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International Myeloma Society

20th Annual Meeting and Exposition

SEPTEMBER 27-30, 2023

Megaron Athens International Conference Centre | Athens, Greece

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International Myeloma Society

CLINICAL LYMPHOMA, MYELOMA & LEUKEMIA

Volume 23, Supplement 2
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Abstracts of the 20th International Myeloma Society Annual Meeting

Athens, Greece
September 27–30, 2023

About the 20th IMS Annual Meeting

The 20th International Myeloma Society Annual Meeting, under the auspices of the International Myeloma Society (IMS), is devoted to fostering scientific and clinical exchange on the latest breakthroughs in multiple myeloma and related plasma cell disorders. Scientific programming at the 20th IMS Annual Meeting will cover the latest genomic advances, new drug targets and agents, immunotherapeutic approaches including Car T-cell therapies, COVID-19 in multiple myeloma, and more.

This book compiles the abstracts from oral and poster session presentations at the 20th IMS Annual Meeting held at the Megaron Athens International Conference Centre in Athens, Greece from September 27–30, 2023. The abstracts are reproduced as submitted by the author and accepted by the Scientific Program Committee. They appear in order of abstract code and track.

About the International Myeloma Society

The International Myeloma Society (IMS) is a professional, scientific, and medical society established to bring together clinical and experimental scientists involved in the study of myeloma.

The purpose of this society is to promote research, education, clinical studies (including diagnosis and treatment), workshops, conferences, and symposia on all aspects of multiple myeloma worldwide.

The IMS is a membership organization comprised of basic research scientists, and clinical investigators in the field along with physicians and other healthcare practitioners.

IMS is governed by a Board of Directors representing practices from around the world and encourages and promotes the study of this expanding field through its annual meeting.

Clinical Lymphoma, Myeloma and Leukemia is the official journal of the International Myeloma Society (IMS).

Table of Contents

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CLINICAL LYMPHOMA, MYELOMA & LEUKEMIA

Volume 23, Supplement 2
September 2023

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Abstracts of the 20th International Myeloma Society Annual Meeting

Clinical Lymphoma, Myeloma & Leukemia, Vol. 23, No. S2, S1-S356, 2023

ORAL PRESENTATIONS

OA-01

Exploiting microbiota commensals to potentiate immunotherapy and delay multiple myeloma evolution

Laura Lucia Cogrossi[1], Roberto Ferrarese[2], Matteo Grioni[2], Paola Zordan[2], Benedetta Mattorre[2], Marco Lorenzoni[2], Greta Meregalli[2], Anna Policastro[2], Sofia Sisti[1], Arianna Brevi[3], Marta Chesi[4], Leif Bergsagel[4], Nicola Clementi[1], Nicasio Mancini[5], Bellone Matteo[2]

[1]San Raffaele Scientific Institute; [2]Vita-Salute San Raffaele University; [3]University California San Diego; [4]Mayo Clinic Arizona; [5]Insubria University

Introduction: Although asymptomatic smoldering multiple myeloma (SMM) often precedes symptomatic MM, most patients affected by SMM are only offered active observation, which increases their frustration and anxiety. A link between gut microbiota and MM aggressiveness has been proposed. We previously showed that the human commensal Prevotella heparinolytica (P.h.) expands Th17 cells that migrate from the gut to the bone marrow (BM) where they favor the expansion of neoplastic plasma cells. At odds, P. melaninogenica (P.m.) limits Th17 cell expansion, thus restraining MM aggressiveness. Similarly, in SMM patients, higher levels of BM IL-17 predicted accelerated disease. Because the gut microbiota also contributes to the clinical efficacy of immune checkpoint blockade (ICB) and neoplastic plasma cells selectively express PD-L1, we hypothesized that modulation of the gut microbiota by P.m. limits the expansion of Th17 cells in mice affected by asymptomatic MM, thus fully exploiting the therapeutic potential of anti-PD-L1 against MM. **Methods:** C57BL/6J mice challenged with MM cells and Vk*MYC mice affected by asymptomatic MM were treated with P.m. and/or anti-PD-L1 and disease progression was monitored by paraprotein quantification in blood. Anemia provided clinical evidence of symptomatic disease. Modification of the gut microbiota composition after the treatment were assessed by16S rRNASeq and shotgun metagenomics. At sacrifice, gut, spleen and BM were analyzed by flow cytometry. To clarify the mechanism of Th17 induction by the gut microbiota, we conducted in vitro assays. **Results:** Administration of P.m. to mice challenged with Vk*MYC-derived MM cells increased the therapeutic efficacy of anti-PD-L1 antibodies limiting the expansion of Th17 cells. Translating the approach in the context of SMM-to-MM evolution, treatment with P.m. in transgenic Vk*MYC mice at the phase of asymptomatic (Early)-MM significantly delayed the progression towards symptomatic (Late)-MM. When P.m. was combined with anti-PD-L1 we further delayed the evolution from Early-MM to Late-MM. Mechanistically, P.m. restrained the expansion of gut-born Th17 cells in the BM without dampening the antitumor cytotoxic response elicited by the ICB. Thus, combination of P.m. and anti-PD-L1 resulted in more favorable Th17/T regulatory cell ratio and CD8/Th17 ratio in the BM. P.m. polarized intestinal DCs to produce less Th17-polarizing cytokines compared to P.h., which conversely promoted Th17 expansion. In vitro stimulation of both human and mouse DCs with P.m. or its conditioned medium reduced polarization of naïve T cells to Th17 cells compared to P.h. **Conclusions:** Taken together, our data support the development of microbiota-based strategies in combination with ICB to treat full-blown MM and to prevent progression of patients affected by asymptomatic SMM to full-blown disease.

OA-02

α-NKG2A blockade overcomes multiple myeloma resistance to BCMA and NKG2D CAR-NKAE cells

Jessica Encinas[1,2], Almudena García-Ortiz[1,2], Elena Maroto-Martín[1,2], Eva Castellano[1,2], Raquel Oliva[1,2], Rafael Alonso[3], Teresa Cedena[3], Alejandra Leivas[1,2], Laura García García[4,5], Beatriz Martín-Antonio[5], Guillermo Suñe[6], Dean Lee[7], Rao Prabhala[8], Daniel Powell Jr.[9], Paula Río[4,5], Joaquín Martínez-López[10], Antonio Valeri[1,2]

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Introduction: CAR NK cells have emerged as a promising, safer and off-the-self therapy for cancer patients. However, inhibitory

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OA-02

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Introduction: CAR NK cells have emerged as a promising, safer and off-the-self therapy for cancer patients. However, inhibitory

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immune checkpoints (IC) can constrain their anti-tumor efficacy, as occurs in CAR-T. HLA-E is overexpressed in several tumors, including metastatic cells, and correlates with a poor prognosis. Here, we have studied the impact of HLA-E and NKG2A expression in a high cohort of MM patients at different stages and we propose the combination of α-NKG2A blocking antibodies with BCMA and NKG2D-CAR NK cell immunotherapies to enhance their anti-MM efficacy. **Methods:** HLA-E and NKG2A expression was analysed in bone marrow (BM) samples from healthy donors (HD) (n=18) and MM patients (n=71) and IFNγ from these sera was quantified. HLA-E modulation by IFNγ and bortezomib (BTZ) as well as the efficacy of α-NKG2A blocking monotherapy against plasma cells (PC), within BM mononuclear cells (BMMCs) cultures, were also studied by multiparametric flow cytometry (MFC). Activated and expanded NK (NKAE) cells were obtained from HD' peripheral blood MCs (PBMCs) after stimulation with irradiated K562-mb21-41BBL cells and IL-2. NKAE cells were then purified and lentivirally transduced with either BCMA or NKG2D CAR. The combination activity of these CAR therapies with mouse and human α-NKG2A antibodies was tested in vitro against primary MM cells, PBMCs and CD34+ cells, by MFC and calcein-release assays, and in vivo using NSG-Tg hIL-15 mice bearing U-266 ffLucGFP MM cells. **Results:** MM patients at relapse/progression exhibit higher HLA-E expression in malignant PC compared to healthy populations and elevated NKG2A expression in NK cells. IFNγ, highly increased in MM patients' BM sera, augments HLA E expression. BTZ can diminish this effect in sensitive MM cells but not in BTZ resistant, suggesting HLA-E/NKG2A as an important IC in this relapse/refractory setting. However, mouse or human α-NKG2A monotherapy treatment does not restore MM patients' NK cells anti tumor efficacy. BCMA-CAR and NKG2D-CAR NKAE cells also have an elevated NKG2A expression and release high levels of IFNγ that augment HLA-E levels in MM cells. In this instance, the combination of CAR NKAE therapies with mouse or human α NKG2A antibodies significantly increases their cytotoxicity, degranulation and IFNγ release against MM cells along with a lack of toxicity against HD' PBMCs and CD34+ from MM patients. Differential immunophenotype after α NKG2A blockade in CAR NKAE cells is being studied by Cytof. Notably, human α-NKG2A pretreatment in NKG2D-CAR NKAE cells have significantly increased mice survival, controlling the tumor in treated mice. α-NKG2A combination with BCMA-CAR therapy is being tested. **Conclusions:** HLA-E and NKG2A are overexpressed in malignant PC and NK cells, respectively, from relapse/progression MM patients. Despite the lack of efficacy of α-NKG2A monotherapy, the combination of α NKG2A antibodies with BCMA and NKG2D-CAR therapies is able to overcome MM CAR target independent resistance in vitro and in vivo.

OA-03

Bispecific T-cell engager response is driven by pre-treatment CD8+ effector memory cells and inhibited by TIGIT+ Tregs in relapsed/refractory multiple myeloma

Ross Firestone[1], Devin McAvoy[1], Tala Shekarkhand[1], Edith Serrano[1], Issam Hamadeh[1], Alice Wang[1], Menglei Zhu[1], Dhwani Patel[1], Carlyn Rose Tan[1], Malin Hultcrantz[1], Sham Mailankody[1], Hani Hassoun[1], Urvi Shah[1], Neha Korde[1], Kylee Maclachlan[1], Heather Landau[1], Michael Scordo[1], Gunjan Shah[1], Oscar Lahoud[1], Sergio Giralt[1], Kinga Hosszu[1], David Chung[1], Alexander Lesokhin[1], Saad Usmani[1]

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Introduction: Teclistamab (Tec) is a CD3 x BCMA bispecific antibody approved for treating relapsed/refractory (RR) multiple myeloma (MM) based on the results of the MajesTEC-1 trial (Usmani S, et al. Lancet 2021, Moreau P, et al. N Engl J Med 2022), where patients with exposure to prior anti-BCMA therapy were excluded. While the therapy demonstrated impressive efficacy, little is known about clinical and patient-specific immunophenotypic predictors of response to therapy. Additionally, the efficacy of Tec in patients with prior anti-BCMA therapy exposure has yet to be assessed. **Methods:** We performed an IRB-approved study profiling the peripheral blood T-cell repertoire from pre-treatment PBMC samples from a 14-patient sub cohort (9 responders, 5 non-responders) of commercial Tec patients via high-dimensional spectral cytometry using a 33-color panel including lineage (CD4, CD8, CD25, CD127, CD45RA, CD45RO, CCR7, CD62L, CD28, CD95), exhaustion (PD-1, LAG3, TIM3, CTLA-4, TIGIT, OX-40, 4-1BB, ICOS, BTLA, CD57), and activation markers (CD69, HLA-DR, CD25, CD27) among others. We also performed a retrospective analysis of clinical outcomes for 41 commercial Tec patients (7 median prior lines of therapy, 23/41 (56%) with prior anti-BCMA therapy exposure) treated as of 05/01/2023. Results were correlated to MM cell BCMA expression. **Results:** Tec responders had enrichment for both CD8+ effector memory T-cells (>6-fold increase, p = 0.03) and CD8+ effector memory cells re-expressing CD45RA (>5-fold increase, p = 0.02). Tec non-responders were enriched for TIGIT+ Tregs (3-fold increase, p = 0.03). No differences between PD-1, CTLA-4, LAG-3 or TIM-3 expression were observed in responders vs non-responders. Clinical outcome analysis identified a high CD8+:CD4+ ratio as predictive of response, and CRS during step-up dosing was strongly associated with Tec efficacy. Among the 31/41 response evaluable patients, the overall response rate for commercial Tec patients with prior anti-BCMA therapy exposure was 58% (11/19 patients) and was similar for anti-BCMA therapy naïve patients. No differences in BCMA expression were noted between responding and non-responding patients or between anti-BCMA exposed and anti-BCMA therapy naïve patients. **Conclusions:** Tec is an effective therapy in RRMM even in patients with prior anti-BCMA therapy exposure. A pre-Tec T-cell population enriched with highly cytotoxic effector T-cells associates with response to therapy, while suppressive TIGIT+ Tregs associate with nonresponse, suggesting a potential therapeutic role for TIGIT blockade or CD25+ cell depletion to enhance the therapeutic efficacy of Tec and other bispecific antibodies. Clinical and translational data from additional enrolled patients will be presented at the meeting.

immune checkpoints (IC) can constrain their anti-tumor efficacy, as occurs in CAR-T. HLA-E is overexpressed in several tumors, including metastatic cells, and correlates with a poor prognosis. Here, we have studied the impact of HLA-E and NKG2A expression in a high cohort of MM patients at different stages and we propose the combination of α-NKG2A blocking antibodies with BCMA and NKG2D-CAR NK cell immunotherapies to enhance their anti-MM efficacy. **Methods:** HLA-E and NKG2A expression was analysed in bone marrow (BM) samples from healthy donors (HD) (n=18) and MM patients (n=71) and IFNγ from these sera was quantified. HLA-E modulation by IFNγ and bortezomib (BTZ) as well as the efficacy of α-NKG2A blocking monotherapy against plasma cells (PC), within BM mononuclear cells (BMMCs) cultures, were also studied by multiparametric flow cytometry (MFC). Activated and expanded NK (NKAE) cells were obtained from HD' peripheral blood MCs (PBMCs) after stimulation with irradiated K562-mb21-41BBL cells and IL-2. NKAE cells were then purified and lentivirally transduced with either BCMA or NKG2D CAR. The combination activity of these CAR therapies with mouse and human α-NKG2A antibodies was tested in vitro against primary MM cells, PBMCs and CD34+ cells, by MFC and calcein-release assays, and in vivo using NSG-Tg hIL-15 mice bearing U-266 ffLucGFP MM cells. **Results:** MM patients at relapse/progression exhibit higher HLA-E expression in malignant PC compared to healthy populations and elevated NKG2A expression in NK cells. IFNγ, highly increased in MM patients' BM sera, augments HLA E expression. BTZ can diminish this effect in sensitive MM cells but not in BTZ resistant, suggesting HLA-E/NKG2A as an important IC in this relapse/refractory setting. However, mouse or human α-NKG2A monotherapy treatment does not restore MM patients' NK cells anti tumor efficacy. BCMA-CAR and NKG2D-CAR NKAE cells also have an elevated NKG2A expression and release high levels of IFNγ that augment HLA-E levels in MM cells. In this instance, the combination of CAR NKAE therapies with mouse or human α NKG2A antibodies significantly increases their cytotoxicity, degranulation and IFNγ release against MM cells along with a lack of toxicity against HD' PBMCs and CD34+ from MM patients. Differential immunophenotype after α NKG2A blockade in CAR NKAE cells is being studied by Cytof. Notably, human α-NKG2A pretreatment in NKG2D-CAR NKAE cells have significantly increased mice survival, controlling the tumor in treated mice. α-NKG2A combination with BCMA-CAR therapy is being tested. **Conclusions:** HLA-E and NKG2A are overexpressed in malignant PC and NK cells, respectively, from relapse/progression MM patients. Despite the lack of efficacy of α-NKG2A monotherapy, the combination of α NKG2A antibodies with BCMA and NKG2D-CAR therapies is able to overcome MM CAR target independent resistance in vitro and in vivo.

OA-03

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Ross Firestone[1], Devin McAvoy[1], Tala Shekarkhand[1], Edith Serrano[1], Issam Hamadeh[1], Alice Wang[1], Menglei Zhu[1], Dhwani Patel[1], Carlyn Rose Tan[1], Malin Hultcrantz[1], Sham Mailankody[1], Hani Hassoun[1], Urvi Shah[1], Neha Korde[1], Kylee Maclachlan[1], Heather Landau[1], Michael Scordo[1], Gunjan Shah[1], Oscar Lahoud[1], Sergio Giralt[1], Kinga Hosszu[1], David Chung[1], Alexander Lesokhin[1], Saad Usmani[1]

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Introduction: Teclistamab (Tec) is a CD3 x BCMA bispecific antibody approved for treating relapsed/refractory (RR) multiple myeloma (MM) based on the results of the MajesTEC-1 trial (Usmani S, et al. Lancet 2021, Moreau P, et al. N Engl J Med 2022), where patients with exposure to prior anti-BCMA therapy were excluded. While the therapy demonstrated impressive efficacy, little is known about clinical and patient-specific immunophenotypic predictors of response to therapy. Additionally, the efficacy of Tec in patients with prior anti-BCMA therapy exposure has yet to be assessed. **Methods:** We performed an IRB-approved study profiling the peripheral blood T-cell repertoire from pre-treatment PBMC samples from a 14-patient sub cohort (9 responders, 5 non-responders) of commercial Tec patients via high-dimensional spectral cytometry using a 33-color panel including lineage (CD4, CD8, CD25, CD127, CD45RA, CD45RO, CCR7, CD62L, CD28, CD95), exhaustion (PD-1, LAG3, TIM3, CTLA-4, TIGIT, OX-40, 4-1BB, ICOS, BTLA, CD57), and activation markers (CD69, HLA-DR, CD25, CD27) among others. We also performed a retrospective analysis of clinical outcomes for 41 commercial Tec patients (7 median prior lines of therapy, 23/41 (56%) with prior anti-BCMA therapy exposure) treated as of 05/01/2023. Results were correlated to MM cell BCMA expression. **Results:** Tec responders had enrichment for both CD8+ effector memory T-cells (>6-fold increase, p = 0.03) and CD8+ effector memory cells re-expressing CD45RA (>5-fold increase, p = 0.02). Tec non-responders were enriched for TIGIT+ Tregs (3-fold increase, p = 0.03). No differences between PD-1, CTLA-4, LAG-3 or TIM-3 expression were observed in responders vs non-responders. Clinical outcome analysis identified a high CD8+:CD4+ ratio as predictive of response, and CRS during step-up dosing was strongly associated with Tec efficacy. Among the 31/41 response evaluable patients, the overall response rate for commercial Tec patients with prior anti-BCMA therapy exposure was 58% (11/19 patients) and was similar for anti-BCMA therapy naïve patients. No differences in BCMA expression were noted between responding and non-responding patients or between anti-BCMA exposed and anti-BCMA therapy naïve patients. **Conclusions:** Tec is an effective therapy in RRMM even in patients with prior anti-BCMA therapy exposure. A pre-Tec T-cell population enriched with highly cytotoxic effector T-cells associates with response to therapy, while suppressive TIGIT+ Tregs associate with nonresponse, suggesting a potential therapeutic role for TIGIT blockade or CD25+ cell depletion to enhance the therapeutic efficacy of Tec and other bispecific antibodies. Clinical and translational data from additional enrolled patients will be presented at the meeting.

OA-04

Single cell multi-omic dissection of response and resistance to chimeric antigen receptor T cells against BCMA in relapsed multiple myeloma

Nora Grieb[1], Ronald Weiss[1], Jaren Sia[1], Michael Rade[1], Luise Fischer[1], Patrick Born[1], Stephan Fricke[2], Paul Franz[2], Jonathan Scolnick[3], Stacy Xu[3], Anne Sophie Kubasch[1], Ronny Baber[1], Song Yau Wang[1], Sandra Hoffmann[1], Enrica Bach[1], Klaus Metzeler[1], Marco Herling[1], Madlen Jentzsch[1], Georg-Nikolaus Franke[1], Ulrich Sack[1], Kristin Reiche[2], Ulrike Köhl[2], Uwe Platzbecker[1], Vladan Vucinic[1], Maximilian Merz[1]

[1]University Hospital of Leipzig; [2]Fraunhofer IZI; [3]Singleron Biotechnologies

Introduction: Robust biomarkers of response and resistance to chimeric antigen receptor (CAR) T cell therapy in patients with relapsed/refractory multiple myeloma (RRMM) are lacking. We conducted a longitudinal single-cell multi-omics study to identify factors predicting response to BCMA-directed CAR T cells. **Methods:** Peripheral blood samples from 10 patients (8 Ide-cel; 2 Cilta-cel) were collected on the day of leukapheresis and 30 days after CAR T cell treatment. Bone marrow biopsies were performed on day 30 after CAR T cell therapy. We used 57 oligonucleotide-coupled antibodies for surface proteome analysis. Libraries for single cell BCR, TCR and RNA were generated using the 10x genomics 5' chemistry. Cell types were annotated with Seurat and WNN. scCODA identified cell type composition changes. InferCNV detected CNVs in malignant plasma cells. Ligand-receptor signaling was inferred with iTalk and CellPhoneDB. CAR T cell in vitro functionality was tested through cytotoxicity assays. For analyses patients were divided by their response to CAR T cell therapy on day 30 after infusion (CR: n=5, no CR: n=5). **Results:** We sequenced 178,142 cells (median 7,990 cells/sample, range 1,569-10,972 cells) and already observed differences between patients in CR and no CR at leukapheresis. CR patients harbored more CD8+ TEM and NK cells but fewer monocytes. Non-responders showed recurrently higher PIM kinase expression in monocytes, dendritic and NK cells as well as higher protein expression of immune checkpoints on monocytes (CD39) and NK cells (CD94). Cell-cell interaction analysis identified inhibitory communication of monocytes with NK and CD8+ T cells in non-responders. Since we detected an immunosuppressive environment in non-responders at leukapheresis, we aimed at characterizing the functionality of manufactured CAR T cells. CAR T cells isolated from patients in CR and no CR at day 7 post-infusion, effectively eliminated MM cells (U-266), indicating that also CAR T cells from non-responders remained functional in vitro. Comparing single-cell transcriptomes of CAR T cells isolated from patients in CR who received Cilta-cel or Ide-cel, we noticed an upregulation of genes associated with cell cycle regulation, exhaustion/senescence, and chemotaxis in Cilta-cel CAR T cells. Surface proteomics revealed that hyperexpanded CAR T cells displayed a more exhausted and senescent phenotype, characterized by higher expression levels of immune checkpoints and NK cell receptors (PD1, CD57, CD94), as well as lower expression levels of markers associated with activation. In contrast, non-hyperexpanded CAR T cell clonotypes exhibited a protein expression profile marked by downregulation of exhaustion/senescence markers (e.g., TIM-3, KLRB1, KLRG1, and CD337). **Conclusions:** Our study indicates an association between an immunosuppressive microenvironment that is already present at time of leukapheresis and resistance to CAR T cell therapy in RRMM.

OA-05

Efficacy of forimtamig, a GPRC5DxCD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM): analysis of patient and disease-related factors associated with responses

Simon Harrison[1], Caroline Hasselbalch Riley[2], Salomon Manier[3], Sung-Soo Yoon[4], Antonio Pinto[5], Titouan Cazaubiel[6], Anna Guidetti[7], Rakesh Popat[8], Cyrille Touzeau[9], Enrique Ocio[10], Fritz Offner[11], Paula Rodríguez-Otero[12], Ilaria Rizzello[13], María-Victoria Mateos[14], Ann-Marie Bröske[15], Iryna Dekhtiarenko[16], Natalie Dimier[17], Jan Eckmann[15], Hans-Joachin Helms[18], Wolfgang Jacob[15], Meike Schneider[18], Nassim Sleiman[18], Martin Weisser[15], Carmelo Carlo-Stella[19]

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Introduction: Forimtamig, a GPRC5DxCD3 T-cell-engaging bispecific antibody (BsAb), is currently being evaluated in patients (pts) with RRMM. In a first-in-human Phase 1a dose-escalation study (BP42233; NCT04557150), forimtamig induced deep and durable responses in heavily pre-treated pts and had a safety profile consistent with its MOA and target expression (Carlo-Stella et al. ASH 2022). We evaluated clinical responses in high-risk subgroups. **Methods:** Eligible pts had RRMM and ≥1 prior line(s) of therapy (LOT), and were refractory to a PI and an IMiD. Pts received

OA-04

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OA-05

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forimtamig target doses of 0.018–10mg either IV or SC with prior administration of 2 step doses. Efficacy was evaluated in the following subgroups: age ≥65 years, >4 prior LOT, triple-class and penta-drug refractory disease, prior BCMA-targeted therapy, high-risk cytogenetics (del(17p), t(4;14), t(14;16)), 1q21 gain (irrespective of other high-risk aberrations), ISS disease Stage III at baseline, high tumor burden (>median sBCMA at baseline), and presence of soft tissue plasmacytoma (bone-based and extramedullary). The primary endpoint was objective response rate (ORR) assessed per IMWG criteria. **Results:** As of January 25, 2023, 120 pts in the efficacy-evaluable population had received forimtamig during the dose escalation. Median age was 63 years, and median time from diagnosis to enrollment was 6.2 years (range: 0.4–30.7). ORR across all dose levels was 66.7% (very good partial response or better: 54.2%), with a median duration of response of 12.2 months (range: 0.03–20.8) and 61.3% of responders with ongoing responses at cut-off. High ORRs were observed across all risk groups. ORRs in pts aged ≥65 years (n=52) and in pts with >4 LOT (n=49) were 71.2% and 63.3%, respectively. Pts with high-risk cytogenetics (n=33) had an ORR of 63.4%, while those with 1q21 gain (n=15) had an ORR of 86.7%. ORRs in pts with triple-class (n=81) and penta-drug (n=45) refractory disease were 60.5% and 57.8%, respectively. Twenty-nine pts had received prior BCMA-targeted therapy (n=19 with antibody-drug conjugates [ADCs], n=5 with BsAbs, and n=5 with CAR T-cells, including n=3 with ADCs and BsAbs or CAR T-cells). ORRs were 51.2% in all pts, 47.4% in ADC, 42.9% in BsAb, and 66.7% in CAR T-cell. ORRs in pts with ISS disease Stage III (n=24) and extramedullary disease (n=28), factors known to be of prognostic relevance for T-cell-directed therapy, were 70.8% and 50.0%, respectively. Levels of sBCMA, a potential novel biomarker for tumor load and disease monitoring, above (n=54) and below (n=55) the median at baseline (327 ng/ml) were associated with ORRs of 55.6% and 80.0%, respectively. **Conclusions:** Forimtamig induced objective responses in all subgroups and showed high clinical activity in pts with high-risk features that are known to be clinically relevant in T-cell-directed therapy. Optimization of the forimtamig dose and schedule is ongoing, as well as evaluation of long-term treatment benefit, including in pts with high-risk disease.

OA-06

Robust in vivo expansion and long-term persistence of anti-BCMA CAR T cells, PHE885, manufactured in <2 days on the T-Charge platform

Shuntaro Ikegawa[1], Rao Prabhala[1], Adam Sperling[1], Sarah Nikiforow[1], David Quinn[2], Dexiu Bu[2], Jennifer Mataraza[2], David Pearson[2], Lawrence Rispoli[2], Marc Credi[2], Nina Orwitz[2], Laksmi Potluri[3,4], Yohei Arihara[1], Carol Reynolds[1], Michela Ansuinelli[1], Tuyet Nguyen[1], Serena Vita[2], Nikhil Munshi[5], Jerome Ritz[1]

[1]Dana-Farber Cancer Institute; [2]Novartis Institutes for BioMedical Research; [3]Wayne State University; [4]DMC Sinai Grace Hospital; [5]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/Harvard Medical School

Introduction: BCMA targeted CAR-T cell therapy has clinical benefits for patients with r/r MM, but long manufacturing times and poor in vivo persistence remain unresolved problems. The T-charge platform is a novel rapid manufacturing process that reduces manufacturing time to < 2 days and preserves less-differentiated T cells in the CAR-T product. Here, we present correlative data from the ongoing Phase I trial in r/r MM (NCT04318327) of PHE885, a fully human product manufactured using the T-Charge platform. **Methods:** We studied serial samples from 32 patients who received PHE885 at the Dana-Farber Cancer Institute. PHE885 manufacturing and CAR T cell persistence were assessed in apheresis samples (APH), final product (FP), and peripheral blood (PB) following infusion using flow cytometry and CyTOF. Bulk T cell receptor (TCR) sequencing was used to monitor PHE885 repertoire diversity over time. Serum cytokines and soluble BCMA were also measured. **Results:** We have previously reported a 98% overall response rate (ORR) across all dose levels (2.5-20x10^6 CAR-T cells) and 100% ORR at >5x10^6 cell dose. Here we report immune assessment of the product and after in vivo expansion. The proportion of stem-like memory T cells (TSCM) in FP was preserved following manufacturing. CyTOF and TCR sequencing revealed that TSCM in FP had a highly activated and proliferative phenotype and significantly higher TCR repertoire diversity than memory T cells. PHE885 CAR T cells expanded rapidly after infusion reaching median peak levels of 3,118 cells/ul (range 373 to 17,865) in PB at a median of 14 days (range 10 to 27) after infusion. Cytokine release syndrome (CRS) occurred with expansion of CAR-T cells and was associated with increased serum levels of IFNg, TNFa, and IL-6. While the peak CAR-T expansion was not associated with the dose of PHE885, the frequency of TSCM in FP positively correlated with the expansion of CAR-T on day 14 after infusion. CAR-T cells at day 14 after infusion were predominately effector memory (TEM) and exhibited a highly activated and proliferative phenotype. Following peak expansion there was emergence of effector memory cells expressing CD45RA (TEMRA) over time. CAR-T cells during peak expansion in vivo had higher levels of TCR repertoire diversity than non-CAR-T cells, and post-infusion CAR-T cells shared significantly more TCR clonotypes with TSCM than with memory T cells in FP, suggesting that the highly heterogeneous CAR-T clones at peak expansion were derived from TSCM clones in FP. High levels of PHE885 persistence were observed with transgene detectable by qPCR in 67% of patients, and >10% of CD3+ T cells by flow cytometry in 39% of patients at 6 months. In patients with long-term persistence, CAR-T cells maintained a highly diverse TCR repertoire. **Conclusions:** The T-charge rapid manufacturing platform successfully preserved TSCM clones in the FP leading to a highly heterogeneous and proliferative CAR-T expansion with durable persistence.

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OA-06

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OA-07

Phase I Study of BCMA CAR-T using instant manufacturing platform or traditional production process for relapsed/refractory multiple myeloma therapy

Hui Liu[1], Ting Wang[1], Yazi Yang[1], Ru Feng[1], Jiangtao Li[1], Chunli Zhang[1], Jiefei Bai[1], Yanping Ding[2], Guanghua Liu[2], Fei Wu[2], Xinan Lu[2], Ting He[2]

[1]Beijing Hospital; [2]Beijing Imunopharm Technology Co., Ltd.

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OA-08

GPRC5D-targeted CAR-T cell therapy in patients with relapsed or refractory multiple myeloma progressing after or refractory to BCMA CAR-T cell therapy: updated eesults from a phase 2 clinical trial

Jieyun Xia[1], Zhenyu Li[2], Hujun Li[1], Zhiling Yan[2], Mengdi Xu[1], Kailin Xu[2]

[1]The Affiliated Hospital of Xuzhou Medical University; [2]Blood Diseases Institute, Xuzhou Medical University, Xuzhou, Jiangsu, China

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OA-07

Phase I Study of BCMA CAR-T using instant manufacturing platform or traditional production process for relapsed/refractory multiple myeloma therapy

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toxic effects were reported. One (9%) patient had a grade 1 nail change. One patient died of intracranial hemorrhage 29 days after CAR-T cell infusion, and no abnormal coagulation was observed. **Conclusions:** Our study demonstrates anti-GPRC5D CAR T-cell therapy are clinical active with a favorable safety profile in pts who do not respond to or relapse after anti-BCMA CAR T-cell therapy.

OA-09

Combination of forimtamig with standard of care improves depth and duration of response in preclinical models of multiple myeloma

Jan Eckmann[1], Pablo Umana[2], Christian Klein[2], Tanja Fauti[2], Carina Hage[2], Stefanie Lechner[2], Bruno Paiva[3,4], Aintzane Zabaleta[3], Laura Blanco[3]

[1]Roche Innovation Center Munich, Penzberg, Germany; [2]Roche/Genentech; [3]Clínica Universidad de Navarra (CUN), Centro de Investigación Médica Aplicada (CIMA LAB Diagnostics), IDISNA; [4]CIBERONC

Introduction: Forimtamig (forimtamig) is a 2:1 GPRC5D T cell bispecific antibody with high clinical response rates of > 60% in relapsed or refractory multiple myeloma (MM) patients. **Methods:** Here, we highlight the therapeutic potential of combining forimtamig with standard of care (SoC) agents in MM using clinically relevant ex vivo and in vivo models of myeloma **Results:** We combined forimtamig with carfilzomib, daratumumab and/or pomalidomide in bone marrow aspirate samples from MM patients. Tumor lysis increased 2-fold from 40% to 80% when forimtamig was combined with daratumumab or with daratumumab and pomalidomide while combination with pomalidomide or carfilzomib showed no further increase in response. Antitumor effects were associated with increase of CD69 and PD-1 on CD8+ T cells and secretion of IFNg, MIP1a and granzyme A. Activation of CD8+ TILs was increased in combination with pomalidomide as shown by a 4-fold increased cytokine release and elevated surface expression of CD137 and CD25 compared to forimtamig alone. Forimtamig induced activation of NK cells, as measured by CD25 and CD107a expression which was increased 3-fold in combination with daratumumab and increased further for the triple combination with pomalidomide. A combination with carfilzomib did not change the activation status of autologous TILs or NK cells. Next, we explored any effect of SoC combinations on depth and durability of response in tumor-bearing humanized mice using a fixed duration schedule. Combination with pomalidomide resulted in faster onset of regressions in 20% of mice and increased tumor cell lysis (65% vs 45%) at the end of cycle 1 (C1). However, the progression free survival (PFS) rate of 53% achieved by forimtamig monotherapy at 3 weeks after last dosing was not improved overall. Although daratumumab combination had no impact on the depth of early responses, the PFS rate increased by 10%. carfilzomib induced rapid onset of regressions in 70% of mice in C1 and showed the highest PFS rate of 70%. To test potential effects of SoC combinations on cytokine release syndrome (CRS), we measured cytokine levels in serum of mice 48h after treatment initiation. In line with our ex vivo results, pomalidomide combination further increased serum levels of IFNg, IL2 and TNFa compared to forimtamig alone while daratumumab induced only a moderate increase of TNFa. In contrast, we observed a slight decrease in cytokine release in combination with carfilzomib. **Conclusions:** Synergistic anti-tumoral and NK stimulatory effects suggest a benefit of daratumumab combination in patients with high tumor burden and high risk of developing CRS. Broad immunomodulatory effects of pomalidomide could help sustain T cell responses in patients but may increase the risk of CRS. Considering the importance of balancing CRS and efficacy, carfilzomib was identified as another promising combination partner for forimtamig.

OA-10

Four years treatment with zoledronic acid is superior to two years in protection against progressive bone disease in multiple myeloma

Michael Gundesen[1], Fredrik Schjesvold[2], Annette Juul Vangsted[3], Carsten Helleberg[3], Einar Haukås[4], Trine Silkjær[5], Elena Manuela Teodorescu[6], Bo Amdi Jensen[7], Tobias Slørdahl[8], Jon Thor Asmussen[9], Hareth Nahi[10], Niels Abildgaard[1,11], Thomas Lund[1,11]

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OA-09

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of progressive bone disease, and if this can be achieved without unacceptable high risk of BON. **Methods:** Patients with newly diagnosed symptomatic MM were included and randomized after 2 years ZOL treatment to either two additional years of monthly IV ZOL treatment or observation. Patients with progressive bone disease (PBD) just prior to randomization did not proceed to randomization but remained on ZOL treatment. Patients were followed with monthly visits and blood samples. Bone imaging by low-dose whole body CT was performed every 6 months and quality of life questionnaire data were sampled every 3 months. Moreover, bone imaging was performed when clinically indicated. Criteria for PBD were ≥25% increase in size of existing osteolytic lesions or new osteolytic lesions (both at least 10 mm increase/diameter), new fractures, or lesions needing irradiation therapy or surgery. **Results:** A total of 192 patients with myeloma were randomized, median follow up after randomization was 21.6 months. In total, 8 cases of PBD were found in the ZOL arm and 18 cases were found in the observational arm. Risk of PBD was significantly lower in the ZOL arm (hazard ratio: 0.38, 95% CI (0.17-0.88), p = 0.024). The incidence of BON after 2 years was 3.6% and not different between the two groups. We found no difference in overall survival between the ZOL arm and the observational arm **Conclusions:** Four years of monthly zoledronic acid are superior to two years treatment in protection against progressive bone disease in multiple myeloma.

OA-11

Utility of 18FDG-PET/CT for risk prediction in relapsed/refractory multiple myeloma patients undergoing CAR-T cell therapy: analysis of baseline and early assessment scans after one and three months

Luis-Esteban Tamariz-Amador[1], Ana Alfonso-Pierola[1], Sofia Huerga-Dominguez[1], Maria Panizo-Inoges[1], Maria-Luisa Palacios-Berraquero[2], Sara Villar[1], Maria Marcos-Jubilar[1], Victoria Betech-Antar[1], Evelyn Valencia-Espinoza[1], Jose Rifon[1], Felipe Prosper[1], Jesús San-Miguel[3], Maria-Jose Garcia-Velloso[1], Paula Rodríguez-Otero[1]

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Introduction: Chimeric antigen receptor (CAR) T-cells are an effective treatment for relapsed/refractory multiple myeloma (RRMM) patients. Unfortunately, a significant number relapse during the first two years. The predictive value of positron emission tomography/computed tomography (18FDG-PET/CT) in this group of patients has not been established. Our aim is to assess the utility of 18FDG-PET/CT for risk prediction in RRMM patients undergoing CAR-T cell therapy. **Methods:** Sixty-two patients received CAR-T cell therapy between April 2018 and February 2023. 18FDG-PET/CT was performed at baseline for all patients, and 1 and 3 months after infusion for 57 (92%) and 51 (82%) patients, respectively. We analyzed the presence of focal lesions (FL), paramedullary (PMD), and extramedullary disease (EMD); bone marrow (BM) and FL uptake measured by Deauville score. 18FDG-PET/CT was positive if Deauville scores ≥4 was found for any of the previous variables. **Results:** Out of 62 baseline exams, 49 (79%) were positive. At baseline the presence of hypermetabolic EMD was the only variable associated with worse progression-free (PFS) (hazard ratio [HR] 4.8 [95%CI 2.0 – 11.3; P < .001]) and overall survival (OS) (HR 2.9 [95%CI 1.2 – 6.8; P = .018]). In terms of response evaluation, 33 out of 57 (58%) and 18 out of 51 (35%) scans were positive 1 and 3 months after infusion, respectively. A negative scan at 3 months was associated with improved PFS (median 16 months [95%CI 12 – 19] vs. 6.8 [95%CI 3.4 – 10.3]; P = .04) and OS (median 34 months [95%CI 16 – 52]; vs. 11 [95%CI 7.6 – 15]; P = .012). Interestingly, the assessment at month 1 did not detect any differences in PFS (P = .28), although it did reveal statistically significant differences in OS (median 34 vs. 13 months; P = .021). The presence of hypermetabolic FL with Deauville = 4 did not significantly impact PFS when compared to FL with a Deauville ≤ 3 at both month 1 (median NR vs. 14.5 months; P = 0.23) and 3 (median 18 vs. 8.1 months; P = 0.33). Furthermore, the persistence of hypermetabolic EMD at 3 months was associated with shorter PFS (HR 18.2 [95%CI 5.0 – 65.9]; P < .001) and OS (HR 5.7 [95%CI 1.8 – 18.4; P = .003]). Conversely to basal scans, persistent hypermetabolic PMD at month 3 was associated with shorter PFS (median 3.7 months [95%CI 3.6 – 3.9] vs. 14.5 [95%CI 9.0 – 19.9]; P < .001) (HR 6.2 [95%CI 1.9 – 21.1]; P = .002) and OS (median 7.8 months [95%CI 3.4 – 12.2] vs. 34.2 [95%CI 19.9 – 45.6]; P < .001) (HR 8.3 [95%CI 2.5 – 27.6]; P = .001). **Conclusions:** In conclusion, our study suggests that 18FDG-PET/CT is a valuable tool for staging and prognostication in patients with RRMM treated with CAR-T cells. Based on our results, the optimal timing for response assessment is 3 months after infusion and the persistence of FL uptake with Deauville score = 4 should be evaluated with caution along with other exams.

OA-12

Predictors of unsustained measurable residual disease (MRD) negativity in transplant-eligible multiple myeloma (MM) patients

Camila Guerrero[1], Noemi Puig[2], Teresa Cedena[3], Maria-Jose Calasanz[4], Norma Gutierrez[5], Manuela Fernandez-Guijarro[6], Albert Oriol[7], Rafael Rios[8], Miguel Teodoro Hernandez Garcia[9], Rafael Martinez-Martinez[10], Joan Bargay[11], Felipe de Arriba de la Fuente[12], Luis Palomera[13], Ana Pilar Gonzalez-Rodriguez[14], Marta-Sonia Gonzalez-Perez[15], Alberto Orfao[16], María-Victoria Mateos[17], Joaquin Martinez-Lopez[3], Laura Rosinol[18], Joan Bladé[19], Juan José Lahuerta Palacios[20], Jesús San-Miguel[21], Bruno Paiva[4]

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of progressive bone disease, and if this can be achieved without unacceptable high risk of BON. **Methods:** Patients with newly diagnosed symptomatic MM were included and randomized after 2 years ZOL treatment to either two additional years of monthly IV ZOL treatment or observation. Patients with progressive bone disease (PBD) just prior to randomization did not proceed to randomization but remained on ZOL treatment. Patients were followed with monthly visits and blood samples. Bone imaging by low-dose whole body CT was performed every 6 months and quality of life questionnaire data were sampled every 3 months. Moreover, bone imaging was performed when clinically indicated. Criteria for PBD were ≥25% increase in size of existing osteolytic lesions or new osteolytic lesions (both at least 10 mm increase/diameter), new fractures, or lesions needing irradiation therapy or surgery. **Results:** A total of 192 patients with myeloma were randomized, median follow up after randomization was 21.6 months. In total, 8 cases of PBD were found in the ZOL arm and 18 cases were found in the observational arm. Risk of PBD was significantly lower in the ZOL arm (hazard ratio: 0.38, 95% CI (0.17-0.88), p = 0.024). The incidence of BON after 2 years was 3.6% and not different between the two groups. We found no difference in overall survival between the ZOL arm and the observational arm **Conclusions:** Four years of monthly zoledronic acid are superior to two years treatment in protection against progressive bone disease in multiple myeloma.

OA-11

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OA-12

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OA-11

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OA-12

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Introduction: The role of sustained MRD negativity as a biomarker to stop treatment is being investigated in transplant-eligible MM. Thus, it is important to identify risk-factors of MRD resurgence and/or progressive disease (PD) among patients achieving undetectable MRD to avoid undertreating them. **Methods:** Transplant-eligible MM patients enrolled in the GEM2012MENOS65/GEM2014MAIN clinical trials who achieved MRD negativity by NGF (limit of detection, 2x10-6) were analyzed. A multivariate Fine-Gray statistical model was applied to the dataset, subsequently fitting a weighted Cox model to assess the cumulative incidence of MRD resurgence and/or PD. Death without PD was considered a competing event. **Results:** A total of 267/458 (58%) patients achieved MRD negativity by NGF after induction (n=125), HDT/ASCT (n=77), consolidation (n=32) or after the first year of maintenance therapy (n=33) and were eligible for the analysis. After a median follow-up of 73 months since the first MRD negative assessment, 145/267 (54%) patients remained progression-free and had sustained MRD negativity until last time to follow up, while 111/267 (42%) patients had MRD resurgence (n=71) and/or PD (n=40), and 11/267 (4%) patients died without PD. The overall cumulative incidence of an MRD resurgence and/or PD event at 73 months was 44%. Time from achievement of first MRD negativity until MRD resurgence was similar in patients with or without subsequent disease progression (21 [8-34] and 25 [13-47] months, respectively, P=.188). The median PFS since MRD resurgence until PD or death was 39 months. The only prognostic factors at diagnosis that predicted MRD resurgence and/or PD were an International staging system (ISS) 3 and ≥0.01% CTCs. LDH levels and the R-ISS were not significantly associated, while a high-risk cytogenetic status tended towards significance. Treatment randomization with Bu-Mel or Mel-200 HDT in the GEM2012MENOS65 trial, and with IRD vs RD in the GEM2014MAIN trial also had no impact. Patients who achieved MRD negativity after induction (< 6 months) had significantly lower risk of MRD resurgence and/or PD than those who achieved MRD negativity at a later time point. Because of the potential complementarity provided by patients' ISS, CTC levels (≥0.01%) and the time to achievement of first MRD negative assessment, the three risk factors were modeled for a more accurate prediction of MRD resurgence and/or PD. Accordingly, patients having none versus one versus two or more risk factors showed 5-year rates of MRD resurgence and/or PD of 16%, 33% and 57%, respectively (P<.001). **Conclusions:** We present a dynamic model to predict the risk of MRD resurgence and/or PD after MRD negativity. This dynamic model relies on three easily measurable risk factors. The insights it offers can prove valuable in the careful selection of transplant-eligible MM patients for whom treatment cessation due to MRD negativity is being investigated in clinical trials or its implementation is being considered in routine practice.

OA-13

Increased levels of circulating tumor cells correlate with adverse clinical outcomes and distinct biological features in newly diagnosed patients with multiple myeloma

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Introduction: Circulating tumor cells (CTCs) have shown an independent prognostic value in transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM). In this study, we aimed to evaluate the optimal clinical CTC cut-off for both TE and transplant ineligible (TI) NDMM pts, using the high-sensitive next generation flow-cytometry (NGF). Moreover, we performed matched analysis of both bone marrow (BM) and peripheral blood (PB) to highlight any possible inconsistencies between the two sites. **Methods:** We studied 550 NDMM pts; 210 (38%) were TE and 340 (62%) were TI. NGF was used for the detection of clonal cells in both BM and PB. To define the optimal clinical cut-off of CTCs, we performed various multivariable regression models including CTCs, ISS (or R-ISS), cytogenetic status and LDH, and selected the one with the best performance. The median follow-up period was 41 months (range: 5-66 months). The BM niche profiling was examined with mass cytometry (CyTOF, n=15 pts) and various multicolor flow cytometry panels (n=199

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Introduction: The role of sustained MRD negativity as a biomarker to stop treatment is being investigated in transplant-eligible MM. Thus, it is important to identify risk-factors of MRD resurgence and/or progressive disease (PD) among patients achieving undetectable MRD to avoid undertreating them. **Methods:** Transplant-eligible MM patients enrolled in the GEM2012MENOS65/GEM2014MAIN clinical trials who achieved MRD negativity by NGF (limit of detection, 2x10-6) were analyzed. A multivariate Fine-Gray statistical model was applied to the dataset, subsequently fitting a weighted Cox model to assess the cumulative incidence of MRD resurgence and/or PD. Death without PD was considered a competing event. **Results:** A total of 267/458 (58%) patients achieved MRD negativity by NGF after induction (n=125), HDT/ASCT (n=77), consolidation (n=32) or after the first year of maintenance therapy (n=33) and were eligible for the analysis. After a median follow-up of 73 months since the first MRD negative assessment, 145/267 (54%) patients remained progression-free and had sustained MRD negativity until last time to follow up, while 111/267 (42%) patients had MRD resurgence (n=71) and/or PD (n=40), and 11/267 (4%) patients died without PD. The overall cumulative incidence of an MRD resurgence and/or PD event at 73 months was 44%. Time from achievement of first MRD negativity until MRD resurgence was similar in patients with or without subsequent disease progression (21 [8-34] and 25 [13-47] months, respectively, P=.188). The median PFS since MRD resurgence until PD or death was 39 months. The only prognostic factors at diagnosis that predicted MRD resurgence and/or PD were an International staging system (ISS) 3 and ≥0.01% CTCs. LDH levels and the R-ISS were not significantly associated, while a high-risk cytogenetic status tended towards significance. Treatment randomization with Bu-Mel or Mel-200 HDT in the GEM2012MENOS65 trial, and with IRD vs RD in the GEM2014MAIN trial also had no impact. Patients who achieved MRD negativity after induction (< 6 months) had significantly lower risk of MRD resurgence and/or PD than those who achieved MRD negativity at a later time point. Because of the potential complementarity provided by patients' ISS, CTC levels (≥0.01%) and the time to achievement of first MRD negative assessment, the three risk factors were modeled for a more accurate prediction of MRD resurgence and/or PD. Accordingly, patients having none versus one versus two or more risk factors showed 5-year rates of MRD resurgence and/or PD of 16%, 33% and 57%, respectively (P<.001). **Conclusions:** We present a dynamic model to predict the risk of MRD resurgence and/or PD after MRD negativity. This dynamic model relies on three easily measurable risk factors. The insights it offers can prove valuable in the careful selection of transplant-eligible MM patients for whom treatment cessation due to MRD negativity is being investigated in clinical trials or its implementation is being considered in routine practice.

OA-13

Increased levels of circulating tumor cells correlate with adverse clinical outcomes and distinct biological features in newly diagnosed patients with multiple myeloma

Ioannis Kostopoulos[1], Ioannis Ntanasis-Stathopoulos[1], Pantelis Rousakis[1], Panagiotis Malandrakis[1], Chrysanthi Panteli[1], Evangelos Eleutherakis-Papaiakovou[1], Nikolaos Angelis[1], Vassiliki Spiliopoulou[1], Rodanthi-Eleni Syrigou[1], Georgia Dimitrakopoulou[1], Despina Fotiou[1], Magdalini Migkou[1], Maria Gavriatopoulou[1], Efstathios Kastritis[1], Meletios Dimopoulos[1], Ourania Tsitsilonis[1], Evangelos Terpos[1]

[1]National and Kapodistrian University of Athens, Athens, Greece

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pts) that allowed the detection of 32 distinct immune populations. **Results:** CTCs were detected in 493/550 (89.6%) pts with a median value of 0.01% of all nucleated cells. Increased levels of CTCs correlated with advanced ISS stage (0.002%, 0.007% and 0.037% for pts with ISS-I, ISS-II and ISS-III respectively, p< 0.0001), high risk cytogenetics (median: 0.038% vs. 0.006% in standard risk, p< 0.0001), and higher levels of b2-microglobulin and BM infiltration. Pts with phenotypic inconsistencies between BM and PB had higher levels of CTCs and more often a diffuse MRI pattern than those with a phenotypic agreement (40% vs.10%, p< 0.01). The optimal clinical cut-off of CTCs was defined at 0.02%, stratifying pts in two different prognostic groups with high and low CTCs [median PFS: 40 months vs. not reached (NR), HR: 2.59, 95% CI:1.71-3.91, p< 0.0001]. In the multivariable analysis the 0.02% cut-off was independent from ISS and/or cytogenetics and was clinically relevant for both TI (median PFS: 47 vs. 23 months, p< 0.0001) and TE pts (median PFS: NR in both categories, p< 0.01). The 2-year probability of MRD negativity was 45% and 67% for pts with high and low CTCs; median time to MRD negativity was 34 vs. 17 months, respectively (HR:1.7, 95% CI:1.2-2.4, p=0.002). Of note, pts with high CTCs who achieved MRD negativity, modulated their unfavorable risk status and showed a similar PFS with those who had low CTCs. Beyond prognostication, pts with high CTC levels showed unique BM immune profiles characterized by increased levels of T cells, NK cells, TAMs and an increased memory/naive B cell ratio. **Conclusions:** The presence of CTC at a level of >0.02% confers an adverse prognostic factor for NDMM pts, irrespective of their transplant status. Since the liquid biopsy is a better representative of the entire tumor load than a tissue biopsy sample, the analysis of CTCs may serve as the new hallmark for the real-time evaluation of a patient's disease and immune status.

OA-14

Persistent bone marrow and imaging MRD negativity may guide the duration of lenalidomide maintenance following ASCT in patients with multiple myeloma

Panagiotis Malandrakis[1], Ioannis Ntanasis-Stathopoulos[1], Ioannis Kostopoulos[1], Maria Gavriatopoulou[1], Foteini Theodorakakou[1], Despina Fotiou[1], Magdalini Migkou[1], Maria Roussou[1], Vassiliki Spiliopoulou[1], Evangelos Eleutherakis-Papaiakovou[1], Efstathios Kastritis[1], Ourania Tsitsilonis[1], Meletios Dimopoulos[1], Evangelos Terpos[1]

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Introduction: Autologous stem cell transplantation (ASCT) and lenalidomide maintenance is the standard of care for eligible patients with newly diagnosed multiple myeloma (MM). Sustained marrow and imaging minimal residual disease (MRD) correlate with prolonged progression-free (PFS) and overall survival (OS). It is essential to define the optimal duration of maintenance and reveal criteria to discontinue maintenance. **Methods:** We prospectively included patients with newly diagnosed MM from 1/1/2016 to 31/12/2019. MRD (Euroflow) was assessed in patients with stringent complete remission (sCR) and then at 6, 12, 24, and 36 months after the initiation of lenalidomide maintenance. Patients with at least 3 consecutive MRD negative results and after 36 months of maintenance underwent PET/CT. If patients had achieved imaging MRD negativity, they discontinued lenalidomide maintenance and MRD was performed every 6 months thereafter. If a patient converted from MRD negative to positive or if the patient relapsed from sCR, lenalidomide maintenance was restarted. **Results:** Overall, 151 patients received induction with proteasome inhibitor-based regimens (VCD, VRD) and underwent ASCT. During a median follow-up of 70 months (range 6-84 months) from the time of ASCT, 44 (29.1%) patients had disease progression and 20 (13.2%) patients died. Out of 107 patients who did not progress or die, 42 (39.2%) patients achieved sustained bone marrow MRD negativity and imaging MRD negativity at 3 years after maintenance initiation. Thus, they discontinued lenalidomide maintenance. Their median age at MM diagnosis was 56 years (range 43-66). Twenty-one (50%) patients were males, whereas 52.4% had IgG, 26.2% had IgA and 21.4% had light chain MM. The patient distribution per ISS was ISS 1 63.4%, ISS 2 19.5% and ISS 3 17.1%, whereas per R-ISS was RISS-1 57.5%, RISS-2 35% and RISS-3 7.5%. The median follow up time from maintenance discontinuation for all patients was 16 months (range 1-31). Six months after discontinuation of lenalidomide maintenance, 39 out of 41 patients were found to be MRD negative. At 12 months post-lenalidomide discontinuation, 36 out of 38 patients continued to be MRD negative. At 18 months, all evaluable patients (n=18) remained MRD negative. At 24 months, 13 out of 14 patients were MRD negative and at 30 months all 4 evaluable patients were MRD negative. Overall, five patients restarted treatment with lenalidomide monotherapy after converting from MRD negative to MRD positive following the initial completion of maintenance. One patient progressed and received second line of treatment. Only one patient who discontinued maintenance died for reasons not related to multiple myeloma, and with no symptoms of disease progression. **Conclusions:** Sustained MRD negativity after 3 years lenalidomide maintenance may guide the safe discontinuation of maintenance, although this has to be proven in prospective randomized clinical trials.

OA-15

Serial MRD assessments as a surrogate for long term progression free survival

Nishanth Thalambedu[1], Phillip Farmer[1], Robert Smith[1], Daisy Alapat[1], Carolina Schinke[1], Sharmilan Thanendrarajan[1], John Shaughnessy[1], Fenghuang Zhan[1], Maurizio Zangari[1], Samer Al Hadidi[1], Frits van Rhee[1]

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Introduction: The introduction of novel agents in myeloma together with high dose chemotherapy has made it possible to strive for an operational cure at least in a proportion of patients. However, this requires long-term follow-up, which is outside the scope of many clinical trials. MRD negativity has been associated

pts) that allowed the detection of 32 distinct immune populations. **Results:** CTCs were detected in 493/550 (89.6%) pts with a median value of 0.01% of all nucleated cells. Increased levels of CTCs correlated with advanced ISS stage (0.002%, 0.007% and 0.037% for pts with ISS-I, ISS-II and ISS-III respectively, p< 0.0001), high risk cytogenetics (median: 0.038% vs. 0.006% in standard risk, p< 0.0001), and higher levels of b2-microglobulin and BM infiltration. Pts with phenotypic inconsistencies between BM and PB had higher levels of CTCs and more often a diffuse MRI pattern than those with a phenotypic agreement (40% vs.10%, p< 0.01). The optimal clinical cut-off of CTCs was defined at 0.02%, stratifying pts in two different prognostic groups with high and low CTCs [median PFS: 40 months vs. not reached (NR), HR: 2.59, 95% CI:1.71-3.91, p< 0.0001]. In the multivariable analysis the 0.02% cut-off was independent from ISS and/or cytogenetics and was clinically relevant for both TI (median PFS: 47 vs. 23 months, p< 0.0001) and TE pts (median PFS: NR in both categories, p< 0.01). The 2-year probability of MRD negativity was 45% and 67% for pts with high and low CTCs; median time to MRD negativity was 34 vs. 17 months, respectively (HR:1.7, 95% CI:1.2-2.4, p=0.002). Of note, pts with high CTCs who achieved MRD negativity, modulated their unfavorable risk status and showed a similar PFS with those who had low CTCs. Beyond prognostication, pts with high CTC levels showed unique BM immune profiles characterized by increased levels of T cells, NK cells, TAMs and an increased memory/naive B cell ratio. **Conclusions:** The presence of CTC at a level of >0.02% confers an adverse prognostic factor for NDMM pts, irrespective of their transplant status. Since the liquid biopsy is a better representative of the entire tumor load than a tissue biopsy sample, the analysis of CTCs may serve as the new hallmark for the real-time evaluation of a patient's disease and immune status.

OA-14

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OA-15

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with a deeper response and better progression free survival (PFS). Herein, we examine whether serial MRD measurements in the first 5 years after diagnosis can serve as a surrogate for long-term outcome. **Methods:** 1744 patients received a single or tandem autologous stem cell transplant for newly diagnosed myeloma. Standard demographic variables were collected. Bone marrow examinations were performed every 6-12 months and subjected to 8-color flow cytometry with a sensitivity of 10-5. All patients had at least 3 serial MRD tests performed in the first 5 years. Patients were allocated to three groups: Group 1 patients (n=487) had 3 serial MRD negative tests in the first 5 years and remained MRD negative. Group 2 patients (n=872) had both negative and positive MRD tests. Group 3 patients (n=385) were always MRD positive at every test. PFS was calculated using the Kaplan-Meier method from the date of first autologous stem cell transplant (ASCT) and compared with the log-rank test. The study was approved by the institutional IRB. **Results:** The median age was 62.7 (range 29.4-85.9); 716 were >65 years. There were 303 (25.7%), 721 (61.0%) and 157 (13.3%) patients with R-ISS stage, R-ISS stage 2 and R-ISS stage 3 respectively. An elevated LDH (>190) was present in 410/1739 (23.6%). Abnormal cytogenetics were present in 410/1739 (50.6%). 1744 patients received one ASCT and 945 two ASCT (54.2%). High risk GEP was present in 209/1190 (17.6%). Overall, the median follow-up was 4.4 years (range: 0.1-17.3) Group 1 and Group 2 patients had a similar median MRD tests performed in the first 5 years post ASCT: 10 (range 3-24) and 9 (range 3-23) respectively. Group 3 had a lower median MRD test due to more early relapses (7:range 3-29) A similar observation applied to the total number of MRD test performed in each group; Group 1 median 11 tests (range 3-31), Group 2 median 12 tests (range 3-35), and Group 3 median 7 tests (range 3-29). The PFS at 5 years landmarked from first ASCT for group 1,2 and 3 were respectively 90, 48 and 8%.The PFS at 10 years were respectively 74, 30 and 1%. These differences were highly statistically different (P< 0.001). Group 3 were more likely to be older (p-value< 0.001), have baseline ISS and RISS stage III disease (p-value< 0.001 and 0.045), have abnormal cytogenetics profile (p-value< 0.001), abnormal FLC (p-value< 0.001) and have a high-risk GEP profile (p-value=0.0319) compared to Group 2 patients. **Conclusions:** Achievement of 3 serial MRD negative tests in the first 5 years of therapy is predictive of an excellent long-term outcome with few treatment failures.

OA-16

The rs9344 G risk allele upregulates CCND1 expression through t(11;14) and PAX5 in multiple myeloma

Hongwei Tang[1], Huihuang Yan[1], Suganti Shivaram[1], Neeraj Sharma[1], James Smadbeck[1], Cinthya Zepeda-Mendoza[1], Shulan Tian[1], Yan Asmann[2], Celine Vachon[1], Marcella Kaddoura[3], Francesco Maura[3], Leif Bergsagel[4], Vincent Rajkumar[1], Shaji Kumar[1], Eran Elhaik[5], Esteban Braggio[4], Linda Baughn[1]

[1]Mayo Clinic Rochester; [2]Mayo Clinic Florida; [3]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami; [4]Mayo Clinic Arizona; [5]Lund University

Introduction: Multiple myeloma (MM) is an incurable plasma cell malignancy characterized by recurrent primary cytogenetic abnormalities such as t(11;14)(q13;q32), resulting in upregulation of CCND1. While the G allele of rs9344 (c.723G>A, p.Pro241) in exon 4 of the CCND1 gene is the most significant susceptibility allele for t(11;14) by GWAS, the mechanism of how rs9344 contributes to MM remains unknown. **Methods:** We studied 1,359 patients with MM including two independent and ancestrally diverse cohorts (CoMMpass and Tempus). We analyzed whole exome and RNA-seq data and performed a multivariate generalized linear model (GLM). We also analyzed ATAC-seq and ChIP-seq data of the GM12878 normal lymphoblastoid cell line (heterozygous for rs9344 G/A) and MM patient samples. The t(11;14)+ U266 and KMS12 PE cell lines were used for biological confirmation. QRT-PCR was used to assess the expression of CCND1 in U266 cells before and after PAX5 knockdown (KD) with siRNAs and KMS12 PE engineered cell lines with G>A substitution at rs9344. P-values < 0.05 (two-side) were considered statistically significant. **Results:** The rs9344 G risk allele was associated with t(11;14) MM (OR=1.88, P-value =3.2x10-5 in CoMMpass and OR=1.54, P-value =0.002 in Tempus cohorts). In cells heterozygous for rs9344 (A/G), the G allele occurred in cis with the t(11;14) in 80.34% (95%CI: 64.92–98.32%) of cases demonstrating a biological preference for the G allele in t(11;14). Among t(11;14) cases, the G allele was associated with a significant increase of H3K27ac, H3K4me3, H3K4me1 and chromatin accessibility (P-value=9.2 x10-3-7.3 x10-16) demonstrating an allele-specific regulatory role for rs9344 within the CCND1 locus. Further, using ENCODE ChIP-seq data from the GM12878 cell line, we identified a PAX5 binding site within CCND1, with the binding motif being one base-pair centromeric to rs9344. The G allele was associated with increased PAX5 signal relative to the A allele (P-value =1.09E-01). We reason that the increased binding of PAX5 to the G allele contributed to increased expression of CCND1. This was supported by the observations of the increased PAX5 expression in t(11;14) relative to non-t(11;14) MM patient samples, and the increased CCND1 expression within the t(11;14) subgroup with the G allele: 21.98% (95%CI:18.06-25.8%, P-value =1.3 x 10-26) in CoMMpass and 14.48% (95%CI:9.32-19.64%, P-value =5.2 x 10-8) in Tempus. PAX5 KD in U266 cells resulted in a reduction in CCND1 expression and conversion of AA to GG using CRISPR/Cas9 in KMS12 PE cells was associated with an increase in CCND1 expression, confirming the associations of t(11;14) with rs9344 (P-value ≤ 0.002) and with CCND1 (P-value ≤ 1.2x10-143). **Conclusions:** We demonstrate a novel enhancer involving rs9344 and its interaction with PAX5 together with t(11;14) accounting for 98% (95%CI:86.51–100%) of CCND1 expression. Future studies will explore how this association contributes to increased risk of t(11;14) MM.

OA-17

Tracking the earliest genomic events in multiple myeloma life-history

Anthony Cirrincione[1], Alexandra Poos[2,3], Marcella Kaddoura[1], Bachisio Ziccheddu[1], Kylee Maclachlan[4], Monika Chojnacka[1],

with a deeper response and better progression free survival (PFS). Herein, we examine whether serial MRD measurements in the first 5 years after diagnosis can serve as a surrogate for long-term outcome. **Methods:** 1744 patients received a single or tandem autologous stem cell transplant for newly diagnosed myeloma. Standard demographic variables were collected. Bone marrow examinations were performed every 6-12 months and subjected to 8-color flow cytometry with a sensitivity of 10-5. All patients had at least 3 serial MRD tests performed in the first 5 years. Patients were allocated to three groups: Group 1 patients (n=487) had 3 serial MRD negative tests in the first 5 years and remained MRD negative. Group 2 patients (n=872) had both negative and positive MRD tests. Group 3 patients (n=385) were always MRD positive at every test. PFS was calculated using the Kaplan-Meier method from the date of first autologous stem cell transplant (ASCT) and compared with the log-rank test. The study was approved by the institutional IRB. **Results:** The median age was 62.7 (range 29.4-85.9); 716 were >65 years. There were 303 (25.7%), 721 (61.0%) and 157 (13.3%) patients with R-ISS stage, R-ISS stage 2 and R-ISS stage 3 respectively. An elevated LDH (>190) was present in 410/1739 (23.6%). Abnormal cytogenetics were present in 410/1739 (50.6%). 1744 patients received one ASCT and 945 two ASCT (54.2%). High risk GEP was present in 209/1190 (17.6%). Overall, the median follow-up was 4.4 years (range: 0.1-17.3) Group 1 and Group 2 patients had a similar median MRD tests performed in the first 5 years post ASCT: 10 (range 3-24) and 9 (range 3-23) respectively. Group 3 had a lower median MRD test due to more early relapses (7:range 3-29) A similar observation applied to the total number of MRD test performed in each group; Group 1 median 11 tests (range 3-31), Group 2 median 12 tests (range 3-35), and Group 3 median 7 tests (range 3-29). The PFS at 5 years landmarked from first ASCT for group 1,2 and 3 were respectively 90, 48 and 8%.The PFS at 10 years were respectively 74, 30 and 1%. These differences were highly statistically different (P< 0.001). Group 3 were more likely to be older (p-value< 0.001), have baseline ISS and RISS stage III disease (p-value< 0.001 and 0.045), have abnormal cytogenetics profile (p-value< 0.001), abnormal FLC (p-value< 0.001) and have a high-risk GEP profile (p-value=0.0319) compared to Group 2 patients. **Conclusions:** Achievement of 3 serial MRD negative tests in the first 5 years of therapy is predictive of an excellent long-term outcome with few treatment failures.

OA-16

The rs9344 G risk allele upregulates CCND1 expression through t(11;14) and PAX5 in multiple myeloma

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OA-16

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OA-17

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[1]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami; [2]Department of Hematology, Oncology and Rheumatology, Heidelberg University Hospital, Heidelberg, Germany; [3]Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [4]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City NY, USA; [5]Myeloma Research Program, NYU Langone, Perlmutter Cancer Center; [6]Cytogenetics Laboratory, Department of Pathology, Memorial Sloan Kettering Cancer Center; [7]Hematopathology Service, Department of Pathology, Memorial Sloan Kettering Cancer Center; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [10]Internal Medicine V, GMMG Study Group at University Hospital Heidelberg, Heidelberg, Germany; [11]University Medical Center of Hamburg-Eppendorf, Hamburg, Germany; [12]Hematology and Blood and Marrow Transplant; [13]GMMG Study Group at University Hospital Heidelberg, Heidelberg, Germany; [14]University Hospital Heidelberg

Introduction: Hyperdiploidy (HRD) and immunoglobulin translocations (IGH) are historically considered initiating genomic events in MM pathogenesis, often acquired decades prior the diagnosis. **Methods:** To investigate the existence of genomic events acquired before known MM initiating events we interrogated WGS data from 323 patients with newly diagnosed MM (NDMM). CoMMpass WGS were included as validation (n=752 NDMM). Our analytical and chronological workflow was developed by integrating single nucleotide variants (SNV), structural variants (SV) and copy number variants (CNV) comprising two main steps. First, we estimated molecular time (i.e. corrected ratio between duplicated and non-duplicated clonal SNV) of large and clonal chromosomal duplications and identified the earliest set of chromosomal gains in each patient. Second, within each early large chromosomal gain we identified clonal SV mediating CNV loss. A deletion on a gain can generate three possible scenarios: 1) one of the duplicated alleles is lost after the gain (i.e. post-gain) causing a CNV jump from 3:1 to 2:1 (total alleles:minor alleles); 2) there is a deletion before the duplication (i.e., pre-gain) causing a CNV jump from 3:1 to 1:0. 3) the deletion occurs on the minor, non-duplicated allele, causing a CNV jump from 3:1 to 2:0. Timing the deletion in relation with the chromosomal duplication is impossible in this scenario. **Results:** Molecular time data were generated for 257 patients, 65.8% of which were HRD without IGH translocations. Pre-gain deletions acquired before the earliest multi-chromosomal gain events were detected in 22 patients (8.7%). Post-gain deletions were observed in 88 patients (34.2%). Pre-gain events tended to involve more tumor suppressor genes (TSG) such as TCF3, ATM and TRAF3. While post gain events often occurred near oncogenes such as PIK3CA, KLHL6, and BCL10. Surprisingly, one patient exhibited a pre-gain ATM/BIRC3 deletion on a 11q gain caused by a t(11;14)(CCND1;IGH). Because the gain and translocation occurred simultaneously, the deletion occurred before both events. This is the first evidence of a driver event prior to an early IGH translocation. As validation, we investigated the MMRF CoMMpass study (n=752). Because of the low coverage not allowing for molecular time estimation, we limited our analysis to HRD without IGH translocation. Pre-gain and post-gain deletions were observed in 10.1% (44/434) and 64.1% (278/434) of patients, respectively. Combined WGS/RNAseq analysis showed pre-gain deletions inducing loss of function in TSG such as TRAF3, RAD51B, and DNMT3A. In contrast post-gain deletions induced a more heterogenous impact with loss of function in TSG and gain of function of oncodrivers such as BCL6 and USP6. **Conclusions:** Thanks to the development of a new WGS-based chronological model, we revealed, for the first time, the existence of SV acquired before canonical initiating events in newly diagnosed MM patients.

OA-18

Identification of therapy-induced clonal evolution and resistance pathways in MRD clones in multiple myeloma through single-cell sequencing

Jian Cui[1], Xiaoyun Li[1,2], Shuhui Deng[1,2], Xin Gao[1,2], Lugui Qiu[1,2], Gang An[1,2]

[1]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union Medical College; [2]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem,

Introduction: In multiple myeloma (MM), the leading cause of disease progression, exhibits intratumoral heterogeneity that enables adaptability, limits therapeutic success, and remains incompletely understood. Previous studies have confirmed that clonal evolution frequently occurs at disease follow-up, and the patterns of clonal evolution between diagnosis and relapse correlates with patient outcomes. However, it remains unclear whether clonal evolution occurs as early as after induction therapy. Additionally, the mechanisms of malignant plasma cells (PCs) resistance after induction therapy have only been partly resolved. Here, we use single-cell RNA sequencing (scRNA-seq) to identify the clonal architecture at diagnosis and after induction therapy, and elucidate the resistance pathways occurs early after upfront therapy. **Methods:** In this study, we analyzed single-cell RNA sequencing from 19 patients with newly diagnosed MM (NDMM), paired bone marrow (BM) samples after 2-4 cycles of proteasome inhibitor (PI) plus immunomodulatory drugs (IMiDS)-based induction therapy were collected and underwent scRNA-seq. By tracing transcriptional and cytogenetic PCs clones over time and performing differential expression analysis, we defined different patterns of clonal evolution and identified potential resistant pathways. **Results:** In our cohort, 12 patients were identified with more than 30 PCs in the BM samples sequenced after induction therapy. Among them, our analysis of the transcriptional and cytogenetic clonal dynamics in MM patients identified three main trajectories: patients with sensitive PC clones or clone that responds to treatment with >90% of the malignant PCs replaced with seemingly health PCs (3/12 patients, 25%); in

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patients with a resistant clone that did not respond or only very partly responded to treatment, > 50% of the malignant PCs were found in the BM post-treatment (5/12 patients, 42%); and patients with clonal selection, indicating that the significant clone has been replaced by a small or undetectable clone at baseline (4/12 patients, 33%). For these four patients identified with clonal selection, one was observed with branching evolution, and the other three were observed with differential evolution. Transcriptional differences among sensitive clones, resistant clones, and selective clones were detected based on a pairwise comparison of the gene expressions. A large number of differentially expressed genes with reported MM resistant-related functions were observed in the resistant clones, including previously reported 1q-related genes such as CKS1B, HNRNPU, and H3F3A; cell cycle- and cell proliferation-related genes such as TUBA1B, STMN1, and HMGB2. For selective clones, an evident activation of the NF-kB signaling pathway was observed. **Conclusions:** Together, our study confirms that clonal dynamics of the evolving PC clones may occur early after upfront therapy, and reveals that the acquisition of therapeutic resistant pathways is associated with early adaptation to treatment.

OA-19

Comprehensive genomic characterization of response and resistance to daratumumab – based quadruplet induction in newly diagnosed multiple myeloma patients

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[1]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City NY, USA; [2]Memorial Sloan Kettering Cancer Center, New York City NY, USA; [3]Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center; [4]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami; [5]Myeloma Research Program, NYU Langone, Perlmutter Cancer Center; [6]University of Miami; [7]Myeloma Research, UCL Cancer Institute; [8]Cytogenetics Laboratory, Department of Pathology, Memorial Sloan Kettering Cancer Center; [9]Hematopathology Service, Department of Pathology, Memorial Sloan Kettering Cancer Center; [10]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA

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OA-20

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OA-20

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OA-19

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OA-20

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María-Victoria Mateos[10], Joaquin Martinez-Lopez[3], Maria-Jose Calasanz[2], Ramon Garcia-Sanz[1]

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Introduction: Smoldering multiple myeloma (SMM) precedes multiple myeloma (MM). The risk of progression of SMM patients is not uniform, thus different progression-risk models have been developed, although they are mainly based on clinical parameters. Genomic predictors of progression have been defined for untreated SMM, but their usefulness in the context of trials evaluating upfront treatment in high risk SMM (HR SMM) has not been explored yet, precluding the identification of baseline genomic alterations leading to drug resistance. **Methods:** We carried out NGS and FISH studies on 57 HR SMM patients treated in the GEM-CESAR trial (NCT02415413). CD138+ plasma cells were isolated from the bone marrow; after DNA extraction, a custom NGS panel was used to sequence 145 Kb from 666 target regions, allowing the detection of SNV and indels located in 38 genes previously reported in the literature as relevant in MM. FISH studies included probes to detect the following alterations: t(4;14), t(14;16), del17p, t(11;14), 1q gain or amplification (+1q), del1p and structural aberrations in the MYC locus. **Results:** According to the 2014 IMWG definition, 44 patients met the current criteria to be considered HR SMM at diagnosis, while the remaining 13 cases, originally classified as ultra−high risk (UHR), had active disease at baseline following the actual criteria. The median number of SNV/indels per patient was 1 (range: 0−9), with 11/57 patients (19.3%) harboring no alterations in the studied genes. The mutational profile of these patients was enriched in alterations involving well-known drivers in MM (KRAS, NRAS, DIS3, FAM46C). MAPK pathway gene mutations were the most abundant (52.6%), followed by those belonging to RNA and protein processing (22.8%). In 7 patients we identified more than one SNV and/or indel in the same gene (multihit mutations). Concerning cytogenetics, frequencies were closer to symptomatic MM, although some aberrations were enriched in HR SMM compared to the general SMM population [t(4;14) and +1q]. On the contrary, 1p deletions were infrequent (3.8%) and double-hit TP53 alterations absent. Interestingly, FGFR3 mutations were frequently accompanied by t(4;14): 7/8 cases with FGFR3 mutations also harbored the translocation. Previously described risk factors of progression in SMM (mutations in the MAPK pathway, structural alterations affecting MYC and aberrations in the DNA repair pathway) did not predict early biological or clinical progression. In our cohort, NRAS mutations (HR: 5.45, 95% CI: 1.57−18.93, p=0.008) and the co-occurrence of t(4;14) with FGFR3 mutations (HR: 6.75, 95% CI: 1.87−24.34, p=0.004) were associated with a higher risk of biological progression. **Conclusions:** The mutational profile of HR SMM patients is similar to symptomatic MM. If validated in larger studies, t(4;14) plus FGFR3 mutations, or NRAS mutations, could be used to predict resistance and a shorter time to disease progression.

OA-21

Dysregulated APOBEC3B promotes cell proliferation and DNA damage in multiple myeloma

Afsaneh Panahi[1], Sarah Grasedieck[2], Faezeh Borzooee[3], Matthew Jarvis[4], Reuben Harris[4], Mani Larijani[5], Kevin Song[6], Arefeh Rouhi[1], Florian Kuchenbauer[7]

[1]BCCRC/UBC; [2]UBC; [3]BCCRC; [4]University of Minnesota; [5]SFU; [6]Vancouver General Hospital, Vancouver, BC, Canada; [7]BCCRC/VGH

Introduction: Previous research on APOBEC3B (A3B) in multiple myeloma (MM) has predominantly focused on APOBEC mutation signatures. However, the role of A3B mRNA expression level and its impact on MM cellular characteristics remains poorly understood. This study aims to investigate the prognostic significance of A3B mRNA expression in MM progression and explore its downstream effects through in vitro experiments. **Methods:** The prognostic significance of A3B mRNA expression level in the CoMMpass dataset was investigated using Univariate Cox regression and Kaplan-Meier Curve analysis. Additionally, a pathways analysis (KEGG/REACTOME) was conducted to identify biological functions that were significantly overrepresented in genes correlated with A3B expression. Lentiviral knockdown (KD) and overexpression (OE) of A3B were performed in MM cell lines, followed by RNA-seq and pathway analysis to identify shared pathways through parallel analysis. The obtained results were subsequently tested and validated in vitro. **Results:** A3B expression level showed the highest hazard ratio (HROS:2.60; HRPFS:2.32, p20%) and exhibiting high A3B mRNA expression levels (4th quartile) display a significant (p< 0.05) enrichment of APOBEC-induced genomic mutations, along with a worse prognosis (median PFS: 500 days), in comparison to patients with intermediate (2nd and 3rd quartile) (median PFS: 1000 days) and low (1st quartile) A3B expression levels (median PFS: 1900 days). **Conclusions:** These findings highlight the substantial involvement of A3B in cell proliferation and genomic instability in MM. This identifies A3B as a promising candidate for targeted interventions aimed at mitigating DNA damage and genomic instability in MM cells, particularly among patients with del(17p).

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OA-22

TiMMing: developing an innovative suite of bioinformatic tools to harmonize and track the origin of copy number alterations in the evolutionary history of multiple myeloma

Andrea Poletti[1], Jean-Baptiste Alberge[2], Gaia Mazzocchetti[1], Vincenza Solli[1], Ajsi Kanapari[1], Enrica Borsi[3], Ilaria Vigliotta[1], Marina Martello[1], Silvia Armuzzi[1], Barbara Taurisano[1], Ignazia Pistis[3], Elena Zamagni[1], Lucia Pantani[1], Serena Rocchi[1], Katia Mancuso[1], Paola Tacchetti[1], Ilaria Rizzello[3], Michele Cavo[3], Irene Ghobrial[2], Carolina Terragna[3]

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Introduction: Multiple Myeloma (MM) is a hematologic cancer with heterogeneous and complex genomic landscape, where Copy Number Alterations (CNAs) play a key role in the disease's pathogenesis and prognosis. It is of biological and clinical interest to study the temporal occurrence of early alterations, as they play a disease "driver" function by deregulating key tumor pathways. **Methods:** This study presents an innovative bioinformatic suite consisting of five bioinformatics tools (BOBaFit, RemasterCNA, RAPH, ComphyNumber and TestClonality) created for the purpose of harmonizing Copy Number data across different genomic platforms and tracing the origin of CNAs throughout the evolutionary history of MM. To this aim, large cohorts of newly-diagnosed MM (NDMM, N=1582) and Smoldering-MM (SMM, N=282) were aggregated. **Results:** The tools developed in this study enabled the harmonization of CNAs as obtained from different genomic platforms (i.e. WGS, ULP-WGS, WES, SNP array) in order to obtain the highest statistical power. Therefore, the high numerosity of these cohorts was harnessed for both 1) the identification of novel genes characterized as MM focal "driver" alterations through the optimized use of GISTIC tool (including NFKB2, NOTCH2, MAX and EVI5 and MYC-ME2-enhancer genes), and 2) the generation of an innovative timing model based on Bradley-Terry approach and implemented with the introduction of a statistical method aimed at introducing statistical confidence intervals for CNAs analysis. By applying this model on both NDMM and SMM cohorts, it has been possible to identify specific CNAs (1q(CKS1B)amp, 13q(RB1)del, 11q(CCND1)amp and 14q(MAX)del) that were categorized as "early/driver" events. A high level of precision was guaranteed by the narrow confidence intervals in the timing estimates. These CNAs were proposed as critical MM alterations, playing a critical role in the evolutionary history of both SMM and NDMM. Importantly, among the identified events, CKS1B amp and RB1 del were previously poorly characterized from an evolutionary point of view and uncertainly classified between primary and secondary events, while MAX del represents a completely new discovered MM driver alteration. Finally, a stepwise backward-forward Cox Regression survival model was employed to identify all the independent genomic alterations having the greatest effect on patients' outcomes (i.e. Progression Free and Overall Survival), named deletion of RB1, amplification of CKS1B, amplification of MYC, amplification NOTCH2 and deletion-mutation of TRAF3. **Conclusions:** In conclusion, the study highlighted the existence of previously unrecognized "early-drivers" MM CNAs, whose impact on patients' survival has been demonstrated. These CNAs might improve MM patients' stratification and contribute to precisely assess patients' prognosis. **Acknowledgements:** BolognAIL ONLUS, AIRC19-IG22059.

OA-23

Resolving therapy resistance mechanisms in multiple myeloma by multi-omics subclone analysis

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[1]Department of Hematology, Oncology and Rheumatology, Heidelberg University Hospital, Heidelberg, Germany; [2]Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Division Computational Genomics and Systems Genetics, German Cancer Research Center (DKFZ), Heidelberg, Germany; [4]Open Lab for Single Cell Sequencing (scOpenLab), German Cancer Research Center (DKFZ) and BioQuant, Heidelberg, Germany; [5]Division of Chromatin Networks, German Cancer Research Center (DKFZ) and BioQuant, Heidelberg, Germany; [6]University Hospital Würzburg; [7]National Center for Tumor Diseases (NCT), Heidelberg, Germany; [8]Internal Medicine V, GMMG Study Group at University Hospital Heidelberg, Heidelberg, Germany; [9]Dept. of Medicine V Hematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany

Introduction: Intratumor heterogeneity as a clinical challenge becomes most evident after several treatment lines when multi-drug resistant subclones accumulate. With the hypothesis that the characterization of resistance mechanisms at the subclonal level is key to identify common vulnerabilities, we performed a longitudinal single-cell (sc) sequencing study in relapsed/refractory multiple myeloma (RRMM). **Methods:** scRNA- and ATAC-sequencing together with whole genome sequencing (WGS) was performed for 15 RRMM patients with longitudinal samples (T1/T2). Tumor subclones were identified based on copy number aberrations in both sc readouts. To match transcriptome and epigenome of each subclone, a WGS-guided clustering approach was developed and combined with mitochondrial DNA mutations. Cell-cell interactions between subclones and the bone marrow microenvironment (BME) were identified using CellChat. **Results:** Analyzing the impact of treatment on individual subclones, we found converging adaptation

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mechanisms in patients with stable evolution or only minor changes in the subclonal architecture. Specifically, 86% (range: 64-96%) of therapy-induced changes in gene expression were shared across individual subclones for each patient and the same was seen for transcription factor (TF) motif activities (93 % shared (range: 71-95 %)). This included a significant upregulation of genes and TF motifs of the NFKB pathway upon MEK/BRAF inhibition and of heat-shock proteins upon proteasome inhibition. Next, we focused on patients with major subclonal changes and found evidence for a role of the BME in differential treatment response. Global gene expression and chromatin accessibility analysis in a patient treated with an MCL1 inhibitor revealed subclonal differences in expression of the cell-cell interaction molecule CD44. According to CellChat, CD44 mediated a subclone-specific interaction with monocytes and dendritic cells that was lost upon MCL1 inhibition. Extending the interaction analysis to all patients with multiple subclones, on average 32 ligand-receptor interactions were predicted per patient. Notably, 20% of them were not shared between subclones. These unshared interactions were mainly mediated by the intercellular adhesion molecule (ICAM) signaling network. Despite this heterogeneity in ICAMs, they still represent a potential treatment target. We found ICAM1 to be significantly upregulated upon treatment (p=0.02), including a patient with ICAM1-mediated interactions in all subclones at T2, which were not detectable at T1. In line with this, we found a higher co-accessibility at the ICAM1 promoter and motif activity for TFs regulating ICAM1 such as IRF4 in all subclones. **Conclusions:** Our multi-omics approach of individual subclones integrates multiple layers of resistance. These mechanisms can occur in parallel, which emphasizes the development of strategies that target shared vulnerabilities across individual subclones.

OA-24

Sequential and persistent loss of BCMA and GPRC5D after bispecific antibodies in multiple myeloma revealed by whole genome sequencing

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Introduction: We and others have recently identified biallelic hits in genes coding for immunotherapy targets in Multiple Myeloma (MM) as a mechanism of resistance, such as in BCMA. Similarly, biallelic events in the GPRC5D locus on chromosome 12p have been linked to antigen loss and relapse from GPRC5D targeted therapies. As we are entering an era in which BCMA and GPRC5D targeting agents are approved and available, the question how to sequentially treat patients with anti-BCMA and anti-GPRC5D agents becomes imminent. A more profound knowledge about the selective pressure of sequential immunotherapy on the clonal architecture in MM is key to inform successful sequencing strategies. **Methods:** We applied serial whole genome sequencing (WGS, 100x coverage, 2x151 bp, NovaSeq instrument) and immunohistochemistry (IHC) studies in a patient with RRMM who was treated with 10 lines of therapy with literally all available drugs including BCMA and GPRC5D targeting agents. **Results:** WGS revealed several illustrating genomic events: First, a homozygous BCMA deletion conferring antigen loss after treatment with a BCMA targeting T-cell redirecting bispecific antibody. This biallelic hit was characterized by monosomy 16 and a small deletion on the remaining allele of 586 kb. IHC confirmed BCMA loss on the protein level. Second, 2.5 years later, the patient was treated with a GPRC5D targeting bispecific antibody and again achieved deep remission lasting for 15-months. At subsequent relapse WGS displayed an acquired 12p deletion of 23.3 Mb including GPRC5D and IHC confirmed GPRC5D loss to underlie relapse. The homozygous BCMA deletion was persistent at this time point, highlighting two sequential evolutionary bottlenecks. Next to the loss of immunotargets, two additional genetic lesions associated to the therapy applied were tracked in this patient: the SBS-MM1 signature, in 12.8% of mutations, which is linked to melphalan exposure, and a clonal truncating mutation in CRBN (p.Gln8Ter), inducing IMiD resistance, that was developed upon 3rd line treatment. **Conclusions:** Immunotherapy is an evolutionary bottleneck in the treatment of MM, selecting for antigen loss variants. Sequential mono-immunotherapies may enforce such selection, arguing for multi-specific strategies to circumvent antigen loss. Tumor-intrinsic mechanisms largely explain resistance in our exemplary patient, highlighting WGS of purified MM cells as a promising diagnostic tool to follow-up patients in the era of novel immunotherapies., In our patient the genome could be read as a book in which prior therapies had been noted.

OA-25

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that resemble the maturation stages of post germinal centre B cells through to PCs. These clonal subpopulations include rare MM cells that resemble CD20+CD38-CD138-Irf4- Xbp1s- B cells, CD20-CD38-CD138-Irf4-Xbp1s- pre-plasmablasts and CD38+CD138-Irf4+XBP1s+ pre-PCs, as well as tumor-bulk CD38+CD138+IRF4+Xbp1s+ PCs. MM progenitors possess all of the chromosomal translocations and copy number variations (CNV) present in MM PCs including ploidy changes, translocations such as t(4;14), t(14;16) and t(11;14), and secondary aberrations such as gain(1q), del(1p) and del(17p). To examine if MM progenitor cells also possess the single nucleotide variations (SNV) present within MM PCs, and are thus fully malignant, and to track MM progenitor subpopulations within patients over time, we performed WES (n=60) plus CC-Seq (n=210) on purified cell subpopulations from 17 patients, including 5 whom we sampled serially over >3 years. Five cellular subpopulations were isolated from each BM, and each was sequenced to a depth of 4–20,000x. From these data, SNVs in tumor-bulk MM PCs were regularly detected in MM progenitors, although the low frequency of progenitors often prevented capture of complete SNV profiles. Notably, analyses of serial BM samples taken pre and post treatment suggests that relapsing MM PCs typically do not derive from pre-treatment PCs, and often lack multiple SNVs present in pre-treatment PCs. Instead, crucially, relapsing MM PCs commonly derive from MM progenitor cells, as relapse-specific SNVs present in relapsing PCs were detected within MM B cells and progenitor cells isolated from BMs collected up to 3 years prior to relapse. Moreover MM progenitors were also detected as the sole MRD in PC-negative patients. **Conclusions:** MM B cells and progenitors possess all of the genomic aberrations required for full malignant potential. Tracking of these cells in vivo in patients by their SNV profile implicates them as the cellular origin of disease relapse. Cure of MM requires eradication of MM progenitor cells.

OA-26

Single-cell analysis reveals disease induced perturbations of monocytes in the bone marrow and peripheral blood of multiple myeloma patients

Jian Cui[1], Xiaoyun Li[1,2], Xin Gao[1,2], Lugui Qiu[1,2], Gang An[1,2]

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Introduction: A growing body of evidence has indicated impaired function or compositional changes of monocytes in inflammatory disorders, such as acute respiratory syndrome and covid-19. In multiple myeloma (MM) tumor microenvironment, activation of type I interferon pathway and dysregulated expression of major histocompatibility complex type II genes are observed in classical monocytes, which result in loss of antigen presentation of monocytes. The proportions of BAFF+PD-L1+ monocytes in the bone marrow also correlate with survival of myeloma patients following chimeric antigen-receptor T cell therapy. Nevertheless, the mechanisms underlying monocytes defects in MM remain poorly addressed, at least in part by the lack of large scale scRNA-seq studies. **Methods:** To resolve the heterogeneous bone marrow (BM) and peripheral blood (PB) monocyte subpopulations and their transcriptional factors between healthy donors (HD) and MM patients. We performed scRNA-seq on monocytes of 7 newly diagnosed MM (NDMM) patients and 12 HD. Specifically, 3 and 5 BM samples and 9 and 7 PB samples of 12 HD and 7 NDMM patients were obtained and sequenced. **Results:** Here, we employed scRNA-seq technology to systematically analyze 26,683 BM and 82,328 circulating monocytes, and genetically defined their subpopulations. We constructed a precise atlas of human PB and BM monocytes, identified seven subpopulations in both BM and PB—including S100A12, HLA, ISG15, CD16, proinflammatory, and intermediate in both BM and PB; megakaryocyte-like in PB; and proliferating subset in BM. Differential expression analysis on the BM and PB monocytes showed that a large number of type I interferon (IFN) signaling pathway genes (e.g. IFI27, IFI6, ISG15) were overexpressed in MM compared with HD. Genes encoding major complement system components and class II major histocompatibility complex molecules (MHC class II) were more highly expressed in MM compared to HD, indicating higher inflammatory and phagocytic potential of MM monocytes. However, relative to HD, T-cell attraction-related genes (e.g. CCL3 and CCL4) were markedly downregulated in MM, and T-cell suppression-related genes (e.g. IDO1, CD274 and PDCD1LG2) were markedly upregulated in MM. Furthermore, we identified two monocyte differentiation pathways in both BM and PB, and discovered that BM monocyte feature type I IFN-associated alterations in differentiation in patients with MM as well as dysregulated patterns at transcriptome. Finally, we included 10 MM patients as a validation cohort, by tracking the alterations in transcriptome and differentiation during treatment using scRNA-seq. Our results indicated that type I IFN signaling pathway activation and alterations in differentiation was partially alleviated for BM monocytes in MM by antitumor therapy. **Conclusions:** Our results provided further insight into transcriptional and differentiation alterations occurring in the BM and PB monocytes from patients with MM and explored mechanisms of immune evasion associated with monocytes.

OA-27

Single cell transcriptomics reveals the impact of tumor cell interactions with the bone marrow immune microenvironment in the progression of multiple myeloma

Parvathi Sudha[1], Mohammad Abu Zaid[1], Travis Johnson[2], Vivek Chopra[3], Cedric Dos Santos[3], Michael Nixon[3], Faiza Zafar[3], Habib Hamidi[3], Attaya Suvannasankha[4], Sherif Farag[1], Kelvin Lee[1], Rafat Abonour[5], Brian Walker[1]

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that resemble the maturation stages of post germinal centre B cells through to PCs. These clonal subpopulations include rare MM cells that resemble CD20+CD38-CD138-Irf4- Xbp1s- B cells, CD20-CD38-CD138-Irf4-Xbp1s- pre-plasmablasts and CD38+CD138-Irf4+XBP1s+ pre-PCs, as well as tumor-bulk CD38+CD138+IRF4+Xbp1s+ PCs. MM progenitors possess all of the chromosomal translocations and copy number variations (CNV) present in MM PCs including ploidy changes, translocations such as t(4;14), t(14;16) and t(11;14), and secondary aberrations such as gain(1q), del(1p) and del(17p). To examine if MM progenitor cells also possess the single nucleotide variations (SNV) present within MM PCs, and are thus fully malignant, and to track MM progenitor subpopulations within patients over time, we performed WES (n=60) plus CC-Seq (n=210) on purified cell subpopulations from 17 patients, including 5 whom we sampled serially over >3 years. Five cellular subpopulations were isolated from each BM, and each was sequenced to a depth of 4–20,000x. From these data, SNVs in tumor-bulk MM PCs were regularly detected in MM progenitors, although the low frequency of progenitors often prevented capture of complete SNV profiles. Notably, analyses of serial BM samples taken pre and post treatment suggests that relapsing MM PCs typically do not derive from pre-treatment PCs, and often lack multiple SNVs present in pre-treatment PCs. Instead, crucially, relapsing MM PCs commonly derive from MM progenitor cells, as relapse-specific SNVs present in relapsing PCs were detected within MM B cells and progenitor cells isolated from BMs collected up to 3 years prior to relapse. Moreover MM progenitors were also detected as the sole MRD in PC-negative patients. **Conclusions:** MM B cells and progenitors possess all of the genomic aberrations required for full malignant potential. Tracking of these cells in vivo in patients by their SNV profile implicates them as the cellular origin of disease relapse. Cure of MM requires eradication of MM progenitor cells.

OA-26

Single-cell analysis reveals disease induced perturbations of monocytes in the bone marrow and peripheral blood of multiple myeloma patients

Jian Cui[1], Xiaoyun Li[1,2], Xin Gao[1,2], Lugui Qiu[1,2], Gang An[1,2]

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Introduction: Alterations within the bone marrow microenvironment (BMME) may contribute to the progression of multiple myeloma (MM) from its precursor stages. The significance of the BMME and the role of different immune cell types in the progression of myeloma could identify novel therapeutic approaches to prevent the progression of disease. Here we investigated the frequency of different immune cell types in the BMME at different stages of myeloma and their interactions with the tumor cells. **Methods:** BM aspirates from smoldering multiple myeloma (SMM; n=10), newly diagnosed multiple myeloma (NDMM; n=23), and relapsed/refractory multiple myeloma (RRMM; n=22) patients were collected from the Indiana Myeloma Registry. BM mononuclear cells were isolated by Ficoll and underwent CD138 magnetic bead selection into CD138+ and CD138- fractions. CD138- samples underwent scRNA and TCR sequencing (10X Genomics) and CD138+ samples underwent multiomic analysis (10x Genomics). CD138- data was normalized, integrated, and clusters were annotated for cell type using Seurat (v4), resulting in 315,533 high quality immune cells. Significant proportional and gene expression differences between clusters at different disease stages were calculated. Quantitative analysis on intercellular communication networks were analyzed between single cell clusters of matched CD138+ cells and CD138- samples using CellChat (v1.6.0). **Results:** Integration of all 55 CD138- samples resulted in 36 immune cell subclusters. Despite patient heterogeneity, significant changes in the immune cell proportions were identified as the disease progressed; a substantial decrease in CD4 memory T cells from NDMM to RRMM (P< 0.0001) (SMM=15.7%; NDMM=13.4%; RRMM=4%) whereas CD4 T effector cells significantly increased from NDMM to RRMM (P=0.005) (SMM=10.8%; NDMM=8.7%; RRMM=11.9%) and CD8 T MAIT cells decreased from NDMM to RRMM (P=0.002). CD56 natural killer cells increased (SMM=1.6%; NDMM=2.7%; RRMM=5.2%; P< 0.05) as did CD16 monocyte cell clusters (SMM=0.9%; NDMM=1.9%; RRMM=4.3%; P< 0.05). Regarding tumor-BMME intercellular communication, we observed known APRIL-BCMA and BAFF-BCMA/BAFF-TACI interactions between myeloid dendritic cells or monocyte clusters and tumor cell clusters. Our single cell data shows these interactions decreased from SMM to NDMM and RRMM (P< 0.05). In addition, RRMM samples had a significant increase in MIF-CD74/CXCR4 interactions between tumor cells and myeloid dendritic cells compared to SMM and NDMM cells (P< 0.05), which can contribute to the immune evasion of myeloma cells and limit the effectiveness of immune-based therapies. **Conclusions:** Immune cell subgroups change as the disease progresses from SMM to NDMM and RRMM, as do their interactions with myeloma cells possibly resulting in increased resistance through immune evasion and MIF signaling mechanisms.

OA-28

Unraveling the heterogeneity of multiple myeloma associated with therapy resistance by single-cell RNA sequencing

Takahiro Kamiya[1,2], Motohiko Oshima[1], Shuhei Koide[1], Yaeko Nakajima-Takagi[1], Kazumasa Aoyama[1], Satoshi Kaito[1], Naoki Itokawa[1], Masayuki Yamashita[1], Noriko Doki[3], Keisuke Kataoka[2,4], Atsushi Iwama[1]

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Introduction: Multiple myeloma (MM) is a malignancy of clonal plasma cells with identical VDJ recombination of immunoglobulin loci (called repertoire) and extensive genome or transcriptome heterogeneity. Even though many new treatment modalities have been developed to extend patient survival, most cases remain incurable. Recent evidence suggests that intra-tumor heterogeneity underlies the therapy resistance, but its details remain largely unknown. **Methods:** To understand the comprehensive architecture, we subdivided bone marrow (BM) cells from MM patients at different disease stages (n=8) into 11 fractions by flow cytometry (FCM) and performed bulk RNA sequencing (bulk RNA-seq). Using BM cells with MM sorted by the panel established based on clonal repertoire distribution, we performed single-cell RNA sequencing (scRNA-seq) coupled with VDJ targeted sequencing (scVDJ-seq) (n=11) including those at diagnosis and in remission with minimal residual disease (MRD). **Results:** RNA sequencing-based profiling of repertoire revealed that tumor cells are also detected in Lineage marker– (Lin–)/ CD19–/CD38++/CD138– fraction other than the main fraction (Lin–/CD19–/CD38++/CD138+) regardless of disease stage. An analysis of scRNA-seq coupled with scVDJ-seq on Lin–/CD19–/CD38+ fraction, without CD138 gating, discriminated MM cells (20084 cells) clearly from others. By integration with gene signatures established from bulk RNA-seq of CD138+ and CD138– MM cells (n=12), the heterogeneity on the CD138 axis was also unraveled. FCM analysis confirmed that CD138– MM cells were present at a rate of less than 10% across the disease stages (n=59), which showed unique morphology, methylation of histone H3K4 and cell cycle status distinct from CD138+ cells. Primary cell culture and trajectory/velocity analysis of scRNA-seq suggested that heterogeneity along the CD138 axis might be regulated by epigenetic plasticity. Interestingly, we identified unique clusters in the CD138– population which tended to remain at high proportions after treatment. They were characterized by low expression of MHC class-I genes and BCMA as well as 198 upregulated genes, including MCL1, MALAT1, NEAT1, which have been previously implicated in treatment resistance. We systematically interrogated their dependencies in growth of MM cells using a custom CRISPR/Cas9 screening system and narrowed down several important genes. Analysis of public databases showed

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OA-28

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that high expression of a part of these genes, including RNA-binding protein 39 (RBM39), are significantly associated with poor prognosis. We confirmed that RBM39 is indispensable for the MM cells by CRISPR/Cas9-mediated knockout and pharmacological protein degradation. **Conclusions:** We achieved a complete view of MM diversity that was not limited by cell surface antigens or transcriptome characteristics by using repertoire clonality. Our results highlight a novel subpopulation as a candidate therapeutic target for cure.

OA-29

First results from the randomized portion of a phase 2 study of venetoclax plus carfilzomib-dexamethasone vs carfilzomib-dexamethasone in patients with t(11;14) relapsed/refractory multiple myeloma

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Introduction: Venetoclax (Ven) is a potent, oral BCL-2 inhibitor under investigation for t(11;14)+ relapsed/refractory multiple myeloma (RRMM). The dose-finding part of a Phase 2 study (NCT02899052) of Ven plus carfilzomib (K) and dexamethasone (d) in RRMM showed an overall response rate (ORR) of 80%, and ORR was higher in patients (pts) who were t(11;14)+ vs t(11;14)– (92 vs 75%; Costa, Blood Adv. 2021;5:3748). Here, we report initial safety and efficacy data in patients with t(11;14)+ RRMM treated with Ven (400 or 800 mg) combined with K (70 mg/m^2) and d (Ven400Kd or Ven800Kd) vs Kd alone in the dose-finding and randomized parts of the study. **Methods:** Pts with t(11;14)+ RRMM were randomized 5:3:5 to receive K (70 mg/m^2 weekly) and d (40 mg) plus daily Ven (Ven400Kd or Ven800Kd), or Kd alone. Pts in the randomized part had ≥1 prior line of therapy (LOT); pts in dose finding had 1–3 prior LOT. Primary objectives of the randomized part were to assess safety and efficacy. Secondary objectives were to assess progression-free survival (PFS), overall survival (OS), time to response (TTR), time to progression (TTP), and duration of response (DOR). Efficacy was analyzed in pts randomized to Ven400Kd, enrolled during dose finding or randomized to Ven800Kd, and randomized to Kd. Safety was analyzed in those who received ≥1 dose of study treatment. **Results:** At the 19 Jan 2023 cutoff, 48 randomized pts and 8 pts from dose finding were included (Ven400Kd, n=17; Ven800Kd, n=20; Kd, n=19); 1 pt in the Kd group was not treated. Pts had median age of 70.5–73 years, median 2 prior LOT, and had prior exposure to proteasome inhibitors (89–94%), immunomodulatory drugs (85–89%), and anti-CD38 mAb (24–47%). Treatment-emergent adverse events (TEAEs) occurring at ≥50% in any group (Ven400Kd vs Ven800Kd vs Kd) were diarrhea (65 vs 75 vs 6%), nausea (53 vs 55 vs 28%), fatigue (35 vs 50 vs 22%), and vomiting (0 vs 50 vs 11%). Grade ≥3 TEAEs occurred in 88, 85, and 72% of pts. Grade ≥3 TEAEs occurring at ≥20% in any group were lymphopenia (18 vs 30 vs 6%), neutropenia (12 vs 25 vs 11%), and hypertension (24 vs 15 vs 17%). Few Grade ≥3 cardiac disorders occurred (0 vs 5 vs 6%). Grade ≥3 infection rates were higher in the VenKd groups vs Kd (29 vs 20 vs 11%). At median follow-ups (range) of 16.8 (5.8–30.8), 21.1 (2.2–65.8), and 11.5 (0.0–28.3) months in the Ven400Kd, Ven800Kd, and Kd groups, respectively, corresponding ORRs (95% CI) were 94% (71–100), 95% (75–100), and 58% (34–80). Complete response (CR)/stringent CR rates were 29, 50, and 11%, respectively. Median TTR was 1.0, 1.0, and 2.4 months. 12-month PFS estimates were 67, 85, and 79%, with median PFS of 42.4 months (hazard ratio vs Kd=0.613 [95% CI, 0.153–2.456]) in the Ven800Kd group and not reached (NR) in the Ven400Kd and Kd groups. Medians for OS, TTP, and DOR were NR in any group. More mature data will be presented. **Conclusions:** Treatment with VenKd was well tolerated and produced favorable responses in >90% of pts with t(11;14)+ RRMM. Enrollment is ongoing.

OA-30

Critical roles of CRIP1 in promoting cell survival and bortezomib resistance by enhancing proteasome activity and autophagy in multiple myeloma

Zhen Yu[1], Peixia Tang[1], Zhenshu Xu[2], Mu Hao[1], Lugui Qiu[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China.; [2]Hematology Department Fujian Medical University Union Hospital, Fujian Institute of Hematology

Introduction: Although proteasome inhibitors (PIs) have transformed management of multiple myeloma (MM), drug resistance emerges through induction of the aggresome & autophagy pathway as a compensatory protein clearance mechanism. Accordingly, autophagy inhibitors used in association to conventional anti-MM drugs might enforce the effect against resistant MM cells and render autophagy a new therapeutic target.

that high expression of a part of these genes, including RNA-binding protein 39 (RBM39), are significantly associated with poor prognosis. We confirmed that RBM39 is indispensable for the MM cells by CRISPR/Cas9-mediated knockout and pharmacological protein degradation. **Conclusions:** We achieved a complete view of MM diversity that was not limited by cell surface antigens or transcriptome characteristics by using repertoire clonality. Our results highlight a novel subpopulation as a candidate therapeutic target for cure.

OA-29

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OA-31

Efficacy of bispecific antibodies in the treatment of extramedullary disease and high risk cytogenetics in relapsed multiple myeloma: a systematic review

Charan Vegivinti[1,2], Jaison Lawrence Alexander Santhi[3], Lawrence Liu[4], M Bakri Hammami[1,2], Rahul Thakur[1], Ananta Ghimire[5], Nagarathna Poojary[5], Murali Mohan Reddy Gopireddy[5], Anusha Manoj Kallamvalappil[6], Sahas Reddy Jitta[7], Nikita Chintapally[8], Nishi Shah[9,2], Murali Janakiram[4]

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Introduction: Bispecific antibodies (BsAbs) are effective treatments for relapsed multiple myeloma (MM). The purpose of this systematic review is to determine the efficacy of BsAbs in the management of extramedullary disease (EMD) and high risk cytogenetic abnormalities (HRCAs) in relapsed MM. **Methods:** A systematic literature search was conducted to identify clinical trials that investigated BsAbs in MM using the PubMed database and ASH-submitted abstracts using search terms (bispecific antibodies) AND (multiple myeloma). Our search on PubMed yielded 263 studies, of which 7 were clinical trials; of these, 5 were included, and 6 ASH abstracts were included. Cochrane-Q test and I^2 statistic were used to assess the statistical heterogenicity. A fixed effect model was used for low statistical heterogeneity ($P > 0.05$ in Cochrane-Q test and I^2 50%). Categorical outcomes were summarized by pooled proportion with 95% CI. **Results:** Overall response rates (ORRs) of the entire cohort were reported in 660 patients across 9 studies. The ORRs for EMD and HRCAs were reported in 3 (n=78) and 4 (n=100) studies, respectively. The ORR of the entire cohort was 0.65 [95% CI; 0.57; 0.74). The ORR of each BsAb was 0.70 (0.51-0.85; Chari et al, 2022) for talquetamab, 0.63 (0.55-0.70; Moreau et al, 2022) for teclistamab, and 0.61 (0.52-0.70; Bahlis et al, 2022) for elranatamab. The ORRs in MM with EMD and HRCAs with 95% CI were 0.38 [0.28; 0.49] and 0.60 [0.51; 0.70], respectively. Among the studies that reported the ORR in EMD, talquetamab (Chari et al, 2022) has the highest ORR of 0.45 (0.17; 0.77), followed by elranatamab (Bahlis et al, 2022) of 0.38 (0.23; 0.55), and teclistamab (Moreau el al, 2022) of 0.36 (0.19; 0.56). There is no significant difference in the ORR between the drugs with respect to EMD status. In studies that reported the ORR in HRCAs, talquetamab (Chari et al, 2022) had an ORR of 0.67 (0.17; 0.77) followed by teclistamab (Moreau el al, 2022) of 0.61 (0.43; 0.76), and elranatamab (Bahlis et al, 2022) of 0.55 (0.36; 0.73). Similarly, there is no significant difference in the ORR between the drugs with respect to HRCA status. The above results demonstrate that ORR in EMD is lower when compared to the entire cohort. **Conclusions:** Despite 11 clinical trials done with bispecific antibodies only 4 had reported EMD responses. This needs to be improved and clinical trials should report EMD responses distinctly as it directly informs clinical decisions. EMD responses are significantly lower than the full cohort ORR however it is encouraging that responses to high risk multiple myeloma (HRMM) closely approximate ORR of these agents. Further analysis is needed to see whether ORR and PFS correlate for HRMM. Evidence was insufficient to establish the relative superiority of one BsAb over another with EMD and combination therapies should be explored for EMD in myeloma.

OA-32

The impact of genomics to identify novel immunotherapeutic targets in multiple myeloma

Enze Liu[1], Parvathi Sudha[1], Mohammad Abu Zaid[1], Travis Johnson[2], Vivek Chopra[3], Cedric Dos Santos[3], Michael Nixon[3], Habib Hamidi[3], Attaya Suvannasankha[4], Kelvin Lee[1], Rafat Abonour[5], Brian Walker[1]

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Our previous study identified that CRIP1 was a high-risk gene that overexpressed in drug-resistance MM cells in post-treatment patient samples. However, the molecular mechanism of CRIP1 in myelomagenesis has not been fully understood. In this study, we evaluated the mechanism of CRIP1-mediated PIs resistance and MM cell aggressive proliferation. **Methods:** An inducible CRIP1-shRNA vector and CRIP1 overexpress vector were constructed to explore the role of CRIP1 in MM. Co-IP(Co-Immunoprecipitation) with TAP/MS (Tandem affinity purification/Mass spectrum) was performed to detect the binding of USP7, CRIP1 and PA200. Myeloma xenograft model was used to determine the role of CRIP1 to promote proliferation of MM cells and induce BTZ resistance in vivo. **Results:** Our data showed that CRIP1 was overexpressed in MM cells especially in patients with RRMM (relapsed/refractory MM). CRIP1 overexpression is linked to inferior outcome in patients with MM even those undergoing bortezomib (BTZ) treatment. CRIP1 promoted MM cell proliferation, invasion and decreased PIs sensitivity in MM cells. More important, CRIP1 overexpression stabilized PA200 and against PIs induced MM cell apoptosis by enhancing the proteasome activity and autophagy. Co-IP and TAPMS analysis indicated that CRIP1 promoted the deubiquitination and stabilization of PA200 by binding with USP7. Strikingly, our study elucidated for the first time that CRIP1 and PA200 were both the substrates of USP7. CRIP1 worked as a scaffold protein and played critical roles in BTZ resistance by forming the complex with USP7 and PA200. In vitro and in vivo studies further confirmed that the USP7 or PSME4 inhibition reduces CRIP1 induced BTZ - resistance in MM. **Conclusions:** In summary, CRIP1 was overexpressed in MM cells and correlated with inferior outcome of MM patients. CRIP1 induced drug resistance to proteasome inhibitors by promoting proteasome activity and autophagy in MM. CRIP1 promoted PA200 bound with USP7 through facilitating proteasome activity and autophagy and induced the BTZ resistance of MM cells. Blocking CRIP1/USP7/PA200 signal pathway would be an ideal strategy for MM therapy which can suppress proteasome activity and autophagy simultaneously.

OA-31

Efficacy of bispecific antibodies in the treatment of extramedullary disease and high risk cytogenetics in relapsed multiple myeloma: a systematic review

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Introduction: Bispecific antibodies (BsAbs) are effective treatments for relapsed multiple myeloma (MM). The purpose of this systematic review is to determine the efficacy of BsAbs in the management of extramedullary disease (EMD) and high risk cytogenetic abnormalities (HRCAs) in relapsed MM. **Methods:** A systematic literature search was conducted to identify clinical trials that investigated BsAbs in MM using the PubMed database and ASH-submitted abstracts using search terms (bispecific antibodies) AND (multiple myeloma). Our search on PubMed yielded 263 studies, of which 7 were clinical trials; of these, 5 were included, and 6 ASH abstracts were included. Cochrane-Q test and I^2 statistic were used to assess the statistical heterogenicity. A fixed effect model was used for low statistical heterogeneity ($P > 0.05$ in Cochrane-Q test and I^2 50%). Categorical outcomes were summarized by pooled proportion with 95% CI. **Results:** Overall response rates (ORRs) of the entire cohort were reported in 660 patients across 9 studies. The ORRs for EMD and HRCAs were reported in 3 (n=78) and 4 (n=100) studies, respectively. The ORR of the entire cohort was 0.65 [95% CI; 0.57; 0.74). The ORR of each BsAb was 0.70 (0.51-0.85; Chari et al, 2022) for talquetamab, 0.63 (0.55-0.70; Moreau et al, 2022) for teclistamab, and 0.61 (0.52-0.70; Bahlis et al, 2022) for elranatamab. The ORRs in MM with EMD and HRCAs with 95% CI were 0.38 [0.28; 0.49] and 0.60 [0.51; 0.70], respectively. Among the studies that reported the ORR in EMD, talquetamab (Chari et al, 2022) has the highest ORR of 0.45 (0.17; 0.77), followed by elranatamab (Bahlis et al, 2022) of 0.38 (0.23; 0.55), and teclistamab (Moreau el al, 2022) of 0.36 (0.19; 0.56). There is no significant difference in the ORR between the drugs with respect to EMD status. In studies that reported the ORR in HRCAs, talquetamab (Chari et al, 2022) had an ORR of 0.67 (0.17; 0.77) followed by teclistamab (Moreau el al, 2022) of 0.61 (0.43; 0.76), and elranatamab (Bahlis et al, 2022) of 0.55 (0.36; 0.73). Similarly, there is no significant difference in the ORR between the drugs with respect to HRCA status. The above results demonstrate that ORR in EMD is lower when compared to the entire cohort. **Conclusions:** Despite 11 clinical trials done with bispecific antibodies only 4 had reported EMD responses. This needs to be improved and clinical trials should report EMD responses distinctly as it directly informs clinical decisions. EMD responses are significantly lower than the full cohort ORR however it is encouraging that responses to high risk multiple myeloma (HRMM) closely approximate ORR of these agents. Further analysis is needed to see whether ORR and PFS correlate for HRMM. Evidence was insufficient to establish the relative superiority of one BsAb over another with EMD and combination therapies should be explored for EMD in myeloma.

OA-32

The impact of genomics to identify novel immunotherapeutic targets in multiple myeloma

Enze Liu[1], Parvathi Sudha[1], Mohammad Abu Zaid[1], Travis Johnson[2], Vivek Chopra[3], Cedric Dos Santos[3], Michael Nixon[3], Habib Hamidi[3], Attaya Suvannasankha[4], Kelvin Lee[1], Rafat Abonour[5], Brian Walker[1]

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Introduction: Immunotherapies have shown promise in treating MM, although this has been limited to relapsed and refractory MM. However, their application is limited by short remission, potential toxicity, and genomic heterogeneity. Here, we used genomic subgroups and high-risk markers to identify additional potential therapeutic targets with low predicted toxicity and high specificity to MM and genomic subgroups. **Methods:** RNA-seq data from 754 newly diagnosed MM (NDMM) and 98 relapsed and refractory MM (RRMM) samples with genomic annotation from the CoMMpass study were utilized. 32 NDMM and 43 RRMM in-house samples were used as validation. Genes with high surface potential were prioritized by annotations from 5 databases and annotation from the Human Protein Atlas was used to evaluate off-target toxicity. Candidates were further filtered to have high surface potential (>3 databases), low toxicity (normalized TPM>50 in 3). Candidates were identified at both the population and cytogenetic subgroup levels. **Results:** We identified 847 genes with high cell surface potential, of which 599 had low predicted off-target toxicity. 48 genes with high expression were identified as candidates in both the NDMM and RRMM population, all of which were validated with consistently high expression in the validation set. They included established targets such as SLAMF7/CD319, TNFRSF17/BCMA, GPRC5D, CD38, and FCRL5/FcRH5 as well as novel targets such as EVI2B, CD53, CD79A, CD79B, and CD48. High expression of CD53 and CD48 was also associated with poor progression-free survival with quartile analysis (p=0.03, p=0.01, logrank test). By splitting the population into cytogenetic subgroups 25 more candidates were identified, including significantly upregulated ROBO3 in t(4;14), SPN in t(14;16),t(14;20) and t(4;14) and MS4A1/CD20 in t(11;14) and t(14;16). SPN expression was significantly associated with overall survival in the three subgroups (p=0.0005, logrank test). 11 unique candidates were identified for other high-risk subgroups including 1q amp, biallelic TP53, and t(MYC). Some candidates were also associated with high-risk subgroups such as GPRC5D, IL6R and SPN which showed significantly elevated expression with increasing copies of 1q (p< 0.001, p< 0.001, p< 0.04, respectively). Using the DepMap database, IL6R was essential in the 1q-gained cell-line OCI-MY7 indicating that immune escape from this target may be difficult in some patients. **Conclusions:** Our studies demonstrated the existence of novel increased expression of genes encoding surface proteins in NDMM patient samples that maintained their expression levels or increased when being exposed to existing standard of care in MM. In some instances, these genes associate with existing cytogenetic subgroups and may serve as novel proteins that can be further targeted by immune-related therapies.

OA-33

Aberrant B cell differentiation induce plasma cell malignancy

Jiaojiao Guo[1], Yaru Li[2], Qing Li[3], Zhenhao Liu[4], Ruiqi Zhou[5], Zhengjiang Li[5], Nihan He[5], Tao Cheng[3], Hebing Chen[2], Wen Zhou[6]

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Introduction: Multiple myeloma (MM) is the second most common hematological malignancy. It is generally believed that MM cells develop from either B cells or plasma cells differentiated from hematopoietic stem cells (HSCs) in the bone marrow (BM). However, the nature of the earliest precursors of MM cells is still poorly defined. **Methods:** Screening the cellular origin of important genetic variation in MM patients and the key factor in cell subsets using scRNA-seq and scATAC-seq combined plasma cell differentiation. By using FISH and scPCR technology to verify the important genetic variation and differential genes of MM cell origin. Gene editing technology and adoptive B cell transplantation mouse model to verify the malignant transformation effect of screening key factor. **Results:** Firstly, we sorted HSCs, B cells and plasma cell of new diagnosis MM for scRNA-seq and scATAC-seq sequencing. Principal component analysis revealed the number of B cells declined and abnormal proportion. Further time pseudotime analysis found that MM patients with abnormal differentiation compared with the healthy donor, and "memory B" like subgroups had the potential to differentiate into plasma cells. By using inferCNV analysis, we found 1q amplification (1qAmp) could be detected in plasma cell and B cells but no HSCs. Furthermore we found that 1qAmp+ B cells have a CD24-FCRL5+phenotype. The use of FISH to validate clinical specimens further confirms this result. Finally, we sorted CD24-FCRL5+subgroups induction in vitro found that they had stronger differentiation potential of plasma cell. Suggesting that the CD24-FCRL5+ B cell subset is the cellular origin of 1qAmp. In vitro induced differentiation results display interference with FCRL5 expression inhibited B cell proliferation and plasma cell differentiation by used cas9 tag mice. The results were also confirmed by MM patients. The adoptive B cell transplantation by Vκmyc mice confirmed that over expression of FCRL5 promotes B cell malignant transformation and bone destruction. Further omics data analysis found that the open region of FCRL5 chromatin had SPI1 binding site, and FCRL5 upregulated the expression of proliferation related gene MCL1 and B cell differentiation gene IRF4. CHIP qPCR verified that SPI1 directly bound to the promoter region of MCL1 and IRF4. It is suggested that FCRL5 can promote B cell malignancy by recruiting SPI1 and regulating MCL1 and IRF4. **Conclusions:** Evidence from our previous study has demonstrated that the 1q amplification,

[2]Department of Biostatistics and Health Data Science, School of Medicine, Indiana University; [3]Genentech Inc.; [4]Indiana University Simon Cancer Center and Roudebush VAMC, Indianapolis, IN, USA; [5]Indiana University School of Medicine, Indianapolis, IN, USA

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OA-33

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which is one of the most common cytogenetic abnormalities of MM, is detected in CD24-FCRL5+B cell sub-population by single-cell omics. Interestingly, FCRL5 drives MM malignant transformation through the promotive process of B cell proliferation and plasma cell differentiation.Our research will not only provide novel insights for the origin and mechanism of MM with different genetic events, but also provide a new intervention strategy for refractory and relapsed from the perspective of cell origin of MM.

OA-34

Feasibility of a novel academic anti-BCMA chimeric antigen receptor T-cell (CART) (HBI0101) for the treatment of relapsed and refractory AL amyloidosis

Eyal Lebel[1], Shlomit Kfir-erenfeld[1], Nathalie Asherie[1], Sigal Grisariu[1], Batia Avni[1], Shlomo Elias[1], Miri Assayag[1], Tatyana Dubnikov[1], Nomi Zalcman[1], Marjorie Pick[1], Eran Zimran[1], Adir Shaulov[1], Yaël Cohen[2,3], Irit Avivi[2], Cyrille Cohen[4], Polina Stepensky[1], Moshe Gatt[1]

[1]Hadassah Medical center; [2]Tel-Aviv Sourasky (Ichilov) Medical Center; [3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [4]Bar-Ilan University

Introduction: While anti-BCMA chimeric antigen receptor T-cell therapy (CART) have proven safe and efficient in multiple myeloma (MM), its application to AL amyloidosis (AL), has been restricted, due to the frailty of this population and rarity of disease. HBI0101 therapy is a novel anti-BCMA CAR T-based therapy developed at Hadassah Medical Center for MM treatment. In a phase Ia/b study (NCT04720313), HBI0101 has demonstrated manageable safety with therapeutic efficacy in over 50 MM patients. Although BCMA targeting in AL has been questioned because of relatively low expression of this antigen on AL plasma cells (PC), we have previously reported that this level of expression is sufficient to enable PC eradication by HBI0101 CART ex vivo. Based on this observation, we have included 8 AL patients in our study, which represent the largest cohort of AL treated with BCMA-CART reported so far. **Methods:** Eight AL patients with relapsed/refractory disease were included, with a median of 6 prior lines of therapy (range: 3-10), all resistant to their last line. Six patients were penta-refractory, and five were resistant to belantamab. Seven of eight had cardiac involvement, including 4 with MAYO-stage IIIa/IIIb. The patients were treated within the following cohorts: 1 received $150x10^6$ CART cells, 2 received $450x10^6$ and 5 received $800x10^6$. Two of the patients were treated on a compassionate basis due to concomitant myelodysplastic syndrome (MDS) / ECOG 4 performance status. **Results:** Adverse events (AEs) were manageable, with cytokine-released syndrome (CRS) observed in 6/8 (grade 1-2- 4 patients; grade 3 - 2 patients). Hematologic AEs included: grade 3-4 neutropenia in 5/8, Grade 2-3 anemia in 2 patients, and in one case worsening to grade 4 of pre-existing thrombocytopenia. Two patients developed initial AL related organ deterioration, subsequently resolved. None of the patients developed immune effector cell-associated neurotoxicity syndrome (ICANs). There were no treatment-related deaths. HBI0101 therapy induced remarkable responses in these 8 heavily pretreated AL patients, achieving overall response rate of 100%, including a fast and efficient complete response in 5 patients, a very good partial response in 2, and a partial response in 1 patient. Minimal residual disease (MRD) negativity based on flow cytometry 10^{-5} was achieved in 5/8. The hematologic responses translated to clinical improvement in all patients, while 6/8 thus far met the official criteria for organ responses. With a median follow-up that is still short (7.3 months (m), range: 2.5-16.5), the median duration of response thus far is 5m (range: 2.5-16.5). **Conclusions:** In the largest cohort of AL patients reported to date, we demonstrated acceptable toxicity in this frail population, and remarkable efficacy translating into organ responses. Our data suggests that BCMA-CART modality may become a powerful clinical tool to improve organ function and survival even in advanced AL patients.

OA-35

High-throughput plasma proteomics to define the precursor multiple myeloma proteome and identify candidate high-risk disease biomarkers of progression

Elizabeth Lightbody[1], DR Mani[2], Hasmik Keshishian[2], Habib El-Khoury[1], Ankit Dutta[1], Hadley Barr[1], Namrata Udeshi[2], Michael Agius[1], Luca Bertamini[1], Nang Kham Su[1], Cody Boehner[1], Laura Hevenor[1], Katherine Towle[1], Christian Cea-Curry[1], Grace Fleming[1], Jacqueline Perry[1], Erica Horowitz[1], Maya Davis[1], Anna Cowan[1], Daniel Auclair[3], Catherine Marinac[1], Michael Gillette[2], Steven Carr[2], Irene Ghobrial[1]

[1]Dana-Farber Cancer Institute; [2]Broad Institute of MIT and Harvard; [3]AstraZeneca

Introduction: Multiple Myeloma (MM) develops from precursors Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM). Bone marrow (BM) biopsies are not routine in precursor disease management and only few proteins within peripheral blood (PB) suggest progressive disease. PB proteome profiling may better help track disease; however, the dynamic range of the plasma proteome has limited detection depth for MS-based proteomics without depleting abundant proteins and fractionating the samples after digestion to peptides. We perform the first comprehensive plasma proteomic profiling study using advanced multiplex immunoassays on patients across the MM disease continuum and sequential samples from progressive and stable disease. **Methods:** We performed plasma profiling for 3000 proteins using the Olink® Explore 3072 library and Proximity Extension Assay (PEA) technology. Proteins were recognized by multiplexed antibodies labelled with DNA oligonucleotides that upon binding come into proximity, hybridize, and are extended to generate a unique sequence for protein identification with sequencing. We profiled 423 plasma samples from 348 individuals, including healthy controls (n=58), MGUS (n=67), SMM (n=179), MM (n=44), as well as sequential samples from patients with progressive (n=27) and stable disease with matched clinical follow-up time. Precursor defined samples from progressors range 1.03-

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[1]Hadassah Medical center; [2]Tel-Aviv Sourasky (Ichilov) Medical Center; [3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [4]Bar-Ilan University

Introduction: While anti-BCMA chimeric antigen receptor T-cell therapy (CART) have proven safe and efficient in multiple myeloma (MM), its application to AL amyloidosis (AL), has been restricted, due to the frailty of this population and rarity of disease. HBI0101 therapy is a novel anti-BCMA CAR T-based therapy developed at Hadassah Medical Center for MM treatment. In a phase Ia/b study (NCT04720313), HBI0101 has demonstrated manageable safety with therapeutic efficacy in over 50 MM patients. Although BCMA targeting in AL has been questioned because of relatively low expression of this antigen on AL plasma cells (PC), we have previously reported that this level of expression is sufficient to enable PC eradication by HBI0101 CART ex vivo. Based on this observation, we have included 8 AL patients in our study, which represent the largest cohort of AL treated with BCMA-CART reported so far. **Methods:** Eight AL patients with relapsed/refractory disease were included, with a median of 6 prior lines of therapy (range: 3-10), all resistant to their last line. Six patients were penta-refractory, and five were resistant to belantamab. Seven of eight had cardiac involvement, including 4 with MAYO-stage IIIa/IIIb. The patients were treated within the following cohorts: 1 received $150x10^6$ CART cells, 2 received $450x10^6$ and 5 received $800x10^6$. Two of the patients were treated on a compassionate basis due to concomitant myelodysplastic syndrome (MDS) / ECOG 4 performance status. **Results:** Adverse events (AEs) were manageable, with cytokine-released syndrome (CRS) observed in 6/8 (grade 1-2- 4 patients; grade 3 - 2 patients). Hematologic AEs included: grade 3-4 neutropenia in 5/8, Grade 2-3 anemia in 2 patients, and in one case worsening to grade 4 of pre-existing thrombocytopenia. Two patients developed initial AL related organ deterioration, subsequently resolved. None of the patients developed immune effector cell-associated neurotoxicity syndrome (ICANs). There were no treatment-related deaths. HBI0101 therapy induced remarkable responses in these 8 heavily pretreated AL patients, achieving overall response rate of 100%, including a fast and efficient complete response in 5 patients, a very good partial response in 2, and a partial response in 1 patient. Minimal residual disease (MRD) negativity based on flow cytometry 10^{-5} was achieved in 5/8. The hematologic responses translated to clinical improvement in all patients, while 6/8 thus far met the official criteria for organ responses. With a median follow-up that is still short (7.3 months (m), range: 2.5-16.5), the median duration of response thus far is 5m (range: 2.5-16.5). **Conclusions:** In the largest cohort of AL patients reported to date, we demonstrated acceptable toxicity in this frail population, and remarkable efficacy translating into organ responses. Our data suggests that BCMA-CART modality may become a powerful clinical tool to improve organ function and survival even in advanced AL patients.

OA-35

High-throughput plasma proteomics to define the precursor multiple myeloma proteome and identify candidate high-risk disease biomarkers of progression

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Introduction: Multiple Myeloma (MM) develops from precursors Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM). Bone marrow (BM) biopsies are not routine in precursor disease management and only few proteins within peripheral blood (PB) suggest progressive disease. PB proteome profiling may better help track disease; however, the dynamic range of the plasma proteome has limited detection depth for MS-based proteomics without depleting abundant proteins and fractionating the samples after digestion to peptides. We perform the first comprehensive plasma proteomic profiling study using advanced multiplex immunoassays on patients across the MM disease continuum and sequential samples from progressive and stable disease. **Methods:** We performed plasma profiling for 3000 proteins using the Olink® Explore 3072 library and Proximity Extension Assay (PEA) technology. Proteins were recognized by multiplexed antibodies labelled with DNA oligonucleotides that upon binding come into proximity, hybridize, and are extended to generate a unique sequence for protein identification with sequencing. We profiled 423 plasma samples from 348 individuals, including healthy controls (n=58), MGUS (n=67), SMM (n=179), MM (n=44), as well as sequential samples from patients with progressive (n=27) and stable disease with matched clinical follow-up time. Precursor defined samples from progressors range 1.03-

5.88yrs prior to diagnosis, with a median clinical follow-up time of 7.05yrs. T-tests, ANOVAs, and a linear mixed effect model identified proteins across disease stages, progression status, and time with results adjusted for multiple testing using the Benjamini-Hochberg Method. **Results:** We captured circulating levels of proteins highly expressed on the surface of plasma cells, including CD38, SDC1, BCMA and SLAMF7, highlighting the ability of PEA technology to detect clinically relevant therapeutic targets. We identified proteins that significantly discriminated MGUS, SMM, and NDMM from healthy donors (n=222, 423, 494). Top classifiers included proinflammatory cytokines IL1, IL5, IL6, IL16, and IL18 which are known to create a BM environment that promotes malignant cell development by suppressing the microenvironment, promoting cellular adhesion, or increasing angiogenesis. Consistent with previous findings, baseline BCMA levels were significantly elevated in progressors vs. non-progressors, further supporting the potential utility of BCMA measurements for disease monitoring. Four novel proteins vital for calcium homeostasis and integrin-mediated cell adhesion significantly increased from healthy to MM and in progressors vs. non-progressors, nominating these proteins as candidate biomarkers of high-risk disease. **Conclusions:** We performed the most comprehensive plasma proteomics study to date on MM disease stages and identified candidate high-risk disease biomarkers. Additional studies are underway to validate candidates and integrate proteins into risk stratification models.

OA-36

SBCMA predicts progression and is a biomarker of response in myeloma precursor disease followed on prospective studies

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*[1]The University of Texas MD Anderson Cancer Center; [2]Siriraj Hospital, Mahidol University, Bangkok, Thailand; [3]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City NY, USA; [4]Mount Sinai Medical Center, New York, NY, USA; [5]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami; *RO and EM equal contribution*

Introduction: Current evidence from retrospective studies supports serum(s)BCMA as a novel biomarker in the diagnosis, prognosis, response and surveillance in myeloma precursor disease (MPD): monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Independent prospective validation of sBCMA is essential. We analyzed prospectively collected serum samples of MPD patients enrolled on clinical studies. **Methods:** A total of 730 samples belonging to 187 patients were included in the study [624 samples from 150 patients in ORIGIN (Observational prospective Research study In monoclonal Gammopathies leading to myeloma NCT02726750); 26 samples from 13 patients with int. and high-risk SMM treated with pembrolizumab (NCT02603887) and 80 samples from 24 high-risk SMM patients in ISAMAR treated with isatuximab (ISA) (NCT02960555)]. sBCMA levels were measured in triplicate by enzyme-linked immunosorbent assay (ELISA) with human anti-BCMA/TNFRSF17 antibody from R&D systems (catalogue# DY193). SPSSv20 was used for statistical analysis, Mann-Whitney and ANOVA tests were used for non-parametric and parametric comparisons, respectively. **Results:** In ORIGIN, where untreated MGUS and/or SMM patients are followed prospectively until progression, the baseline sBCMA was significantly lower in MGUS vs SMM patients, [44.4 (IQR20.2-67.5) vs 59.4 (IQR34.3-120.8) ng/mL; p=0.006]. Longitudinal analysis showed that MGUS progressors (to SMM) (n=4) and SMM progressors (to MM) (n=13) had increasing sBCMA over time. The median sBCMA level at baseline, 1, and 3 years was 62.7 (IQR32.3 – 257.4), 81.3 (IQR27.9 – 239.2), and 139.5 (IQR123.9 – 139.5) ng/mL in MGUS-> SMM and 11.6 (2.6 – 45), 14.7 (4.3 – 61.3) and 27.8 (9.2 – 80.1) ng/mL in SMM->MM patients. MGUS patients (n=4) that progressed to SMM had a higher baseline sBCMA compared to non-progressor MGUS (n=54) [62.8 (IQR32.3 – 257.4) vs 43.3 (IQR15.7 – 64.3) ng/mL; p=0.236]. SMM patients who were treated with either pembrolizumab or ISA monotherapy on protocol and did not progress to MM (n=30) had lower baseline sBCMA compared to SMM progressors (n=7) (82.3 (IQR62.3 – 148.4) vs 176 (IQR101.7 – 330.7) ng/mL, p=0.078. In ISAMAR, sBCMA significantly decreased after treatment with ISA [baseline sBCMA 101.5 (IQR70.9 – 181.3)), after 30 cycles 14.9 (IQR9.3 – 69.3) ng/mL (p< 0.001)]. Correlation analysis of the serum paraprotein, i:u sFLC ratio and sBCMA throughout treatment showed significant reduction in all 3 parameters, but the slope of sBCMA decrease after treatment was significantly more pronounced than in the ratio or paraprotein (p< 0.001). **Conclusions:** sBCMA can be used for prediction of progression in MPD, where it may be an independent biomarker. Additionally, it may be used in response monitoring in MPD treatment allowing for faster assessment of response compared to traditional blood markers.

OA-37

Optimization of the 20/2/20 risk stratification model for patients with smoldering multiple myeloma through integration of the evolving patterns of monoclonal protein and serum free light chains

Annika Werly[1], Thomas Hielscher[2], Niels Weinhold[3,4], Kosima Zürn[1], Anna Jauch[5,6], Marc Raab[3], Carsten Müller-Tidow[3,7], Hartmut Goldschmidt[8], Elias Mai[3,8]

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5.88yrs prior to diagnosis, with a median clinical follow-up time of 7.05yrs. T-tests, ANOVAs, and a linear mixed effect model identified proteins across disease stages, progression status, and time with results adjusted for multiple testing using the Benjamini-Hochberg Method. **Results:** We captured circulating levels of proteins highly expressed on the surface of plasma cells, including CD38, SDC1, BCMA and SLAMF7, highlighting the ability of PEA technology to detect clinically relevant therapeutic targets. We identified proteins that significantly discriminated MGUS, SMM, and NDMM from healthy donors (n=222, 423, 494). Top classifiers included proinflammatory cytokines IL1, IL5, IL6, IL16, and IL18 which are known to create a BM environment that promotes malignant cell development by suppressing the microenvironment, promoting cellular adhesion, or increasing angiogenesis. Consistent with previous findings, baseline BCMA levels were significantly elevated in progressors vs. non-progressors, further supporting the potential utility of BCMA measurements for disease monitoring. Four novel proteins vital for calcium homeostasis and integrin-mediated cell adhesion significantly increased from healthy to MM and in progressors vs. non-progressors, nominating these proteins as candidate biomarkers of high-risk disease. **Conclusions:** We performed the most comprehensive plasma proteomics study to date on MM disease stages and identified candidate high-risk disease biomarkers. Additional studies are underway to validate candidates and integrate proteins into risk stratification models.

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OA-37

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OA-36

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OA-37

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Diseases (NCT), Heidelberg, Germany; [8]Internal Medicine V, GMMG Study Group at University Hospital Heidelberg, Heidelberg, Germany

Introduction: The 20/2/20 model represents the prevailing standard of risk stratification for patients with smoldering multiple myeloma (SMM). This study aims at optimization of the 20/2/20 model by integrating evolving patterns of serum M-protein and involved serum free light chains (sFLC) as risk factors to more accurately identify patients at high risk who benefit from intensified monitoring or early therapeutic interventions. **Methods:** In this study we retrospectively included 339 patients diagnosed with SMM between 2010 and 2022, who met the 2014 IMWG diagnostic criteria (Rajkumar SV et al., Lancet Oncol., 2014). Through cutoff analyses, we defined evolving patterns of serum M-protein and involved sFLC. We then compared the performance of the Mayo2018 (BMPC >20%, M-protein > 2g/dl, FLCr >20; 0 points = low risk, 1 point = intermediate risk, ≥2 points = high risk; Lakshman A et al., BCJ, 2018), IMWG2020 (as Mayo2018 plus cytogenetic abnormalities (t(4;14), t(14;16), +1q21 and/or del13q); 0 points = low risk, 1 point = low intermediate risk, 2 points = intermediate risk, ≥3 points = high risk; Mateos MV et al., BCJ, 2020) and gradual IMWG2020 (gradual scoring system for M-protein, BMPC, FLCr and cytogenetic abnormalities; Mateos MV et al., BCJ, 2020) models enhanced by the dynamic risk factor "evolving M-protein and/or evolving sFLC" at one year from diagnosis to the respective standard models, using the c-index. **Results:** Based on optimal cut-point search and clinical applicability we defined the independent risk factors evolving M-protein as a >10% and >0,2g/dl increase in M-protein (49/222 patients (22%), HR=5.02, 95% CI [2.86;8.81], p25% and >50mg/l increase in involved sFLC (14/178 patients (8%), HR=3.66, 95% CI [1.60;8.38], p< 0.002) within one year from diagnosis. 58/179 patients (32%) had an evolving M-protein and/or evolving sFLC phenotype resulting in an increased risk of progression (HR=6.41, 95% CI [3.19;12.86], p< 0,001). At one year, 10 of 78 patients migrated from low to intermediate risk and 19 of 56 patients from intermediate to high risk in the Mayo2018 model when adding the evolving phenotype. At one year the combined risk factor „evolving M-protein and/or evolving sFLC" improved discrimination of the risk groups when added to the Mayo2018 model (c-statistics for static model: 0.750 vs. dynamic model: 0.783, p=0.165). Similarly, the IMWG2020 (static: 0.745 vs. dynamic: 0.805, p=0.014) and gradual IMWG2020 (static: 0.753 vs. dynamic: 0.828, p=0.005) models improved prognostication when expanded by dynamic M-protein/sFLC. **Conclusions:** Through integration of the dynamic risk factor "evolving M-protein and/or evolving sFLC" in the current risk stratification models of SMM, a crucial aspect of individual disease dynamics is taken into account. Our results show that the dynamic M-protein/sFLC models are superior to standard models. Independent validation of the analyses is in preparation.

OA-38

Physical activity interventions to improve functional performance in patients with multiple myeloma

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Introduction: Frailty is a frequent limitation for treatment and an adverse prognostic factor for multiple myeloma (MM) patients. In other settings, including oncology, physical exercise has been shown to be beneficial in improving patients' fitness. The IMWG has developed a frailty score based on patient-reported parameters. There are, however, only limited data on the safety and efficacy of physical exercise in MM to improve functional performance, especially with bone disease present. To address this gap in knowledge, we performed a two-arm non-randomized pilot exercise study in MM patients. **Methods:** Patients self-selected into one of two active interventions: a six-month, twice weekly, in person, supervised resistance training (strength training group, STG) and a six-month behavioral intervention using fitness trackers with regular remote prompts to motivate patients to achieve 150-300 active minutes per week (walking group, WG). The non-randomized design allowed patients to participate in the remote arm if they lived too far from the institution to attend regular training sessions or had COVID-19-related concerns. After informed consent, a patient's most recent imaging results were reviewed in an interdisciplinary tumor board; the patient was either cleared for participation, cleared with limitations, or declined for participation. Assessments of functional parameters occurred after three and six months of the intervention and three and six months after the intervention. **Results:** A total of 87 patients were informed of the trial. Of those, 44 patients refused to participate, mostly due to travel distance. Of the 43 enrolled patients, 24 chose the STG and 20 the WG. For different reasons, including the COVID-19 pandemic, five patients did not complete the trial. The tumor board recommended restrictions for seven patients (e.g., no overhead exercises; no impact exercises). There were no significant differences between the groups in terms of age, BMI, sex, race, ECOG performance status, disease response, disease status, and likelihood of completing the intervention. The combined study sample showed significant improvements in mobility (AM-PAC Basic Mobility Short Form, P< 0.01), six-minute walk test (6MWT, P< 0.01), 30-second sit-to-stand test (30STS, P< 0.01), timed up-and-go test (TUG, P< 0.01), and pain (visual analogue scale, P< 0.01) during the intervention. The 30STS remained significantly improved six months after the intervention, while the gains made in mobility and the TUG were partially lost. The gains in 6MWT and pain were not significantly changed after the intervention. **Conclusions:** In this pilot study, both the STG and the WG were feasible in patients with MM and led to improvements in relevant parameters of functional capacity. This work lays the foundation for future exercise interventions aimed at improving physical function and resilience in MM patients undergoing systemic treatment.

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Introduction: The 20/2/20 model represents the prevailing standard of risk stratification for patients with smoldering multiple myeloma (SMM). This study aims at optimization of the 20/2/20 model by integrating evolving patterns of serum M-protein and involved serum free light chains (sFLC) as risk factors to more accurately identify patients at high risk who benefit from intensified monitoring or early therapeutic interventions. **Methods:** In this study we retrospectively included 339 patients diagnosed with SMM between 2010 and 2022, who met the 2014 IMWG diagnostic criteria (Rajkumar SV et al., Lancet Oncol., 2014). Through cutoff analyses, we defined evolving patterns of serum M-protein and involved sFLC. We then compared the performance of the Mayo2018 (BMPC >20%, M-protein > 2g/dl, FLCr >20; 0 points = low risk, 1 point = intermediate risk, ≥2 points = high risk; Lakshman A et al., BCJ, 2018), IMWG2020 (as Mayo2018 plus cytogenetic abnormalities (t(4;14), t(14;16), +1q21 and/or del13q); 0 points = low risk, 1 point = low intermediate risk, 2 points = intermediate risk, ≥3 points = high risk; Mateos MV et al., BCJ, 2020) and gradual IMWG2020 (gradual scoring system for M-protein, BMPC, FLCr and cytogenetic abnormalities; Mateos MV et al., BCJ, 2020) models enhanced by the dynamic risk factor "evolving M-protein and/or evolving sFLC" at one year from diagnosis to the respective standard models, using the c-index. **Results:** Based on optimal cut-point search and clinical applicability we defined the independent risk factors evolving M-protein as a >10% and >0,2g/dl increase in M-protein (49/222 patients (22%), HR=5.02, 95% CI [2.86;8.81], p25% and >50mg/l increase in involved sFLC (14/178 patients (8%), HR=3.66, 95% CI [1.60;8.38], p< 0.002) within one year from diagnosis. 58/179 patients (32%) had an evolving M-protein and/or evolving sFLC phenotype resulting in an increased risk of progression (HR=6.41, 95% CI [3.19;12.86], p< 0,001). At one year, 10 of 78 patients migrated from low to intermediate risk and 19 of 56 patients from intermediate to high risk in the Mayo2018 model when adding the evolving phenotype. At one year the combined risk factor „evolving M-protein and/or evolving sFLC" improved discrimination of the risk groups when added to the Mayo2018 model (c-statistics for static model: 0.750 vs. dynamic model: 0.783, p=0.165). Similarly, the IMWG2020 (static: 0.745 vs. dynamic: 0.805, p=0.014) and gradual IMWG2020 (static: 0.753 vs. dynamic: 0.828, p=0.005) models improved prognostication when expanded by dynamic M-protein/sFLC. **Conclusions:** Through integration of the dynamic risk factor "evolving M-protein and/or evolving sFLC" in the current risk stratification models of SMM, a crucial aspect of individual disease dynamics is taken into account. Our results show that the dynamic M-protein/sFLC models are superior to standard models. Independent validation of the analyses is in preparation.

OA-38

Physical activity interventions to improve functional performance in patients with multiple myeloma

Jens Hillengass[1], Michaela Hillengass[1], Hillary Jacobson[1], Rikki Cannioto[1], Bryan Wittmeyer[1], Kirsten Moysich[1], Janine Joseph[1]

[1]Roswell Park Comprehensive Cancer Center

Introduction: Frailty is a frequent limitation for treatment and an adverse prognostic factor for multiple myeloma (MM) patients. In other settings, including oncology, physical exercise has been shown to be beneficial in improving patients' fitness. The IMWG has developed a frailty score based on patient-reported parameters. There are, however, only limited data on the safety and efficacy of physical exercise in MM to improve functional performance, especially with bone disease present. To address this gap in knowledge, we performed a two-arm non-randomized pilot exercise study in MM patients. **Methods:** Patients self-selected into one of two active interventions: a six-month, twice weekly, in person, supervised resistance training (strength training group, STG) and a six-month behavioral intervention using fitness trackers with regular remote prompts to motivate patients to achieve 150-300 active minutes per week (walking group, WG). The non-randomized design allowed patients to participate in the remote arm if they lived too far from the institution to attend regular training sessions or had COVID-19-related concerns. After informed consent, a patient's most recent imaging results were reviewed in an interdisciplinary tumor board; the patient was either cleared for participation, cleared with limitations, or declined for participation. Assessments of functional parameters occurred after three and six months of the intervention and three and six months after the intervention. **Results:** A total of 87 patients were informed of the trial. Of those, 44 patients refused to participate, mostly due to travel distance. Of the 43 enrolled patients, 24 chose the STG and 20 the WG. For different reasons, including the COVID-19 pandemic, five patients did not complete the trial. The tumor board recommended restrictions for seven patients (e.g., no overhead exercises; no impact exercises). There were no significant differences between the groups in terms of age, BMI, sex, race, ECOG performance status, disease response, disease status, and likelihood of completing the intervention. The combined study sample showed significant improvements in mobility (AM-PAC Basic Mobility Short Form, P< 0.01), six-minute walk test (6MWT, P< 0.01), 30-second sit-to-stand test (30STS, P< 0.01), timed up-and-go test (TUG, P< 0.01), and pain (visual analogue scale, P< 0.01) during the intervention. The 30STS remained significantly improved six months after the intervention, while the gains made in mobility and the TUG were partially lost. The gains in 6MWT and pain were not significantly changed after the intervention. **Conclusions:** In this pilot study, both the STG and the WG were feasible in patients with MM and led to improvements in relevant parameters of functional capacity. This work lays the foundation for future exercise interventions aimed at improving physical function and resilience in MM patients undergoing systemic treatment.

OA-39

Development and validation of a prognostic survival model with patient reported outcomes for older adults with multiple myeloma

Hira Mian[1], Rinku Sutradhar[2], Matthew Cheung[3], Anastasia Gayowsky[4], Jason Tay[5], Amaris Balitsky[1], Tanya Wildes[6], Arleigh McCurdy[7], Alissa Visram[8], Irwindeep Sandhu[9], Hsien Seow[1]

[1]McMaster University, Hamilton, Ontario, Canada; [2]University of Toronto; [3]Sunnybrook Health Sciences Centre; [4]ICES McMaster; [5]University of Calgary; [6]University of Nebraska Medical Centre; [7]University of Ottawa; [8]The Ottawa Hospital; [9]University of Alberta, Edmonton, AB, Canada

Introduction: Existing prognostic tools in multiple myeloma (MM) are designed specifically for clinicians and incorporate variables often unknown to MM patients (i.e. cytogenetics). Developing prognostic tools for patient use represents an important step in empowering patients to understand their prognosis and engage in shared decision making. Incorporating patient reported outcomes (PROs) may represent an opportunity for developing prognostic tools. The implementation of standardized cancer symptom assessment in clinics in Ontario, Canada since 2007 provides a unique opportunity to evaluate the prognostic ability of PROs. The objective of our study was to develop and validate a prognostic score for overall survival among transplant ineligible newly-diagnosed multiple myeloma (TI NDMM) patients incorporating PROs. **Methods:** This was a retrospective population-based, prognostic study using administrative data of all patients with TI NDMM in Ontario diagnosed between Jan 2007-Dec 2019. Index date was defined as one year following diagnosis to ensure only patients who did not receive a transplant in first line were included. Patients were randomly selected for model derivation (75%) and validation (25%). The derivation cohort was used to develop a multivariable Cox proportional hazards regression model with backward stepwise variable selection to predict the risk of death one year following index date. Baseline covariates at index date included demographic characteristics, clinical information, health care utilization, performance status, and PROs using the Edmonton Symptom Assessment Score, which measures 9 common cancer symptoms (e.g. pain, dyspnea) on a 10-point scale, where 7-10 is high burden. **Results:** There were 2356 TI NDMM patients identified. The median age was 75 with 42.2% female sex. The majority of patients (90.3%) had received a novel drug (IMID and/or PI) following diagnosis. The following factors were associated with an increased risk of death: age >80 (HR 1.11), previous history of congestive heart failure (HR 1.52), CRAB symptoms at diagnosis (HR 1.61), distance of >50 km to cancer center (HR 1.25), radiation received in the year prior (HR 1.48), no novel drugs received in the year prior (HR 1.36), emergency department (HR 1.55) or hospitalization (HR 2.13) in the prior 6-months, poor performance status (ECOG 3-4 HR 1.76) and increasing number of symptoms with high burden (HR 1.56) in the prior 6-months. Model discrimination in the validation cohort was high with C-statistic of 0.74, and calibration plots indicated strong agreement between observed and predicted risks. **Conclusions:** To our knowledge, this represents one of the first prognostic models developed in NDMM designed specifically for patients, using easily available variables that can be easily completed by patients themselves including PROs. This survival prognostic tool may improve communication regarding prognosis and shared decision making among older adults with MM and their health care providers.

OA-40

Frailty and initial treatment intensity in patients newly diagnosed with multiple myeloma

Clark DuMontier[1], Jennifer La[2], John Bihn[3], June Corrigan[3], Cenk Yilidrim[3], Mayuri Dharne[3], Hamza Hassan[4], Sarvari Yellapragada[5], Gregory Abel[6], J Michael Gaziano[1], Nhan Do[4], Mary Brophy[4], Dae Kim, Nikhil Munshi[8], Nathanael Fillmore[2], Jane Driver[1]

[1]VA Boston Healthcare System and Brigham and Women's Hospital/ Harvard Medical School; [2]VA Boston Healthcare System and Harvard School of Medicine; [3]VA Boston Healthcare System; [4]Boston Medical Center and Chobanian and Avedisian School of Medicine, Boston University; [5]VA Houston and Baylor College of Medicine; [6]Dana-Farber Cancer Institute/Harvard Medical School; [7]Harvard Medical School and Hebrew SeniorLife and Marcus Institute for Aging Research; [8]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/Harvard Medical School

Introduction: Randomized controlled trial data suggest that initiation of the more intensive triplet bortezomib-lenalidomide-dexamethasone (VRd) versus the less intensive doublet lenalidomide-dexamethasone (Rd) in patients newly diagnosed with multiple myeloma (MM) confers superior survival, but it is uncertain whether this survival benefit generalizes to frail patients treated in practice. **Methods:** We identified all patients newly diagnosed with MM who were initiated on either VRd or Rd in the national U.S. Veterans Affairs Healthcare System. We measured frailty using the electronic Veterans Affairs Frailty Index (VA-FI), which has been validated in veterans with and without cancer. Using established cutoffs, we identified patients who were moderate-severely frail (VA-FI ≥ 0.3), mildly frail (VA-FI 0.20-0.29), and nonfrail (VA-FI < 0.2). To reduce imbalance in potential confounding across treatment groups within frailty categories, we matched patients on MM stage and on a propensity score (1:1 nearest-neighbor with a caliper of 1%) that was modeled on the probability of being initially treated with VRd vs. Rd as a function of age, sociodemographics, comorbidity, and MM-specific covariates. We used Cox proportional hazards models to evaluate differences in mortality between veterans initiated on VRd and veterans initiated on Rd. Our secondary outcome was incidence of unplanned hospitalizations within one year of treatment initiation. **Results:** We identified 2573 patients newly diagnosed with MM who were initiated either on VRd (990) or Rd (1583), spanning years 2004-2020. After matching, patients who were moderate-severely frail were older than non-frail patients (median age 71.1 years vs. 67.6 years), had a higher prevalence of stage III MM (32.9% vs. 19.5%), and had a higher prevalence of myeloma-related health deficits. VRd vs. Rd was associated with lower mortality (HR = 0.81, 95% CI = 0.70 - 0.94) in the overall population. Moderate-severely

OA-39

Development and validation of a prognostic survival model with patient reported outcomes for older adults with multiple myeloma

Hira Mian[1], Rinku Sutradhar[2], Matthew Cheung[3], Anastasia Gayowsky[4], Jason Tay[5], Amaris Balitsky[1], Tanya Wildes[6], Arleigh McCurdy[7], Alissa Visram[8], Irwindeep Sandhu[9], Hsien Seow[1]

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OA-40

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frail patients demonstrated the strongest association between VRd vs. Rd and lower mortality (HR 0.74, 95% CI 0.56 - 0.97), whereas the association was weaker in mildly frail (HR 0.80, 95% CI 0.61 - 1.05) and nonfrail patients (HR 0.86, 95% CI 0.67 - 1.10). Although there was a modestly higher incidence of hospitalizations associated with VRd vs. Rd (incidence rate ratio [IRR] 1.22, 95% CI 1.1 - 1.34) in the overall population, this association weakened in moderate-severely frail patients (IRR 1.14, 95% CI 0.96 - 1.36). **Conclusions:** Our findings not only confirm the mortality benefit of VRd over Rd in U.S. veterans newly diagnosed with MM, but also suggest that this benefit is strongest in patients with the highest levels of frailty, countering historical recommendations to consider doublets in this population. These findings argue that a frail patient's cancer should be considered as a treatable cause of their frailty wherein more intensive treatment may be more effective.

OA-41

Iberdomide, bortezomib, and dexamethasone (IberVd) in transplant-ineligible newly diagnosed multiple myeloma (NDMM): results from the CC-220-MM-001 trial

Darrell White[1], Brea Lipe[2], Mercedes Gironella Mesa[3], Ruben Niesvizky[4], Albert Oriol[5], Anna Sureda Balari[6], Manisha Bhutani[7], Cristina Encinas[8], Abdullah Khan[9], Michael Amatangelo[10], Kexin Jin[10], Thomas Solomon[10], Kevin Hong[10], Alpesh Amin[10], Paulo Maciag[10], Niels van de Donk[11], Sagar Lonial[12]

[1]Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; [2]The Department of Medicine, University of Rochester Medical Center, Rochester, NY, USA; [3]Hematology Department, Vall d'Hebron Hospital, Barcelona, Spain; [4]Division of Oncology & Hematology, Weill Cornell Medicine, New York, NY, USA; [5]Catalan Institute of Oncology and Josep Carreras Institute, Hospital Germans Trias i Pujol, Badalona, Spain; [6]Hematology Department, Institut Català d'Oncologia - Hospitalet, IDIBELL, University of Barcelona, Barcelona, Spain; [7]Division of Plasma Cell Disorders, Department of Hematologic Oncology & Blood Disorders, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [8]Hospital General Universitario Gregorio Marañón (HGUGM), IiSGM, Madrid, Spain; [9]The James Cancer Hospital and Solove Research Institute, Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [10]Bristol Myers Squibb, Princeton, NJ, USA; [11]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Department of Hematology, Amsterdam, Netherlands, and Cancer Center Amsterdam, Amsterdam, Netherlands; [12]Winship Cancer Institute, Emory University, Atlanta, GA, USA

Introduction: In patients (pts) with transplant-ineligible (TNE) NDMM, the immunomodulatory drug (IMiD®) lenalidomide forms a standard of care in combination with bortezomib (BORT) and dexamethasone (DEX). Iberdomide (IBER) is a novel, potent oral cereblon E3 ligase modulator (CELMoD™) with increased tumoricidal activity and immune-modulatory effects compared with IMiD agents. IBER has shown preclinical synergistic activity in combination with BORT, and IberVd has shown promising preliminary efficacy and safety in pts with relapsed/refractory MM in the ongoing phase 1/2 CC-220-MM-001 trial (NCT02773030). Here we report results from the dose-expansion cohort of IberVd in pts with TNE NDMM. **Methods:** Eligible pts had untreated symptomatic NDMM, no autologous stem cell transplant planned, nor ineligibility due to age or comorbidities. Oral IBER was given on days (D) 1–14 of each 21-d cycle in Cycle (C)1–8 and D1–21 of each 28-d cycle in ≥C9 in combination with subcutaneous BORT (starting at 1.3mg/m^2) on D1, 4, 8, and 11 of each 21-d cycle and oral DEX on D1, 2, 4, 5, 8, 9, 11, and 12 of each 21-d cycle in C1–8, and weekly in ≥C9 (20 or 10mg if >75 y of age in C1–8; 40 or 20mg if >75 y in ≥C9). Endpoints included preliminary efficacy and safety, pharmacokinetics, and minimal residual disease assessment. **Results:** As of March 3, 2023, 18 pts received IberVd (1 pt 1.0mg; 17 pts 1.6mg). Median age was 77.5 (57–84) y and 11 (61.1%) pts had high-risk cytogenetics. Median follow-up was 10.5 mo. Median treatment (Tx) duration was 48.4 (3.0–65.0) wk; 14 (77.8%) pts continued on Tx. Two pts withdrew from the study before completing a Tx cycle (1 lost to follow-up, 1 consent withdrawal); no pts withdrew due to IBER-related Tx-emergent adverse events (TEAEs). Grade (Gr) 3–4 TEAEs occurred in 70.6% pts; most common were neutropenia (17.6%) and infections (17.6%, including pneumonia [11.8%]). Two (11.8%) pts had Gr 3–4 peripheral neuropathy. Occurrence of other Gr 3–4 TEAEs was low. Eleven (64.7%) and 6 (35.3%) pts had IBER dose interruptions and reductions due to TEAEs, respectively. Overall response rate in the intention-to-treat population was 88.9% (95% CI, 65.3–98.6) with 4 stringent complete responses, 5 complete responses (CR), 5 very good partial responses (VGPR), and 2 partial responses; 2 pts were not evaluable. Overall, 9 (50.0%) pts achieved ≥CR, and 14 (77.8%) pts achieved ≥VGPR. Median time to response was 3.1 (3.0–17.0) wk; 68.6% of pts responded in < 6 wk. Pharmacodynamic data showed that IBER Tx led to robust substrate degradation (median >50% decrease) and immune stimulation (177% median increase in T-cell proliferation) when combined with Vd. **Conclusions:** IberVd showed high efficacy with deep, ongoing responses in this cohort of mostly older pts with TNE NDMM. The safety profile was manageable with no new safety signals, and no pts discontinued due to AEs. These data support further assessment of IBER combinations in the frontline setting.

OA-42

Second primary malignancies after tandem autologous hematopoietic stem cell transplantation for patients with multiple myeloma treated on earlier total therapy protocols

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[1]Myeloma Center, University of Arkansas for Medical Sciences; [2]Jordan university of science and technology

frail patients demonstrated the strongest association between VRd vs. Rd and lower mortality (HR 0.74, 95% CI 0.56 - 0.97), whereas the association was weaker in mildly frail (HR 0.80, 95% CI 0.61 - 1.05) and nonfrail patients (HR 0.86, 95% CI 0.67 - 1.10). Although there was a modestly higher incidence of hospitalizations associated with VRd vs. Rd (incidence rate ratio [IRR] 1.22, 95% CI 1.1 - 1.34) in the overall population, this association weakened in moderate-severely frail patients (IRR 1.14, 95% CI 0.96 - 1.36). **Conclusions:** Our findings not only confirm the mortality benefit of VRd over Rd in U.S. veterans newly diagnosed with MM, but also suggest that this benefit is strongest in patients with the highest levels of frailty, countering historical recommendations to consider doublets in this population. These findings argue that a frail patient's cancer should be considered as a treatable cause of their frailty wherein more intensive treatment may be more effective.

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Introduction: In patients (pts) with transplant-ineligible (TNE) NDMM, the immunomodulatory drug (IMiD®) lenalidomide forms a standard of care in combination with bortezomib (BORT) and dexamethasone (DEX). Iberdomide (IBER) is a novel, potent oral cereblon E3 ligase modulator (CELMoD™) with increased tumoricidal activity and immune-modulatory effects compared with IMiD agents. IBER has shown preclinical synergistic activity in combination with BORT, and IberVd has shown promising preliminary efficacy and safety in pts with relapsed/refractory MM in the ongoing phase 1/2 CC-220-MM-001 trial (NCT02773030). Here we report results from the dose-expansion cohort of IberVd in pts with TNE NDMM. **Methods:** Eligible pts had untreated symptomatic NDMM, no autologous stem cell transplant planned, nor ineligibility due to age or comorbidities. Oral IBER was given on days (D) 1–14 of each 21-d cycle in Cycle (C)1–8 and D1–21 of each 28-d cycle in ≥C9 in combination with subcutaneous BORT (starting at 1.3mg/m^2) on D1, 4, 8, and 11 of each 21-d cycle and oral DEX on D1, 2, 4, 5, 8, 9, 11, and 12 of each 21-d cycle in C1–8, and weekly in ≥C9 (20 or 10mg if >75 y of age in C1–8; 40 or 20mg if >75 y in ≥C9). Endpoints included preliminary efficacy and safety, pharmacokinetics, and minimal residual disease assessment. **Results:** As of March 3, 2023, 18 pts received IberVd (1 pt 1.0mg; 17 pts 1.6mg). Median age was 77.5 (57–84) y and 11 (61.1%) pts had high-risk cytogenetics. Median follow-up was 10.5 mo. Median treatment (Tx) duration was 48.4 (3.0–65.0) wk; 14 (77.8%) pts continued on Tx. Two pts withdrew from the study before completing a Tx cycle (1 lost to follow-up, 1 consent withdrawal); no pts withdrew due to IBER-related Tx-emergent adverse events (TEAEs). Grade (Gr) 3–4 TEAEs occurred in 70.6% pts; most common were neutropenia (17.6%) and infections (17.6%, including pneumonia [11.8%]). Two (11.8%) pts had Gr 3–4 peripheral neuropathy. Occurrence of other Gr 3–4 TEAEs was low. Eleven (64.7%) and 6 (35.3%) pts had IBER dose interruptions and reductions due to TEAEs, respectively. Overall response rate in the intention-to-treat population was 88.9% (95% CI, 65.3–98.6) with 4 stringent complete responses, 5 complete responses (CR), 5 very good partial responses (VGPR), and 2 partial responses; 2 pts were not evaluable. Overall, 9 (50.0%) pts achieved ≥CR, and 14 (77.8%) pts achieved ≥VGPR. Median time to response was 3.1 (3.0–17.0) wk; 68.6% of pts responded in < 6 wk. Pharmacodynamic data showed that IBER Tx led to robust substrate degradation (median >50% decrease) and immune stimulation (177% median increase in T-cell proliferation) when combined with Vd. **Conclusions:** IberVd showed high efficacy with deep, ongoing responses in this cohort of mostly older pts with TNE NDMM. The safety profile was manageable with no new safety signals, and no pts discontinued due to AEs. These data support further assessment of IBER combinations in the frontline setting.

OA-42

Second primary malignancies after tandem autologous hematopoietic stem cell transplantation for patients with multiple myeloma treated on earlier total therapy protocols

Samer Al Hadidi[1], Obada Ababneh[2], Carolina Schinke[1], Sharmilan Thanendrarajan[1], Clyde Bailey[1], Guido Tricot[1], John Shaughnessy[1], Fenghuang Zhan[1], Jeffrey Sawyer[1], Bart Barlogie[1], Maurizio Zangari[1], Frits van Rhee[1]

[1]Myeloma Center, University of Arkansas for Medical Sciences; [2]Jordan university of science and technology

frail patients demonstrated the strongest association between VRd vs. Rd and lower mortality (HR 0.74, 95% CI 0.56 - 0.97), whereas the association was weaker in mildly frail (HR 0.80, 95% CI 0.61 - 1.05) and nonfrail patients (HR 0.86, 95% CI 0.67 - 1.10). Although there was a modestly higher incidence of hospitalizations associated with VRd vs. Rd (incidence rate ratio [IRR] 1.22, 95% CI 1.1 - 1.34) in the overall population, this association weakened in moderate-severely frail patients (IRR 1.14, 95% CI 0.96 - 1.36). **Conclusions:** Our findings not only confirm the mortality benefit of VRd over Rd in U.S. veterans newly diagnosed with MM, but also suggest that this benefit is strongest in patients with the highest levels of frailty, countering historical recommendations to consider doublets in this population. These findings argue that a frail patient's cancer should be considered as a treatable cause of their frailty wherein more intensive treatment may be more effective.

OA-41

Iberdomide, bortezomib, and dexamethasone (IberVd) in transplant-ineligible newly diagnosed multiple myeloma (NDMM): results from the CC-220-MM-001 trial

Darrell White[1], Brea Lipe[2], Mercedes Gironella Mesa[3], Ruben Niesvizky[4], Albert Oriol[5], Anna Sureda Balari[6], Manisha Bhutani[7], Cristina Encinas[8], Abdullah Khan[9], Michael Amatangelo[10], Kexin Jin[10], Thomas Solomon[10], Kevin Hong[10], Alpesh Amin[10], Paulo Maciag[10], Niels van de Donk[11], Sagar Lonial[12]

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Introduction: The use of high-dose chemotherapy followed by tandem autologous hematopoietic stem cell transplantation (auto-HSCT) has resulted in improved outcomes for patients with multiple myeloma (MM) While auto-HSCT is recognized as a standard of care for newly diagnosed transplant-eligible MM patients due to the improved long-term disease control and survival it provides, the exposure to high-dose chemotherapy is associated with an increased risk of second primary malignancies (SPMs), with a subset of SPMs categorized as second hematologic malignancies (SHM). Our study aims to provide the incidence of SPMs and SHMs on patients treated on TT I-IIIB based on long-term follow up **Methods:** Patients enrolled on total therapy I (NCT00580372), II (NCT00083551), IIIA (NCT00081939) and IIIB (NCT00572169) between 1989-2008 were included. Patients were treated at the University of Arkansas for Medical Sciences with combination-based chemotherapy, tandem auto-HSCT and maintenance therapy, and followed for development of SPMs and SHMs. **Results:** Among 1379 patients with newly diagnosed MM enrolled on four TT trials with a median follow up range of 15-25 years. SPMs (including SHMs and excluding non-melanoma skin cancer) occurred in 11.8% of patients of which 64.4% of SPMs were solid tumors (most common were prostate cancer (n=22), colorectal cancer (n=20), breast cancer (n=15), lung cancer (n=11), and bladder cancer (n=7). A total of 4.2% (n=58) of patients developed a SHM. SHMs include acute lymphoblastic leukemia (ALL) (n=4), acute myeloid leukemia (2.4%, n=33), myelodysplastic syndrome (0.7%, n=9), B-cell lymphoma (n=10), chronic myelomonocytic leukemia (n=1) and unspecified leukemia (n=1). Median time to first SHM in patients treated on TT I, TT II (+thalidomide), TT II (-thalidomide), TT IIIA, TTIIIB were 10.7, 7.67, 10.3, 5.56, and 6.23 years, respectively. No statistical difference between risk of SHMs and enrollment on specific clinical trial, was observed. However, all four ALL cases occurred in patients who were exposed to an immunomodulatory drug. No difference in SPMs were observed in patients treated on TT IIIB when compared to TT IIIA. **Conclusions:** The occurrence of SHMs in patients who were treated with tandem-autologous hematopoietic stem cell transplantation on earlier TT protocols and followed up for a median of more than 15 years was 4.2%. The risk of AML and/or MDS was 3.1%. Our long-term follow up indicates that the risk of developing SHMs is relatively low. With the improvement in long-term outcomes of MM patients it is important to consider the risk of developing various cancers and consider appropriate.

OA-43

Analysis of sustained MRD-negativity and progression-free survival of Isa-KRd in high-risk newly diagnosed multiple myeloma – additional data from planned interim analysis of the GMMG-CONCEPT trial

Lisa Leypoldt[1,2,3], Diana Tichy[4], Britta Besemer[5], Mathias Hänel[6], Marc Raab[7], Christoph Mann[8], Markus Munder[9], Hans Christian Reinhardt[10], Axel Nogai[11], Martin Görner[12], Yon-Dschun Ko[13], Maike de Wit[14], Hans Salwender[15], Christof Scheid[16], Ullrich Graeven[17], Rudolf Peceny[18], Peter Staib[19], Annette Dieing[20], Hermann Einsele[21], Anna Jauch[22], Manola Zago[23], Axel Benner[24], Carsten Bokemeyer[25], Hartmut Goldschmidt[26], Katja Weisel[27]

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Introduction: While novel treatments have improved prognosis for most multiple myeloma (MM) patients (pts), survival remains poor for pts with high-risk (HR) disease. Achievement of minimal residual disease negativity (MRD–) correlates with better survival outcome and is particularly important for HR MM pts. The academic, multi-center phase II GMMG-CONCEPT trial (NCT03104842)

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OA-43

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investigates the quadruplet isatuximab, carfilzomib, lenalidomide, and dexamethasone in newly diagnosed (ND) HR MM pts both transplant-eligible (TE) and ineligible (TNE). The planned interim analysis (IA) on the primary endpoint (EP) demonstrated MRD– after consolidation (CONS) with 67.7% and 54.2% for TE and TNE pts, respectively (Weisel, ASH 2022 #759). Here, we show data on sustained MRD– and progression-free survival (PFS). **Methods:** HR MM is defined by ISS stage 2 or 3 and any of del17p, t(4;14), t(14;16), or >3 copies 1q21 (amp1q21) as HR cytogenetic aberration (HRCA). All pts receive Isa-KRd induction, CONS, and Isa-KR maintenance. TE pts undergo high-dose therapy while TNE pts receive 2 extra cycles Isa-KRd. PFS is defined as combined EP of progressive disease or death, whichever occurs first. Data cutoff was on Dec. 1, 2022. **Results:** The IA population for the primary EP consists of 125 pts (99 TE-ITT-IA, 26 TNE-ITT) according to trial design; sustained MRD– and PFS is based on the full first cohort (127 TE, 26 TNE). Median age was 58 (range 35-73) and 74 (64-87) years for the TE-ITT-IA and TNE-ITT population. All pts had HR MM, del17p was the most common HRCA (n=44, 44.4% [TE]; n=11, 42.3% [TNE]), followed by t(4;14) (n=42, 42.4% [TE]; n=6, 23.1% [TNE]) and amp1q21 (n=31, 31.3% [TE]; n=14, 53.8% [TNE]). 31 (31.3%) of 91 evaluable TE and 7 (26.9%) of 24 evaluable TNE pts had ≥2 HRCA marking ultra-HR (30.4% overall). As reported, the CONCEPT trial significantly met its primary EP (MRD– rates after CONS: 67.7% in TE and 54.2% in TNE pts [NGF, 10-5]). Of 106 TE pts reaching MRD– at any timepoint (84.4%), it was sustained for ≥6 and ≥12 months in 90 (72.0%) and 80 (64.0%) pts. Results for 18 TNE pts with MRD– (69.2%) were slightly lower (susMRD–6mo: n=14, 53.8%; susMRD–12mo: n=12, 46.2%). With a median follow-up of 40 (33) months for TE (TNE) pts, the median PFS was not reached in either study arm. Exploratory PFS analysis showed 1-Y-PFS rates of 86.4% (95% CI: 80.5-92.6) for TE-ITT and 75.1% (59.7-94.5) for TNE-ITT pts. 2-Y-PFS rates were 78.3% (71.4-85.9) for TE-ITT and 62.6% (46.0-85.3) for TNE-ITT. Additional subgroup analyses showed that pts with elevated LDH or ≥2 HRCA or del17p were least likely to reach MRD– and had shortened PFS. Since the last report, no new safety signals occurred. **Conclusions:** Isa-KRd induces high rates of sustained MRD– in ND HRMM, translating into a median PFS that was not yet reached. Of the HR markers, elevated LDH, co-existence of ≥2 HRCA, and del17p are associated with lower MRD– and PFS rates, helping to identify the subgroups of HR MM at highest risk.

OA-44

Pomalidomide, bortezomib, and dexamethasone vs bortezomib and dexamethasone in relapsed or refractory multiple myeloma (OPTIMISMM): final survival outcomes from a randomized, open-label, phase 3 trial

Meral Beksac[1], Paul Richardson[2], Albert Oriol[3], Jindriska Lindsay[4], Fredrik Schjesvold[5], Monica Galli[6], Münci Yağcı[7], Alessandra Larocca[8], Katja Weisel[9], Xin Yu[10], Cynthia Donahue[11], Jorge Acosta[12], Teresa Peluso[12], Meletios Dimopoulos[13]

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investigates the quadruplet isatuximab, carfilzomib, lenalidomide, and dexamethasone in newly diagnosed (ND) HR MM pts both transplant-eligible (TE) and ineligible (TNE). The planned interim analysis (IA) on the primary endpoint (EP) demonstrated MRD– after consolidation (CONS) with 67.7% and 54.2% for TE and TNE pts, respectively (Weisel, ASH 2022 #759). Here, we show data on sustained MRD– and progression-free survival (PFS). **Methods:** HR MM is defined by ISS stage 2 or 3 and any of del17p, t(4;14), t(14;16), or >3 copies 1q21 (amp1q21) as HR cytogenetic aberration (HRCA). All pts receive Isa-KRd induction, CONS, and Isa-KR maintenance. TE pts undergo high-dose therapy while TNE pts receive 2 extra cycles Isa-KRd. PFS is defined as combined EP of progressive disease or death, whichever occurs first. Data cutoff was on Dec. 1, 2022. **Results:** The IA population for the primary EP consists of 125 pts (99 TE-ITT-IA, 26 TNE-ITT) according to trial design; sustained MRD– and PFS is based on the full first cohort (127 TE, 26 TNE). Median age was 58 (range 35-73) and 74 (64-87) years for the TE-ITT-IA and TNE-ITT population. All pts had HR MM, del17p was the most common HRCA (n=44, 44.4% [TE]; n=11, 42.3% [TNE]), followed by t(4;14) (n=42, 42.4% [TE]; n=6, 23.1% [TNE]) and amp1q21 (n=31, 31.3% [TE]; n=14, 53.8% [TNE]). 31 (31.3%) of 91 evaluable TE and 7 (26.9%) of 24 evaluable TNE pts had ≥2 HRCA marking ultra-HR (30.4% overall). As reported, the CONCEPT trial significantly met its primary EP (MRD– rates after CONS: 67.7% in TE and 54.2% in TNE pts [NGF, 10-5]). Of 106 TE pts reaching MRD– at any timepoint (84.4%), it was sustained for ≥6 and ≥12 months in 90 (72.0%) and 80 (64.0%) pts. Results for 18 TNE pts with MRD– (69.2%) were slightly lower (susMRD–6mo: n=14, 53.8%; susMRD–12mo: n=12, 46.2%). With a median follow-up of 40 (33) months for TE (TNE) pts, the median PFS was not reached in either study arm. Exploratory PFS analysis showed 1-Y-PFS rates of 86.4% (95% CI: 80.5-92.6) for TE-ITT and 75.1% (59.7-94.5) for TNE-ITT pts. 2-Y-PFS rates were 78.3% (71.4-85.9) for TE-ITT and 62.6% (46.0-85.3) for TNE-ITT. Additional subgroup analyses showed that pts with elevated LDH or ≥2 HRCA or del17p were least likely to reach MRD– and had shortened PFS. Since the last report, no new safety signals occurred. **Conclusions:** Isa-KRd induces high rates of sustained MRD– in ND HRMM, translating into a median PFS that was not yet reached. Of the HR markers, elevated LDH, co-existence of ≥2 HRCA, and del17p are associated with lower MRD– and PFS rates, helping to identify the subgroups of HR MM at highest risk.

OA-44

Pomalidomide, bortezomib, and dexamethasone vs bortezomib and dexamethasone in relapsed or refractory multiple myeloma (OPTIMISMM): final survival outcomes from a randomized, open-label, phase 3 trial

Meral Beksac[1], Paul Richardson[2], Albert Oriol[3], Jindriska Lindsay[4], Fredrik Schjesvold[5], Monica Galli[6], Münci Yağcı[7], Alessandra Larocca[8], Katja Weisel[9], Xin Yu[10], Cynthia Donahue[11], Jorge Acosta[12], Teresa Peluso[12], Meletios Dimopoulos[13]

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OA-45

Pharmacokinetic and correlative analysis of ciltacabtagene autoleucel in patients with lenalidomide-refractory multiple myeloma in the CARTITUDE-4 trial

Carlos Fernández de Larrea[1], Simon Harrison[2], Joaquín Martínez-López[3], María-Victoria Mateos[4], Albert Oriol[5], Niels van de Donk[6], Duncan Purtill[7], Reuben Benjamin[8], Michele Cavo[9], Paolo Corradini[10], Dominik Dytfeld[11], Katherine Li[12], Arnob Banerjee[12], Shirley Shih-Yu Chang[12], Pharavee Jaiprasart[12], Ana Slaughter[13], Carolina Lonardi[14], Jordan Schecter[15], William Deraedt[16], Diana Chen[17], Tzu-min Yeh[15], Nitin Patel[18], Dong Geng[18], Chang-Ki Min[19], Christopher Strouse[20]

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Introduction: CARTITUDE-4 is an open-label, randomized controlled trial (NCT04181827) comparing the CAR-T therapy ciltacabtagene autoleucel (cilta-cel) with physician's choice of standard of care (SOC) in lenalidomide (len)-refractory patients (pts) with multiple myeloma (MM). Cilta-cel significantly improved median progression-free survival (PFS) vs SOC (hazard ratio, 0.26 [95% CI, 0.18–0.38]; P< 0.0001) in the intent-to-treat population at a median follow-up of 15.9 months. Here, we report pharmacokinetic (PK) and correlative analyses in the 176 pts who received cilta-cel as study treatment. **Methods:** Eligible pts were len-refractory with 1–3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug and had an ECOG performance status score of ≤1. Pts randomized to cilta-cel underwent apheresis, received physician's choice of pomalidomide-based bridging treatment, and then 1 cilta-cel infusion (target dose 0.75×10^6 CAR+ viable T cells/kg) 5–7 d after lymphodepletion. The primary endpoint was PFS. PK was assessed by both CAR transgene levels and flow cytometry (CAR+ T cells per microliter in peripheral blood). Expression levels of BCMA on plasma cells in bone marrow aspirate (BMA) were assessed by flow cytometry. A ligand binding assay was used to quantify serum soluble BCMA (sBCMA). **Results:** As of Aug 2022, among the 176 pts who received cilta-cel as study treatment, CD3+CAR+ cells in blood peaked at median 13 d post infusion (mean, 1451 cells/μL; SD, 6169 cells/μL) and remained detectable for median 57 d (range, 13–631). Mean AUC00-28d of CD3+CAR+ cells in blood was 11,710 cells/μL (SD, 56,994 cells/μL). In 13 pts with progressive disease (PD) and available data, we did not observe a reappearance or re-expansion of CD3+CAR+ cells in blood at PD; CAR+ T cells were below the lower limit of quantification (LLOQ; 2 cells/mL) in all pts. sBCMA decreased following cilta-cel infusion in all patients, becoming undetectable (LLOQ, 0.25000 μg/L) at median day 56. At PD, results for sBCMA and proportion of BCMA+ MM cells in BMA were available for 3 and 6 pts respectively. After an initial decline following cilta-cel infusion, sBCMA levels either returned to or exceeded baseline levels at PD. Similar findings were observed in the 6 pts with available data on the proportion of BCMA+ MM cells in bone marrow. **Conclusions:** CAR transgene and cellular levels in CARTITUDE-4 were concordant with observations in CARTITUDE-1 and showed similar expansion and persistence profiles. Based on the samples available at data cut-off, sBCMA levels and proportion of BCMA+ MM cells return to levels at or above baseline at time of relapse, without reappearance or re-expansion of CD3+CAR+ cells in blood. Study follow-up is ongoing, and more samples may be available with additional follow-up. Understanding mechanisms of resistance is an area of interest which will ultimately assist with the sequencing of MM therapies.

OA-46

Epigenetic regulation of CD38/48 by KDM6A mediates NK cell response in multiple myeloma

Jiye Liu[1], Lijie Xing[2], Jiang Li[3], Kenneth Wen[1], Ning Liu[4], Yuntong Liu[1], Keiji Kurata[1], Eugenio Morelli[1], Annamaria Gulla[5], Nikhil Munshi[6], Paul Richardson[1], Teru Hideshima[1], Kenneth Anderson[7]

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Introduction: CARTITUDE-4 is an open-label, randomized controlled trial (NCT04181827) comparing the CAR-T therapy ciltacabtagene autoleucel (cilta-cel) with physician's choice of standard of care (SOC) in lenalidomide (len)-refractory patients (pts) with multiple myeloma (MM). Cilta-cel significantly improved median progression-free survival (PFS) vs SOC (hazard ratio, 0.26 [95% CI, 0.18–0.38]; P< 0.0001) in the intent-to-treat population at a median follow-up of 15.9 months. Here, we report pharmacokinetic (PK) and correlative analyses in the 176 pts who received cilta-cel as study treatment. **Methods:** Eligible pts were len-refractory with 1–3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug and had an ECOG performance status score of ≤1. Pts randomized to cilta-cel underwent apheresis, received physician's choice of pomalidomide-based bridging treatment, and then 1 cilta-cel infusion (target dose 0.75×10^6 CAR+ viable T cells/kg) 5–7 d after lymphodepletion. The primary endpoint was PFS. PK was assessed by both CAR transgene levels and flow cytometry (CAR+ T cells per microliter in peripheral blood). Expression levels of BCMA on plasma cells in bone marrow aspirate (BMA) were assessed by flow cytometry. A ligand binding assay was used to quantify serum soluble BCMA (sBCMA). **Results:** As of Aug 2022, among the 176 pts who received cilta-cel as study treatment, CD3+CAR+ cells in blood peaked at median 13 d post infusion (mean, 1451 cells/μL; SD, 6169 cells/μL) and remained detectable for median 57 d (range, 13–631). Mean AUC00-28d of CD3+CAR+ cells in blood was 11,710 cells/μL (SD, 56,994 cells/μL). In 13 pts with progressive disease (PD) and available data, we did not observe a reappearance or re-expansion of CD3+CAR+ cells in blood at PD; CAR+ T cells were below the lower limit of quantification (LLOQ; 2 cells/mL) in all pts. sBCMA decreased following cilta-cel infusion in all patients, becoming undetectable (LLOQ, 0.25000 μg/L) at median day 56. At PD, results for sBCMA and proportion of BCMA+ MM cells in BMA were available for 3 and 6 pts respectively. After an initial decline following cilta-cel infusion, sBCMA levels either returned to or exceeded baseline levels at PD. Similar findings were observed in the 6 pts with available data on the proportion of BCMA+ MM cells in bone marrow. **Conclusions:** CAR transgene and cellular levels in CARTITUDE-4 were concordant with observations in CARTITUDE-1 and showed similar expansion and persistence profiles. Based on the samples available at data cut-off, sBCMA levels and proportion of BCMA+ MM cells return to levels at or above baseline at time of relapse, without reappearance or re-expansion of CD3+CAR+ cells in blood. Study follow-up is ongoing, and more samples may be available with additional follow-up. Understanding mechanisms of resistance is an area of interest which will ultimately assist with the sequencing of MM therapies.

OA-46

Epigenetic regulation of CD38/48 by KDM6A mediates NK cell response in multiple myeloma

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Introduction: Daratumumab (Dara) is a therapeutic antibody against CD38, which triggers both direct and immune-mediated cytotoxicity in multiple myeloma (MM) cells. Although Dara combination therapies have high efficacy, relapse due to Dara resistance is common. **Methods:** To identify tumor-intrinsic genes involved in resistance to Dara, we performed two CRISPR knockout (KO) screens, and RNA-seq in KDM6A KO cells. **Results:** At the first screen, we found 433 genes that were positively correlated with MM cytotoxicity triggered by Dara and primary NK cells. 16 of these genes were also correlated with cytolytic activity in most of the 36 cancer types we analyzed in the TCGA database. Dara efficacy is closely associated with the expression of CD38, with nonresponders having lower CD38 expression. Therefore, our second screen used CRISPR to find genes whose KO caused the lowest expression of CD38 (bottom 5%). KDM6A was the top-ranked gene out of the set of overlapping genes from these two screens. We confirmed that KDM6A KO significantly decreased CD38 expression (>2 times, p< 0.01) and that re-introducing KDM6A into KDM6A KO cells restored the expression of CD38 and Dara-induced cytotoxicity. KDM6A encodes lysine-specific demethylase 6A, which demethylates lysine 27 of histone H3 (H3K27) to promote gene expression. In fact, when we compared the CD38 promoter area between KDM6A KO and control cells using ChIP-seq and ChIP qPCR, we found that the H3K27me3 level was higher in KDM6A KO cells. Conversely, the re-introduction of KDM6A into KDM6A-KO cells decreased the H3K27me3 level. Concordantly, Dara-resistant cell lines had lower CD38 expression and higher levels of H3K27me3 at the CD38 promoter. Interestingly, we found that CD38 overexpression only partially restored the sensitivity of KDM6A KO cells to Dara treatment, suggesting other mechanisms for KDM6A. We performed RNA-seq in KDM6A KO cells and found that CD48, an NK-activating ligand, was downregulated. Overexpression of CD48 in KDM6A KO cells significantly increased secretion of Granzyme B and Perforin by NK cells, restoring the activity of NK cells and re-sensitizing KDM6A KO cells to Dara treatment. These data suggest that KDM6A not only regulates CD38 expression but also NK cell activity by CD48 regulation, thereby modulating the efficacy of Dara. KDM6A acts to oppose the EZH2/PRC2 complex by demethylating H3K27me3, and we found that Tazemetostat (Taze), an FDA-approved EZH2 inhibitor, increased the expression of CD38 and CD48 at the protein, mRNA, and surface expression levels, especially in KDM6A-KO cells. Importantly, Taze also restored the sensitivity of KDM6A KO cells to Dara-mediated NK cell cytotoxicity. **Conclusions:** Taken together, our data reveal that KDM6A assists in Dara targeting by upregulating CD38 and in Dara cytotoxicity by modulating NK activity through CD48 regulation. By imitating its function using an FDA-approved inhibitor, we may overcome Dara resistance and improve patient outcomes in MM.

OA-47

Additional analysis of CARTITUDE-4: Cilta-cel vs standard of care (PVd or DPd) in lenalidomide-refractory patients with multiple myeloma and 1–3 prior lines of therapy

Salomon Manier[1], Jesús San-Miguel[2], Binod Dhakal[3], Kwee Yong[4], Joaquín Martínez-López[5], Albert Oriol[6], Duncan Purtill[7], Hasib Sidiqi[7], Shinsuke Iida[8], Anne Mylin[9], Roberto Mina[10], Lionel Karlin[11], William Deraedt[12], Nikoletta Lendvai[13], Carolina Lonardi[14], Ana Slaughter[15], Jordan Schecter[13], Katherine Li[16], Diana Chen[17], Jane Gilbert[18], Tzu-min Yeh[13], Erika Florendo[19], Lida Pacaud[19], Nitin Patel[19], Hermann Einsele[20]

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OA-47

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1 cilta-cel infusion (target dose, 0.75×10^6 CAR+ viable T cells/kg) 5–7 days after start of lymphodepletion. Pts randomized to SOC received physician's choice of PVd or DPd until progression. Primary endpoint was PFS, analyzed using a weighted method to focus on PFS after the period during which both arms were on the same tx. Subgroup analyses of PFS was reported with HRs and 95% CIs. **Results:** Pts were randomized between July 2020 and November 2021. As of November 1, 2022, median follow-up was 15.9 mo (range, 0.1–27). 208 pts were randomized to cilta-cel (of whom 176 received cilta-cel) and 211 to SOC. Arms were balanced at baseline; 32.5% of pts had 1 prior LOT and 6.2% were ISS stage III. 61.2% of pts had high-risk cytogenetics (ie, del(17p), t(14;16), t(4;14) or gain/amp(1q)); 22.0% had ≥2 high-risk abnormalities. 18.9% had soft tissue plasmacytomas, 20.5% had bone marrow plasma cells ≥60%, and 15.0% of pts had triple-class refractory disease. 12.9% of pts received PVd; 87.1% received DPd. Cilta-cel significantly improved PFS vs SOC in all subgroups analyzed, including pts aged < 65 yrs, HR 0.24 (95% CI, 0.15–0.38), and 65–75 yrs, 0.34 (0.19–0.61); with 1 prior LOT, 0.35 (0.19–0.66); ISS stage III, 0.33 (0.11–0.95); ≥1 cytogenetic high-risk abnormality, 0.25 (0.16–0.38); ≥2 high-risk abnormalities, 0.33 (0.17–0.64); soft tissue plasmacytomas, 0.39 (0.21–0.75); bone marrow plasma cells ≥60%, 0.28 (0.14–0.59); triple-class refractory disease, 0.15 (0.05–0.39), as well as pts treated with PVd, 0.31 (0.13–0.72) and DPd, 0.26 (0.18–0.39). **Conclusions:** Cilta-cel significantly improved PFS across all analyzed subgroups of the ITT population, including by age, in those with high-risk features, after first relapse, and vs both SOC regimens. Benefit shown was similar to that seen in the overall ITT population, confirming efficacy of a single cilta-cel infusion in a range of clinically relevant MM subgroups.

OA-48

Isatuximab plus carfilzomib and dexamethasone versus carfilzomib and dexamethasone in patients with relapsed multiple myeloma (IKEMA): final overall survival analysis

Kwee Yong[1], Thomas Martin[2], Meletios Dimopoulos[3], Joseph Mikhael[4], Marcelo Capra[5], Thierry Facon[6], Roman Hájek[7], Ivan Špička[8], Ross Baker[9], Kihyun Kim[10], Gracia Martinez[11], Chang-Ki Min[12], Ludek Pour[13], Xavier Leleu[14], Albert Oriol[15], Youngil Koh[16], Kenshi Suzuki[17], France Casca[18], Sandrine Macé[19], Marie-Laure Risse[19], Philippe Moreau[20]

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Introduction: Isatuximab (Isa) is an anti-CD38 monoclonal antibody approved in combination with carfilzomib (K) and dexamethasone (d) for patients (pts) with relapsed multiple myeloma (MM) after ≥1 prior therapy, based on the primary progression-free survival (PFS) analysis of the Phase 3 IKEMA study (HR: 0.531; 99% CI: 0.318–0.889; one-sided p=0.0007; NCT03275285). At final PFS analysis 2 years later with a median follow-up of 43.96 months, the median PFS was reached — 35.65 mo (Isa-Kd) vs 19.15 mo (Kd). Here we report the final overall survival (OS) results from IKEMA planned 3 years after the primary PFS analysis. **Methods:** Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n=179) or Kd (n=123). Treatment was given until progressive disease, unacceptable toxicity, or pt wish. Safety was assessed in all treated pts. **Results:** As of 7 February 2023 (cutoff), with a median follow-up of 56.61 mo, 42 (23.5%) and 7 (5.7%) pts in the Isa-Kd and Kd arms were still on treatment (tx); 81 (45.3%) and 66 (53.7%), respectively, discontinued due to progressive disease. Median tx duration was longer with Isa-Kd vs Kd (94.0 vs 61.9 weeks). A trend toward an OS benefit was observed with Isa-Kd vs Kd (median OS not reached [NR; 95% CI: 52.172–NR] vs 50.6 mo [95% CI: 38.932–NR]; HR: 0.855; 95% CI: 0.608–1.202; nominal one-sided p=0.1836). A sensitivity analysis censoring COVID-19 deaths showed consistent results (HR: 0.803; 95% CI: 0.564–1.142). Time to next tx (TTNT) was in favor of Isa-Kd (median 43.99 [95% CI: 31.31–NR] vs 25.0 [95% CI: 17.938–31.31] mo; HR: 0.583; 95% CI: 0.429–0.792; nominal one-sided p=0.0002), as was second progression-free survival (PFS2; median 47.18 [95% CI: 38.965–57.922] vs 32.36 [95% CI: 23.129–40.016] mo; HR: 0.663; 95% CI: 0.491–0.895; nominal one-sided p=0.0035). The difference between arms in median PFS2 (14.82 mo) remains very close to the difference in median PFS (16.50 mo). More pts in the Kd vs Isa-Kd arm received further anti-myeloma therapies that included those with novel mechanisms of action (MoA; 65.9% vs 49.7%) and further anti-CD38 agents (63.0% vs 29.2%). The safety profiles of both arms were comparable to those in the interim and final PFS analyses. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 84.2% (Isa-Kd) and 73.0% (Kd) of pts, while serious TEAEs occurred in 71.2% and 60.7% of pts. TEAEs leading to tx discontinuation occurred in 13.6% Isa-Kd and 18.0% Kd pts. Despite longer exposure, both arms had a similar incidence of cardiac failure (Isa-Kd: 8.5%; Kd: 8.2%). **Conclusions:** This final OS analysis shows a meaningful trend for OS benefit with Isa-Kd vs Kd despite subsequent tx with anti-CD38 agents, introduction of tx with novel MoA among further therapies, and the COVID-19 pandemic. Improvements in TTNT and PFS2 were observed, and sustained PFS benefit still observed at PFS2. The Isa-Kd safety profile

1 cilta-cel infusion (target dose, 0.75×10^6 CAR+ viable T cells/kg) 5–7 days after start of lymphodepletion. Pts randomized to SOC received physician's choice of PVd or DPd until progression. Primary endpoint was PFS, analyzed using a weighted method to focus on PFS after the period during which both arms were on the same tx. Subgroup analyses of PFS was reported with HRs and 95% CIs. **Results:** Pts were randomized between July 2020 and November 2021. As of November 1, 2022, median follow-up was 15.9 mo (range, 0.1–27). 208 pts were randomized to cilta-cel (of whom 176 received cilta-cel) and 211 to SOC. Arms were balanced at baseline; 32.5% of pts had 1 prior LOT and 6.2% were ISS stage III. 61.2% of pts had high-risk cytogenetics (ie, del(17p), t(14;16), t(4;14) or gain/amp(1q)); 22.0% had ≥2 high-risk abnormalities. 18.9% had soft tissue plasmacytomas, 20.5% had bone marrow plasma cells ≥60%, and 15.0% of pts had triple-class refractory disease. 12.9% of pts received PVd; 87.1% received DPd. Cilta-cel significantly improved PFS vs SOC in all subgroups analyzed, including pts aged < 65 yrs, HR 0.24 (95% CI, 0.15–0.38), and 65–75 yrs, 0.34 (0.19–0.61); with 1 prior LOT, 0.35 (0.19–0.66); ISS stage III, 0.33 (0.11–0.95); ≥1 cytogenetic high-risk abnormality, 0.25 (0.16–0.38); ≥2 high-risk abnormalities, 0.33 (0.17–0.64); soft tissue plasmacytomas, 0.39 (0.21–0.75); bone marrow plasma cells ≥60%, 0.28 (0.14–0.59); triple-class refractory disease, 0.15 (0.05–0.39), as well as pts treated with PVd, 0.31 (0.13–0.72) and DPd, 0.26 (0.18–0.39). **Conclusions:** Cilta-cel significantly improved PFS across all analyzed subgroups of the ITT population, including by age, in those with high-risk features, after first relapse, and vs both SOC regimens. Benefit shown was similar to that seen in the overall ITT population, confirming efficacy of a single cilta-cel infusion in a range of clinically relevant MM subgroups.

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Isatuximab plus carfilzomib and dexamethasone versus carfilzomib and dexamethasone in patients with relapsed multiple myeloma (IKEMA): final overall survival analysis

Kwee Yong[1], Thomas Martin[2], Meletios Dimopoulos[3], Joseph Mikhael[4], Marcelo Capra[5], Thierry Facon[6], Roman Hájek[7], Ivan Špička[8], Ross Baker[9], Kihyun Kim[10], Gracia Martinez[11], Chang-Ki Min[12], Ludek Pour[13], Xavier Leleu[14], Albert Oriol[15], Youngil Koh[16], Kenshi Suzuki[17], France Casca[18], Sandrine Macé[19], Marie-Laure Risse[19], Philippe Moreau[20]

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Introduction: Isatuximab (Isa) is an anti-CD38 monoclonal antibody approved in combination with carfilzomib (K) and dexamethasone (d) for patients (pts) with relapsed multiple myeloma (MM) after ≥1 prior therapy, based on the primary progression-free survival (PFS) analysis of the Phase 3 IKEMA study (HR: 0.531; 99% CI: 0.318–0.889; one-sided p=0.0007; NCT03275285). At final PFS analysis 2 years later with a median follow-up of 43.96 months, the median PFS was reached — 35.65 mo (Isa-Kd) vs 19.15 mo (Kd). Here we report the final overall survival (OS) results from IKEMA planned 3 years after the primary PFS analysis. **Methods:** Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n=179) or Kd (n=123). Treatment was given until progressive disease, unacceptable toxicity, or pt wish. Safety was assessed in all treated pts. **Results:** As of 7 February 2023 (cutoff), with a median follow-up of 56.61 mo, 42 (23.5%) and 7 (5.7%) pts in the Isa-Kd and Kd arms were still on treatment (tx); 81 (45.3%) and 66 (53.7%), respectively, discontinued due to progressive disease. Median tx duration was longer with Isa-Kd vs Kd (94.0 vs 61.9 weeks). A trend toward an OS benefit was observed with Isa-Kd vs Kd (median OS not reached [NR; 95% CI: 52.172–NR] vs 50.6 mo [95% CI: 38.932–NR]; HR: 0.855; 95% CI: 0.608–1.202; nominal one-sided p=0.1836). A sensitivity analysis censoring COVID-19 deaths showed consistent results (HR: 0.803; 95% CI: 0.564–1.142). Time to next tx (TTNT) was in favor of Isa-Kd (median 43.99 [95% CI: 31.31–NR] vs 25.0 [95% CI: 17.938–31.31] mo; HR: 0.583; 95% CI: 0.429–0.792; nominal one-sided p=0.0002), as was second progression-free survival (PFS2; median 47.18 [95% CI: 38.965–57.922] vs 32.36 [95% CI: 23.129–40.016] mo; HR: 0.663; 95% CI: 0.491–0.895; nominal one-sided p=0.0035). The difference between arms in median PFS2 (14.82 mo) remains very close to the difference in median PFS (16.50 mo). More pts in the Kd vs Isa-Kd arm received further anti-myeloma therapies that included those with novel mechanisms of action (MoA; 65.9% vs 49.7%) and further anti-CD38 agents (63.0% vs 29.2%). The safety profiles of both arms were comparable to those in the interim and final PFS analyses. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 84.2% (Isa-Kd) and 73.0% (Kd) of pts, while serious TEAEs occurred in 71.2% and 60.7% of pts. TEAEs leading to tx discontinuation occurred in 13.6% Isa-Kd and 18.0% Kd pts. Despite longer exposure, both arms had a similar incidence of cardiac failure (Isa-Kd: 8.5%; Kd: 8.2%). **Conclusions:** This final OS analysis shows a meaningful trend for OS benefit with Isa-Kd vs Kd despite subsequent tx with anti-CD38 agents, introduction of tx with novel MoA among further therapies, and the COVID-19 pandemic. Improvements in TTNT and PFS2 were observed, and sustained PFS benefit still observed at PFS2. The Isa-Kd safety profile

was consistent with previous analyses, supporting it as a standard-of-care therapy for relapsed MM pts. Funding: Sanofi.

OA-49

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OA-50

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BCMA (sBCMA) by LC-MS/MS with immunoaffinity capture. Tumor biomarkers were assessed by flow cytometry using bone marrow (BM) aspirates. Differential gene expression and Gene Set Variation Analysis of cell signature enrichment scores were assessed by RNAseq using baseline and on-treatment CD138- BM cells. **Results:** In peripheral blood (PB), sBCMA accumulated in pts with progressive disease, though levels remained constant with successive treatment cycles in pts with stable disease. Changes in PB activation markers occurred between 24h and 8d after first infusion, though were not observed in Tira mono treated pts. Transient upregulation of CD69+CD25+ CD4 T cells occurred in a subset of T+D treated pts, while a trend of NK/NKT CD69 upregulation was observed earlier and at a greater magnitude in two of three T+D+A treated pts when compared to T+D. Notably, NK absolute counts decreased by C1D8 in combination arms, consistent with Dara-mediated effects. Frequencies of PB Ki-67+HLA-DR+ CD8 T cells were transiently upregulated by C1D8 in pts receiving T+D+A, and in a subset of T+D treated pts. In the BM, the frequency of PD-1+ CD8 T cells significantly increased between C1D15 and C2D1 in T+D and to a greater extent in T+D+A treated pts. Additional transcriptomic analysis to interrogate modulation of gene expressions and cell signatures over treatment is ongoing, however, initial reports suggest T+D treatment significantly increased NK, CD8 T cell, and macrophage signatures within the BM, but this was not observed with Tira alone. **Conclusions:** The study demonstrated that PD changes in NK and T cell activation in the periphery are among the earliest biomarkers of T+D activity, and that the addition of Atezo may potentiate CD8 T cell responses, suggesting that Tira + Atezo combinations may improve pt outcomes. This is the first clinical study to evaluate biomarkers of novel checkpoint inhibitor combinations in R/R MM, and additional analyses are ongoing to better characterize patient populations that will benefit most from dual checkpoint blockade combinations.

OA-51

Preliminary recommendations for prevention and management of infections, hypogammaglobulinemia, and neutropenia during treatment with teclistamab based on experience from the MajesTEC-1 study

Niels van de Donk[1], Ajay Nooka[2], Cesar Rodriguez[3], María-Victoria Mateos[4], Katherine Chastain[5], Arnob Banerjee[6], Rachel Kobos[5], Keqin Qi[7], Raluca Verona[6], Margaret Doyle[8], Thomas Martin[9], Salomon Manier[10]

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POSTER PRESENTATIONS

P-001

The bone marrow stroma influences extrinsic apoptotic signaling and results in resistance to BCMA CAR-T cell induced cell death

James Ackley[1], Samuel McCachren[1], Sagar Lonial[1], Damian Green[2], Stanley Riddell[2], Geoffrey Hill[2], Madhav Dhodapkar[1], Lawrence Boise[1]

[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]Fred Hutchinson Cancer Center

BCMA (sBCMA) by LC-MS/MS with immunoaffinity capture. Tumor biomarkers were assessed by flow cytometry using bone marrow (BM) aspirates. Differential gene expression and Gene Set Variation Analysis of cell signature enrichment scores were assessed by RNAseq using baseline and on-treatment CD138- BM cells. **Results:** In peripheral blood (PB), sBCMA accumulated in pts with progressive disease, though levels remained constant with successive treatment cycles in pts with stable disease. Changes in PB activation markers occurred between 24h and 8d after first infusion, though were not observed in Tira mono treated pts. Transient upregulation of CD69+CD25+ CD4 T cells occurred in a subset of T+D treated pts, while a trend of NK/NKT CD69 upregulation was observed earlier and at a greater magnitude in two of three T+D+A treated pts when compared to T+D. Notably, NK absolute counts decreased by C1D8 in combination arms, consistent with Dara-mediated effects. Frequencies of PB Ki-67+HLA-DR+ CD8 T cells were transiently upregulated by C1D8 in pts receiving T+D+A, and in a subset of T+D treated pts. In the BM, the frequency of PD-1+ CD8 T cells significantly increased between C1D15 and C2D1 in T+D and to a greater extent in T+D+A treated pts. Additional transcriptomic analysis to interrogate modulation of gene expressions and cell signatures over treatment is ongoing, however, initial reports suggest T+D treatment significantly increased NK, CD8 T cell, and macrophage signatures within the BM, but this was not observed with Tira alone. **Conclusions:** The study demonstrated that PD changes in NK and T cell activation in the periphery are among the earliest biomarkers of T+D activity, and that the addition of Atezo may potentiate CD8 T cell responses, suggesting that Tira + Atezo combinations may improve pt outcomes. This is the first clinical study to evaluate biomarkers of novel checkpoint inhibitor combinations in R/R MM, and additional analyses are ongoing to better characterize patient populations that will benefit most from dual checkpoint blockade combinations.

OA-51

Preliminary recommendations for prevention and management of infections, hypogammaglobulinemia, and neutropenia during treatment with teclistamab based on experience from the MajesTEC-1 study

Niels van de Donk[1], Ajay Nooka[2], Cesar Rodriguez[3], María-Victoria Mateos[4], Katherine Chastain[5], Arnob Banerjee[6], Rachel Kobos[5], Keqin Qi[7], Raluca Verona[6], Margaret Doyle[8], Thomas Martin[9], Salomon Manier[10]

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POSTER PRESENTATIONS

P-001

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[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]Fred Hutchinson Cancer Center

BCMA (sBCMA) by LC-MS/MS with immunoaffinity capture. Tumor biomarkers were assessed by flow cytometry using bone marrow (BM) aspirates. Differential gene expression and Gene Set Variation Analysis of cell signature enrichment scores were assessed by RNAseq using baseline and on-treatment CD138- BM cells. **Results:** In peripheral blood (PB), sBCMA accumulated in pts with progressive disease, though levels remained constant with successive treatment cycles in pts with stable disease. Changes in PB activation markers occurred between 24h and 8d after first infusion, though were not observed in Tira mono treated pts. Transient upregulation of CD69+CD25+ CD4 T cells occurred in a subset of T+D treated pts, while a trend of NK/NKT CD69 upregulation was observed earlier and at a greater magnitude in two of three T+D+A treated pts when compared to T+D. Notably, NK absolute counts decreased by C1D8 in combination arms, consistent with Dara-mediated effects. Frequencies of PB Ki-67+HLA-DR+ CD8 T cells were transiently upregulated by C1D8 in pts receiving T+D+A, and in a subset of T+D treated pts. In the BM, the frequency of PD-1+ CD8 T cells significantly increased between C1D15 and C2D1 in T+D and to a greater extent in T+D+A treated pts. Additional transcriptomic analysis to interrogate modulation of gene expressions and cell signatures over treatment is ongoing, however, initial reports suggest T+D treatment significantly increased NK, CD8 T cell, and macrophage signatures within the BM, but this was not observed with Tira alone. **Conclusions:** The study demonstrated that PD changes in NK and T cell activation in the periphery are among the earliest biomarkers of T+D activity, and that the addition of Atezo may potentiate CD8 T cell responses, suggesting that Tira + Atezo combinations may improve pt outcomes. This is the first clinical study to evaluate biomarkers of novel checkpoint inhibitor combinations in R/R MM, and additional analyses are ongoing to better characterize patient populations that will benefit most from dual checkpoint blockade combinations.

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POSTER PRESENTATIONS

P-001

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Introduction: BCMA targeted CAR-T therapy is effective at inducing disease remission in heavily pretreated relapsed refractory Multiple Myeloma (MM) patients with a cumulative overall response rate of 85.2%, however, duration has been disappointing. Bone marrow microenvironment (BMM)-derived IL6 is a survival signal for MM cells and is known to promote drug resistance. CAR-T therapy induces an immune response, resulting in increased IL6. With this in mind, we investigated the impact of the BMM and IL6 on CAR-T induced cell death in MM. **Methods:** MM cell lines were exposed to BCMA-CAR-T cells or CD95L for 24 hours and cell death measured via Annexin V staining. CD3, CD38, and mCherry expression were used to distinguish T cells, MM cells, and HS-5 stromal cells respectively. In stromal coculture (SCC) and conditioned media (SCM) assays, MM cells were preincubated for 1 hour before T cell addition. Caspase 8 activity was measured with an IETD-FMK fluorometric assay. **Results:** SCC protected all 3 MM cell lines tested from CAR-T induced cell death while SCM protected 2 of the 3 cell lines. CAR-T CD107a surface expression remained consistent between control and SCC/SCM groups indicating no change in T cell activation. Gene editing to ablate CD95 expression protected 3 of 4 MM cell lines demonstrating its importance in CAR-T induced cell death. Therefore, to determine the mechanism of protection we focused on the effects of SCC, SCM, and IL6 on rCD95L killing. All were sufficient to protect myeloma cells from rCD95L. Loss of mitochondrial-mediated apoptosis through the deletion of BID or BAX/BAK protected 2 of 4 cell lines from rCD95L, indicating that rCD95L induces type 1 (mitochondria-independent) or type 2 (mitochondria-dependent) death in a cell line specific manner. When type 2 cells deficient in mitochondrial apoptosis were cultured in SCM and exposed to rCD95L, there was no enhancement of protection beyond SCM alone. In contrast, when type 1 cells deficient in mitochondrial apoptosis were exposed to rCD95L, the combination of SCM and BAK/BAX DKO protected the type 1 cells beyond SCM alone suggesting an effect upstream of the mitochondria. Consistent with this possibility, SCM inhibits CD95L induced activation of caspase 8 in both type 1 and type 2 cells lines. **Conclusions:** These results demonstrate that the BMM can induce MM cell intrinsic protection against CAR-T therapy in part due to soluble stromal factors. This protection may be due in part to inhibition of the extrinsic apoptotic pathway. Stromal factors including IL6 inhibit rCD95L induced type 1 induced cell death through a reduction in Caspase 8 activity. We hypothesize that reduced caspase 8 activity changes a type 1 cell death signal to a type 2 death signal that can be inhibited by anti-apoptotic BCL2 family.

P-002

Impact of bridging therapy (BT) on outcome of relapsed refractory multiple myeloma (RRMM) with Ide-cel CAR T-cell therapy: real-world experience from the U.S. myeloma CAR T consortium

Aimaz Afrough[1], Hamza Hashmi[2], Doris Hansen[3], Surbhi Sidana[4], Chul Ahn[5], Danai Dima[6], Ciara Freeman[3], Omar Castaneda Puglianini[3], M Hakan Kocoglu[7], Shebli Atrash[8], Peter Voorhees[9], Leyla Shune[10], Gary Simmons[11], Douglas Sborov[12], Christopher Ferreri[13], Charlotte Wagner[14], Krina Patel[15], Jack Khouri[16], Larry Anderson[1], Yi Lin[17]

[1]Cellular Therapy and Hematologic Malignancies Program, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center; [2]Medical University of South Carolina; [3]Moffiitt Cancer Center; [4]Stanford University; [5]University of Texas Southwestern; [6]Cleveland Clinic Taussig Cancer Institute; [7]University of Maryland, Baltimore, MD, USA; [8]Levine Cancer Institute; [9]Levine Cancer Institute-Atrium Health Wake Forest University School of Medicine; [10]University of Kansas Medical Center; [11]Virgina Commonwealth University; [12]University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA; [13]The University of Texas MD Anderson Cancer Center; [14]Department of Pharmacy, University of Utah Hospitals and Clinics, Huntsman Cancer Institute; [15]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [16]Taussig Cancer Institute, Cleveland Clinic; [17]Mayo Clinic, Rochester, MN, USA

Introduction: Ide-cel is an FDA-approved treatment for RRMM patients (pts). However, there is limited data on how BT for disease control during its manufacturing process affects clinical outcomes. **Methods:** Eleven US academic centers contributed data to this analysis without involvement from the manufacturer. By 5/1/2022, 235 pts had undergone leukapheresis, with 214 infused with a median follow up of 9 months (mos). BT was given between leukapheresis and CAR-T infusion. **Results:** In this analysis, 79% of pts (n=170) received BT, which included alkylator-based in 35.5%, steroid and or IMiD/Ab combos (IMiD combos) in 14%, PI combinations (PI combos) in 12%, and selinexor in 10%. BT recipients had higher ECOG PS 2-4, R-ISS 2-3, ferritin, and CRP before lymphodepleting (LD) chemo, however, no difference among BT subgroups. No difference in prior lines of therapy or penta-refractory between BT and No BT (NBT) groups or BT subgroups. Median cycle of the BT was 1 (1-7), with overall response rate (ORR) of 12%, with no difference among BT subgroups. Incidence and severity of CRS and ICANs were comparable in BT and NBT. However, pts who received BT had a longer median hospital stay compared to NBT, particularly in the alkylator/selinexor subgroups. There were no significant difference in cytopenias at day 90 post CAR-T between the BT and NBT or BT subgroups. For the 73% (n=157) evaluable for day 90 response, there was no difference in the complete or ORR between the BT and NBT groups (41% vs. 52%; p=0.2 and 84% vs. 87.5%, p=0.8, respectively). Median PFS was worse at 8.1 mos in BT vs 11.5 mos in NBT (p=0.03). Among BT subgroups, PFS was the longest with IMiD combos with median PFS not reached (NR), comparable to NBT, and was significantly longer than all other BT subgroups (p=0.01). The median OS was 13.8 mos with BT and NR in NBT (p=.002). In BT subgroup analysis, alkylators group had a shorter OS, although, this was not significant (p=.06). There was no significant difference in PFS and OS in relationship to response to BT (p=.6 and p=.9, respectively). **Conclusions:** Pts without BT had longer PFS and OS post ide-cel, likely reflective of less aggressive disease. Those who received BT with steroid/IMiD and Ab combos had similar PFS as NBT. However, BT choice is complicated by disease severity and should be evaluated per patient circumstances.

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P-003

Clinical outcomes among multiple myeloma and lymphoma patients taking beta-blockers undergoing CAR-T therapy

Kristina Balandan[1], Yi Hwa[1], Radhika Bansal[1], Arushi Khurana[1], Patrick Johnston[1], Stephen Ansell[1], Nora Bennani[1], Moritz Binder[1], David Dingli[1], Morie Gertz[1], Suzanne Haymann[1], Prashant Kapoor[1], Taxiarchis Kourelis[1], Shaji Kumar[1], Jonas Paludo[1], Rahma Warsame[1], Yucai Wang[1], Joselle Cook[1], Urshila Durani[1], Yi Lin[1], Angela Dispenzieri[1]

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Introduction: The antineoplastic effect of beta blockers (BB) has been widely explored in solid tumors but understudied in hematologic malignancies. We previously reported that BB improved overall survival (OS) and reduced myeloma specific death among patients receiving various multiple myeloma (MM) therapies, and improved progression free survival (PFS) in patients treated with pomalidomide / dexamethasone. No studies have done to explore the antitumor effect in lymphoma. This retrospective study evaluated the outcomes of patients taking BB who received CAR-T therapy for MM and non-Hodgkin lymphoma (NHL). **Methods:** We identified 217 patients received CAR-T at Mayo Clinic between January 2018 and September 2022 for MM (n=63) and NHL (n=154). BB usage was extracted from patient records. Peri-CART BB intake was defined as ≥ 3 months BB intake prior to and post CAR-T to evaluate CRS and neurotoxicity. Post-CART BB usage groups, defined as ≥ 3 months of BB intake following CAR-T, were compared to evaluate PFS and OS from CAR-T. OS from diagnosis was analyzed between patients with BB intake of ≥ 3 months at any time after diagnosis and no-BB usage group. Kaplan-Meier method was used to estimate the PFS and OS. **Results:** During the peri-CAR-T period, there were 46 BB users and 171 non-BB users (median age of 67 versus 61 years, p=0.0005). Both groups had male predominance (70% in BB and 58% in no-BB patients). The time from diagnosis to CAR-T was not significantly different between the BB group and the non-BB group (55 months vs 30 months; p=0.88) nor were there significant differences between two groups in ECOG score, prior-line therapies and, if received, bridging therapy. The patients with peri-CART BB consumption, compared to no-BB group, were less likely to develop CRS (71.7% vs 83.6%, p=.06) and had significantly lower severity of CRS (grade ≥ 2: 23.9% vs 43.9%; p=0.01) but comparable ICANS rates. The median follow-up from CAR-T and from diagnosis for surviving patients was 13.2 months and 5.1 years, respectively. The 47 (15 MM, 32 NHL) patients who took BB post-CART, compared to 170 (48 MM, 122 NHL) patients with no post-CART BB intake, had superior PFS (11.1 vs 6.3 months in all patients; 12.2 vs 8.3 months in MM; 7.7 vs 4.7 months in NHL) and superior 1-year OS from CAR-T (81% vs 67% in all patients; 93% vs 79% in MM; 75% vs 62% in NHL). The 60 (16 MM, 44 NHL) patients who took BB at any time after diagnosis had higher 10-year OS from diagnosis than no-BB intake group (64% vs 45%, p=.0105 in all patients; 74% vs 50% in MM, p NS; 57% vs 42% in NHL, p=.007). Comparison of PFS and OS from CAR-T as well as OS from diagnosis in MM did not reach statistical significance due to small sample size and shorter follow up. **Conclusions:** BB intake among patients receiving CAR-T therapy showed reduced risks for CRS and was associated with more favorable survival outcomes. The result warrants further investigation for anti-cancer effect of BB in CAR-T and other immunotherapies.

P-004

Expansion, persistence, and characteristics of autologous, BHV-1100 ARMored memory-like NK cells infused prior to autologous stem cell transplant in MRD+, newly diagnosed multiple myeloma patients

Grace Birch[1], Juliana Vergara-Cadavid[1], Michela Ansuinelli[1], Tuyet Nguyen[1], Carol Reynolds[1], Soo Im[1], Hope Wei[1], Sarah Hogan[1], Elizabeth Kendricken[1], Adam Sperling[1], Omar Nadeem[1], Shonali Midha[1], Jacob Laubach[1], Alissa Rybicki[2], Steven Schnittman[2], Elyse Stock[2], Sarah Nikiforow[1], Jerome Ritz[1], Robert Soiffer[1], Giada Bianchi[3], Rizwan Romee[1]

[1]Dana Farber Cancer Institute; [2]Biohaven Pharmaceuticals; [3]Brigham and Women/s Hospital/Harvard Medical School/Dana Farber Cancer Institute

Introduction: Autologous stem cell transplant (ASCT) improves MRD negativity and prolongs progression free survival in newly diagnosed multiple myeloma (MM) patients. MM NK cells are dysfunctional, negatively impacting outcomes. BHV-1100, an Antibody Recruiting Molecule (ARM), binds to CD38 target cell antigen and recruits NK cells for ADCC. Allogeneic, cytokine induced memory-like (CIML) NK cells effectively treat myeloid disorders. It is not known if autologous CIML NK cells can be obtained and, when coated with BHV-1100, would improve ASCT outcomes in MM. **Methods:** We designed a first-in-human study of autologous CIML NK cells coated ex-vivo with BHV-1100 for MRD+, newly diagnosed MM patients undergoing ASCT. Cells were manufactured in house from non-mobilized lymphapheresis. CIML NK cells were obtained via overnight incubation of enriched NK cells with IL-12 (10ng/ml), IL-15 (100ng/ml), and IL-18 (50ng/ml) and subsequently coated with BHV-1100. The product was infused fresh on D0 after standard melphalan 200 mg/m^2 myeloablative conditioning and followed by stem cells infusion. Low dose IL2 (1 mIU/m^2) was administered SQ starting on D+1, QOD for 7 doses. **Results:** This is an ongoing trial (NCT04634435) with a median follow-up of 191 days. We are herein reporting data on in vivo expansion and functional characterization of ARMored CIML NK for the first 4 patients. CIML NK cells were manufactured with a 100% success rate and infused at a target dose of 5-10x10^6 cells. Patients received between 3.9-6.0x10^6/Kg stem cells. Engraftment based on recovery of neutrophil count occurred on D+12-D+14. There was a 3.5-fold expansion of NK cells in the peripheral blood from D+7 (from 11.1% to 41%) to D+28 that persisted until D+60 (25% total PBMC). Most expanded NK cells were CD56dim, CD16high, KIR high and CD57high. CD57 and KIR expression increased over time from D+7 to D+60, whereas NKG2A expression

P-003

Clinical outcomes among multiple myeloma and lymphoma patients taking beta-blockers undergoing CAR-T therapy

Kristina Balandan[1], Yi Hwa[1], Radhika Bansal[1], Arushi Khurana[1], Patrick Johnston[1], Stephen Ansell[1], Nora Bennani[1], Moritz Binder[1], David Dingli[1], Morie Gertz[1], Suzanne Haymann[1], Prashant Kapoor[1], Taxiarchis Kourelis[1], Shaji Kumar[1], Jonas Paludo[1], Rahma Warsame[1], Yucai Wang[1], Joselle Cook[1], Urshila Durani[1], Yi Lin[1], Angela Dispenzieri[1]

[1]Mayo Clinic

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decreased, indicating expansion of mature, activated and cytotoxic NK cells. Regulatory T cells increased by D+7 (3% vs 15% total PBMC) and returned to baseline after D+14. The functional capacity of the infused product was tested in vitro against MOLP8 MM cell line. The BHV-1100 ARMored cells had a higher killing capacity compared to untreated CIML NK cells and were stable for up to 24 hours (92.6% target cell death vs 91.1% at 0H, 90.8% vs 81% at 4H and 75.3 vs 73.8% at 24H, E:T ratio 2:1). ARMored cells also showed increased IFNγ (53% vs 37.5%) and CD107a (26% vs 14.9%) production compared to untreated CIML NK cells. **Conclusions:** Autologous, BHV-1100 ARMored CIML NK cells have enhanced anti-MM activity in vitro and expand and persist in vivo with peak at D+28 after infusion. This represents an innovative approach to boost autologous cancer immunosurveillance in the context of ASCT. Aside from anticipated infusion reactions, no severe/unexpected adverse events were noted; longer follow up is required to assess safety and efficacy.

P-005

Association of baseline soluble BCMA with measures of disease burden and response to linvoseltamab: a comprehensive analysis in patients with relapsed/refractory multiple myeloma (RRMM)

Anita Boyapati[1], Joshua Richter[2], Attaya Suvannasankha[3], Hans Lee[4], Erica Chio[1], Yariv Houvras[1], Nikhil Singh[1], Tao Liang[1], Jihua Chen[1], Anasuya Hazra[1], Yuan Zhu[1], Irene Noguera-Troise[1], Karen Rodriguez Lorenc[1], Glenn Kroog[1]

[1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [2]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Indiana University Simon Cancer Center and Roudebush VAMC, Indianapolis, IN, USA; [4]Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Introduction: B-cell maturation antigen (BCMA) is a receptor expressed in normal and malignant plasma cells, which is cleaved to release the ectodomain, known as soluble BCMA (sBCMA). sBCMA concentrations range from normal to very high in patients with MM, and high concentrations reduce the ability of BCMA-directed therapies to induce cytotoxicity of MM cells in vitro (Frerichs, et al. Clin Cancer Res. 2020). Based on these data and correlations of sBCMA to plasma cell levels and M protein in patients with MM (Ghermezi, et al. Haematologica. 2017), it was hypothesized that high circulating sBCMA may reflect high disease burden and correlate with lower response to plasma cell-targeting T-cell engagers (Girgis, et al. Blood Adv. 2023). Since MM cells vary in their secretion of disease proteins, we evaluated the relationship between sBCMA and M protein, involved free light chains (FLCs), IgA, and bone marrow (BM) plasma cells. We also assessed response to linvoseltamab, a BCMA×CD3 bispecific antibody, in patients with RRMM with high vs low baseline sBCMA. **Methods:** A sandwich ELISA was established for human sBCMA, with a sensitivity of 1.56 ng/mL in neat serum. Baseline serum samples were collected from 2 clinical trials in RRMM (NCT03761108 and NCT04083534; N=302 for sBCMA analysis). Baseline levels of M protein, FLC kappa, FLC lambda, and IgA were quantified using standard techniques. Baseline BM plasma cells were quantified using EuroFlow at a central laboratory. Spearman correlations were performed to assess the relationships between sBCMA and disease parameters. To assess correlation between baseline sBCMA and objective response rate (ORR) in patients treated with the recommended Ph 2 dose (RP2D) of linvoseltamab (N=117), an analysis by baseline sBCMA concentrations according to tertiles was performed. **Results:** Baseline sBCMA ranged from 17.1–10,200 ng/mL. Median concentrations in our studies were higher than in other reports in RRMM (Girgis, et al. Blood Adv. 2023). Baseline sBCMA was correlated to serum M protein (rho=0.42, P=3.1 e-08), and modestly correlated to involved FLC (rho=0.67, P=6.2 e-08). Correlations to IgA in patients with IgA myeloma at baseline were also modest (rho=0.52, P=1.1 e-05). Correlation of sBCMA to pretreatment BM aspirate plasma cells was weak (rho=0.26, P=00062). Overall ORR was 71% in the cohort of patients treated at the RP2D of linvoseltamab 200 mg. The ORRs according to tertiles of baseline sBCMA were 91.7% (≤210 ng/mL), 70.6% (>210–≤607 ng/mL), and 55.9% (>607–≤4460 ng/mL). **Conclusions:** In contrast to previous data indicating that sBCMA is highly correlated with disease burden, our study demonstrates variable correlations to secretory proteins in patients with RRMM. While prior studies suggested that patients with high baseline sBCMA may have a low response to bispecific therapeutics targeting BCMA and GPRC5D, our study shows that a high ORR can be achieved with linvoseltamab 200 mg in patients with RRMM, including in those with high sBCMA concentrations.

P-006

SBCMA has utility for early response monitoring in the blood and is correlated with forimtamig pharmacodynamic activity, clinical response and MRD

Iryna Dekhtiarenko[1], Jan Attig[1], Hans-Joachin Helms[1], Iva Lelios[1], Inga Clausen[1], Wolfgang Jacob[1], Meike Schneider[1], Martin Weisser[1], Carmelo Carlo-Stella[2], Salomon Manier[3], Simon Harrison[4], Rakesh Popat[5], Caroline Hasselbalch Riley[6], Ann-Marie Bröske[7]

[1]Roche Pharma Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland; [2]Department of Oncology and Hematology, Humanitas Cancer Center, Humanitas Clinical and Research Center and Department of Biomedical Sciences, Humanitas University, Rozzano, Italy; [3]Centre Hospitalier Universitaire de Lille, Université de Lille, Lille, France; [4]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia; [5]NHS University College London Hospital, London, United Kingdom; [6]Rigshospitalet, Copenhagen, Denmark; [7]Roche Innovation Center Munich, Penzberg, Germany

Introduction: Forimtamig is a GPRC5DxCD3 T-cell engaging bispecific antibody that induces T-cell directed Multiple Myeloma

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P-005

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(MM) cell killing and has shown promising clinical activity in a Phase I study in patients (pts) with relapsed refractory MM (NCT04557150; Carlo-Stella et al. ASH 2022). Soluble B-cell maturation antigen (sBCMA) was demonstrated to correlate with tumor burden, is a potential prognostic marker and, having shorter half-life compared to other peripheral MM disease markers, is a promising early response predictor in MM (Nakamura et al. EHA 2022, Girgis et al. Blood Adv. 2023). Here, we investigate sBCMA as a blood-based surrogate marker of clinical response and disease monitoring for forimtamig treatment. **Methods:** Plasma samples were collected in the NCT04557150 dose-escalation study. sBCMA and cytokines were quantified with Protein ELLA System. Peripheral blood immune cells were monitored with flow cytometry and minimal residual disease (MRD) was measured by next generation sequencing. Pts were grouped by age, prior therapy, refractory status, ISS score, cytogenetic risk (high risk: del(17p), t(4;14), t(14;16)) and objective response (responder [≥PR] or non-responder [< PR]). All pts provided informed consent. Updated data will be presented. **Results:** At cut-off (January 25, 2023), 109/120 pts were biomarker evaluable. Baseline sBCMA levels did not significantly differ between pt groups defined by age, refractory status, ISS score, number of prior therapy lines, prior anti-CD38 or anti-BCMA therapy. Pts with high-risk cytogenetics (n=30) tend to have higher baseline levels of sBCMA than standard risk pts (n=16); median: 619.5 ng/mL vs 271.0 ng/mL, p=0.0439. Patients with baseline sBCMA concentrations below median had a higher ORR (above and below median ORR of 55.6% and 80.0%, respectively). A drop in sBCMA levels was detected as early as C1D8 (median=-22.4%) reaching a median of -88.8% by C2D1 in responding pts, whereas sBCMA concentrations increased in non-responding pts (median of 6.7% and 5.1% at C1D8 and C2D1, respectively). Pts with an early drop of sBCMA showed higher likelihood of strong T-cell margination (86% vs. 15%), increase in T-cell proliferation (76% vs. 28%) and modest increase in inflammatory cytokine release compared to those pts without an early drop of sBCMA. ≥50% decrease in sBCMA levels at C2D1 was associated with higher rate of MRD negativity at the same time point: 10-5 MRD neg reported for 13 out of 32 pts (40.6%). All pts not reaching the 50% sBCMA threshold level at C2D1 were MRD positive (n=9). **Conclusions:** sBCMA is a blood-based biomarker that is easily applicable, cost effective, and has potential prognostic value. For the first time, our data indicates a correlation of sBMCA decrease with T-cell activation and MRD negativity. Based on the results of our study, sBCMA may be used as a patient-centric and dynamic surrogate biomarker of response complementary to MRD in the future.

P-007

Prognostic impact of corticosteroid and tocilizumab use on the efficacy of chimeric antigen receptor T-cell therapy for relapsed/refractory multiple myeloma

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Introduction: Chimeric antigen receptor T-cell (CAR-T) therapy targeting B-cell maturation antigen (BCMA) or G protein-coupled receptor, class C, group 5, member D (GPRC5D) has shown unprecedented efficacy in patients (pts) with relapsed/refractory multiple myeloma (RRMM). Immune-related adverse events (irAEs) such as cytokine release syndrome (CRS) and neurotoxicity may occur early in treatment. Whilst immune-suppressive agents such as tocilizumab (TCZ) and corticosteroids (CS) are used to manage irAEs, a potential concern is a negative effect on CAR-T efficacy and survival outcomes. Here, we evaluated the prognostic impact of TCZ and CS use within 30 days of CAR-T infusion. **Methods:** This was a single-center, retrospective cohort study involving RRMM pts aged ≥18 years and treated with commercial/investigational anti-BCMA or anti-GPRC5D CAR-T therapy from April 2017 to September 2022. Fisher's exact test was used to determine whether CS use influenced the overall response rate (ORR; ≥PR as per IMWG Criteria). We also performed a 30-day landmark analysis using multivariable Cox proportional hazards models to evaluate the impact of TCZ administration and CS administration/dosing on progression-free survival (PFS) and overall survival (OS). **Results:** Among the 102 pts included (46% female), the median age was 62 years (range, 37-79) and median number of prior lines of therapy was 6 (range, 2-20). Triple-class refractoriness (TCR), extramedullary disease (EMD), and high-risk cytogenetics were present in 83%, 49%, and 70% of pts, respectively. Anti-BCMA CAR-T was used in 93 pts (91%), and anti-GPRC5D CAR-T in 9 pts (9%). After CAR-T infusion, 77% of pts developed CRS (35% grade 1; 34% grade 2; 8% grade 3) and 14% developed neurotoxicity (8% grade 1; 4% grade 2; 2% grade 3). A total of 42 pts (41%) and 29 pts (28%) received TCZ and CS within 30 days post-infusion, respectively. No significant difference in ORR was observed between pts who received CS and those that did not (66% vs 83%; P=0.089). Following a 30-day landmark analysis, both PFS and OS were significantly inferior in pts with EMD with hazard ratio (HR) of 1.86 (95% confidence interval [CI], 1.05-3.29; P=0.034) and 3.88 (95% CI, 1.71-8.76; P20 mg vs ≤20 mg). Similarly, there was no significant difference in either PFS (HR, 1.06; 95% CI, 0.55-2.04; P=0.87) or OS (HR, 1.03; 95% CI, 0.40-2.68; P=0.95) in pts who received TCZ versus those that did not. **Conclusions:** CS and TCZ treatment for irAEs does not appear to compromise CAR-T efficacy or survival outcomes in RRMM pts. These results support the timely and appropriate use of these drugs for attenuating CAR-T-related toxicities.

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P-008

Idecabtagene vicleucel (ide-cel) vs standard regimens in triple-class–exposed (TCE) relapsed and refractory multiple myeloma (RRMM): KarMMa-3 subgroup analysis in patients receiving bridging therapy

Hermann Einsele[1], Paula Rodríguez-Otero[2], Bertrand Arnulf[3], Krina Patel[4], Salomon Manier[5], Luciano Costa[6], Nizar Bahlis[7], Annemiek Broijl[8], Christine Chen[9], Ingerid Weum Abrahamsen[10], Michel Delforge[11], Usama Gergis[12], Marc Raab[13], Seema Singhal[14], Rafat Abonour[15], Anna Truppel-Hartmann[16], Rashmi Bhatnagar[17], Jasper Felten[18], Andrea Caia[18], Fan Wu[18], Julia Piasecki[18], Mark Cook[19], Sikander Ailawadhi[20]

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Introduction: Ide-cel, a BCMA-directed CAR T cell therapy (Tx), significantly improved median progression-free survival (mPFS; 13.3 vs 4.4 mo; HR 0.49; P< 0.001) and overall response rates (ORR; 71 vs 42%; P< 0.001) vs standard (std) regimens in patients (pts) with TCE RRMM in KarMMa-3 (NCT03651128). Optional bridging Tx (BTx) was allowed for disease control in pts randomized to ide-cel. Outcomes in pts in ide-cel arm who received BTx are reported. **Methods:** Pts in KarMMa-3 randomized to ide-cel could receive ≤1 cycle of BTx, selected by investigator before randomization and dependent on last prior Tx. This post hoc analysis based disease burden (DB) on measurable disease pre-leukapheresis (LK; serum/urine M-protein, M-protein, or difference between involved/uninvolved free light chain). Pts who received BTx were grouped based on DB change from LK to ide-cel (≥25% increase; ≥25% decrease; no change). Efficacy (PFS, ORR, complete response rate [CRR], duration of response [DOR]) and safety of ide-cel were assessed. **Results:** Of 254 pts randomized to ide-cel, 213 received BTx; 200 were evaluable for change in DB before ide-cel (DPd, n=45; DVd, n=20; IRd, n=25; Kd, n=26; EPd, n=59; other, n=25) (increase, n=59 [28%]; decrease, n=32 [15%]; no change, n=109 [51%]). Median number of cycles was 1 for all BTx regimens. A higher percentage of pts with increased disease had baseline high-risk MM characteristics (extramedullary plasmacytoma, increase, 41%; decrease, 16%; no change, 24%; high-risk cytogenetics, increase, 53%; decrease, 25%; no change, 38%; triple-class–refractory disease, increase, 90%; decrease, 63%; no change, 59%). mPFS (95% CI) was numerically longer in pts with decrease vs increase or no change (increase, 6.9 [2.4–11.8]; decrease, 20.7 [11.2–NR]; no change, 15.1 [12.4–17.3] mo). ORR (95% CI) was numerically higher in pts with decrease vs increase or no change (increase, 56% [43–69]; decrease, 97% [91–100]; no change, 80% [72–87]), with deeper (CRR: increase, 32%; decrease, 56%; no change, 39%), more durable (mDOR [95% CI]: increase, 9.3 [7.5–17.3]; decrease, 18.6 [8.6–NR]; no change, 12.9 [10.9–21.4] mo) responses. Any-grade (G; increase, 90%; decrease, 97%; no change, 96%) and G3/4 adverse event (AE; increase, 81%; decrease, 84%; no change, 95%) incidence was similar between groups. G5 AEs occurred in 15% (increase), 6% (decrease) and 13% (no change); serious AEs in 42%, 25%, and 44%, respectively. Any-G cytokine release syndrome occurred in 80% (increase), 94% (decrease), and 84% (no change); G3/4 in 7%, 3%, and 4%, respectively. Any-G investigator-identified neurotoxicity occurred in 24% (increase), 3% (decrease), and 13% (no change); G3/4 in 3%, 0%, and 4%, respectively. **Conclusions:** Ide-cel resulted in longer mPFS and greater response in pts with TCE RRMM who had decrease/no change versus increase in DB with BTx. Regardless of change in DB, ide-cel safety profile was consistent. Effective BTx is an important consideration for ide-cel Tx in TCE RRMM.

P-009

Cellular dynamics following CAR T cell therapy are associated with response, resistance and cytokine release syndrome in relapsed/refractory myeloma

Luise Fischer[1], Ronald Weiss[1], Nora Grieb[1], Michael Rade[1], Patrick Born[1], Andreas Boldt[1], Stephan Fricke[2], Paul Franz[2], Simone Heyn[1], Anne Sophie Kubasch[1], Ronny Baber[1], Song Yau Wang[1], Enrica Bach[1], Sandra Hoffmann[1], Jule Ussmann[1], Klaus H. Metzeler[1], Marco Herling[1], Madlen Jentzsch[1], Georg-Nikolaus Franke[1], Ulrich Sack[1], Kristin Reiche[2], Uwe Platzbecker[1], Vladan Vucinic[1], Maximilian Merz[1], Ulrike Köhl[2]

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Introduction: Data on cellular (CAR) T cell dynamics after treatment and the association with response or the occurrence of cytokine release syndrome (CRS) are limited. We performed a longitudinal flow cytometry study to analyze dynamics of CAR T cells and bystander T cells after infusion and correlated findings with CRS and outcome. **Methods:** We analyzed 29 patients treated with commercial CAR T cell products (Ide-cel/Cilta-cel). Based on their response on day 30 following CAR T cell infusion, patients were separated into two groups (CR:n=14, no CR:n=15). To assess longitudinal cellular dynamics of (CAR) T cells, peripheral blood was collected at day of re-infusion (d 0) as well as days 7, 14, 30

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[1]University Hospital of Leipzig; [2]Fraunhofer IZI*

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and 100 after infusion. CAR T cells were detected using a biotin labeled BCMA CAR detection reagent. The T cell compartment was furthermore differentiated by flow cytometry into CD4+/CD8+ CAR T cells and into thymic emigrants, naïve T cells, effector and central memory T cells as well as naïve and memory regulatory T cells. **Results:** We found no correlation between infused number of CAR T cells and in vivo expansion of CAR T cells as well as with response and outcome. Peak CAR T cell expansion was detected after two weeks and was predominantly represented by CD8+ cells. Significantly higher numbers of CAR T cells were detected in the first week and first month following infusion in patients in CR (d7: median 63.4/µl vs 7/µl, p=0.046; d30: median 48/µl vs 3/µl, p=0.031). We also observed significant differences between patients in CR as compared to patients with suboptimal response in the non-CAR T cell compartment. While patients not in CR exhibited significantly higher numbers of naïve CD4+ and CD8+ T cells as well as naïve regulatory T cells during the first months after treatment, patients in CR harbored a significantly higher proportion of CD4+ and CD8+ effector memory T cells one moths after treatment (CD4+:58% vs 33% of all CD4+ T cells,p=0.002; CD8+:59% vs 47%,p=0.018). Overall, 17 patients (59%) developed a CRS (grade 1:n=15,grade 2:n=2). Patients developing a CRS showed significantly higher numbers of CAR T cells in the first week (median 104/µl vs 8/µl, p=0.011) and first month (median 19/µl vs 1/µl, p=0.002) following reinfusion. The expansion of CD8+ effector memory T cells two weeks after infusion was significantly correlated to the occurrence of CRS (CRS: median 191/µl vs no CRS: 46/µl, p=0.006). In patients without CRS, significantly higher numbers of central memory CD4+ (median 35/µl vs 12/µl, p=0.007) and CD8+ T cells (median 10/µl versus 3/µl, p=0.019) as well as naïve CD8+ cells (median 1.3/µl vs 0.1/µl, p=0.021) were observed during the first week. **Conclusions:** Longitudinal analyses of CAR T cells and non-transduced T cells show that their numbers correlate with outcome and toxicity of CAR T cell therapy in patients with multiple myeloma. Our study identified patients at risk for relapse and CRS based on the post-treatment cellular dynamics.

P-010

Tumor-intrinsic features associated with progression-free survival (PFS) in patients (pts) with relapsed and refractory multiple myeloma (RRMM) treated with idecabtagene vicleucel (ide-cel)

Nicholas Stong[1], Ethan Thompson[1], Amy Xu[1], Julie Rytlewski[1], Arnaud Amzallag[1], Timothy Campbell[1], Sundar Jagannath[2], Nikhil Munshi[3], Julia Piasecki[1], Debashree Basudhar[1], Maria Ortiz-Estévez[1], Shari Kaiser[1], Nathan Martin[1], Erin Flynt[4]

[1]Bristol Myers Squibb, Princeton, NJ, USA; [2]Mount Sinai Medical Center, New York, NY, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/Harvard Medical School; [4]Bristol Myers Squibb, Summit, NJ, USA

Introduction: Ide-cel, a B-cell maturation antigen chimeric antigen receptor T cell therapy, has demonstrated frequent, deep, durable responses in pts with RRMM in the KarMMa (NCT03361748), KarMMa-2 (NCT03601078), and KarMMa-3 (NCT03651128) trials. A previous analysis of KarMMa showed comparable efficacy of ide-cel across molecular high-risk/resistance (HR/R) features such as biallelic p53 inactivation, 1q amplification, t(4;14), and CRBN dysregulation, and identified a baseline gene expression pattern (PC4) associated with PFS (Martin N, et al. Hemasphere 2022;6:(S6):1452). We aimed to identify additional genomic features associated with ide-cel efficacy in KarMMa and KarMMa-2 and evaluate samples from pts in KarMMa-3 as an independent validation cohort. **Methods:** Transcriptional and genomic profiles were assessed at baseline in CD138+ cells from bone marrow from pts in KarMMa, KarMMa-2 cohort 1, and KarMMa-3. Gene copy number aberrations were evaluated for associations with response. Analyses were post hoc and exploratory, and a P value, or false discovery rate (FDR), of < 0.05 was used to identify associations of interest. **Results:** In evaluable pts in KarMMa (n=70), single copy number loss was observed at 2 loci that associated with PFS, a broad region across 14q (n=16) and deletion at 1p31.2 (n=6). These were generally independent and together represented 30% (21/70) of pts. Both were associated with shorter median PFS (mPFS) in KarMMa (cohort mPFS, 8.8 mo, n=128; Munshi et al. N Engl J Med 2021;384:705–716) after FDR correction (del 14q, mPFS, 4.0 mo; del 1p31.2, mPFS, 2.3 mo). No pt with 1p loss had a best overall response (BOR) better than partial response. Pts with loss vs non-loss of 14q had similar BOR distribution, but poorer mPFS within each BOR (10.4 vs 29.7 mo for loss vs non-loss in pts with complete response/stringent complete response). Due to small sample size in KarMMa-2 cohort 1 (n=18), these data were aggregated with those from KarMMa. When combined, previously described associations with HR/R features were maintained except for biallelic p53 inactivation, which showed a stronger association with shorter PFS in the aggregate dataset (n=83, P=0.04) than in KarMMa (n=65, P=0.09). KarMMa-3 (n=210) analysis is ongoing and will be used as a validation cohort for these findings. Consistent trends for the association of the PC4 gene signature with PFS were observed in KarMMa-2 but were not statistically significant and limited by sample size. **Conclusions:** Two novel genomic HR/R features associated with PFS were identified using samples from KarMMa; validation is ongoing using samples from KarMMa-3. The PC4 gene signature was consistent in 2 RRMM cohorts. A modest association between biallelic p53 disruption and PFS emerged with increased sample size and will be studied in KarMMa-3.
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P-011

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Jan Frenking[1,2], Joseph Kauer[1], Marina Hajiyianni[1,3], Elias Mai[1,3], Christian Michel[1], Lilli Sester[1,2], Lukas John[1,2], Carsten Müller-Tidow[1,4],

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P-011

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P-011

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Hartmut Goldschmidt[5], Niels Weinhold[1,2], Anita Schmitt[1], Michael Schmitt[1], Peter Dreger[1], Sandra Sauer[1], Marc Raab[1]

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Introduction: The time span from patient selection for CAR T-cells to actual infusion is challenging. Pre-apheresis and bridging therapies need to be carefully balanced between disease control, toxicities and effects on T cell fitness. The post-CAR-T phase is characterized by cytopenias and immune deficiency. Considering the diversity of therapeutic options in relapsed/refractory multiple myeloma (RRMM), we evaluated the effect of pre-CAR-T treatment regimens on reconstitution of bone marrow and immune function. **Methods:** We performed a retrospective analysis of RRMM patients who received anti-BCMA CAR T-cells at our academic center. At data cutoff (May 22, 2023), 32 patients had undergone T cell apheresis and 29 patients had received idecabtagene vicleucel (ide-cel). We determined the last documented stable or progressive disease state leading to a systemic treatment prior to apheresis ('pre-apheresis therapy'). 'Bridging therapy' was defined as any systemic treatment applied between apheresis and start of lymphodepletion. For analysis of the post-CAR-T phase, bridging therapies were divided into regimens with ≥ 2 (n=11), ≥ 1 (n=15), or no classical cytotoxic/chemotherapeutic (CTX) agents (n=10), with last cytotoxic drug administration ≤ 60 d before lymphodepletion and exclusion of patients with progressive disease and bone marrow infiltration > 5% (n=2) at time of reconstitution analysis. 14/32 patients had received cyclophosphamide, etoposide and dexamethasone (CED) as pre-apheresis therapy (n=4), bridging therapy (n=4) or both (n=6). Other bridging regimens with ≥ 2 CTX agents were CED-carfilzomib (n=1), BEAM (n=1) and pomalidomide-PACE (n=1). **Results:** CAR T cell therapy with ide-cel resulted in an overall response rate (ORR; ≥ PR) of 72% (n=21), despite a high number of cases with R-ISS ≥ 2 (62%; n=18), high-risk cytogenetics (69%; n=20) and extramedullary disease (48%; n=14). With CED as pre-CAR-T treatment, 11/14 (79%) patients achieved at least stable disease. The ORR was 43% (n=6). Analysis of post-CAR-T hematopoietic reconstitution revealed a delayed recovery in patients after ≥ 2 CTX agents compared to all other bridging therapies. This included lower platelet counts at day 28 (p=0.025), day 35 (p=0.005), day 42 (p=0.009) and day 63 (p=0.015). Leukocyte counts were similarly different from day 28 onward, reaching statistical significance at day 35 (p=0.031), day 42 (p=0.030), day 63 (p=0.015) and day 90 (p=0.028). Two patients required stem cell support (both ≥ 2 CTX group). Infections between days 30 and 90 were more common among patients with ≥ 1 CTX bridging agent (18% vs. 67%; p=0.021). **Conclusions:** The clinical efficacy achieved with ide-cel at our center was comparable with previously published data. CED is effective as pre-apheresis and bridging therapy for RRMM patients with high disease burden. However, CTX-intense regimens appear to be associated with an increased risk for prolonged cytopenias and infections after CAR T-cell therapy.

P-012

Safety and efficacy of standard of care (SOC) teclistamab (TEC) in patients with relapsed/refractory multiple myeloma (RRMM), a single center experience

Ariel Grajales-Cruz[1], Sushmita Khadka[2], Brandon Blue[2], Doris Hansen[2], Omar Castaneda Puglianini[2], Ciara Freeman[2], Gabriel De Avila[2], Leonel Ochoa-Bayona[2], Hien Liu[2], Taiga Nishihori[2], Frederick Locke[2], Ken Shain[2], Rachid Baz[1], Melissa Alsina[2]

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Introduction: B- cell maturation antigen (BCMA) directed therapy and particularly bi-specific T cell engagers are a therapeutic option for patients (pts) with RRMM. MajesTEC-1 demonstrated an overall response rate (ORR) at 63%, progression free survival (PFS) of 11.3 months and duration of response (DOR) of 18.4 months. Adverse events were mainly low-grade cytokine release syndrome (CRS) (73%), cytopenias, and infections. TEC was FDA approved in October 2022 for RRMM. **Methods:** We retrospectively evaluated outcomes of 28 pts treated with TEC as SOC at our institution from December 2022 to May 2023. CRS and ICANS were graded per ASTCT consensus, responses per IMWG. This retrospective study was IRB approved. **Results:** All pts would have been ineligible for the MajesTEC-1 trial, due to prior BCMA directed therapy (n=22), cytopenias (n=8), renal impairment (n=5), and performance status (PS) (n=4). At the time of TEC, median age was 66 (range 48-81), and 7 pts (25%) had an ECOG PS ≥2. Thirteen pts (46%) had high risk cytogenetics (defined as del17, t(4;14), t(14;16)), and 15 pts (54%) had gain 1q; 10 (36%) were ultra-high risk (double and triple hit). Median prior lines of therapy (LOT) was 7 (4-15). Twenty-six pts (93%) were triple class refractory, and 12 (43%) were penta refractory. Twenty-two pts (79%) received prior BCMA directed therapy; CAR-T (n=16; 73%), Antibody Drug Conjugate (ADC) (n=2; 9%), or both CAR-T and ADC (n=4; 18%). Responses to prior BCMA directed therapies were as follows: 4 progression of disease (PD), 1 stable disease (SD), 1 minimal response (MR), 2 partial response (PR), 4 very good partial response (VGPR), 8 complete response (CR). Twelve (54%) pts received TEC right after progression from prior BCMA directed therapies. Twelve of thirteen pts (all receiving prior BCMA-directed therapy) tested for BCMA expression were positive by IHC, with 7 expressors responding. Twenty-five pts were evaluable for response at day 30. ORR was 52%, with 24% ≥VGPR and 12% ≥CR. ORR in pts with prior BCMA directed therapy was 44%, with 24% ≥VGPR and 12% ≥CR. Grade 1 CRS was seen in 14 (50%) pts, grade 2 in 3 (11%) pts, and grade 3 in 2 (7%) pts. 6 pts received Tocilizumab for CRS; 2 for grade 1 CRS, 2 for grade 2, and 2 for grade 3. One pt received steroids for grade 3 CRS. Grade 3 ICANS was seen in 1 pt (4%), requiring steroids. Infections were seen in 12 (43%)

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P-012

Safety and efficacy of standard of care (SOC) teclistamab (TEC) in patients with relapsed/refractory multiple myeloma (RRMM), a single center experience

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Introduction: B- cell maturation antigen (BCMA) directed therapy and particularly bi-specific T cell engagers are a therapeutic option for patients (pts) with RRMM. MajesTEC-1 demonstrated an overall response rate (ORR) at 63%, progression free survival (PFS) of 11.3 months and duration of response (DOR) of 18.4 months. Adverse events were mainly low-grade cytokine release syndrome (CRS) (73%), cytopenias, and infections. TEC was FDA approved in October 2022 for RRMM. **Methods:** We retrospectively evaluated outcomes of 28 pts treated with TEC as SOC at our institution from December 2022 to May 2023. CRS and ICANS were graded per ASTCT consensus, responses per IMWG. This retrospective study was IRB approved. **Results:** All pts would have been ineligible for the MajesTEC-1 trial, due to prior BCMA directed therapy (n=22), cytopenias (n=8), renal impairment (n=5), and performance status (PS) (n=4). At the time of TEC, median age was 66 (range 48-81), and 7 pts (25%) had an ECOG PS ≥2. Thirteen pts (46%) had high risk cytogenetics (defined as del17, t(4;14), t(14;16)), and 15 pts (54%) had gain 1q; 10 (36%) were ultra-high risk (double and triple hit). Median prior lines of therapy (LOT) was 7 (4-15). Twenty-six pts (93%) were triple class refractory, and 12 (43%) were penta refractory. Twenty-two pts (79%) received prior BCMA directed therapy; CAR-T (n=16; 73%), Antibody Drug Conjugate (ADC) (n=2; 9%), or both CAR-T and ADC (n=4; 18%). Responses to prior BCMA directed therapies were as follows: 4 progression of disease (PD), 1 stable disease (SD), 1 minimal response (MR), 2 partial response (PR), 4 very good partial response (VGPR), 8 complete response (CR). Twelve (54%) pts received TEC right after progression from prior BCMA directed therapies. Twelve of thirteen pts (all receiving prior BCMA-directed therapy) tested for BCMA expression were positive by IHC, with 7 expressors responding. Twenty-five pts were evaluable for response at day 30. ORR was 52%, with 24% ≥VGPR and 12% ≥CR. ORR in pts with prior BCMA directed therapy was 44%, with 24% ≥VGPR and 12% ≥CR. Grade 1 CRS was seen in 14 (50%) pts, grade 2 in 3 (11%) pts, and grade 3 in 2 (7%) pts. 6 pts received Tocilizumab for CRS; 2 for grade 1 CRS, 2 for grade 2, and 2 for grade 3. One pt received steroids for grade 3 CRS. Grade 3 ICANS was seen in 1 pt (4%), requiring steroids. Infections were seen in 12 (43%)

pts, including viral, bacterial, and fungal. Five (18%) infections were deemed severe and required hospitalization. Prior to TEC, 14 (50%) pts had hypogammaglobulinemia (IgG< 400). After TEC, 8 pts (29%) developed new hypogammaglobulinemia. Eleven (39%) pts had treatment delays, mainly due to CRS and infections. Four pts died; 1 due to infection, and 3 due to progression of disease. **Conclusions:** Pts treated with SOC TEC had a favorable ORR (52%) despite no pts meeting MajesTEC-1 trial eligibility criteria. No new safety signals were identified. Results will be updated with continued follow up.

P-013

Patterns of cytokine release syndrome with teclistamab in relapsed/refractory multiple myeloma with or without prior T-cell redirection therapy

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P-014

Teclistamab in relapsed and refractory multiple myeloma: patients characteristics from post marketing acces (acces precoce) in France

Stéphanie Harel[1], Jean-Marc Schiano de Colella[2], Cecile Sonntag[3], Titouan Cazaubiel[4], Laurent Garderet[5], Sylvie Bouillie[6], Matthieu Javelot[7], Sophie Vernet[7], Aurore Perrot[8]

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pts, including viral, bacterial, and fungal. Five (18%) infections were deemed severe and required hospitalization. Prior to TEC, 14 (50%) pts had hypogammaglobulinemia (IgG< 400). After TEC, 8 pts (29%) developed new hypogammaglobulinemia. Eleven (39%) pts had treatment delays, mainly due to CRS and infections. Four pts died; 1 due to infection, and 3 due to progression of disease. **Conclusions:** Pts treated with SOC TEC had a favorable ORR (52%) despite no pts meeting MajesTEC-1 trial eligibility criteria. No new safety signals were identified. Results will be updated with continued follow up.

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score ≥ 2 was reported for 18.9% and 33,4 % of pts presented with clinically significant comorbidities including hypertension (25,1%), cardiopathy (18%) and renal insufficiency (17,8%). The cytogenetic risk profile was unknown for 35.1% of pts and 21.7% presented with cytogenetic high-risk features, defined as one or more of del17p, t(4,14) or t(14,16). Extramedullary disease was present in 21.2 % of pts. The median number of previous lines of therapy was 4 [3-11]. The percentages of pts having received 3, 4, 5 and ≥6 prior lines were 31.3%, 25.9%, 18.9% and 24% respectively. Pts were previously exposed to lenalidomide and bortezomib (≥97%), daratumumab and pomalidomide (>87%) and carfilzomib (83.2%). 8.6 % pts had been previously treated with a BCMA-targeted therapy. 69.6% pts had triple-class refractory disease and 32 % penta-drug refractory disease. Pts had been included by 230 physicians from 100 different sites: 28 academic hospitals and 72 non-academic centers. The median follow-up was 2.9 [0;6.2] months. As of data cut-off, 38 treatment discontinuations were reported due to disease progression (78.9% with a fatal outcome for 16/30 patients) or toxicity (10.5%). 4 patients died from a treatment-related adverse event. **Conclusions:** This is the largest population of teclistamab patients characterized outside of the clinical trial setting (572 pts included in 6 months). French AP population was heavily pre-treated with clinically significant comorbidities and was slightly older, more frail than patients in the Majestec-1 study population. Academic and non-academic centers have included patients. Only a limited number of treatment discontinuations reported to date.

P-015

A Novel CAR-T cell therapy targeting kappa myeloma antigen for the treatment of multiple myeloma

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Introduction: Multiple myeloma (MM), the second most common blood cancer, is characterized by the accumulation of malignant plasma cells in the bone marrow. Chimeric Antigen Receptor (CAR)-T cell therapy has recently entered the standard of care for relapsed and refractory MM, following the recent FDA-approval of two CAR-T cell products, ide-cel® and cilta-cel®, which target the B cell maturation antigen (BCMA). However, despite impressive response rates, most patients relapse within 1-3 years, highlighting the need to develop novel CAR targets for this disease indication. **Methods:** Kappa (κ) myeloma antigen (KMA) is a tumour specific membrane associated protein expressed on malignant plasma cells in patients with kappa light-chain restricted (κ-type) MM. KMA is absent on normal plasma cells and haematopoietic stem cells, making it an attractive and alternative target antigen for CAR-T cell therapy for MM. The monoclonal antibody, KappaMab (MDX-1097), binds to a conformational epitope on KMA, and has been assessed in phase I, IIa and IIb clinical trials in relapse refractory myeloma patients. Here, we have engineered a lentiviral vector encoding a second-generation CAR expressing a scFv from MDX-1097, fused to a 4-1BB co-stimulatory domain and CD3 zeta chain, to test in preclinical models of MM. **Results:** We successfully generated human anti-KMA CAR-T cells with high and stable CAR expression and a predominately memory T cell phenotype. The CAR-T cells selectively killed KMA-expressing tumour lines and secreted interferon-gamma upon target recognition. Futhermore, a single dose of anti-KMA CAR-T cells demonstrated potent anti-tumour activity in a xenograft model. All mice treated with a 5e6 CAR-T cell dose were alive at 100 days post-treatment, had persisting circulating CAR-T cells and no evidence of disease. **Conclusions:** Our data demonstrates that anti-KMA CAR-T cell therapy is a novel and potent treatment ready to enter a phase I clinical trial for patients with multiple myeloma.

P-016

Disparities in access and practice patterns of BCMA-directed T-cell engager (TCE) therapies in multiple myeloma: a global perspective

Hamza Hassan[1], Mehmet Samur[2], Adam Cohen[3], Hermann Einsele[4], Philippe Moreau[5], Jesus San-Miguel[6], Shaji Kumar[7], María-Victoria Mateos[8], David Avigan[9], Jesus Berdeja[10], Ajai Chari[11], Pieter Sonneveld[12], Francesca Gay[13], Amrita Krishnan[14], Saad Usmani[15], Sundar Jagannath[16], Jacob Laubach[17], Clifton Mo[17], Adam Sperling[17], Omar Nadeem[17], Irene Ghobrial[17], Paul Richardson[17], Kenneth Anderson[18], Nikhil Munshi[19], Shonali Midha[17]

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Introduction: BCMA-directed T cell engager therapies (TCE), chimeric antigen receptor (CAR) T cells and bispecific T cell engagers (BiTEs) have shown remarkable efficacy in relapsed/ refractory multiple myeloma (RRMM) leading to the approval of

score ≥ 2 was reported for 18.9% and 33,4 % of pts presented with clinically significant comorbidities including hypertension (25,1%), cardiopathy (18%) and renal insufficiency (17,8%). The cytogenetic risk profile was unknown for 35.1% of pts and 21.7% presented with cytogenetic high-risk features, defined as one or more of del17p, t(4,14) or t(14,16). Extramedullary disease was present in 21.2 % of pts. The median number of previous lines of therapy was 4 [3-11]. The percentages of pts having received 3, 4, 5 and ≥6 prior lines were 31.3%, 25.9%, 18.9% and 24% respectively. Pts were previously exposed to lenalidomide and bortezomib (≥97%), daratumumab and pomalidomide (>87%) and carfilzomib (83.2%). 8.6 % pts had been previously treated with a BCMA-targeted therapy. 69.6% pts had triple-class refractory disease and 32 % penta-drug refractory disease. Pts had been included by 230 physicians from 100 different sites: 28 academic hospitals and 72 non-academic centers. The median follow-up was 2.9 [0;6.2] months. As of data cut-off, 38 treatment discontinuations were reported due to disease progression (78.9% with a fatal outcome for 16/30 patients) or toxicity (10.5%). 4 patients died from a treatment-related adverse event. **Conclusions:** This is the largest population of teclistamab patients characterized outside of the clinical trial setting (572 pts included in 6 months). French AP population was heavily pre-treated with clinically significant comorbidities and was slightly older, more frail than patients in the Majestec-1 study population. Academic and non-academic centers have included patients. Only a limited number of treatment discontinuations reported to date.

P-015

A Novel CAR-T cell therapy targeting kappa myeloma antigen for the treatment of multiple myeloma

Jane Oliaro[1], Jessica Li[1], Nicole Haynes[1], Katherine Cummins[1], Halley Hilton[2], Rosanne Dunn[2], Simon Harrison[3]

[1]CoE CIT, Peter MacCallum Cancer Centre; [2]HaemaLogiX Ltd, Woolloomooloo, NSW, Australia; [3]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia

Introduction: Multiple myeloma (MM), the second most common blood cancer, is characterized by the accumulation of malignant plasma cells in the bone marrow. Chimeric Antigen Receptor (CAR)-T cell therapy has recently entered the standard of care for relapsed and refractory MM, following the recent FDA-approval of two CAR-T cell products, ide-cel® and cilta-cel®, which target the B cell maturation antigen (BCMA). However, despite impressive response rates, most patients relapse within 1-3 years, highlighting the need to develop novel CAR targets for this disease indication. **Methods:** Kappa (κ) myeloma antigen (KMA) is a tumour specific membrane associated protein expressed on malignant plasma cells in patients with kappa light-chain restricted (κ-type) MM. KMA is absent on normal plasma cells and haematopoietic stem cells, making it an attractive and alternative target antigen for CAR-T cell therapy for MM. The monoclonal antibody, KappaMab (MDX-1097), binds to a conformational epitope on KMA, and has been assessed in phase I, IIa and IIb clinical trials in relapse refractory myeloma patients. Here, we have engineered a lentiviral vector encoding a second-generation CAR expressing a scFv from MDX-1097, fused to a 4-1BB co-stimulatory domain and CD3 zeta chain, to test in preclinical models of MM. **Results:** We successfully generated human anti-KMA CAR-T cells with high and stable CAR expression and a predominately memory T cell phenotype. The CAR-T cells selectively killed KMA-expressing tumour lines and secreted interferon-gamma upon target recognition. Futhermore, a single dose of anti-KMA CAR-T cells demonstrated potent anti-tumour activity in a xenograft model. All mice treated with a 5e6 CAR-T cell dose were alive at 100 days post-treatment, had persisting circulating CAR-T cells and no evidence of disease. **Conclusions:** Our data demonstrates that anti-KMA CAR-T cell therapy is a novel and potent treatment ready to enter a phase I clinical trial for patients with multiple myeloma.

P-016

Disparities in access and practice patterns of BCMA-directed T-cell engager (TCE) therapies in multiple myeloma: a global perspective

Hamza Hassan[1], Mehmet Samur[2], Adam Cohen[3], Hermann Einsele[4], Philippe Moreau[5], Jesus San-Miguel[6], Shaji Kumar[7], María-Victoria Mateos[8], David Avigan[9], Jesus Berdeja[10], Ajai Chari[11], Pieter Sonneveld[12], Francesca Gay[13], Amrita Krishnan[14], Saad Usmani[15], Sundar Jagannath[16], Jacob Laubach[17], Clifton Mo[17], Adam Sperling[17], Omar Nadeem[17], Irene Ghobrial[17], Paul Richardson[17], Kenneth Anderson[18], Nikhil Munshi[19], Shonali Midha[17]

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idecabtagene vicleucel, ciltacabtagene autoleucel and teclistamab by the FDA, EMA and other regulatory agencies. We performed a global survey on accessibility, practice patterns, and toxicity management of commercially available TCE therapies. **Methods:** Clinicians attending the IMS Immune Effector Cell Therapies in Multiple Myeloma Workshop (Boston, USA 2023), in-person or virtually, completed an online survey available for 30 days. **Results:** 87 clinicians from 16 countries (North America 64.4%, Europe 25.3%, Asia 6.9%, Australia 3.4%) completed the survey, most practicing in academic practice (86%), in an urban environment (89%). 77% reported CAR-T cell therapy was approved in their country with 44.8% treating 1-5 patients and 14.9% treating >5 patients per month; 67% reported BiTE therapy was approved in their country with 14.9% treating >5 patients per month. Of evaluable responses (n = 40), 62% administered CAR-T therapy inpatient and 15% administered CAR-T therapy outpatient ≥ 50% of the time. Length of time between decision to treat with CAR-T therapy to infusion was 6-12 weeks for 42% of responders and < 6 weeks for 20%. Most (75%) reported inpatient administration of BiTE therapy step-up dosing; 17.5% reported outpatient step-up dosing administered ≥ 50% of the time. 53% prefer cilta-cel, while 23% reported CAR-T therapy preference depended most on patients' co-morbidities (89%), timing of next available apheresis (67%) and age (56%). Maintenance therapy after CAR-T therapy was reported by 25% and 5% of respondents in 1-10% and 11-50% of their patients, respectively, to "maintain level of response achieved" (50%) or "achieve a deeper level of response" (25%). Tocilizumab was used as cytokine release syndrome (CRS) prophylaxis by one responder (2.5%) due to history of prior CRS. Keppra neurologic prophylaxis was used by 47.5% and 15% of responders for CAR-T and BiTE therapy, respectively. Delayed neurotoxicity with CAR-T was reported in 1-5% of patients by 57.5% of responders and 6-10% by 15%; most common manifestations were other movement/neuromuscular disorder (62%), nerve palsy (55%), and Parkinsonism (45%). Infectious prophylaxis included HSV (92.5%), PJP (90%), bacterial pathogens (55%), fungal pathogens (60%), and IVIG (77.5%). Most respondents (46.3 – 86.5%) reported completing an infectious work-up including CMV, EBV, Hep B/C, and HIV. However, 87.5% have not treated an HIV+ patient with CAR-T therapy due to lack of available data or patient need. **Conclusions:** Trends of TCE use and supportive care in MM vary widely among academic centers across the globe, demonstrating a need for further understanding of disease and toxicity management among the international myeloma community, along with improved access beyond urban centers.

P-017

Real-world efficacy of CAR T-cell therapies: a HealthTree cure hub's study of multiple myeloma patients

Jay Hydren[1], Jorge Arturo Hurtado Martinez[1], Nathan Sweeney[1], Patricia Alejandra Flores Pérez[1], Andrea Isabel Robles Espinoza[1], Jennifer Ahlstrom[1]

[1]HealthTree Foundation

Introduction: Chimeric antigen receptor T-cell (CAR-T) therapy is a promising immunotherapy that is used in the treatment of patients with relapsed and refractory multiple myeloma (RRMM). The purpose of this study was to analyze real-world data (RWD) and assess the effectiveness of CAR T-cell therapies in patients with RRMM. **Methods:** We utilized HealthTree Cure Hub for Multiple Myeloma, an online portal for patients with plasma cell dyscrasias to analyze RWD from 78 patients who either participated in CAR T-cell clinical trials or received this treatment as an approved intervention for multiple myeloma between the years 2017 and 2022. We assessed the effectiveness of CAR T-cell therapies (Abecma [ide-cel], Carvykti [cilta-cel], orva-cel, and other) by using Kaplan-Meier probability to examine event-free survival (EFS), progression-free survival (PFS), and overall survival (OS). EFS was determined by the start of a non-maintenance therapy and PFS was determined by using the IMWG progressive disease criteria. **Results:** Our analysis of the 78 patients found an average age of 63 ± 9.5 at the time of this analysis and an average age of 61 ± 9.5 at the point of initiating CAR-T therapy. The patients had been treated with an average of 6.5 ± 3.4 prior lines of therapy. Over half of patients (51%) were male, 76% were white, and 55% were non-Hispanic or Latino/a. Of the total 78 patients, 40 received Abecma (ide-cel) as their CAR T-cell therapy, 10 received Carvykti (cilta-cel), 7 received orva-cel, and 21 received other (an incidence of 3 or fewer). The median EFS was 30 months for Abecma (ide-cel), 30 months for orva-cel, 43 months for other, and undefined for Carvykti (cilta-cel). The median PFS and OS was undefined for all CAR T-cell therapies. Additionally, our analysis of EFS, PFS, and OS found no significant difference between the four CAR T-cell therapies. **Conclusions:** Our evaluation of real-world data suggests CAR T-cell therapy is a promising treatment strategy for RRMM regardless of therapy. The findings underscore the advantages of utilizing RWD through digital platforms such as HealthTree Cure Hub. This methodology offers a powerful tool to continually assess the impact of emerging therapeutics within the multiple myeloma patient population.

P-018

Prior BCMA-directed bispecific antibody or CAR T is not associated with increased risk of early infections in patients treated with bispecific antibodies

Lawrence Liu[1], Scott R. Goldsmith[2], Sheryl Leahey[2], Carlos Gomez[1], Shawn Streeter[1], Adam Braun[1], Myo Htut[1], Nitya Nathwani[1], Michael Rosenzweig[1], Firoozeh Sahebi[1], Azra Borogovac[1], Arnab Chowdhury[1], Sanjeet Dadwal[1], Amrita Krishnan[1], Murali Janakiram[1]

[1]City of Hope National Comprehensive Cancer Center, Duarte, CA, USA; [2]City Of Hope National Medical Center, Duarte, CA, USA

Introduction: Bispecific antibodies are associated with a higher risk of infections, 50% in a pooled analysis of 1185 patients. Risk factors for early infections with bispecific antibodies remain undefined though hypogammaglobulinemia and neutropenia are postulated to increase risk. **Methods:** We undertook a retrospective analysis of all patients who received bispecific antibodies at our

idecabtagene vicleucel, ciltacabtagene autoleucel and teclistamab by the FDA, EMA and other regulatory agencies. We performed a global survey on accessibility, practice patterns, and toxicity management of commercially available TCE therapies. **Methods:** Clinicians attending the IMS Immune Effector Cell Therapies in Multiple Myeloma Workshop (Boston, USA 2023), in-person or virtually, completed an online survey available for 30 days. **Results:** 87 clinicians from 16 countries (North America 64.4%, Europe 25.3%, Asia 6.9%, Australia 3.4%) completed the survey, most practicing in academic practice (86%), in an urban environment (89%). 77% reported CAR-T cell therapy was approved in their country with 44.8% treating 1-5 patients and 14.9% treating >5 patients per month; 67% reported BiTE therapy was approved in their country with 14.9% treating >5 patients per month. Of evaluable responses (n = 40), 62% administered CAR-T therapy inpatient and 15% administered CAR-T therapy outpatient ≥ 50% of the time. Length of time between decision to treat with CAR-T therapy to infusion was 6-12 weeks for 42% of responders and < 6 weeks for 20%. Most (75%) reported inpatient administration of BiTE therapy step-up dosing; 17.5% reported outpatient step-up dosing administered ≥ 50% of the time. 53% prefer cilta-cel, while 23% reported CAR-T therapy preference depended most on patients' co-morbidities (89%), timing of next available apheresis (67%) and age (56%). Maintenance therapy after CAR-T therapy was reported by 25% and 5% of respondents in 1-10% and 11-50% of their patients, respectively, to "maintain level of response achieved" (50%) or "achieve a deeper level of response" (25%). Tocilizumab was used as cytokine release syndrome (CRS) prophylaxis by one responder (2.5%) due to history of prior CRS. Keppra neurologic prophylaxis was used by 47.5% and 15% of responders for CAR-T and BiTE therapy, respectively. Delayed neurotoxicity with CAR-T was reported in 1-5% of patients by 57.5% of responders and 6-10% by 15%; most common manifestations were other movement/neuromuscular disorder (62%), nerve palsy (55%), and Parkinsonism (45%). Infectious prophylaxis included HSV (92.5%), PJP (90%), bacterial pathogens (55%), fungal pathogens (60%), and IVIG (77.5%). Most respondents (46.3 – 86.5%) reported completing an infectious work-up including CMV, EBV, Hep B/C, and HIV. However, 87.5% have not treated an HIV+ patient with CAR-T therapy due to lack of available data or patient need. **Conclusions:** Trends of TCE use and supportive care in MM vary widely among academic centers across the globe, demonstrating a need for further understanding of disease and toxicity management among the international myeloma community, along with improved access beyond urban centers.

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Jay Hydren[1], Jorge Arturo Hurtado Martinez[1], Nathan Sweeney[1], Patricia Alejandra Flores Pérez[1], Andrea Isabel Robles Espinoza[1], Jennifer Ahlstrom[1]

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Introduction: Chimeric antigen receptor T-cell (CAR-T) therapy is a promising immunotherapy that is used in the treatment of patients with relapsed and refractory multiple myeloma (RRMM). The purpose of this study was to analyze real-world data (RWD) and assess the effectiveness of CAR T-cell therapies in patients with RRMM. **Methods:** We utilized HealthTree Cure Hub for Multiple Myeloma, an online portal for patients with plasma cell dyscrasias to analyze RWD from 78 patients who either participated in CAR T-cell clinical trials or received this treatment as an approved intervention for multiple myeloma between the years 2017 and 2022. We assessed the effectiveness of CAR T-cell therapies (Abecma [ide-cel], Carvykti [cilta-cel], orva-cel, and other) by using Kaplan-Meier probability to examine event-free survival (EFS), progression-free survival (PFS), and overall survival (OS). EFS was determined by the start of a non-maintenance therapy and PFS was determined by using the IMWG progressive disease criteria. **Results:** Our analysis of the 78 patients found an average age of 63 ± 9.5 at the time of this analysis and an average age of 61 ± 9.5 at the point of initiating CAR-T therapy. The patients had been treated with an average of 6.5 ± 3.4 prior lines of therapy. Over half of patients (51%) were male, 76% were white, and 55% were non-Hispanic or Latino/a. Of the total 78 patients, 40 received Abecma (ide-cel) as their CAR T-cell therapy, 10 received Carvykti (cilta-cel), 7 received orva-cel, and 21 received other (an incidence of 3 or fewer). The median EFS was 30 months for Abecma (ide-cel), 30 months for orva-cel, 43 months for other, and undefined for Carvykti (cilta-cel). The median PFS and OS was undefined for all CAR T-cell therapies. Additionally, our analysis of EFS, PFS, and OS found no significant difference between the four CAR T-cell therapies. **Conclusions:** Our evaluation of real-world data suggests CAR T-cell therapy is a promising treatment strategy for RRMM regardless of therapy. The findings underscore the advantages of utilizing RWD through digital platforms such as HealthTree Cure Hub. This methodology offers a powerful tool to continually assess the impact of emerging therapeutics within the multiple myeloma patient population.

P-018

Prior BCMA-directed bispecific antibody or CAR T is not associated with increased risk of early infections in patients treated with bispecific antibodies

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Introduction: Bispecific antibodies are associated with a higher risk of infections, 50% in a pooled analysis of 1185 patients. Risk factors for early infections with bispecific antibodies remain undefined though hypogammaglobulinemia and neutropenia are postulated to increase risk. **Methods:** We undertook a retrospective analysis of all patients who received bispecific antibodies at our

center between Jan 2017 to Feb 2023. The receipt of a bispecific antibody (BisAb) regimen was considered as a treatment event (TE), if a patient received two different BisAb's regimens over a 12-month period it would be considered as two TE. Clinical predictors of risk and infection data within the first 90 days was collected for each event. **Results:** Our cohort contains 90 patients with 123 TE where 40, 48 and 35 represent regimens with BCMA, GPRC5D and FcRH5 respectively. Within these 123 TE, 77 infection episodes were recorded between days 1 and 90. No infections were recorded in 68 TE, while 41 had one infection and 14 with >=2 infections (36 total). The most common infections recorded were - 38% had Upper respiratory tract infection, 15% blood stream, 13% pneumonia, 14% GI, and 9% had CMV viremia/infection, 8% Urinary tract infections and 3% skin infections. Recurrent infections >1 was higher with BCMA directed therapies in the first 90 days (8.4 vs 17.5%). We divided the cohorts into no infection, 1 infection episode and greater than 1 infection episode. We observed no differences in baseline characteristics between the 3 cohorts including- HR, EMD, RISS, ECOG status, number of lines of prior therapy. On treatment parameters - ANC, ALC at D1, IgG levels, receipt of IVIG, CRS grade, tocilizumab use and treatment dose steroids were also not different between the 3 groups [0,1 and 2 infections]. Multivariate analysis showed none of the covariates including receipt of BCMA vs non BCMA BisAb, HR MM, IgG at baseline, prior CART, or prior BCMA directed therapy to be significantly associated with an increased risk of infection. **Conclusions:** Our results demonstrate that early infection within 90 days is not associated with specific baseline risk factors. Importantly our analysis shows that patients who received prior immune engagers are not at an increased risk of early infections and that IgG levels, ALC and ANC were also not predictive. Other risk factors including duration of prior immune engagers should be explored to identify risk factors for recurrent infections.

P-019

Novel combination immunotherapy for relapsed/refractory multiple myeloma (RRMM): initial Phase 1 safety run-in results for cevostamab in combination with pomalidomide and dexamethasone

Tomas Jelinek[1], Andrew Spencer[2], Amrita Krishnan[3], Suzanne Trudel[4], Simon Harrison[5], Madlaina Breuleux[6], Grant Goodman[7], Jiangeng Huang[7], Ameet Mishra[7], Leanne Richardson[8], Jennifer Tsai[7], Ravi Vij[9]

[1]University Hospital Ostrava and University of Ostrava, Ostrava, Czech Republic; [2]Alfred Health-Monash University, Melbourne, VIC, Australia; [3]City of Hope, Duarte, CA, USA; [4]Princess Margaret Cancer Centre and University of Toronto, Toronto, ON, Canada; [5]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia; [6]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [7]Genentech, Inc., South San Francisco, CA, USA; [8]Roche Products Ltd, Welwyn Garden City, United Kingdom; [9]Washington University, St. Louis, MO, USA

Introduction: Cevostamab, a FcRH5xCD3 bispecific antibody that facilitates T-cell directed killing of myeloma cells, has shown encouraging activity as monotherapy in patients (pts) with heavily pre-treated RRMM in a Phase 1 study (GO39775; NCT03275103; Trudel et al. ASH 2021). Combining cevostamab with anti-myeloma agents that augment the activity of T cells may enhance efficacy (Li et al. Mol Cancer Ther 2023). Both daratumumab (dara), an anti-CD38 antibody, and pomalidomide (pom), an immunomodulatory drug (IMiD), exhibit T-cell co-stimulatory effects and are clinically active when administered alone or with dexamethasone (dex) in pts with RRMM (Lonial et al. Lancet 2016; San Miguel et al. Lancet Oncol 2013). CAMMA 1 (GO42552; NCT04910568) is an ongoing Phase 1b study evaluating the safety and activity of cevostamab alone (Arm A) or with pom + dex (Arm B) or dara + dex (Arm C) in pts with RRMM. We present initial data from the Arm B safety run-in, including the first efficacy results for a non-B-cell maturation antigen (BCMA)-targeting bispecific antibody + IMiD combination. **Methods:** Eligible pts must have RRMM and have received ≥2 prior lines of therapy, including ≥1 IMiD and ≥1 proteasome inhibitor. Prior pom exposure is allowed. After a pre-phase with step-up dosing, cevostamab is given intravenously every 2 weeks in Cycles (C) 1–6 (28 days per cycle) and every 4 weeks in C7+. From C1+, pom (4 mg PO) is given on Day (D) 1–21 and dex (20 mg) on D1, 8, 15, and 22. At the investigator's discretion, dex may be eliminated from C5+. Treatment continues until disease progression or unacceptable toxicity. **Results:** At data cut-off (February 20, 2023), 8 pts had been enrolled (median age: 64.5 years). Median prior lines of therapy was 4. All pts were triple-class exposed. Median follow-up was 4.8 months. The objective response rate was 100% (8/8 pts), with one patient (12.5%) in complete response, three pts (37.5%) in very good partial response, and 4 pts (50%) in partial response. At cut-off, all responders (8/8 pts) were in response, with responses deepening over time, and 7/8 pts remained on treatment. Grade (Gr) 3–4 adverse events (AEs) occurred in 7 pts (87.5%) and were most commonly neutropenia (Gr 3: 12.5%; Gr 4: 37.5%). Cytokine release syndrome (CRS) occurred in 7 pts (87.5%), with Gr 3 CRS in 2 pts. Both Gr 3 CRS events occurred during the cevostamab pre-phase prior to the addition of pom and resolved without sequelae. AEs leading to dose modification or interruption occurred in all pts. There were no Gr 5 (fatal) AEs. One patient discontinued study treatment due to a serious AE (Gr 3 drug reaction with eosinophils and systemic symptoms [DRESS]) in the setting of cevostamab, pom, and dapsone exposure. **Conclusions:** Cevostamab plus pom and dex shows promising activity in pts with RRMM and warrants further evaluation to optimize the benefit/risk profile. Biomarker and updated clinical data will be presented.

P-020

Dendritic cell/myeloma fusion vaccine with lenalidomide maintenance following autologous hematopoietic cell transplant (HCT) results in long-term sustained T cell activation and clonotypic expansion

Dimitra Karagkouni[1], Giulia Cheloni[2], Daniela Torres[2], David Chung[3], Nina Shah[4], Natalie Callander[5],

center between Jan 2017 to Feb 2023. The receipt of a bispecific antibody (BisAb) regimen was considered as a treatment event (TE), if a patient received two different BisAb's regimens over a 12-month period it would be considered as two TE. Clinical predictors of risk and infection data within the first 90 days was collected for each event. **Results:** Our cohort contains 90 patients with 123 TE where 40, 48 and 35 represent regimens with BCMA, GPRC5D and FcRH5 respectively. Within these 123 TE, 77 infection episodes were recorded between days 1 and 90. No infections were recorded in 68 TE, while 41 had one infection and 14 with >=2 infections (36 total). The most common infections recorded were - 38% had Upper respiratory tract infection, 15% blood stream, 13% pneumonia, 14% GI, and 9% had CMV viremia/infection, 8% Urinary tract infections and 3% skin infections. Recurrent infections >1 was higher with BCMA directed therapies in the first 90 days (8.4 vs 17.5%). We divided the cohorts into no infection, 1 infection episode and greater than 1 infection episode. We observed no differences in baseline characteristics between the 3 cohorts including- HR, EMD, RISS, ECOG status, number of lines of prior therapy. On treatment parameters - ANC, ALC at D1, IgG levels, receipt of IVIG, CRS grade, tocilizumab use and treatment dose steroids were also not different between the 3 groups [0,1 and 2 infections]. Multivariate analysis showed none of the covariates including receipt of BCMA vs non BCMA BisAb, HR MM, IgG at baseline, prior CART, or prior BCMA directed therapy to be significantly associated with an increased risk of infection. **Conclusions:** Our results demonstrate that early infection within 90 days is not associated with specific baseline risk factors. Importantly our analysis shows that patients who received prior immune engagers are not at an increased risk of early infections and that IgG levels, ALC and ANC were also not predictive. Other risk factors including duration of prior immune engagers should be explored to identify risk factors for recurrent infections.

P-019

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Introduction: Cevostamab, a FcRH5xCD3 bispecific antibody that facilitates T-cell directed killing of myeloma cells, has shown encouraging activity as monotherapy in patients (pts) with heavily pre-treated RRMM in a Phase 1 study (GO39775; NCT03275103; Trudel et al. ASH 2021). Combining cevostamab with anti-myeloma agents that augment the activity of T cells may enhance efficacy (Li et al. Mol Cancer Ther 2023). Both daratumumab (dara), an anti-CD38 antibody, and pomalidomide (pom), an immunomodulatory drug (IMiD), exhibit T-cell co-stimulatory effects and are clinically active when administered alone or with dexamethasone (dex) in pts with RRMM (Lonial et al. Lancet 2016; San Miguel et al. Lancet Oncol 2013). CAMMA 1 (GO42552; NCT04910568) is an ongoing Phase 1b study evaluating the safety and activity of cevostamab alone (Arm A) or with pom + dex (Arm B) or dara + dex (Arm C) in pts with RRMM. We present initial data from the Arm B safety run-in, including the first efficacy results for a non-B-cell maturation antigen (BCMA)-targeting bispecific antibody + IMiD combination. **Methods:** Eligible pts must have RRMM and have received ≥2 prior lines of therapy, including ≥1 IMiD and ≥1 proteasome inhibitor. Prior pom exposure is allowed. After a pre-phase with step-up dosing, cevostamab is given intravenously every 2 weeks in Cycles (C) 1–6 (28 days per cycle) and every 4 weeks in C7+. From C1+, pom (4 mg PO) is given on Day (D) 1–21 and dex (20 mg) on D1, 8, 15, and 22. At the investigator's discretion, dex may be eliminated from C5+. Treatment continues until disease progression or unacceptable toxicity. **Results:** At data cut-off (February 20, 2023), 8 pts had been enrolled (median age: 64.5 years). Median prior lines of therapy was 4. All pts were triple-class exposed. Median follow-up was 4.8 months. The objective response rate was 100% (8/8 pts), with one patient (12.5%) in complete response, three pts (37.5%) in very good partial response, and 4 pts (50%) in partial response. At cut-off, all responders (8/8 pts) were in response, with responses deepening over time, and 7/8 pts remained on treatment. Grade (Gr) 3–4 adverse events (AEs) occurred in 7 pts (87.5%) and were most commonly neutropenia (Gr 3: 12.5%; Gr 4: 37.5%). Cytokine release syndrome (CRS) occurred in 7 pts (87.5%), with Gr 3 CRS in 2 pts. Both Gr 3 CRS events occurred during the cevostamab pre-phase prior to the addition of pom and resolved without sequelae. AEs leading to dose modification or interruption occurred in all pts. There were no Gr 5 (fatal) AEs. One patient discontinued study treatment due to a serious AE (Gr 3 drug reaction with eosinophils and systemic symptoms [DRESS]) in the setting of cevostamab, pom, and dapsone exposure. **Conclusions:** Cevostamab plus pom and dex shows promising activity in pts with RRMM and warrants further evaluation to optimize the benefit/risk profile. Biomarker and updated clinical data will be presented.

P-020

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P-019

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P-020

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Introduction: We have developed a personalized cancer vaccine in which hybridomas are created between patient-derived multiple myeloma (MM) cells and autologous dendritic cells (DCs) such that a broad array of tumor antigens is presented in the context of DC-mediated co-stimulation. BMT CTN 1401 (NCT02728102) is a first-of-its-kind academically led national randomized trial for a personalized cell therapy. We assessed immunologic and clinical response following DC/MM vaccine combined with lenalidomide maintenance (Len) after autoHCT, as compared to maintenance alone. 203 patients were enrolled from 18 centers. To assess the impact of the DC/MM vaccine on the establishment of an anti-MM immune response, we profiled the peripheral blood (PB) immune landscape at the single-cell level pre-/post-vaccination. **Methods:** We performed single-cell immunoprofiling (gene expression + V(D)J sequencing) on 160 PB mononuclear cell (PBMC) samples from 40 patients (DC/MM vaccine/Len/GM-CSF: N=20; Len/GM-CSF: N=10; Len: N=10) collected at enrollment, after 2, and following 3 vaccines (1-year post-transplant). Samples were processed using the 10x Genomics single cell 5' assay. Assessment of samples from the initial cohort (13 vaccinated patients) captured approximately half a million cells, corresponding to 47 cell populations. **Results:** Vaccination with DC/MM fusions as compared to the maintenance therapy alone was associated with a durable expansion of MM reactive T cells at 1-year post-transplant. Preliminary analysis of the vaccine arm identified key immune subsets and provided a detailed characterization of the T-cell landscape (146,373 cells), including subsets of regulatory, effector, and memory compartments. A progressive rise in the relative abundance of CD4 and CD8 T cells was observed after 3 vaccinations compared to the pre-vaccination period. Immune cell repertoire profiling of full-length paired α/β T-cell receptors demonstrated a higher clonotypic expansion of the CD8 effector memory T cells (TCR clonotype frequency > 20) following 2 and 3 vaccinations as compared to pre-vaccination. CD8 T cells showed greater expansion than all other T-cell populations at each time point. Consistent with these findings, a higher proportion of shared epitope/paratope hotspots among the expanded TCR β clonotypes across the vaccinated patients was observed at 1-year post-transplant as compared to the early post-transplant period. The use of BEAM-T 10x Genomics technology is being employed to identify the antigenic targets of the expanded clonotypes. Transcriptomic analysis of the vaccine and control cohorts is being completed. **Conclusions:** Assessment of PBMC samples from vaccinated patients provided a detailed picture of the immune landscape. The constant T cell expansion in patients following vaccination coupled with the shared paratope/epitope hotspots among patients, indicated the TCR cross-reactivity and suggested for the establishment of an anti-MM immune response.

P-021

Durable response to CAR T cell treatment is associated with the downstream triggering of native T cell immunity: a lesson learned from B cell lymphoma patients

Dimitra Karagkouni[1], Giulia Cheloni[2], Yered Pita-Juarez[3], Daniela Torres[2], Eleni Kanata[1], Zachary Avigan[2], Jessica Liegel[3], Dina Stroopinsky[2], Brodie Miles[4], Gayatri Tiwari[4], Jenny Kim[4], Mike Mattie[4], Jacalyn Rosenblatt[3], David Avigan[3], Ioannis Vlachos[3]

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Introduction: CD19-directed CAR T cell therapy results in durable response in a subset of large B cell lymphoma (LBCL) patients in the absence of persistent circulating CAR T cells. We postulated that durable response to CAR T therapy depends on downstream triggering of native T cell immunity. We performed single-cell immunoprofiling on peripheral blood mononuclear cell (PBMC) and RNAseq on baseline tumor from patients participating in the ZUMA 1 study. **Methods:** Single cell immunoprofiling (5' expression + V(D)J, 10x Genomics) was performed on 92 PBMC samples from ZUMA-1 patients (N=32), collected at leukapheresis, 4 weeks, 6- and 12-months post CAR T. RNAseq was performed on FFPE baseline lymphoma samples (N=17). We defined 3 groups: non-responders, relapsed within 1 year from CAR T infusion, and long-term responders. Approximately half a million cells passed the quality check, capturing 73 cellular populations. **Results:** Patients with durable response exhibited significantly higher proportions of CD8 T cells and an increased CD8/CD4 ratio pre-/post-CAR T, compared to the other cohorts. Long-term responders were characterized by a significantly increased cytotoxic signature, mostly pronounced at 4 weeks and 6 months post-CAR T. A higher abundance of CD4 cytotoxic T cells, highly cytotoxic CD8 T cells, as well as of early effector memory and pro-inflammatory CD8 T cells was observed post-CAR T. In contrast, patients with early relapse showed increased levels of regulatory T cells pre-/post-CAR T. In the long-term responder group compared to the patients with refractory or relapsing disease, pairwise comparisons of the TCR proportions before and after CAR T infusion demonstrated a higher

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Introduction: We have developed a personalized cancer vaccine in which hybridomas are created between patient-derived multiple myeloma (MM) cells and autologous dendritic cells (DCs) such that a broad array of tumor antigens is presented in the context of DC-mediated co-stimulation. BMT CTN 1401 (NCT02728102) is a first-of-its-kind academically led national randomized trial for a personalized cell therapy. We assessed immunologic and clinical response following DC/MM vaccine combined with lenalidomide maintenance (Len) after autoHCT, as compared to maintenance alone. 203 patients were enrolled from 18 centers. To assess the impact of the DC/MM vaccine on the establishment of an anti-MM immune response, we profiled the peripheral blood (PB) immune landscape at the single-cell level pre-/post-vaccination. **Methods:** We performed single-cell immunoprofiling (gene expression + V(D)J sequencing) on 160 PB mononuclear cell (PBMC) samples from 40 patients (DC/MM vaccine/Len/GM-CSF: N=20; Len/GM-CSF: N=10; Len: N=10) collected at enrollment, after 2, and following 3 vaccines (1-year post-transplant). Samples were processed using the 10x Genomics single cell 5' assay. Assessment of samples from the initial cohort (13 vaccinated patients) captured approximately half a million cells, corresponding to 47 cell populations. **Results:** Vaccination with DC/MM fusions as compared to the maintenance therapy alone was associated with a durable expansion of MM reactive T cells at 1-year post-transplant. Preliminary analysis of the vaccine arm identified key immune subsets and provided a detailed characterization of the T-cell landscape (146,373 cells), including subsets of regulatory, effector, and memory compartments. A progressive rise in the relative abundance of CD4 and CD8 T cells was observed after 3 vaccinations compared to the pre-vaccination period. Immune cell repertoire profiling of full-length paired α/β T-cell receptors demonstrated a higher clonotypic expansion of the CD8 effector memory T cells (TCR clonotype frequency > 20) following 2 and 3 vaccinations as compared to pre-vaccination. CD8 T cells showed greater expansion than all other T-cell populations at each time point. Consistent with these findings, a higher proportion of shared epitope/paratope hotspots among the expanded TCR β clonotypes across the vaccinated patients was observed at 1-year post-transplant as compared to the early post-transplant period. The use of BEAM-T 10x Genomics technology is being employed to identify the antigenic targets of the expanded clonotypes. Transcriptomic analysis of the vaccine and control cohorts is being completed. **Conclusions:** Assessment of PBMC samples from vaccinated patients provided a detailed picture of the immune landscape. The constant T cell expansion in patients following vaccination coupled with the shared paratope/epitope hotspots among patients, indicated the TCR cross-reactivity and suggested for the establishment of an anti-MM immune response.

P-021

Durable response to CAR T cell treatment is associated with the downstream triggering of native T cell immunity: a lesson learned from B cell lymphoma patients

Dimitra Karagkouni[1], Giulia Cheloni[2], Yered Pita-Juarez[3], Daniela Torres[2], Eleni Kanata[1], Zachary Avigan[2], Jessica Liegel[3], Dina Stroopinsky[2], Brodie Miles[4], Gayatri Tiwari[4], Jenny Kim[4], Mike Mattie[4], Jacalyn Rosenblatt[3], David Avigan[3], Ioannis Vlachos[3]

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Introduction: CD19-directed CAR T cell therapy results in durable response in a subset of large B cell lymphoma (LBCL) patients in the absence of persistent circulating CAR T cells. We postulated that durable response to CAR T therapy depends on downstream triggering of native T cell immunity. We performed single-cell immunoprofiling on peripheral blood mononuclear cell (PBMC) and RNAseq on baseline tumor from patients participating in the ZUMA 1 study. **Methods:** Single cell immunoprofiling (5' expression + V(D)J, 10x Genomics) was performed on 92 PBMC samples from ZUMA-1 patients (N=32), collected at leukapheresis, 4 weeks, 6- and 12-months post CAR T. RNAseq was performed on FFPE baseline lymphoma samples (N=17). We defined 3 groups: non-responders, relapsed within 1 year from CAR T infusion, and long-term responders. Approximately half a million cells passed the quality check, capturing 73 cellular populations. **Results:** Patients with durable response exhibited significantly higher proportions of CD8 T cells and an increased CD8/CD4 ratio pre-/post-CAR T, compared to the other cohorts. Long-term responders were characterized by a significantly increased cytotoxic signature, mostly pronounced at 4 weeks and 6 months post-CAR T. A higher abundance of CD4 cytotoxic T cells, highly cytotoxic CD8 T cells, as well as of early effector memory and pro-inflammatory CD8 T cells was observed post-CAR T. In contrast, patients with early relapse showed increased levels of regulatory T cells pre-/post-CAR T. In the long-term responder group compared to the patients with refractory or relapsing disease, pairwise comparisons of the TCR proportions before and after CAR T infusion demonstrated a higher

abundance of expanded clonotypes within the cytotoxic CD8 and CD4 T cell compartment, followed by gradually increased numbers over the course of the study. Similar shared PB T cell clones and tumor antigen sequences derived from the RNAseq samples, as well as the high mutational burden, observed in a subset of responders, suggest a (neo)antigen-specific response driven by common epitopes. Monocyte and NK cells were less prevalent in responders before treatment, guided by differences in phagocytic monocyte and inhibitory NK cell abundance. Ligand-receptor expression patterns revealed strong cell-cell interactions between phagocytic monocytes and T regulatory cells 6 months post-CAR T, suggesting a negative immunoregulatory role of these cells. **Conclusions:** The application of single-cell immunoprofiling on longitudinal samples from ZUMA-1 patients demonstrated distinct cellular and clonal profiles between long-term responders and patients with relapsed or refractory disease. These findings support our hypothesis of an important role of the non-CAR T immunity in maintaining sustained response to CAR T therapy. Our results can be used to better understand CAR T therapeutic efficacy and inform patient stratification and management across hematological malignancies.

P-022

Development of trogocytosis resistant CAR-NK for multiple myeloma

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Introduction: Multiple Myeloma (MM) remains an incurable disease, with a median survival of 8.6 months in patients refractory to conventional therapies. There is a great interest in translating chimeric antigen receptor (CAR) therapies to MM, where new therapeutic options are direly needed. Both CAR-T cells, now widely used, and CAR-NK cells, still at an experimental stage, must face evasion mechanisms that make tumor cells resistant to CAR-mediated killing. One of these mechanisms, trogocytosis, has emerged as a major hurdle in the effectiveness of CAR therapy, but strategies to overcome it are still lacking. During trogocytosis, NK cells capture and express the membrane and associated proteins of MM cells on their cell surface leading to negative consequences such as fratricide and antigen loss on the target cells. **Methods:** We set up an in vitro model to study the extent to which CAR-NK cells perform trogocytosis with MM cells and assessed if the structure of the CAR would change the amount of trogocytosis that occurred. We took advantage of NK92 cells, a human NK cell line widely used in preclinical studies, that we transduced with a BCMA targeted CAR construct. We labelled MM cells (with variable expression of BCMA) with Cell Trace Violet (CTV) and co incubated the labelled cells with CAR NK cells. Following 1 hr co incubation, we assessed transfer of cell dye as well as other specific MM markers, including BCMA, by flow cytometry. We repeated this assay with CAR structures varying in the affinity of the antigen binding domain for BCMA and the hinge length. **Results:** Consistent with our hypothesis, CTV dye was transferred to CAR NK cells incubated with MM cell lines, along with BCMA. In contrast, after co incubation with BCMA deficient cells, CAR NK cells failed to stain for BCMA and had lower CTV. Importantly, pre incubating CAR NK cells with the trogocytosis inhibitor latrunculin abolished BCMA acquisition from MM cells. Surprisingly, changing the affinity of the binding domain for BCMA did not alter trogocytosis, however, we found that hinge length had a positive correlation with trogocytosis. In the future, we will apply these methods to primary NK and MM cells as well as in vivo to assess the efficacy of our CAR constructs. **Conclusions:** Taken together, these experiments show that BCMA targeted CAR expression in NK cells greatly enhances trogocytosis of MM antigens, including BCMA. In addition, we demonstrated that the structure of the CAR influences the amount of trogocytosis that occurs. Further studies are needed to determine how we can generate trogocytosis-resistant CAR-NK to improve therapy for MM.

P-023

Talquetamab, a G protein–coupled receptor family C group 5 member D × CD3 bispecific antibody, in relapsed/refractory multiple myeloma: efficacy and safety of patient subgroups from monumenTAL-1

Amrita Krishnan[1], Luciano Costa[2], Carolina Schinke[3], Lionel Karlin[4], Daniel Morillo[5], Carmen Martinez-Chamorro[5], Jing Christine Ye[6], Ajai Chari[7], Philippe Moreau[8], Jo Caers[9], Andrzej Jakubowiak[10], Michela Campagna[11], Tara Masterson[12], Brandi Hilder[12], Jaszianne Tolbert[12], Thomas Renaud[13], M. Damiette Smit[14], Christoph Heuck[12], Monique Minnema[15]

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Introduction: Talquetamab (Tal) is a first-in-class GPRC5D×CD3 bispecific antibody that has shown >71% overall response rates (ORRs) and clinically manageable safety in patients (pts) with relapsed/refractory multiple myeloma (RRMM) in the MonumenTAL-1 study. We present subgroup analysis of the efficacy and safety of Tal in pts with disease and clinical features typically associated with poorer outcomes on established myeloma therapies. **Methods:** MonumenTAL-1 (NCT03399799/NCT04634552) is an open-label, single arm, phase 1/2 trial in pts with RRMM.

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Safety and efficacy of pts treated at the recommended phase 2 doses of subcutaneous Tal at 0.4 mg/kg weekly (QW) and 0.8 mg/kg every other week (Q2W) were previously reported. Pt subgroups assessed were age ≥75 years; high-risk cytogenetics [del(17p), t(4;14), and/or t(14;16)]; ISS stage III; renal impairment (baseline function ≤60 mL/min/1.73m^2); triple-class refractory (to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody); and extramedullary disease (EMD; ≥1, including soft tissue plasmacytomas). **Results:** As of Jan 17, 2023, 143 and 145 pts received Tal 0.4 mg/kg QW and 0.8 mg/kg Q2W, respectively. Of these, respectively, 106 (74.1%) and 100 (69.0%) were triple-class refractory; 21 (14.7%) and 32 (22.1%) were ≥75 years; 41 (28.7%) and 37 (25.5%) had high-risk cytogenetics; 28 (19.6%) and 35 (24.1%) were ISS III; 40 (28.0%) and 45 (31.0%) had renal impairment; and 33 (23.1%) and 37 (25.5%) had EMD. Median follow-up for the subgroups was consistent with their respective dose cohorts in the overall population (QW, 19 mo; Q2W, 13 mo). In the Q2W cohort, efficacy was consistent with the broader population (ORR, 72%; 9-mo DOR, 76%; 12-mo PFS, 54%; 12-mo OS, 77%) in the following subgroups: age ≥75 years (ORR, 75%; 9-mo DOR, 92%; 12-mo PFS, 71%; 12-mo OS, 83%), high-risk cytogenetics (ORR, 76%; 9-mo DOR, 78%; 12-mo PFS, 63%; 12-mo OS, 62%), triple-class refractory (ORR, 69%; 9-mo DOR, 73%; 12-mo PFS, 50%; 12-mo OS, 73%) and renal (ORR, 67%; 9-mo DOR, 64%; 12-mo PFS, 40%; 12-mo OS, 72%). Efficacy was lower in ISS III (ORR, 60%; 9-mo DOR, 61%; 12-mo PFS, 38%; 12-mo OS, 67%) and EMD (ORR, 43%; 9-mo DOR, 56%; 12-mo PFS, 27%; 12-mo OS, 65%) subgroups. Trends were similar in the QW cohort. The safety profile among subgroups in both cohorts was generally consistent with the overall population. Rates of discontinuation due to adverse events were higher than the overall population (QW and Q2W, 5–8%) in age ≥75 years (14.3%) and ISS III (10.7%) subgroups in the QW cohort and ISS III (14.3%) and renal (13.3%) subgroups in the Q2W cohort. **Conclusions:** Most pts with traditional high-risk features experience clinical benefit with Tal monotherapy that is consistent with the overall study population. While responses were less consistent in EMD and ISS III subgroups, Tal still provided responses in over one-third and one-half of these pts, respectively.

P-024

Early outcomes and therapy modification strategies in multiple myeloma patients treated with teclistamab, CD3XBCMA BITE: a single center experience

Swarup Kumar[1], Katharine Hooper[1], Jackson Clark[1], Alvaro Alvarez-Soto[1], Allison Rounds[1]

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Introduction: Cellular therapies in Multiple Myeloma have gained attention in recent years with the first commercially available Bispecific T-cell Engaging Monoclonal Antibody (BITE), CD3XBCMA teclistamab being approved for use for patients with relapsed disease following four or more lines of prior therapy in 2022. The impact of early treatment frequency modification as well as predictive immune markers of response are incompletely understood in this patient population. We aimed to assess and characterize early responses to teclistamab in our patient population as well as understand genomic profiling related mutations identifiable through commercially available assays in predicting treatment response. **Methods:** Nine patients who were treated at our health center with teclistamab between November 2022 and February 2023 were included in this analysis. Patients' baseline characteristics, markers of disease response including hematologic, bone marrow molecular, evaluable minimal residual disease (MRD) at three months post dose escalation completion were abstracted. ClonoSEQ® and Tempus xT® 648 gene DNA NGS panel were utilized for MRD tracking and genomic profiling respectively. **Results:** The median age of the patient population was 75 years (41-81) and the median number of prior lines being 6(4-9). 3 patients had IMWG defined high risk FISH abnormalities and 2 patients had EMP prior to therapy. Mean Absolute Lymphocyte Count prior to therapy was 1.16 (x10^3/ul). 7 patients had cytokine release syndrome (CRS) event while 1 patient had immune effector cell related neurotoxicity (ICANS) event. None of the CRS or ICANS events were grade 3 or higher. Mean absolute CD4 count and CD8 count prior to therapy was 550/cu mm and 622/cu mm. At the 3-moth evaluation, 3 patients had achieved a CR, with 2 being stringent CR, MRD-. 1 VGPR, 2 PR and 3 PD were also observed. Of the 3 patients with CR, 2 patients were treated with Q2 weekly dosing immediately following the dose escalation cycle due to patient tolerance issues, one of whom had also achieved a stringent CR. Amongst all patients with response at the 3-month bone marrow evaluation, 1 patient had DNA damage related mutation (CHEK2) whilst 2 had residual CHIP mutations (TET2 and DNMT3A) with prior exposure to multi-agent antineoplastic therapy (DNA damage agents). **Conclusions:** In our limited patient dataset, 6 (66.7%) patients had achieved an early best response of PR or higher, consistent with clinical trial data. Despite treatment frequency modification, two patients achieved a CR with one patient achieving a stringent CR at the 3-month evaluation. Further studies are needed to assess response adapted treatment frequency modification as well as study genomic perturbations that can alter the function of immune cells (T cells) and impact response to BITE.

P-025

Synergistic antitumor activity of the BCMA 2+1 T-cell engager (TCE) alnuctamab (ALNUC; BMS-986349; CC-93269) and CELMoD agents in multiple myeloma (MM) preclinical models

Bruno Paiva[1], Bonny Gaffney[2], Kelven Burnett[2], Paola Castiglioni[2], Ross La Motte-Mohs[3], Michael Angelo[2], Daniel Pierce[4], Isaac Boss[5]

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Safety and efficacy of pts treated at the recommended phase 2 doses of subcutaneous Tal at 0.4 mg/kg weekly (QW) and 0.8 mg/kg every other week (Q2W) were previously reported. Pt subgroups assessed were age ≥75 years; high-risk cytogenetics [del(17p), t(4;14), and/or t(14;16)]; ISS stage III; renal impairment (baseline function ≤60 mL/min/1.73m^2); triple-class refractory (to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody); and extramedullary disease (EMD; ≥1, including soft tissue plasmacytomas). **Results:** As of Jan 17, 2023, 143 and 145 pts received Tal 0.4 mg/kg QW and 0.8 mg/kg Q2W, respectively. Of these, respectively, 106 (74.1%) and 100 (69.0%) were triple-class refractory; 21 (14.7%) and 32 (22.1%) were ≥75 years; 41 (28.7%) and 37 (25.5%) had high-risk cytogenetics; 28 (19.6%) and 35 (24.1%) were ISS III; 40 (28.0%) and 45 (31.0%) had renal impairment; and 33 (23.1%) and 37 (25.5%) had EMD. Median follow-up for the subgroups was consistent with their respective dose cohorts in the overall population (QW, 19 mo; Q2W, 13 mo). In the Q2W cohort, efficacy was consistent with the broader population (ORR, 72%; 9-mo DOR, 76%; 12-mo PFS, 54%; 12-mo OS, 77%) in the following subgroups: age ≥75 years (ORR, 75%; 9-mo DOR, 92%; 12-mo PFS, 71%; 12-mo OS, 83%), high-risk cytogenetics (ORR, 76%; 9-mo DOR, 78%; 12-mo PFS, 63%; 12-mo OS, 62%), triple-class refractory (ORR, 69%; 9-mo DOR, 73%; 12-mo PFS, 50%; 12-mo OS, 73%) and renal (ORR, 67%; 9-mo DOR, 64%; 12-mo PFS, 40%; 12-mo OS, 72%). Efficacy was lower in ISS III (ORR, 60%; 9-mo DOR, 61%; 12-mo PFS, 38%; 12-mo OS, 67%) and EMD (ORR, 43%; 9-mo DOR, 56%; 12-mo PFS, 27%; 12-mo OS, 65%) subgroups. Trends were similar in the QW cohort. The safety profile among subgroups in both cohorts was generally consistent with the overall population. Rates of discontinuation due to adverse events were higher than the overall population (QW and Q2W, 5–8%) in age ≥75 years (14.3%) and ISS III (10.7%) subgroups in the QW cohort and ISS III (14.3%) and renal (13.3%) subgroups in the Q2W cohort. **Conclusions:** Most pts with traditional high-risk features experience clinical benefit with Tal monotherapy that is consistent with the overall study population. While responses were less consistent in EMD and ISS III subgroups, Tal still provided responses in over one-third and one-half of these pts, respectively.

P-024

Early outcomes and therapy modification strategies in multiple myeloma patients treated with teclistamab, CD3XBCMA BITE: a single center experience

Swarup Kumar[1], Katharine Hooper[1], Jackson Clark[1], Alvaro Alvarez-Soto[1], Allison Rounds[1]

[1]University of Connecticut, UCONN Health

Introduction: Cellular therapies in Multiple Myeloma have gained attention in recent years with the first commercially available Bispecific T-cell Engaging Monoclonal Antibody (BITE), CD3XBCMA teclistamab being approved for use for patients with relapsed disease following four or more lines of prior therapy in 2022. The impact of early treatment frequency modification as well as predictive immune markers of response are incompletely understood in this patient population. We aimed to assess and characterize early responses to teclistamab in our patient population as well as understand genomic profiling related mutations identifiable through commercially available assays in predicting treatment response. **Methods:** Nine patients who were treated at our health center with teclistamab between November 2022 and February 2023 were included in this analysis. Patients' baseline characteristics, markers of disease response including hematologic, bone marrow molecular, evaluable minimal residual disease (MRD) at three months post dose escalation completion were abstracted. ClonoSEQ® and Tempus xT® 648 gene DNA NGS panel were utilized for MRD tracking and genomic profiling respectively. **Results:** The median age of the patient population was 75 years (41-81) and the median number of prior lines being 6(4-9). 3 patients had IMWG defined high risk FISH abnormalities and 2 patients had EMP prior to therapy. Mean Absolute Lymphocyte Count prior to therapy was 1.16 (x10^3/ul). 7 patients had cytokine release syndrome (CRS) event while 1 patient had immune effector cell related neurotoxicity (ICANS) event. None of the CRS or ICANS events were grade 3 or higher. Mean absolute CD4 count and CD8 count prior to therapy was 550/cu mm and 622/cu mm. At the 3-moth evaluation, 3 patients had achieved a CR, with 2 being stringent CR, MRD-. 1 VGPR, 2 PR and 3 PD were also observed. Of the 3 patients with CR, 2 patients were treated with Q2 weekly dosing immediately following the dose escalation cycle due to patient tolerance issues, one of whom had also achieved a stringent CR. Amongst all patients with response at the 3-month bone marrow evaluation, 1 patient had DNA damage related mutation (CHEK2) whilst 2 had residual CHIP mutations (TET2 and DNMT3A) with prior exposure to multi-agent antineoplastic therapy (DNA damage agents). **Conclusions:** In our limited patient dataset, 6 (66.7%) patients had achieved an early best response of PR or higher, consistent with clinical trial data. Despite treatment frequency modification, two patients achieved a CR with one patient achieving a stringent CR at the 3-month evaluation. Further studies are needed to assess response adapted treatment frequency modification as well as study genomic perturbations that can alter the function of immune cells (T cells) and impact response to BITE.

P-025

Synergistic antitumor activity of the BCMA 2+1 T-cell engager (TCE) alnuctamab (ALNUC; BMS-986349; CC-93269) and CELMoD agents in multiple myeloma (MM) preclinical models

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Introduction: Cereblon E3 ligase modulator (CELMoD®) agents, including classic immunomodulatory (IMiD®) agents, have antitumor activity in MM. ALNUC is an IgG TCE that binds BCMA and CD3ε in a 2+1 format. ALNUC mediates myeloma cell killing by recruiting T cells to BCMA-expressing target cells, leading to T cell cytotoxic activity. Combining CELMoD agents with ALNUC may enhance antitumor activity. We evaluated the anti-MM potential of ALNUC + pomalidomide (POM) and novel CELMoD agents mezigdomide (MEZI) and iberdomide (IBER) in preclinical models. **Methods:** To evaluate effects of CELMoD agents on ALNUC-mediated T cell anti-MM activity, healthy donor (HD) T cells and/or BCMA-expressing MM cell lines were pretreated with POM, MEZI, IBER, or DMSO for 16 h (T cells) or 72 h (MM cells) prior to coculture; ALNUC was added for 72 h and T cell activation and MM target cell depletion were measured. To evaluate CELMoD agent effects on artificially exhausted T cells, HD CD3+ T cells were pretreated with anti-CD3/CD28 beads and POM, MEZI, IBER, or DMSO for 7 d prior to coculture with MM cells and ALNUC. To determine if CELMoD treatment could reverse T cell dysfunction, pretreatment PBMCs from pts with MM who had response (n=2) or nonresponse (n=3) to ALNUC in a phase 1 trial (NCT03486067) were cocultured with H929 cells. Cocultures were pretreated with MEZI 1 nM for 24 h prior to adding ALNUC. The effects of concurrent and sequential MEZI and ALNUC were studied in a humanized mouse H929 MM xenograft model. **Results:** In cocultures with HD T cells, pretreatment of MM cells with MEZI, IBER, and POM increased ALNUC-induced tumor-cell killing potency and efficacy across all cell lines vs ALNUC alone. ALNUC antitumor activity against the OPM-2 cell line was also enhanced by pretreating T cells with MEZI and IBER, but not POM. MEZI showed the greatest overall enhancement of ALNUC activity. In artificially exhausted HD T cells, enhanced antitumor activity was observed with MEZI and IBER, but not POM, vs DMSO. In a mouse MM xenograft model, priming or concurrent treatment with MEZI enhanced T cell activation, promoted T cell infiltration of tumor tissue, and increased ALNUC-induced tumor clearance. MEZI pretreatment of MM pt-derived PBMCs increased ALNUC-mediated antitumor activity vs control in samples from both responders and nonresponders. **Conclusions:** Combining ALNUC with novel CELMoD agents enhanced T cell mediated antitumor activity in both in vitro and ex vivo MM models. MEZI showed the greatest ability to enhance TCE-mediated antitumor activity while reversing artificial T cell dysfunction/exhaustion. Priming and concurrent treatment with MEZI enhanced ALNUC-induced T cell infiltration and activation in a MM xenograft model. Enhancement of ALNUC T cell antitumor function by MEZI was confirmed using MM patient-derived PBMCs. These results provide a strong biological rationale for combining MEZI or IBER with ALNUC to enhance responses in pts with MM. Presented at ASH 2022. Paiva B et al. Abstract 3135.

P-026

Safety and efficacy of a locally produced novel anti-BCMA chimeric antigen receptor T-cell (CART) (HBI0101) for the treatment of relapsed and refractory multiple myeloma

Eyal Lebel[1], Shlomit Kfir-erenfeld[1], Nathalie Asherie[1], Sigal Grisariu[1], Batia Avni[1], Shlomo Elias[1], Miri Assayag[1], Tatyana Dubnikov[1], Nomi Zalcman[1], Marjorie Pick[1], Eran Zimran[1], Adir Shaulov[1], Yaël Cohen[2,3], Irit Avivi[2], Cyrille Cohen[4], Polina Stepensky[1], Moshe Gatt[1]

[1]Hadassah Medical center; [2]Tel-Aviv Sourasky (Ichilov) Medical Center; [3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [4]Bar-Ilan University

Introduction: Anti-B-cell maturation antigen (BCMA) chimeric antigen receptor T-cell (CART) therapy shows remarkable efficacy in patients with relapsed and/or refractory (R/R) multiple myeloma (MM). HBI0101 is a novel second generation optimized anti-BCMA CART, that was developed in an academic setting. The phase Ia study evaluating HBI0101 (NCT04720313) proved manageable safety profile and initial high efficacy (Asherie, Haematologica 2022). Here we present the updated phase 1a results as well as the phase 1b results including 50 patients treated to date. **Methods:** At Hadassah Medical Center we have developed a new anti-BCMA CAR T with 4-1BB co-stimulatory domain (HBI0101) for the treatment of R/R MM. Following phase 1a study, evaluating the first 20 R/R MM patients with three or more prior lines of therapy, including a PI, IMiD and anti CD38 antibody (infusing $150x10^6$ (n=6), $450x10^6$ (n=7) and $800x10^6$ (n=7) CAR T cells), the phase Ib study further evaluated the infusion of $800x10^6$ CAR T cells. **Results:** Fifty R/R MM patients were included in the phase Ia and Ib cohorts. The median number of prior lines was 5 (3-13) and most (92%) were triple refractory to PI, IMiDs and anti-CD38 antibodies. 30% were penta-refractory and 30% were refractory to belantamab mofadotin. Safety was manageable with grade 3-4 hematological toxicities common (anemia - 54%, thrombocytopenia - 60%, neutropenia & lymphopenia- 100%). Cytokine release syndrome (CRS) occurred in 46/50 (92%), but were mostly (41/46) of grade 1-2, and manageable with frequent use of tocilizumab (70%). No immune effector cell associated neurotoxicity syndrome (ICANS) cases were observed, and no irreversible organ toxicities or treatment related deaths occurred. The overall response rate (ORR) of the established $800x10^6$ CAR T cells was 87%. Of 37 patients treated with this dose, 21 (57%) achieved complete response (CR)/ stringent CR, and 27 (73%) achieved minimal residual disease (MRD) negativity at day +30. At data cutoff, with a median follow-up of 6 months (range 1-17.4), the median progression-free survival was 11 months and the median overall survival was not reached. Although the presence of extra-medullary disease and prior anti-BCMA therapy correlated with worse outcome, high response rates were still observed (ORR of 96%/63% for patients without/with extra-medullary disease, respectively, and 93%/73% for patients without/with prior anti-BCMA therapy, respectively). **Conclusions:** Our findings demonstrate the manageable safety and high efficacy profiles of HBI0101, comparable to those reported of commercial anti-BCMA CART products. These favorable data are encouraging

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and support decentralization of CART production at an academic setting, ensuring a sufficient CART supply in the light of the increasing local demand.

P-027

Hotspot mutations in BCMA extracellular domain lead to differential susceptibility to anti-BCMA targeted immunotherapies

Holly Lee[1], Sungwoo Ahn[1], Ranjan Maity[1], Noemie Leblay[1], Bachisio Ziccheddu[2], Marietta Truger[3], Monika Chojnacka[4], Anthony Cirrincione[5], Michael Durante[2], Remi Tilmont[1], Elie Barakat[1], Mansour Poorebrahim[1], Ola Landgren[4], Hermann Einsele[6], Jean-Baptiste Alberge[7], Jonathan Keats[8,9], Leo Rasche[10], Francesco Maura[4], Paola Neri[11], Nizar Bahlis[11]

[1]University of Calgary; [2]University of Miami; [3]MLL Munich; [4]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami; [5]Sylvester Comprehensive Cancer Center; [6]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany; [7]Harvard Medical School; [8]TGen; [9]City of Hope; [10]University Hospital Würzburg; [11]Arnie Charbonneau Cancer Institute, University of Calgary

Introduction: Mutations in TNFRSF17 extracellular domain were recently reported to mediate escape to anti-BCMA bispecific T cell engagers (TCE). The prevalence of these mutations and how they impact other anti-BCMA therapies remain undefined. Furthermore, it is unclear whether these mutations affect BCMA canonical ligand binding and signaling. We here investigated the impact of hotspot mutations in BCMA extracellular domain on the efficacy of anti-BCMA therapies and the emergence of oncogenic dependencies. **Methods:** In order to define the frequency of TNFRSF17 alterations post anti-BCMA therapies and interrogate their functional significance, we collected CD138+ cells from patients treated with anti-BCMA CAR T/ TCE, and subjected the cells to WGS or single cell CNV analysis. Identified BCMA mutations were cloned and transduced into K562 myelogenous cell line for in vitro functional evaluation. **Results:** Recipients of anti-BCMA therapy (CAR T n=5, TCE n=16, both n=3) were included in this analysis. In patients progressing on anti-BCMA CAR T, only one (20%) had biallelic deletion of TNFRSF17 with no BCMA extracellular domain mutations. In contrast, among patients progressing on anti-BCMA TCE (n=14), mutations in TNFRSF17 were observed in 42.8% including TNFRSF17 biallelic loss (n=1) and extracellular domain mutations (n=5). Monoallelic TNFRSF17 deletion were coupled with p.Arg27Pro in one case, while p.Pro34del, or p.Ser30del were observed in 3 and 2 patients, with one patient harboring both mutations, consistent with convergent evolution. None of these mutations were identified in pre-therapy samples using WGS (100x) and digital PCR (0.1% sensitivity). Lentivirally transduced K562 cells were used to characterize the impact of BCMA mutations on the efficacy of various TCEs and cross resistance to CAR T. Of interest, while these mutations differentially impacted the sensitivities of TCEs based on their geometry and valency, cross resistance was not carried out to CAR T cells. As such, while p.Arg27Po, p.Ser30del, and p.Pro34del abrogated teclistamab mediated T cell killing, T cells transduced with teclistamab based scFv CAR retained cytolytic activity. Therefore, TCE resistance derived from BCMA extracellular domain mutations does not preclude retreatment with another anti-BCMA TCE or CAR T. Functionally, while BCMA extracellular domain mutations abrogated the binding of most anti-BCMA TCEs, they did not impair the binding of Fc-tagged APRIL, p65 nuclear translocation, and ERK phosphorylation. **Conclusions:** Collectively, our studies reveal that convergent evolution of MM clones harboring BCMA extracellular domain mutations selectively evade recognition by anti-BCMA TCEs while retaining the pro-survival signaling of the APRIL-BCMA-NFkB axis. Furthermore, these hotspot mutations do not equally confer resistance to all anti-BCMA TCEs or CAR Ts. Dynamic surveillance and functional evaluation of emerging mutant clones will be required to inform and guide therapy selection and sequence.

P-028

Canadian-made single domain antibody (sdAb) BCMA CAR-T cells for multiple myeloma

Lorenzo Lindo[1], Daniel Waller[1], Lauren Wilkinson[1], Silvia Selleri[1], Mehdi Arbabi-Ghahroudi[2], Scott McComb[2], Leif Bergsagel[3], Marta Chesi[3], Kevin Hay[1]

[1]Terry Fox Laboratory - BC Cancer Research Institute; [2]National Research Council of Canada; [3]Mayo Clinic Arizona

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and support decentralization of CART production at an academic setting, ensuring a sufficient CART supply in the light of the increasing local demand.

P-027

Hotspot mutations in BCMA extracellular domain lead to differential susceptibility to anti-BCMA targeted immunotherapies

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[1]University of Calgary; [2]University of Miami; [3]MLL Munich; [4]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami; [5]Sylvester Comprehensive Cancer Center; [6]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany; [7]Harvard Medical School; [8]TGen; [9]City of Hope; [10]University Hospital Würzburg; [11]Arnie Charbonneau Cancer Institute, University of Calgary

Introduction: Mutations in TNFRSF17 extracellular domain were recently reported to mediate escape to anti-BCMA bispecific T cell engagers (TCE). The prevalence of these mutations and how they impact other anti-BCMA therapies remain undefined. Furthermore, it is unclear whether these mutations affect BCMA canonical ligand binding and signaling. We here investigated the impact of hotspot mutations in BCMA extracellular domain on the efficacy of anti-BCMA therapies and the emergence of oncogenic dependencies. **Methods:** In order to define the frequency of TNFRSF17 alterations post anti-BCMA therapies and interrogate their functional significance, we collected CD138+ cells from patients treated with anti-BCMA CAR T/ TCE, and subjected the cells to WGS or single cell CNV analysis. Identified BCMA mutations were cloned and transduced into K562 myelogenous cell line for in vitro functional evaluation. **Results:** Recipients of anti-BCMA therapy (CAR T n=5, TCE n=16, both n=3) were included in this analysis. In patients progressing on anti-BCMA CAR T, only one (20%) had biallelic deletion of TNFRSF17 with no BCMA extracellular domain mutations. In contrast, among patients progressing on anti-BCMA TCE (n=14), mutations in TNFRSF17 were observed in 42.8% including TNFRSF17 biallelic loss (n=1) and extracellular domain mutations (n=5). Monoallelic TNFRSF17 deletion were coupled with p.Arg27Pro in one case, while p.Pro34del, or p.Ser30del were observed in 3 and 2 patients, with one patient harboring both mutations, consistent with convergent evolution. None of these mutations were identified in pre-therapy samples using WGS (100x) and digital PCR (0.1% sensitivity). Lentivirally transduced K562 cells were used to characterize the impact of BCMA mutations on the efficacy of various TCEs and cross resistance to CAR T. Of interest, while these mutations differentially impacted the sensitivities of TCEs based on their geometry and valency, cross resistance was not carried out to CAR T cells. As such, while p.Arg27Po, p.Ser30del, and p.Pro34del abrogated teclistamab mediated T cell killing, T cells transduced with teclistamab based scFv CAR retained cytolytic activity. Therefore, TCE resistance derived from BCMA extracellular domain mutations does not preclude retreatment with another anti-BCMA TCE or CAR T. Functionally, while BCMA extracellular domain mutations abrogated the binding of most anti-BCMA TCEs, they did not impair the binding of Fc-tagged APRIL, p65 nuclear translocation, and ERK phosphorylation. **Conclusions:** Collectively, our studies reveal that convergent evolution of MM clones harboring BCMA extracellular domain mutations selectively evade recognition by anti-BCMA TCEs while retaining the pro-survival signaling of the APRIL-BCMA-NFkB axis. Furthermore, these hotspot mutations do not equally confer resistance to all anti-BCMA TCEs or CAR Ts. Dynamic surveillance and functional evaluation of emerging mutant clones will be required to inform and guide therapy selection and sequence.

P-028

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P-029

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P-030

First results from the RedirecTT-1 study with teclistamab (tec) + talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM)

Hila Magen[1], Daniel Morillo[2], Moshe Gatt[3], Michael Sebag[4], Kihyun Kim[5], Chang-Ki Min[6], Albert Oriol[7], Enrique Ocio[8], Sung-Soo Yoon[9], María-Victoria Mateos[10], Michael Chu[11], Paula Rodríguez-Otero[12], Irit Avivi[13], Yue Guo[14], Maria Krevvata[14], Michelle Peterson[14], Melissa Beelen[14], Jill Vanak[14], Arnob Banerjee[14], Yaël Cohen[15]

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P-030

First results from the RedirecTT-1 study with teclistamab (tec) + talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM)

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Introduction: Tec is the only approved BCMA×CD3 bispecific antibody with a personalized, weight-based, and flexible dosing schedule for the treatment of triple-class exposed RRMM. Tal, a bispecific antibody targeting the novel myeloma antigen GPRC5D, has shown promising efficacy in pts with RRMM. By simultaneously targeting 2 validated myeloma target antigens, using tec + tal in combination may lead to improved outcomes by overcoming resistance mechanisms, such as antigen escape. Here, we report the first results from the phase 1b RedirecTT-1 trial (NCT04586426) in pts with RRMM. **Methods:** Enrolled pts had MM per International Myeloma Working Group 2016 criteria; were relapsed/refractory or intolerant to the last line of therapy (LOT); were exposed to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 therapy; and had measurable disease. The primary objectives are to evaluate safety and identify a recommended phase 2 regimen (RP2R) for the combination. Responses were investigator-assessed. Adverse events (AEs) were graded per CTCAE v5.0. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT criteria. **Results:** As of Dec 12, 2022, 63 pts had received tec + tal. Median (range) age was 67 years (39–81); median (range) prior LOT was 5 (1–11); 33% (15/45) had high-risk cytogenetics; 78% (49/63) were triple-class refractory; 63% (40/63) were penta-drug exposed; and 43% (27/63) had extramedullary disease (EMD; all bone independent). Median (range) duration of follow-up was 14.4 months (0.5–21.9). The most common treatment-emergent AEs were CRS (81%; grade [gr] 3, 3%, no gr 4), neutropenia (76%; gr 3/4, 75%), and anemia (60%; gr 3/4, 43%). Dose-limiting toxicities (DLTs) were reported at dose level 1 (gr 3 herpetic stomatitis) and dose level 3 (gr 3 AST/ALT elevation). 1 ICANS event was reported at dose level 3. No DLTs were reported at the RP2R. Across all dose levels, overall response rate (ORR) was 84% (52/62) among all evaluable pts and 73% (19/26) among evaluable pts with EMD; rate of complete response or better (≥CR) was 34% (21/62) and 31% (8/26), respectively. At the RP2R, ORR was 92% (12/13) among all evaluable pts and 83% (5/6) among evaluable pts with EMD; rate of ≥CR was 31% (4/13) and 33% (2/6), respectively. Median duration of response has not been reached. Updated data, with 19 additional pts at the RP2R, will be presented. **Conclusions:** In this first combination study of two bispecific antibodies in MM, targeting BCMA and GPRC5D, tec + tal at the RP2R has a manageable safety profile consistent with each of the monotherapies. A 92% ORR was observed in pts with advanced RRMM at the RP2R and an ORR of 83% was achieved in pts with EMD, a high-risk population with unmet need, supporting further evaluation of the combination. © 2023 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2023 ASCO Annual Meeting. All rights reserved.

P-031

Idecabtagene vicleucel (ide-cel) vs standard regimens in patients with triple-class–exposed (TCE) relapsed and refractory multiple myeloma (RRMM): KarMMa-3 subgroup analysis by prior lines of therapy

Salomon Manier[1], Paula Rodríguez-Otero[2], María-Victoria Mateos[3], Hermann Einsele[4], Nizar Bahlis[5], Nikhil Munshi[6], Sikander Ailawadhi[7], Bertrand Arnulf[8], Ajay Nooka[9], Ravi Vij[10], Ingerid Weum Abrahamsen[11], Annemiek Broijl[12], Sundar Jagannath[13], Reuben Benjamin[14], Usama Gergis[15], Douglas Sborov[16], Shinsuke Iida[17], Anna Truppel-Hartmann[18], Zhihong Yang[19], Rashmi Bhatnagar[20], Julia Piasecki[19], Jasper Felten[19], Andrea Caia[19], Mark Cook[21], Rachid Baz[22]

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Introduction: With use of combination therapy (Tx), patients (pts) with RRMM become TCE earlier in their disease course and represent a therapeutic challenge. In the phase 3 KarMMa 3 trial (NCT03651128), ide-cel significantly improved median progression-free survival (mPFS 13.3 vs 4.4 mo; HR 0.49; P< 0.001) and overall response rate (ORR 71% vs 42%; P< 0.001) vs standard (std) regimens in pts with TCE RRMM who received 2–4 prior lines of Tx (LoT). We assessed efficacy and safety of ide-cel vs std regimens across numbers (no.) of prior LoT (2, 3, 4, and 3 or 4) in pts with TCE RRMM in KarMMa 3. **Methods:** Pts with RRMM who received 2–4 prior LoT, were TCE (immunomodulatory agents, proteasome inhibitors, and daratumumab), and had disease refractory to the last regimen were randomized 2:1 to receive ide-cel (range 150–450 x 10^6 CAR+ T cells) or a std regimen (DPd, DVd, IRd, Kd, or EPd); stratification factors included no. of prior LoT (2 vs 3 or 4). Analysis was performed to assess the relationship between soluble BCMA (sBCMA) levels and prior LoT. **Results:** Baseline

Introduction: Tec is the only approved BCMA×CD3 bispecific antibody with a personalized, weight-based, and flexible dosing schedule for the treatment of triple-class exposed RRMM. Tal, a bispecific antibody targeting the novel myeloma antigen GPRC5D, has shown promising efficacy in pts with RRMM. By simultaneously targeting 2 validated myeloma target antigens, using tec + tal in combination may lead to improved outcomes by overcoming resistance mechanisms, such as antigen escape. Here, we report the first results from the phase 1b RedirecTT-1 trial (NCT04586426) in pts with RRMM. **Methods:** Enrolled pts had MM per International Myeloma Working Group 2016 criteria; were relapsed/refractory or intolerant to the last line of therapy (LOT); were exposed to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 therapy; and had measurable disease. The primary objectives are to evaluate safety and identify a recommended phase 2 regimen (RP2R) for the combination. Responses were investigator-assessed. Adverse events (AEs) were graded per CTCAE v5.0. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT criteria. **Results:** As of Dec 12, 2022, 63 pts had received tec + tal. Median (range) age was 67 years (39–81); median (range) prior LOT was 5 (1–11); 33% (15/45) had high-risk cytogenetics; 78% (49/63) were triple-class refractory; 63% (40/63) were penta-drug exposed; and 43% (27/63) had extramedullary disease (EMD; all bone independent). Median (range) duration of follow-up was 14.4 months (0.5–21.9). The most common treatment-emergent AEs were CRS (81%; grade [gr] 3, 3%, no gr 4), neutropenia (76%; gr 3/4, 75%), and anemia (60%; gr 3/4, 43%). Dose-limiting toxicities (DLTs) were reported at dose level 1 (gr 3 herpetic stomatitis) and dose level 3 (gr 3 AST/ALT elevation). 1 ICANS event was reported at dose level 3. No DLTs were reported at the RP2R. Across all dose levels, overall response rate (ORR) was 84% (52/62) among all evaluable pts and 73% (19/26) among evaluable pts with EMD; rate of complete response or better (≥CR) was 34% (21/62) and 31% (8/26), respectively. At the RP2R, ORR was 92% (12/13) among all evaluable pts and 83% (5/6) among evaluable pts with EMD; rate of ≥CR was 31% (4/13) and 33% (2/6), respectively. Median duration of response has not been reached. Updated data, with 19 additional pts at the RP2R, will be presented. **Conclusions:** In this first combination study of two bispecific antibodies in MM, targeting BCMA and GPRC5D, tec + tal at the RP2R has a manageable safety profile consistent with each of the monotherapies. A 92% ORR was observed in pts with advanced RRMM at the RP2R and an ORR of 83% was achieved in pts with EMD, a high-risk population with unmet need, supporting further evaluation of the combination. © 2023 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2023 ASCO Annual Meeting. All rights reserved.

P-031

Idecabtagene vicleucel (ide-cel) vs standard regimens in patients with triple-class–exposed (TCE) relapsed and refractory multiple myeloma (RRMM): KarMMa-3 subgroup analysis by prior lines of therapy

Salomon Manier[1], Paula Rodríguez-Otero[2], María-Victoria Mateos[3], Hermann Einsele[4], Nizar Bahlis[5], Nikhil Munshi[6], Sikander Ailawadhi[7], Bertrand Arnulf[8], Ajay Nooka[9], Ravi Vij[10], Ingerid Weum Abrahamsen[11], Annemiek Broijl[12], Sundar Jagannath[13], Reuben Benjamin[14], Usama Gergis[15], Douglas Sborov[16], Shinsuke Iida[17], Anna Truppel-Hartmann[18], Zhihong Yang[19], Rashmi Bhatnagar[20], Julia Piasecki[19], Jasper Felten[19], Andrea Caia[19], Mark Cook[21], Rachid Baz[22]

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characteristics and high-risk clinical features were generally balanced across prior LoT in each arm. Proportion of pts with triple-class–refractory (TCR) disease increased and median time to progression on last prior Tx decreased from 2 to 4 prior LoT (ide-cel: 50% to 88% and 9.3 to 5.1 mo, respectively), for both arms. At a median follow-up of 18.6 (range 0.4–35.4) mo, PFS improvement for ide-cel vs std regimens was consistent across prior LoT (HR 0.44–0.58). In pts with 2 and 3 or 4 prior LoT, mPFS with ide-cel was 15.1 and 12.0 mo, vs 4.8 and 4.2 mo with std regimens, respectively. The 12-mo PFS rates in the ide-cel arm were 64%, 54%, 46% in pts with 2, 3, 4 prior LoT, respectively. Ide-cel showed numerically higher ORRs (69–74% vs 35–51%) and complete response rates (34–42% vs 2–13%) vs std regimens regardless of prior LoT. Baseline sBCMA levels were similar in pts with 2 vs 3 or 4 prior LoT in both arms; at nadir, a greater proportion of pts in the ide-cel arm with 2 vs 3 or 4 prior LoT cleared sBCMA level (82% vs 68%; P=0.0238). Proportion of pts who had serious AEs was similar in subgroups by prior LoT (ide-cel 51–55%; std regimens 37–39%) vs the overall population (ide-cel 52%; std regimens 38%). Safety profile of ide-cel including cytokine release syndrome (CRS) was similar across prior LoT. Grade 5 CRS occurred in 1 pt each in the 2 and 3 prior LoT subgroups. Investigator-identified neurotoxicity was lowest in pts with 2 prior LoT (2, 7%; 3 or 4, 19%). **Conclusions:** Across prior LoT, the benefit of ide-cel vs std regimens was maintained with consistent safety profile. With increasing LoT, pts were more likely to have TCR disease and numerically poorer efficacy outcomes in both arms. Greater proportion of pts in the ide cel arm with 2 vs 3 or 4 prior LoT had clearance of tumor burden as measured by sBCMA, raising the possibility of earlier ide-cel use in TCE RRMM.

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P-032

Ide-cel versus standard regimens in patients with triple-class–exposed (TCE) relapsed and refractory multiple myeloma (RRMM): a KarMMa-3 analysis in the modified intention to-treat (mITT) population

Salomon Manier[1], Sikander Ailawadhi[2], Paula Rodríguez-Otero[3], Bertrand Arnulf[4], Krina Patel[5], Scott Solomon[6], Rachid Baz[7], Sundar Jagannath[8], Noopur Raje[9], Christoph Scheid[10], María-Victoria Mateos[11], Al-Ola Abdallah[12], Hermann Einsele[13], Sergio Giralt[14], Thomas Mueller Pabst[15], Aurore Perrot[16], Yi Lin[17], Anna Truppel-Hartmann[18], Rashmi Bhatnagar[19], Jasper Felten[20], Andrea Caia[20], Julia Piasecki[20], Mark Cook[21], Philippe Moreau[22]

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Introduction: With use of combination regimens, including immunomodulatory (IMiD®) agents, proteasome inhibitors (PI) and daratumumab, patients (pts) with RRMM become TCE earlier in their treatment (tx), which represents an unmet need. In KarMMa-3 (NCT03651128), ide-cel significantly improved median progression-free survival (mPFS 13.3 vs 4.4 mo; HR 0.49; P< 0.001) and overall response rates (ORR 71% vs 42%; P< 0.001) vs standard (std) regimens in pts with TCE RRMM (Rodriguez-Otero, NEJM 2023). Efficacy was analyzed in the KarMMa-3 intent-to-treat (ITT) population (pop). Here, we report outcomes in the mITT pop of pts who received the study tx to which they were randomly assigned. **Methods:** Pts with RRMM who received 2–4 prior lines of therapy, were TCE (IMiD agents, PI, and daratumumab), and had disease refractory to the last regimen, were randomized 2:1 to receive ide-cel or a std regimen (DPd, DVd, IRd, Kd or EPd). Efficacy (PFS and ORR) and safety were assessed in the mITT pop who received the study tx to which they were randomly assigned. **Results:** Of the 386 pts in the ITT pop, 351 received study tx and constituted the mITT pop (225 pts, ide-cel; 126 pts, std regimens); 35 randomized pts in the ITT pop did not receive ide-cel (n=29) or std regimens (n=6). Of the 29 pts who did not receive ide-cel, 5 did not undergo leukapheresis and 24 underwent leukapheresis but did not receive ide-cel due to physician decision (n=7), eligibility criteria (n=6), death (n=4), adverse events (AEs; n=4), and manufacturing failure (n=3). Six pts did not receive std regimens (consent withdrawal [n=3], physician decision [n=2], and progressive disease [PD; n=1]). In the mITT pop, baseline characteristics were generally balanced between tx arms, and comparable to the ITT pop. Among pts who did not receive ide-cel (n=29), a greater proportion had high-risk features vs the mITT pop (R-ISS stage III [38% vs 9%] and higher tumor burden [52% vs 25%]). In the mITT pop, tx with ide-cel led to longer PFS vs std regimens (mPFS [95% CI], 14.5 [12.2–17.3] vs 4.4 [3.4–5.9] mo; HR 0.43; 95% CI 0.33–0.56). ORR was higher with ide-cel vs std regimens (80% vs 44%), with higher rates of deep response (≥complete response: 44% vs 6%). In the mITT pop, grade 3/4 AEs occurred in 213/225 (95%) and 94/126 (75%) pts in the ide-cel and std regimens arms, respectively; most commonly neutropenia (80% vs 40%), anemia (51% vs 18%) and thrombocytopenia (44% vs 17%). Grade 5 AEs occurred in 12% and 6% of pts, of which 4.9% and 2.4%, respectively, were due to PD. **Conclusions:** In the mITT pop, the benefit of ide-cel over std regimens was consistent with the ITT pop; while the mPFS for std regimens remained same in both pop, the mPFS for ide-cel was longer in the mITT pop than in the ITT pop, reflecting ide-cel efficacy in infused pts.

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P-032

Ide-cel versus standard regimens in patients with triple-class–exposed (TCE) relapsed and refractory multiple myeloma (RRMM): a KarMMa-3 analysis in the modified intention to-treat (mITT) population

Salomon Manier[1], Sikander Ailawadhi[2], Paula Rodríguez-Otero[3], Bertrand Arnulf[4], Krina Patel[5], Scott Solomon[6], Rachid Baz[7], Sundar Jagannath[8], Noopur Raje[9], Christoph Scheid[10], María-Victoria Mateos[11], Al-Ola Abdallah[12], Hermann Einsele[13], Sergio Giralt[14], Thomas Mueller Pabst[15], Aurore Perrot[16], Yi Lin[17], Anna Truppel-Hartmann[18], Rashmi Bhatnagar[19], Jasper Felten[20], Andrea Caia[20], Julia Piasecki[20], Mark Cook[21], Philippe Moreau[22]

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Introduction: With use of combination regimens, including immunomodulatory (IMiD®) agents, proteasome inhibitors (PI) and daratumumab, patients (pts) with RRMM become TCE earlier in their treatment (tx), which represents an unmet need. In KarMMa-3 (NCT03651128), ide-cel significantly improved median progression-free survival (mPFS 13.3 vs 4.4 mo; HR 0.49; P< 0.001) and overall response rates (ORR 71% vs 42%; P< 0.001) vs standard (std) regimens in pts with TCE RRMM (Rodriguez-Otero, NEJM 2023). Efficacy was analyzed in the KarMMa-3 intent-to-treat (ITT) population (pop). Here, we report outcomes in the mITT pop of pts who received the study tx to which they were randomly assigned. **Methods:** Pts with RRMM who received 2–4 prior lines of therapy, were TCE (IMiD agents, PI, and daratumumab), and had disease refractory to the last regimen, were randomized 2:1 to receive ide-cel or a std regimen (DPd, DVd, IRd, Kd or EPd). Efficacy (PFS and ORR) and safety were assessed in the mITT pop who received the study tx to which they were randomly assigned. **Results:** Of the 386 pts in the ITT pop, 351 received study tx and constituted the mITT pop (225 pts, ide-cel; 126 pts, std regimens); 35 randomized pts in the ITT pop did not receive ide-cel (n=29) or std regimens (n=6). Of the 29 pts who did not receive ide-cel, 5 did not undergo leukapheresis and 24 underwent leukapheresis but did not receive ide-cel due to physician decision (n=7), eligibility criteria (n=6), death (n=4), adverse events (AEs; n=4), and manufacturing failure (n=3). Six pts did not receive std regimens (consent withdrawal [n=3], physician decision [n=2], and progressive disease [PD; n=1]). In the mITT pop, baseline characteristics were generally balanced between tx arms, and comparable to the ITT pop. Among pts who did not receive ide-cel (n=29), a greater proportion had high-risk features vs the mITT pop (R-ISS stage III [38% vs 9%] and higher tumor burden [52% vs 25%]). In the mITT pop, tx with ide-cel led to longer PFS vs std regimens (mPFS [95% CI], 14.5 [12.2–17.3] vs 4.4 [3.4–5.9] mo; HR 0.43; 95% CI 0.33–0.56). ORR was higher with ide-cel vs std regimens (80% vs 44%), with higher rates of deep response (≥complete response: 44% vs 6%). In the mITT pop, grade 3/4 AEs occurred in 213/225 (95%) and 94/126 (75%) pts in the ide-cel and std regimens arms, respectively; most commonly neutropenia (80% vs 40%), anemia (51% vs 18%) and thrombocytopenia (44% vs 17%). Grade 5 AEs occurred in 12% and 6% of pts, of which 4.9% and 2.4%, respectively, were due to PD. **Conclusions:** In the mITT pop, the benefit of ide-cel over std regimens was consistent with the ITT pop; while the mPFS for std regimens remained same in both pop, the mPFS for ide-cel was longer in the mITT pop than in the ITT pop, reflecting ide-cel efficacy in infused pts.

P-033

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Introduction: Teclistamab (TEC) is a bispecific BCMA-CD3 directed T-cell antibody (BsAb), which received EMA approval on 8/24/22 and subsequent FDA approval on 10/25/22, based on the MajesTEC-1 study showing high single agent response rates (≥PR in 63.0%) in heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM). Also reported were unique side effects including, cytokine release syndrome (CRS) and neurotoxicity (ICANS), and prompting the FDA/EMA to recommend inpatient monitoring during the initial step-up and first full-dose of TEC. In addition, a high incidence of infections (76.4%; ≥grade 3: 44.8%) have been reported. Thus, the IMF Immunotherapy subgroup embarked on this international analysis of real-word use of Teclistamab in RRMM. **Methods:** Patients treated with Teclistamab at 6 academic centers from 3 countries (US, Greece, Spain), were included. Data was collected up until May 23, 2023. **Results:** 77 patients were included in this analysis; median age was 69 (range 38-91y); 16 pts. (21%) were >75 yrs; 53% male, 68% Caucasian, 15% Hispanic, and 14% Asian. Pts received a median of 6 PLT (range 1-21); 75% were triple-class-refractory (n=44/59), 23% had high-risk cyto/fish and 32% had 1q21 gain. At least 59% of pts would not have been eligible for MajesTEC-1 (51% prior BCMA (n=26 BCMA-CAR, n=8 BCMA-ADC; n=2 BCMA-bisp; n=3 Car+ADC); 13% had CrCl < 30ml/min with 2 on HD). Median number of hospital days was 7 but 26 patients were treated entirely as outpatients (Mayo clinic Rochester and Arizona). CRS was seen in 52% (all grade 1: except 1Gr2, 1Gr4); it generally resolved within 24 hours and was managed with either 1 dose of tocilizumab or 1-4 doses of dex. CRS was more common in patients treated in the inpatient versus outpatient (CRS 64% vs. 35%) setting. CrCl < 30 mls, did not appear to alter the incidence or severity of CRS (55%; all Gr1). ICANS was infrequent (n=5; 7%, 1 pt with Gr 4-Sz requiring HD-steroids and treatment discontinuation). Infections were common, seen in 37% of patients, and the majority of infections were reported as viral URI or CMV reactivation. No CMV organ disease and no Covid deaths occurred. The overall response rate for evaluable patients (n=56) was 61%; (sCR/CR 7; VGPR 19; PR 8; SD 11; PD 11). In pts treated with prior BCMA (n=32) the ORR was 59% (sCR 1; VGPR 14; PR 4; SD 6; PD 7). The most common reason for treatment discontinuation was PD (12%). **Conclusions:** In this Real-World evaluation of Teclistamab, a high ORR was seen 61%, similar to the results of the MajesTEC-1 study. Responses were rapid and are expected to deepen over time (median f/u only 3m). CRS rates were similar to MajesTEC-1 and no unexpected toxicity was noted. Infection rates were low but may increase with longer follow-up. Details regarding the timing and types of infection and the global use of IVIG will be presented. Additional patient data will be presented at the IMS meeting from global IMWG centers.

P-034

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Introduction: ALNUC, a 2+1 T-cell engager (TCE) with bivalent binding to BCMA, demonstrated clinical activity in RRMM in a phase 1 study (NCT03486067). IV ALNUC had a long duration of response (DOR) but resulted in cytokine release syndrome (CRS) in 76% of pts. Subcutaneous (SC) dosing reduced

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CRS rate and severity, allowing higher target doses with promising antitumor activity. We present long-term data from IV pts and safety and efficacy in SC pts treated in the phase 1 study. **Methods:** Pts had ≥3 prior lines of therapy (LOTs), including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 therapy. IV ALNUC was given at target doses of 0.15–10 mg with both fixed and step-up dosing (Costa LJ et al. Blood 2019). SC ALNUC was given on D 1, 4, 8, 15, and 22 of cycle 1 (C1), QW in C2–3, Q2W in C4–6, and Q4W in C7+ (28-d cycles). Step-up doses were given on C1D1 (3 mg) and C1D4 (6 mg), and target doses (≥10 mg) on C1D8 and thereafter. Safety and tolerability were primary objectives. Data cutoff was Nov 9 2022. **Results:** In total, 70 pts received IV ALNUC. Overall response rate (ORR) was 39% (27/70); median DOR was 33.6 mo (95% CI, 10.6–NA). Median PFS was 3.1 mo (95% CI, 1.9–5.5). CRS was reported in 53 (76%) pts, with grade (G) ≥3 in 5 (7%) pts. Of 73 pts treated with SC ALNUC in dose escalation (target dose: 10 mg, 6; 15 mg, 4; 30 mg, 6; 60 mg, 7) and dose expansion (target dose: 10 mg, 19; 30 mg, 21; 60 mg, 10), median age was 64 y; 42% were female. Pts had a median of 4 prior regimens; 93% were refractory to last LOT, 100%/63% had triple-class exposed/refractory MM; 66%/26% had penta-drug exposed/refractory MM. Median follow-up was 4.3 mo (range, 0.5–16.0); 39 (53%) pts were on treatment at data cutoff. Any-G/G3–4 treatment-emergent adverse events occurred in 99%/79% of SC pts; most common were CRS (56%/0%), neutropenia (49%/42%), infections (47%/10%), anemia (41%/25%), and thrombocytopenia (33%/14%). SC pts had CRS limited to G1 (44%) or G2 (12%); 35 pts received ≥1 concomitant medication for CRS, including tocilizumab (30%) and/or corticosteroids (15%). Median time to CRS was 3 d (range, 1–20); median duration was 2 d (range, 1–11). SC ALNUC bioavailability was ~61%; t½ was 15 d. Trough concentrations at the 30-mg target dose exceeded levels predicted for efficacy by C2D1. In 55 efficacy-evaluable pts receiving SC ALNUC, ORR was 53% across all doses and 65% at the 30-mg target dose; 20/29 responders were minimal residual disease (MRD)-evaluable, of whom 16 (80%) were MRD-negative (10e-5 sensitivity) at C2D1 or C4D1. Median time to response was 1.0 mo (95% CI, 0.7–1.3); 25 responses (86%) were ongoing. **Conclusions:** IV ALNUC led to durable responses in heavily pretreated pts with RRMM. SC ALNUC had an improved safety profile vs IV ALNUC, with CRS limited to low-grade, short-lived events. SC ALNUC showed promising dose-dependent antitumor activity and a high proportion of responders were MRD-negative. The phase 1 study is ongoing. Presented at EHA 2023. Wong SW et al. Abstract P883.

P-035

Real world experience of patients treated with teclistamab: a BCMA-directed bispecific T-cell engaging therapy for multiple myeloma

Shonali Midha[1], Houry Leblebjian[1], Jacob Laubach[1], Clifton Mo[1], Adam Sperling[1], Omar Nadeem[1], Giada Bianchi[2], Monique Hartley-Brown[1], Linda Ramsdell[1], Kristen Donadio[1], Emerald Chun[1], Megan Belanger[1], Irina Dobrusin[1], Irene Ghobrial[1], Paul Richardson[1], Kenneth Anderson[3], Nikhil Munshi[4]

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Introduction: Teclistamab is a bispecific t-cell engaging (BiTE) therapy that was approved by the US FDA in October 2022 for treatment of relapsed and refractory multiple myeloma (RRMM) in patients who have received ≥ 4 lines of therapy. We report our initial experience with commercial teclistamab use at the Dana-Farber Cancer Institute/Brigham and Women's Hospital. **Methods:** Patients treated with teclistamab until April 15, 2023 were included in the analysis. Data was collected for baseline demographics, prior therapies, efficacy including response rates (ORR), and safety variables such as rates of cytokine release syndrome (CRS), neurological toxicity (NT), cytopenias and infectious complications. **Results:** 34 patients were treated with teclistamab from December 15, 2022 to April 15, 2023. The median age was 65 (range 51-83), with 10 females (29%) and 24 males (71%). Median prior lines of therapy was 6 (range 4-12) with 55% of patients having had a prior stem cell transplant. Seven patients (21%) had received prior BCMA-directed CAR-T therapy and 10 (29%) had received prior BCMA-targeting antibody-drug conjugate therapy. Twenty-one patients (62%) had at least one high-risk (HR) cytogenetic risk factor among del 17p, t(4;14), t(14;16) or 1q21 gain or amplification with breakdown as follows: 1 HR factor: 11 (32%), 2 HR factors: 9 (26%), 3 HR factors: 1 (3%). Eight patients (24%) had a creatinine clearance < 40 ml/min. Thirteen patients (38%) treated had extramedullary disease (EMD) and 5 (15%) had CNS involvement. Hematologic toxicity included anemia (n=34, 100%, grade ≥3; 62%), neutropenia (n=24, 71%, grade ≥3; 47%), and thrombocytopenia (n=31, 91%, grade ≥3; 53%) with most present prior to treatment. CRS was reported in 19 patients (56%), 12 with grade 1 (35%), 7 with grade 2 (21%) and none with grade 3 or higher. Tocilizumab was used in 8 patients (24%) and dexamethasone was used in 4 patients (12%). Grade 1 neurotoxicity was assessed in 1 patient (3%), which did not require treatment. Eleven (32%) infectious complications were observed with 3 (9%) patients presenting with grade 3 or greater infections requiring hospitalization or urgent intervention, all non-fatal. At a median follow-up of 6 weeks, ORR is 44%, with 3 patients (9%) achieving a complete response (CR), and 10 (29%) achieving VGPR or greater. Thirteen patients have had disease progression or died at the time of data cut-off (38%). The ORRs of those with renal dysfunction (CrCl < 40 ml/min), EMD or ≥1 HR cytogenetic risk factor is 25%, 23% and 48%, respectively. ORR in patients with prior BCMA-targeted therapy exposure is 27%. **Conclusions:** Overall, we observed that teclistamab treatment in a commercial setting generated comparable responses to the previously reported clinical trials without any new toxicity signals. While additional follow up with commercial Teclistamab use in the real-world is needed to validate these results, this study reveals the need for efficacious therapies in high-risk or ultra-high-risk disease.

CRS rate and severity, allowing higher target doses with promising antitumor activity. We present long-term data from IV pts and safety and efficacy in SC pts treated in the phase 1 study. **Methods:** Pts had ≥3 prior lines of therapy (LOTs), including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 therapy. IV ALNUC was given at target doses of 0.15–10 mg with both fixed and step-up dosing (Costa LJ et al. Blood 2019). SC ALNUC was given on D 1, 4, 8, 15, and 22 of cycle 1 (C1), QW in C2–3, Q2W in C4–6, and Q4W in C7+ (28-d cycles). Step-up doses were given on C1D1 (3 mg) and C1D4 (6 mg), and target doses (≥10 mg) on C1D8 and thereafter. Safety and tolerability were primary objectives. Data cutoff was Nov 9 2022. **Results:** In total, 70 pts received IV ALNUC. Overall response rate (ORR) was 39% (27/70); median DOR was 33.6 mo (95% CI, 10.6–NA). Median PFS was 3.1 mo (95% CI, 1.9–5.5). CRS was reported in 53 (76%) pts, with grade (G) ≥3 in 5 (7%) pts. Of 73 pts treated with SC ALNUC in dose escalation (target dose: 10 mg, 6; 15 mg, 4; 30 mg, 6; 60 mg, 7) and dose expansion (target dose: 10 mg, 19; 30 mg, 21; 60 mg, 10), median age was 64 y; 42% were female. Pts had a median of 4 prior regimens; 93% were refractory to last LOT, 100%/63% had triple-class exposed/refractory MM; 66%/26% had penta-drug exposed/refractory MM. Median follow-up was 4.3 mo (range, 0.5–16.0); 39 (53%) pts were on treatment at data cutoff. Any-G/G3–4 treatment-emergent adverse events occurred in 99%/79% of SC pts; most common were CRS (56%/0%), neutropenia (49%/42%), infections (47%/10%), anemia (41%/25%), and thrombocytopenia (33%/14%). SC pts had CRS limited to G1 (44%) or G2 (12%); 35 pts received ≥1 concomitant medication for CRS, including tocilizumab (30%) and/or corticosteroids (15%). Median time to CRS was 3 d (range, 1–20); median duration was 2 d (range, 1–11). SC ALNUC bioavailability was ~61%; t½ was 15 d. Trough concentrations at the 30-mg target dose exceeded levels predicted for efficacy by C2D1. In 55 efficacy-evaluable pts receiving SC ALNUC, ORR was 53% across all doses and 65% at the 30-mg target dose; 20/29 responders were minimal residual disease (MRD)-evaluable, of whom 16 (80%) were MRD-negative (10e-5 sensitivity) at C2D1 or C4D1. Median time to response was 1.0 mo (95% CI, 0.7–1.3); 25 responses (86%) were ongoing. **Conclusions:** IV ALNUC led to durable responses in heavily pretreated pts with RRMM. SC ALNUC had an improved safety profile vs IV ALNUC, with CRS limited to low-grade, short-lived events. SC ALNUC showed promising dose-dependent antitumor activity and a high proportion of responders were MRD-negative. The phase 1 study is ongoing. Presented at EHA 2023. Wong SW et al. Abstract P883.

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Real world experience of patients treated with teclistamab: a BCMA-directed bispecific T-cell engaging therapy for multiple myeloma

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Introduction: Teclistamab is a bispecific t-cell engaging (BiTE) therapy that was approved by the US FDA in October 2022 for treatment of relapsed and refractory multiple myeloma (RRMM) in patients who have received ≥ 4 lines of therapy. We report our initial experience with commercial teclistamab use at the Dana-Farber Cancer Institute/Brigham and Women's Hospital. **Methods:** Patients treated with teclistamab until April 15, 2023 were included in the analysis. Data was collected for baseline demographics, prior therapies, efficacy including response rates (ORR), and safety variables such as rates of cytokine release syndrome (CRS), neurological toxicity (NT), cytopenias and infectious complications. **Results:** 34 patients were treated with teclistamab from December 15, 2022 to April 15, 2023. The median age was 65 (range 51-83), with 10 females (29%) and 24 males (71%). Median prior lines of therapy was 6 (range 4-12) with 55% of patients having had a prior stem cell transplant. Seven patients (21%) had received prior BCMA-directed CAR-T therapy and 10 (29%) had received prior BCMA-targeting antibody-drug conjugate therapy. Twenty-one patients (62%) had at least one high-risk (HR) cytogenetic risk factor among del 17p, t(4;14), t(14;16) or 1q21 gain or amplification with breakdown as follows: 1 HR factor: 11 (32%), 2 HR factors: 9 (26%), 3 HR factors: 1 (3%). Eight patients (24%) had a creatinine clearance < 40 ml/min. Thirteen patients (38%) treated had extramedullary disease (EMD) and 5 (15%) had CNS involvement. Hematologic toxicity included anemia (n=34, 100%, grade ≥3; 62%), neutropenia (n=24, 71%, grade ≥3; 47%), and thrombocytopenia (n=31, 91%, grade ≥3; 53%) with most present prior to treatment. CRS was reported in 19 patients (56%), 12 with grade 1 (35%), 7 with grade 2 (21%) and none with grade 3 or higher. Tocilizumab was used in 8 patients (24%) and dexamethasone was used in 4 patients (12%). Grade 1 neurotoxicity was assessed in 1 patient (3%), which did not require treatment. Eleven (32%) infectious complications were observed with 3 (9%) patients presenting with grade 3 or greater infections requiring hospitalization or urgent intervention, all non-fatal. At a median follow-up of 6 weeks, ORR is 44%, with 3 patients (9%) achieving a complete response (CR), and 10 (29%) achieving VGPR or greater. Thirteen patients have had disease progression or died at the time of data cut-off (38%). The ORRs of those with renal dysfunction (CrCl < 40 ml/min), EMD or ≥1 HR cytogenetic risk factor is 25%, 23% and 48%, respectively. ORR in patients with prior BCMA-targeted therapy exposure is 27%. **Conclusions:** Overall, we observed that teclistamab treatment in a commercial setting generated comparable responses to the previously reported clinical trials without any new toxicity signals. While additional follow up with commercial Teclistamab use in the real-world is needed to validate these results, this study reveals the need for efficacious therapies in high-risk or ultra-high-risk disease.

P-036

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Introduction: Anti-BCMA CAR T-cell therapy is approved for relapsed and refractory multiple myeloma (RRMM) with two available products (idecabtagene vicleucel, ide-cel and ciltacabtagene autoleucel, cilta-cel). Data regarding long-term toxicities in a real-world population is lacking. We report long-term toxicities in patients treated with ide-cel or cilta-cel at Dana-Farber Cancer Institute/Brigham and Women's Hospital. **Methods:** Patients who received an anti-BCMA CAR T-cell infusion for RRMM between 8/9/2021 – 2/22/23 were retrospectively analyzed. Toxicities were divided into early (90d). **Results:** Fifty-four patients, median age 66 yrs. (34-79) received cilta-cel (n = 7, 13%) or ide-cel (n = 47, 87%) and were followed for median 158 days (range 29-395). Median number of prior regimens was 8 (3-15). A total of 13 patients (24%) received prior belantamab mafodotin (blmf). Bridging therapy was used in 41 (76%) patients with most receiving alkylator therapy and 4 on continued blmf. Cytokine release syndrome (CRS) was reported in 76% of patients (G1: n=30, 56%; G2: n=11, 20%) and neurotoxicity in 4 patients (G1: n=2, 7%; G2: n=2, 4%; grade 2: n=2, 4%,). Any-grade cytopenias included: anemia (n=51, 94%), thrombocytopenia (n=45, 83%) and neutropenia (n=45, 83%). Grade ≥3 (high-grade) early cytopenias included neutropenia (n=14, 26%; G3: 19%, G4: 7%) thrombocytopenia (n=13, 24%; G3: 13%, G4: 11%) and anemia (G3: n=1, 2%). High-grade late cytopenias included thrombocytopenia (n=14, 26%; G3: 19%, G4: 7%), neutropenia (n=13, 24%; G3: 13%, G4: 11%) and anemia (G3: n=3, 6%). High-grade prolonged cytopenias included neutropenia (G3: n=6, 11%), thrombocytopenia (n=6, 11%; G3: 7%, G4: 4%), and anemia (G3: n=2, 4%). Ten patients (19%) had one or more prolonged high-grade cytopenias; the median age of patients who recovered counts was 60 (n=5, 50%) versus 74 for those who did not (n=5, 50%). Supportive care for all 10 patients included: IVIg (50%), G-CSF (40%), darbepoeitin alfa (40%), and romiplostim (30%). Eleven patients (20%), median age 68 yrs. (51-75) developed nonfatal infections, with 5 requiring hospitalization. Most common infections involved the respiratory tract (n=9, 17%); 5 patients with COVID-19 and 4 with pneumonia. A total of 41 patients (76%) had hypogammaglobulinemia (< 600 mg/dL), including 9 of the 11 patients (82%) with infections. No treatment related deaths or myeloid neoplasms were observed. Overall response rate was 85% (n=46) with 65% (n=35) achieving a very good partial response or better, including 26% (n=14) with a complete response. A total of 25 patients (46%) had either progressive disease or started new therapy at data cutoff with 12 deaths due to progression. **Conclusions:** This analysis reports less frequent high-grade cytopenias as compared to previous clinical trial data. Number of prior therapies, bridging regimens, and CRS were not found to be predictive of prolonged toxicity.

P-037

BMS-986393 (CC-95266), a G protein-coupled receptor class C group 5 member D (GPRC5D)-targeted CAR T-cell therapy for relapsed/refractory multiple myeloma (RRMM): results from a phase 1 study

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Introduction: Chimeric antigen receptor (CAR) T-cell therapies targeting B cell maturation antigen (BCMA) have shown deep response in RRMM but new targets are needed as most patients (pts) relapse. GPRC5D, an orphan receptor expressed on MM cells with limited expression in other tissues, is a promising therapeutic target for MM. We present safety and efficacy from the Part A dose escalation of CC-95266-MM-001 (NCT04674813), a phase 1, first-in-human, multicenter open-label study of BMS-986393 (CC-95266), a GPRC5D-targeted autologous CAR T-cell therapy, in pts with RRMM. **Methods:** Part A included pts with ≥3 prior lines of therapy, with prior BCMA-directed and CAR T-cell therapies allowed. After leukapheresis and lymphodepletion, pts had a single infusion of BMS-986393. Safety, maximum tolerated dose (MTD), and/or recommended phase 2 dose were primary objectives. **Results:** As of 7 Sept 2022, 33/40 enrolled pts received BMS-986393 at doses of 25, 75, 150, 300, and 450 × 10^6 CAR T cells. Of these, 48% had high-risk cytogenetics and 45% had extramedullary plasmacytomas. Eighteen (55%) pts had received prior BCMA-targeted therapies, including BCMA-directed CAR T-cell therapy (13 pts); 24% had penta-refractory MM. Grade (G) 3/4 treatment-emergent adverse events (TEAEs) occurred in 24/33 (73%) pts; most frequently

P-036

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neutropenia (61%), anemia (21%) and thrombocytopenia (21%). On-target off-tumor TEAEs, all G1, included skin TEAEs (30%), dysgeusia (15%), nail TEAEs (9%) and dysphagia (3%). Dose-limiting toxicities of prolonged (out to day 42) G4 neutropenia and/or thrombocytopenia occurred in 2 pts; MTD was not exceeded. Cytokine release syndrome (CRS) occurred in 21/33 pts (19 G1/2; 2 G3). Immune effector cell-associated neurotoxicity syndrome (ICANS)–type neurotoxicity occurred in 2 pts and was low-grade and reversible with steroid treatment. Overall response rate was 89% (17/19) in efficacy-evaluable pts, including 7/9 pts with prior BCMA-directed therapies including CAR T cells. Median follow-up for treated pts was 3.1 mo (range, 0.1–15.5). At data cutoff, 15/17 pts with a response were ongoing. All 4 pts with available minimal residual disease (MRD) data and best overall response of complete response (CR) were MRD-negative (10^{-5} depth) at 3 mo. BMS-986393 reduced soluble BCMA levels across all dose levels; BMS-986393 exposure showed dose-dependence. **Conclusions:** As of data cutoff, dose escalation of BMS-986393 from 25–450 × 10^6 CAR T cells did not exceed MTD. CRS was mostly G1/2. ICANS-type neurotoxicity was infrequent, low-grade and reversible. A minority of pts had on-target off-tumor TEAEs, all G1. BMS-986393 showed durable responses and efficacy at all tested dose levels, including MRD-negative CRs and in pts previously exposed to BCMA-directed therapies. These preliminary data support GPRC5D-directed CAR T-cell therapy with BMS-986393 for treating RRMM, irrespective of prior BCMA-directed therapy. Part B dose expansion is underway. Updated data will be reported. Presented at EHA 2023. Abst S193.

P-038

Impact of absolute lymphocyte count at pre-apheresis and pre-lymphodepletion on chimeric antigen receptor (CAR)-T therapy outcomes in relapsed refractory multiple myeloma (RRMM)

Noriko Nishimura[1], Jessica Flynn[2], Bruno Costa[3], Sean Devlin[2], Tasmin Farzana[1], Karthik Nath[1], David Chung[4], Heather Landau[4], Oscar Lahoud[2], Michael Scordo[2], Gunjan Shah[2], Hani Hassoun[5], Kylee Maclachlan[5], Malin Hultcrantz[5], Neha Korde[5], Alexander Lesokhin[2], Urvi Shah[5], Carlyn Rose Tan[2], Sergio Giralt[2], Saad Usmani[2], Sham Mailankody[5]

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Introduction: CAR-T cell therapy has been approved for patients with RRMM and 4 or more prior lines of therapy. Due to multiple prior treatments, some patients have a low absolute lymphocyte count (ALC) and data on the prognostic impact of pre-therapy ALC is conflicting. This real-world analysis investigated pre-apheresis (A) and pre-lymphodepletion (LD) ALC, and the ALC reduction between A and LD, on survival outcomes post CAR-T for RRMM. **Methods:** This was a single center, retrospective analysis of 88 patients with RRMM who received CAR-T cell therapy between March 2017 and December 2022. Both commercial (n=22) (BCMA-directed), and investigational (n=66) (BCMA- or GPRC5D-directed) CAR-T were included. We assessed the impact of Pre-A and Pre-LD ALC as well as the reduction in ALC (measured as the difference between pre-LD and pre-A ALC) on the progression-free survival (PFS) and overall survival (OS) using the Cox proportional hazard models. **Results:** The median age was 60 years (range, 37–79), of whom 52% were male. The median number of prior lines of therapy was 7 (range: 2–20). Extramedullary disease (EMD) was present in 51%, and 52% of patients received bridging therapy. The median pre-A and pre-LD ALC was 0.7×10^9/L (range, 0.1–3.4) and 0.7×10^9/L (range, 0.1–3.1), respectively. The median absolute reduction in ALC was 0.0 (range, -2.7 to 2.3). Using the lowest quartiles, low pre-A ALC and low pre-LD ALC were defined as ≤ 0.5×109/L and ≤ $0.4x10^9$/L, respectively. A high reduction was set ≥ 0.27×10^9/L, as described in a prior study. The median follow-up duration post CAR-T infusion was 24 months. There was no significant difference in PFS with either a low vs. high pre-A ALC (HR 1.52, 95% CI 0.92–2.50, p=0.11), low vs. high pre-LD ALC (HR 1.57, 95%CI 0.93–2.68, p=0.10), or a high absolute reduction in ALC between these timepoints (HR 1.39, 95%CI 0.82–2.36, p=0.24). On multivariate analysis, only EMD, high-risk cytogenetics, and ECOG-score of 1/2 were independently associated with a significantly inferior PFS. Regarding OS, on univariate analysis, low pre-LD ALC was significantly associated with a shorter OS (median OS, 13 vs. 29 months, HR 0.47, 95% CI 0.24–0.92, p=0.032), as was presence of EMD, double refractory status, and Revised-International Staging System (R-ISS) of 2/3. Low pre-A ALC and a high absolute reduction in ALC between A and LD (≥0.27) had no significant impact on OS. On multivariate analysis, only EMD was associated with a significantly shorter OS (HR 4.17, 95% CI 1.96–8.87, p< 0.001). **Conclusions:** On multivariate analysis, the pre-A, -pre-LD, and the absolute reduction in ALC prior to CAR-T administration had no significant impact on either PFS or OS. Inferior survival outcomes post-CAR-T appear to be driven by previously recognized factors like the presence of EMD, high-risk cytogenetics, and reduced baseline performance status. Of note, all patients had an ALC > $0.1x10^9$/L and the impact of pre-treatment ALC below this level cannot be assessed from this analysis.

P-039

Vitamin D deficiency and clinical outcomes with chimeric antigen receptor T-cell therapy in relapsed/refractory multiple myeloma

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Introduction: CAR-T cell therapy has been approved for patients with RRMM and 4 or more prior lines of therapy. Due to multiple prior treatments, some patients have a low absolute lymphocyte count (ALC) and data on the prognostic impact of pre-therapy ALC is conflicting. This real-world analysis investigated pre-apheresis (A) and pre-lymphodepletion (LD) ALC, and the ALC reduction between A and LD, on survival outcomes post CAR-T for RRMM. **Methods:** This was a single center, retrospective analysis of 88 patients with RRMM who received CAR-T cell therapy between March 2017 and December 2022. Both commercial (n=22) (BCMA-directed), and investigational (n=66) (BCMA- or GPRC5D-directed) CAR-T were included. We assessed the impact of Pre-A and Pre-LD ALC as well as the reduction in ALC (measured as the difference between pre-LD and pre-A ALC) on the progression-free survival (PFS) and overall survival (OS) using the Cox proportional hazard models. **Results:** The median age was 60 years (range, 37–79), of whom 52% were male. The median number of prior lines of therapy was 7 (range: 2–20). Extramedullary disease (EMD) was present in 51%, and 52% of patients received bridging therapy. The median pre-A and pre-LD ALC was 0.7×10^9/L (range, 0.1–3.4) and 0.7×10^9/L (range, 0.1–3.1), respectively. The median absolute reduction in ALC was 0.0 (range, -2.7 to 2.3). Using the lowest quartiles, low pre-A ALC and low pre-LD ALC were defined as ≤ 0.5×109/L and ≤ $0.4x10^9$/L, respectively. A high reduction was set ≥ 0.27×10^9/L, as described in a prior study. The median follow-up duration post CAR-T infusion was 24 months. There was no significant difference in PFS with either a low vs. high pre-A ALC (HR 1.52, 95% CI 0.92–2.50, p=0.11), low vs. high pre-LD ALC (HR 1.57, 95%CI 0.93–2.68, p=0.10), or a high absolute reduction in ALC between these timepoints (HR 1.39, 95%CI 0.82–2.36, p=0.24). On multivariate analysis, only EMD, high-risk cytogenetics, and ECOG-score of 1/2 were independently associated with a significantly inferior PFS. Regarding OS, on univariate analysis, low pre-LD ALC was significantly associated with a shorter OS (median OS, 13 vs. 29 months, HR 0.47, 95% CI 0.24–0.92, p=0.032), as was presence of EMD, double refractory status, and Revised-International Staging System (R-ISS) of 2/3. Low pre-A ALC and a high absolute reduction in ALC between A and LD (≥0.27) had no significant impact on OS. On multivariate analysis, only EMD was associated with a significantly shorter OS (HR 4.17, 95% CI 1.96–8.87, p< 0.001). **Conclusions:** On multivariate analysis, the pre-A, -pre-LD, and the absolute reduction in ALC prior to CAR-T administration had no significant impact on either PFS or OS. Inferior survival outcomes post-CAR-T appear to be driven by previously recognized factors like the presence of EMD, high-risk cytogenetics, and reduced baseline performance status. Of note, all patients had an ALC > $0.1x10^9$/L and the impact of pre-treatment ALC below this level cannot be assessed from this analysis.

P-039

Vitamin D deficiency and clinical outcomes with chimeric antigen receptor T-cell therapy in relapsed/refractory multiple myeloma

Noriko Nishimura[1], Jessica Flynn[2], Bruno Costa[3], Sean Devlin[2], Tasmin Farzana[1], David Chung[4], Heather Landau[4], Oscar Lahoud[2], Michael Scordo[2], Gunjan Shah[2], Hani Hassoun[5], Kylee Maclachlan[5], Malin Hultcrantz[5], Neha Korde[5], Alexander Lesokhin[2], Urvi Shah[5], Carlyn Rose Tan[2], Sergio Giralt[2], Saad Usmani[2], Sham Mailankody[5], Karthik Nath[1]

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neutropenia (61%), anemia (21%) and thrombocytopenia (21%). On-target off-tumor TEAEs, all G1, included skin TEAEs (30%), dysgeusia (15%), nail TEAEs (9%) and dysphagia (3%). Dose-limiting toxicities of prolonged (out to day 42) G4 neutropenia and/or thrombocytopenia occurred in 2 pts; MTD was not exceeded. Cytokine release syndrome (CRS) occurred in 21/33 pts (19 G1/2; 2 G3). Immune effector cell-associated neurotoxicity syndrome (ICANS)–type neurotoxicity occurred in 2 pts and was low-grade and reversible with steroid treatment. Overall response rate was 89% (17/19) in efficacy-evaluable pts, including 7/9 pts with prior BCMA-directed therapies including CAR T cells. Median follow-up for treated pts was 3.1 mo (range, 0.1–15.5). At data cutoff, 15/17 pts with a response were ongoing. All 4 pts with available minimal residual disease (MRD) data and best overall response of complete response (CR) were MRD-negative (10^{-5} depth) at 3 mo. BMS-986393 reduced soluble BCMA levels across all dose levels; BMS-986393 exposure showed dose-dependence. **Conclusions:** As of data cutoff, dose escalation of BMS-986393 from 25–450 × 10^6 CAR T cells did not exceed MTD. CRS was mostly G1/2. ICANS-type neurotoxicity was infrequent, low-grade and reversible. A minority of pts had on-target off-tumor TEAEs, all G1. BMS-986393 showed durable responses and efficacy at all tested dose levels, including MRD-negative CRs and in pts previously exposed to BCMA-directed therapies. These preliminary data support GPRC5D-directed CAR T-cell therapy with BMS-986393 for treating RRMM, irrespective of prior BCMA-directed therapy. Part B dose expansion is underway. Updated data will be reported. Presented at EHA 2023. Abst S193.

P-038

Impact of absolute lymphocyte count at pre-apheresis and pre-lymphodepletion on chimeric antigen receptor (CAR)-T therapy outcomes in relapsed refractory multiple myeloma (RRMM)

Noriko Nishimura[1], Jessica Flynn[2], Bruno Costa[3], Sean Devlin[2], Tasmin Farzana[1], Karthik Nath[1], David Chung[4], Heather Landau[4], Oscar Lahoud[2], Michael Scordo[2], Gunjan Shah[2], Hani Hassoun[5], Kylee Maclachlan[5], Malin Hultcrantz[5], Neha Korde[5], Alexander Lesokhin[2], Urvi Shah[5], Carlyn Rose Tan[2], Sergio Giralt[2], Saad Usmani[2], Sham Mailankody[5]

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Introduction: CAR-T cell therapy has been approved for patients with RRMM and 4 or more prior lines of therapy. Due to multiple prior treatments, some patients have a low absolute lymphocyte count (ALC) and data on the prognostic impact of pre-therapy ALC is conflicting. This real-world analysis investigated pre-apheresis (A) and pre-lymphodepletion (LD) ALC, and the ALC reduction between A and LD, on survival outcomes post CAR-T for RRMM. **Methods:** This was a single center, retrospective analysis of 88 patients with RRMM who received CAR-T cell therapy between March 2017 and December 2022. Both commercial (n=22) (BCMA-directed), and investigational (n=66) (BCMA- or GPRC5D-directed) CAR-T were included. We assessed the impact of Pre-A and Pre-LD ALC as well as the reduction in ALC (measured as the difference between pre-LD and pre-A ALC) on the progression-free survival (PFS) and overall survival (OS) using the Cox proportional hazard models. **Results:** The median age was 60 years (range, 37–79), of whom 52% were male. The median number of prior lines of therapy was 7 (range: 2–20). Extramedullary disease (EMD) was present in 51%, and 52% of patients received bridging therapy. The median pre-A and pre-LD ALC was 0.7×10^9/L (range, 0.1–3.4) and 0.7×10^9/L (range, 0.1–3.1), respectively. The median absolute reduction in ALC was 0.0 (range, -2.7 to 2.3). Using the lowest quartiles, low pre-A ALC and low pre-LD ALC were defined as ≤ 0.5×109/L and ≤ $0.4x10^9$/L, respectively. A high reduction was set ≥ 0.27×10^9/L, as described in a prior study. The median follow-up duration post CAR-T infusion was 24 months. There was no significant difference in PFS with either a low vs. high pre-A ALC (HR 1.52, 95% CI 0.92–2.50, p=0.11), low vs. high pre-LD ALC (HR 1.57, 95%CI 0.93–2.68, p=0.10), or a high absolute reduction in ALC between these timepoints (HR 1.39, 95%CI 0.82–2.36, p=0.24). On multivariate analysis, only EMD, high-risk cytogenetics, and ECOG-score of 1/2 were independently associated with a significantly inferior PFS. Regarding OS, on univariate analysis, low pre-LD ALC was significantly associated with a shorter OS (median OS, 13 vs. 29 months, HR 0.47, 95% CI 0.24–0.92, p=0.032), as was presence of EMD, double refractory status, and Revised-International Staging System (R-ISS) of 2/3. Low pre-A ALC and a high absolute reduction in ALC between A and LD (≥0.27) had no significant impact on OS. On multivariate analysis, only EMD was associated with a significantly shorter OS (HR 4.17, 95% CI 1.96–8.87, p< 0.001). **Conclusions:** On multivariate analysis, the pre-A, -pre-LD, and the absolute reduction in ALC prior to CAR-T administration had no significant impact on either PFS or OS. Inferior survival outcomes post-CAR-T appear to be driven by previously recognized factors like the presence of EMD, high-risk cytogenetics, and reduced baseline performance status. Of note, all patients had an ALC > $0.1x10^9$/L and the impact of pre-treatment ALC below this level cannot be assessed from this analysis.

P-039

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Introduction: Vitamin D (VitD) deficiency is a potentially modifiable risk factor for poor outcomes in relapsed/refractory multiple myeloma (RRMM). Recent studies demonstrated that VitD deficiency may be associated with inferior survival in recipients of autologous stem-cell transplant (ASCT) (Eicher, Hem Onc, 2020). Additionally, we previously demonstrated that VitD insufficiency is associated with inferior clinical outcomes in patients with B-cell lymphoma treated with CD19-directed chimeric antigen receptor T-cell therapy (CAR-T) (Nath, TCT, 2022). The role of circulating vitamin D in patients with RRMM treated with CAR-T is currently unknown. Here, we evaluated the impact of vitamin D status on clinical outcomes in this patient population. **Methods:** We performed a single-center, retrospective analysis of adult patients with RRMM who received commercial or investigational CAR-T between 04/2017–09/2022 and had a serum vitamin D (25[OH]D) measured pre-CAR-infusion. Vitamin D deficiency was defined as < 20ng/mL as per the Endocrine Society guidelines. Cox proportional hazards models were used to assess the impact of pre-CAR-T vitamin D status on progression-free survival (PFS) and overall survival (OS). **Results:** Of the 102 patients with RRMM who received CAR-T, 61 patients had a pre-CAR infusion vitamin D level available. The median age of the 61 patients was 62 years (range, 38-79), with 57% males. Patients were heavily pretreated with a median 6 prior lines of therapy (range, 2 – 14), and 97% had a prior ASCT. Triple-class refractoriness (TCR), extramedullary disease (EMD), and high-risk cytogenetics (HRC) were observed in 80%, 52%, and 70% of patients, respectively. Baseline characteristics were overall comparable between vitamin D deficient (< 20ng/mL; n= 11) and vitamin D replete (≥20ng/mL; n=50) patients. On univariate analysis, vitamin D deficient compared to replete patients had a significantly inferior PFS (median PFS, 3.5 months vs. 6.5months, HR of 2.24, 95% Confidence Interval [CI] 1.09-4.59, p=0.041). These differences-maintained significance in a multivariate analysis adjusting for baseline characteristics (age, gender, ECOG performance status, HRC, EMD, penta-refractory status) (HR of 2.53, 95%CI 1.14–5.66, p=0.032). There was no significant difference in OS based on vitamin D status in both the univariate and multivariate analysis. Only EMD and decreased performance status (ECOG 1 or 2) was an independently significant poor prognostic factor for OS. **Conclusions:** In this modest cohort of patients with RRMM, VitD deficiency (< 20ng/mL) prior to CAR-T cell therapy was potentially associated with inferior PFS. However, the small sample size and the possibility of residual confounding precludes concrete conclusions. Future studies with larger cohorts of patients will be needed to confirm these findings.

P-040

Idecabtagene vicleucel (ide-cel) versus standard regimens in patients with triple-class-exposed (TCE) relapsed and refractory multiple myeloma (RRMM): a KarMMa-3 high-risk subgroup analysis

Krina Patel[1], Paula Rodríguez-Otero[2], Salomon Manier[3], Rachid Baz[4], Marc Raab[5], Michele Cavo[6], Natalie Callander[7], Luciano Costa[8], Philippe Moreau[9], Scott Solomon[10], Christine Chen[11], Noopur Raje[12], Christoph Scheid[13], Michel Delforge[14], Jeremy Larsen[15], Thomas Mueller Pabst[16], Kenshi Suzuki[17], Anna Truppel-Hartmann[18], Zhihong Yang[18], Julia Piasecki[19], Jasper Felten[19], Andrea Caia[19], Mark Cook[20], Sergio Giralt[21], María-Victoria Mateos[22]

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Introduction: Despite improvements in the treatment landscape of RRMM, outcomes remain poor in patients (pts) with high-risk features such as cytogenetic abnormalities, advanced-disease stage, high tumor burden (HTB), presence of extramedullary plasmacytoma (EMP), and triple-class refractory disease (TCRMM). Ide-cel, a BCMA-directed CAR T cell therapy, significantly improved median progression-free survival (mPFS; 13.3 vs 4.4 mo; HR 0.49; P< 0.001) and overall response rate (ORR; 71 vs 42%; P< 0.001) vs standard (std) regimens in the overall population of pts with TCE RRMM in KarMMa-3 (NCT03651128). Here we assess efficacy and safety of ide-cel vs std regimens in high-risk subgroups in KarMMa-3. **Methods:** In KarMMa-3, pts with RRMM who received 2–4 prior regimens, who were TCE (immunomodulatory agent, proteasome inhibitor [PI], and daratumumab), and had disease refractory to the last regimen, were randomized 2:1 to receive ide-cel (target dose range: 150–450x10^6 CAR+ T cells) or a std regimen (DPd, DVd, IRd, Kd, or EPd, based on prior regimen, per investigator). Efficacy was assessed in high-risk groups including pts with cytogenetic

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P-040

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abnormalities (del[17p], t[4;14], or t[14;16]), R-ISS stage III disease, HTB (≥50% CD138+ plasma cells in bone marrow), EMP (soft-tissue-only and soft-tissue bone-related plasmacytomas), and TCRMM (refractory to ≥1 each of an IMiD® agent, a PI, and an anti-CD38 antibody). **Results:** Baseline demographics and disease characteristics were balanced between arms. Median time to progression on the last prior regimen was short in pts treated with both ide-cel vs std regimens in all high-risk subgroups: cytogenetic abnormalities (5.6 vs 6.7 mo), R-ISS stage III disease (3.9 vs 3.5 mo), HTB (5.1 vs 6.2 mo), EMP (5.1 vs 5.1 mo), and TCRMM (5.6 vs 5.8 mo). At a median follow-up of 18.6 mo (range 0.4–35.4), mPFS was longer in pts treated with ide-cel vs std regimens in all high-risk subgroups: cytogenetic abnormalities (11.9 vs 4.2 mo; HR 0.608), R-ISS stage III disease (5.2 vs 3.0 mo; HR 0.861), HTB (11.0 vs 4.9 mo; HR 0.595), EMP (7.2 vs 2.0 mo; HR 0.401), and TCRMM (11.2 vs 3.5 mo; HR 0.458). ORRs (cytogenetic abnormalities [64.5 vs 37.7%], R-ISS stage III [45.2 vs 28.6%], HTB [64.8 vs 52.9%], EMP [55.7 vs 18.8%], and TCRMM [64.0 vs 31.5%]) and complete response rates (CRR; cytogenetic abnormalities [31.8 vs 4.9%], R-ISS stage III [16.1 vs 7.1%], HTB [31.0 vs 8.8%], EMP [23.0 vs 3.1%], and TCRMM [33.5 vs 1.1%]) were improved in pts treated with ide-cel vs std regimens in all high-risk subgroups. Safety data will be presented. **Conclusions:** Pts treated with ide-cel had a lower risk of disease progression or death and higher odds of achieving an overall response (with higher CRRs) vs pts who received std regimens, regardless of baseline high-risk disease. These results support use of ide-cel in pts with TCE RRMM, including those with difficult-to-treat, high-risk disease. Previously presented at European Hematology Association Meeting 2023, presentation S195.

P-041

Efficacy and safety of BCMA-specific CAR T cell-based therapy in relapsed/refractory multiple myeloma patients with extramedullary disease

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Introduction: Relapsed/refractory (R/R) multiple myeloma (MM) patients with extramedullary disease (EMD) have an unfavorable prognosis and no effective treatment. B-cell maturation antigen (BCMA)-specific chimeric antigen receptor (CAR) T-cell therapies have shown promising efficacy in R/R MM; however, data on patients with EMD remain limited. We aimed to assess the efficacy and safety of CAR T-cell therapy in R/R MM patients with EMD. **Methods:** We conducted a retrospective multi-institutional study of 55 R/R MM patients confirmed with EMD at referral. The definition of EMD included (1) soft tissue masses in extraosseous locations resulting from hematogenous spread (EM-E) and (2) bone-related plasmacytomas that extend via disruption of cortical bones into contiguous soft tissues (EM-B). The overall response, long-term outcomes, and safety were assessed. We also characterized differential response between medullary and extramedullary disease, analyzed unique attributes of compartmental toxicity, and explored patterns of relapse in the setting of EMD. **Results:** The infusion resulted in an overall response rate of 90.9% (95% confidence interval [CI], 80.4-96.1) in medullary disease and 70.9% (95% CI, 57.9-81.2) in EMD (P=0.008). Discrepant outcomes between medullary and extramedullary response were observed, with suboptimal and delayed overall response and shortened duration of response in the setting of EMD. With a median follow-up of 27.3 months, the median progression-free survival was 8.7 months (95% CI, 3.7-18.8), and the median overall survival was 16.0 months (95% CI, 13.5-20.1). Local cytokine release syndrome (CRS) was depicted in 21.8% patients and was associated with the occurrence of systemic CRS (r = 0.322; P = 0.017). 80% patients experienced post-infusion progression in EMD, and BCMA+ progression constituted the main pattern of progression in EMD. Landmark analysis was conducted to compare OS in patients who progressed versus remained progression-free at the 6-month landmark time point. We demonstrated that progression before 6 months post-infusion is strongly associated with an increased risk of death (HR = 11.15 [95% CI, 3.49 to 35.60]; P < 0.001). **Conclusions:** Our study shows that anti-BCMA CAR-T therapy has provided apparent therapeutic advantage over the existing drugs in response rate and long-term survival. We describe a discrepancy between medullary and extramedullary response towards CAR T-cell therapy. We suggest that BCMA-specific CAR T cell-based therapy may have limited efficacy in EMD, perhaps due to insufficient expansion and persistence of CAR T cells within the microenvironment.

P-042

Early infections in myeloma patients treated with anti-BCMA bispecific antibodies

Jakub Radocha[1], Ludek Pour[2], Tomas Jelinek[3], Jiri Minarik[4], Alexandra Jungova[5], Denisa Novakova[1], Martin Stork[2], Ludmila Muronova[6], Tomas Pika[4], Roman Hájek[3]

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Introduction: Myeloma patients treated with anti-BCMA bispecific antibodies (bsAb) are at high risk of developing infections due to subsequent depletion of immunoglobulins (IG) and T cell exhaustion. Preventive measures include IG replacement, but no firm recommendations about timing and target levels exist. We aimed to describe early infection incidence, severity, and IgG levels in patients treated with anti-BCMA bsAb. **Methods:** We retrospectively

abnormalities (del[17p], t[4;14], or t[14;16]), R-ISS stage III disease, HTB (≥50% CD138+ plasma cells in bone marrow), EMP (soft-tissue-only and soft-tissue bone-related plasmacytomas), and TCRMM (refractory to ≥1 each of an IMiD® agent, a PI, and an anti-CD38 antibody). **Results:** Baseline demographics and disease characteristics were balanced between arms. Median time to progression on the last prior regimen was short in pts treated with both ide-cel vs std regimens in all high-risk subgroups: cytogenetic abnormalities (5.6 vs 6.7 mo), R-ISS stage III disease (3.9 vs 3.5 mo), HTB (5.1 vs 6.2 mo), EMP (5.1 vs 5.1 mo), and TCRMM (5.6 vs 5.8 mo). At a median follow-up of 18.6 mo (range 0.4–35.4), mPFS was longer in pts treated with ide-cel vs std regimens in all high-risk subgroups: cytogenetic abnormalities (11.9 vs 4.2 mo; HR 0.608), R-ISS stage III disease (5.2 vs 3.0 mo; HR 0.861), HTB (11.0 vs 4.9 mo; HR 0.595), EMP (7.2 vs 2.0 mo; HR 0.401), and TCRMM (11.2 vs 3.5 mo; HR 0.458). ORRs (cytogenetic abnormalities [64.5 vs 37.7%], R-ISS stage III [45.2 vs 28.6%], HTB [64.8 vs 52.9%], EMP [55.7 vs 18.8%], and TCRMM [64.0 vs 31.5%]) and complete response rates (CRR; cytogenetic abnormalities [31.8 vs 4.9%], R-ISS stage III [16.1 vs 7.1%], HTB [31.0 vs 8.8%], EMP [23.0 vs 3.1%], and TCRMM [33.5 vs 1.1%]) were improved in pts treated with ide-cel vs std regimens in all high-risk subgroups. Safety data will be presented. **Conclusions:** Pts treated with ide-cel had a lower risk of disease progression or death and higher odds of achieving an overall response (with higher CRRs) vs pts who received std regimens, regardless of baseline high-risk disease. These results support use of ide-cel in pts with TCE RRMM, including those with difficult-to-treat, high-risk disease. Previously presented at European Hematology Association Meeting 2023, presentation S195.

P-041

Efficacy and safety of BCMA-specific CAR T cell-based therapy in relapsed/refractory multiple myeloma patients with extramedullary disease

Yue Kun Qi[1], Zhenyu Li[1], Kailin Xu[2]

[1]The Affiliated Hospital of XuZhou Medical University; [2]Blood Diseases Institute, Xuzhou Medical University, Xuzhou, Jiangsu, China

Introduction: Relapsed/refractory (R/R) multiple myeloma (MM) patients with extramedullary disease (EMD) have an unfavorable prognosis and no effective treatment. B-cell maturation antigen (BCMA)-specific chimeric antigen receptor (CAR) T-cell therapies have shown promising efficacy in R/R MM; however, data on patients with EMD remain limited. We aimed to assess the efficacy and safety of CAR T-cell therapy in R/R MM patients with EMD. **Methods:** We conducted a retrospective multi-institutional study of 55 R/R MM patients confirmed with EMD at referral. The definition of EMD included (1) soft tissue masses in extraosseous locations resulting from hematogenous spread (EM-E) and (2) bone-related plasmacytomas that extend via disruption of cortical bones into contiguous soft tissues (EM-B). The overall response, long-term outcomes, and safety were assessed. We also characterized differential response between medullary and extramedullary disease, analyzed unique attributes of compartmental toxicity, and explored patterns of relapse in the setting of EMD. **Results:** The infusion resulted in an overall response rate of 90.9% (95% confidence interval [CI], 80.4-96.1) in medullary disease and 70.9% (95% CI, 57.9-81.2) in EMD (P=0.008). Discrepant outcomes between medullary and extramedullary response were observed, with suboptimal and delayed overall response and shortened duration of response in the setting of EMD. With a median follow-up of 27.3 months, the median progression-free survival was 8.7 months (95% CI, 3.7-18.8), and the median overall survival was 16.0 months (95% CI, 13.5-20.1). Local cytokine release syndrome (CRS) was depicted in 21.8% patients and was associated with the occurrence of systemic CRS (r = 0.322; P = 0.017). 80% patients experienced post-infusion progression in EMD, and BCMA+ progression constituted the main pattern of progression in EMD. Landmark analysis was conducted to compare OS in patients who progressed versus remained progression-free at the 6-month landmark time point. We demonstrated that progression before 6 months post-infusion is strongly associated with an increased risk of death (HR = 11.15 [95% CI, 3.49 to 35.60]; P < 0.001). **Conclusions:** Our study shows that anti-BCMA CAR-T therapy has provided apparent therapeutic advantage over the existing drugs in response rate and long-term survival. We describe a discrepancy between medullary and extramedullary response towards CAR T-cell therapy. We suggest that BCMA-specific CAR T cell-based therapy may have limited efficacy in EMD, perhaps due to insufficient expansion and persistence of CAR T cells within the microenvironment.

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P-043

Leveraging wearable devices for remote patient monitoring facilitate earlier CRS detection following CAR-T therapy in relapsed/refractory multiple myeloma (RRMM): early results from an IIT

Sridevi Rajeeve[1], Matt Wilkes[2], Nicole Zahradka[2], Nicholas Calafat[2], Kseniya Serebyrakova[1], Katerina Kappes[1], Hayley Jackson[1], Nicole Buchenholz[1], Sarita Agte[3], Santiago Thibaud[1], Larysa Sanchez[1], Shambavi Richard[1], Joshua Richter[1], Cesar Rodriguez[1], Hearn Jay Cho[1], Ajai Chari[1], Sundar Jagannath[1], Adriana Rossi[1], Samir Parekh[1]

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P-044

Evaluation of the efficacy and safety of two different linvoseltamab Phase 2 dose regimens: results from LINKER-MM1

Joshua Richter[1], Naresh Bumma[2], Madhav Dhodapkar[3], James Hoffman[4], Hans Lee[5], Attaya Suvannasankha[6], Michelle DeVeaux[7], Dhruti Chokshi[7], Anita Boyapati[7], Anasuya Hazra[7], Karen Rodriguez Lorenc[7], Glenn Kroog[7], Yariv Houvras[7], Sundar Jagannath[8]

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P-044

Evaluation of the efficacy and safety of two different linvoseltamab Phase 2 dose regimens: results from LINKER-MM1

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Introduction: Linvoseltamab is a BCMA×CD3 bispecific antibody (Ab) that has shown promising efficacy and generally manageable safety in patients (pts) with relapsed/refractory multiple myeloma (MM) (Lee et al. ASCO 2023). To optimize dose selection, two Ph 2 dose cohorts (50 and 200 mg) were studied in LINKER-MM1 (NCT03761108). Here, we report a detailed comparison of results from these two cohorts. **Methods:** LINKER-MM1 enrolled adults with MM who progressed on/after ≥3 lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 Ab; the Ph 2 portion also included pts who were ≥triple class (PI/IMiD/anti-CD38 Ab) refractory. A protocol amendment permitted pts who progressed during 4–12 wks on 50 mg to escalate to 200 mg. Primary endpoint was objective response rate (ORR). **Results:** This analysis assessed efficacy and safety in 221 pts (200 mg [n=117] vs 50 mg [n=104]; data cut-off, Feb 28, 2023): aged ≥75 yrs, 26% (200 mg) vs 16% (50 mg); non-White race, both 29%; high-risk cytogenetics, 36% vs 24%; extramedullary plasmacytomas, both 14%; bone marrow plasma cells ≥50%, 22% vs 35%; median soluble BCMA, both 377 ng/mL. The majority of pts (74% [200 mg] vs 88% [50 mg]) were ≥triple class refractory. Median duration of follow-up was 5.6 mo (200 mg) and 7.7 mo (50 mg). ORR was greater at 200 mg (71%) than 50 mg (50%). Higher ORRs were also seen with 200 vs 50 mg across prespecified subgroups, including by age (18–65 yrs, ORR: 66% vs 42%; ≥65–75 yrs, 79% vs 56%; ≥75 yrs, 68% vs 59%), race (White, 73% vs 45%; non-White, 65% vs 64%), disease stage (ISS stage I, 73% vs 53%; stage II, 73% vs 63%; stage III, 59% vs 25%), functional status (ECOG PS 0, 67% vs 51%; PS 1, 73% vs 50%), serum M protein (< 1.06 g/dL, 84% vs 58%; ≥1.06 g/dL, 57% vs 47%), involved free light chain (< 536 mg/L, 83% vs 55%; ≥536 mg/L, 54% vs 45%), and refractory (refr) status (triple-refr, 68% vs 50%; quad-refr, 77% vs 52%; penta-refr, 61% vs 48%). Median PFS was 7.9 mo at 50 mg and not reached at 200 mg. Dose was escalated from 50 to 200 mg in 8 pts; 75% achieved a VGPR. Treatment-emergent AEs (TEAEs) occurred in all pts (Grade [Gr] ≥3: 79%) at 200 mg and 98% (Gr ≥3: 79%) at 50 mg. Overall, the TEAE profile was similar in both cohorts. The most common TEAE for both doses was cytokine release syndrome (200 mg: 45% [Gr 3: 1%] vs 50 mg: 55% [Gr 3: 2%]); other common TEAEs (>30%) were cough (33% vs 32%), neutropenia (32% vs 28%), fatigue (32% vs 29%), diarrhea (32% vs 28%), anemia (27% vs 40%), and arthralgia (26% vs 31%). There were more opportunistic infections at 200 mg (8% vs 2%). **Conclusions:** Linvoseltamab 200 mg showed higher efficacy than 50 mg. Notably, high ORRs with 200 mg were seen across subgroups, even in high-risk and high tumor burden subgroups. Supporting the higher dose, some pts who progressed on 50 mg responded after dose escalating to 200 mg. With a similar safety profile across both doses, these data indicate 200 mg as the recommended dose for future studies.

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Early treatment with bispecific T-cell redirectors (teclistamab or talquetamab) + daratumumab in newly diagnosed high-risk multiple myeloma: an open-label, phase 2, pilot study (GEM-TECTAL)

Paula Rodríguez-Otero, María-Victoria Mateos, Juan José Lahuerta Palacios, Joan Bladé, Christoph Heuck, Rachel Kobos, Claire Albrecht, Margaret Doyle, Kathleen Gray, Jesús San-Miguel

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Introduction: Trial in progress. Treatment (tx) advancements in recent decades have improved outcomes for patients (pts) with multiple myeloma (MM). However, a subset of pts with high-risk (HR) MM continues to have poor outcomes due to a range of pt- and disease-based factors, with median overall survival (OS) < 24 months. Pts with HRMM have poorly defined treatment options and are often underrepresented in clinical trials; those who fail to achieve MRD negativity after frontline therapy have a particularly high unmet medical need. This phase 2, open-label, multicenter, nonrandomized, pilot study aims to investigate a novel, individualized approach to tx, evaluating the efficacy and safety of teclistamab (tec) + daratumumab (dara) and talquetamab (tal) + dara in pts with HR newly diagnosed (ND) MM, with an early rescue intervention (ERI) guided by MRD assessment. **Methods:** Eligible pts are aged ≥18 years with NDMM per International Myeloma Working Group diagnostic criteria, are eligible for transplant and aged ≤70 years, or are fit pts ineligible for transplant with an Eastern Cooperative Oncology Group performance status of 0 or 1. Pts will have ≥1 of the following HRMM features: adverse cytogenic abnormalities (del[17p], t[4;14], t[14;16], or 1q amplifications detected by fluorescence in situ hybridization), Revised International Staging System (R-ISS) stage 3, and presence of extramedullary disease (EMD). 50% of pts will be ultra-high risk: R-ISS stage 3 or "double hit" (≥2 HR cytogenic abnormalities) or 1 HR cytogenic abnormality and EMD. Induction therapy will consist of dara, bortezomib, lenalidomide, and dexamethasone (D-VRd) and response evaluation, including MRD assessment by multiple techniques. All pts will then receive tec + dara (intensification phase). Following subsequent MRD assessment, pts will be stratified by MRD status. MRD-negative pts will receive tec + dara (maintenance therapy) for a pre-defined period of time. MRD-positive pts will receive tal + dara (ERI) before reassessment. Pts who convert to MRD-negative status will receive tal + dara for a pre-defined period of time; MRD-positive

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Trial in progress: linvoseltamab, a BCMAxCD3 bispecific antibody, in a Phase 1b multi-cohort study of combination regimens for patients with relapsed/refractory multiple myeloma

Paula Rodríguez-Otero[1], Nisha Joseph[2], Shaji Kumar[3], Xavier Leleu[4], Salomon Manier[5], Meletios Dimopoulos[6], María-Victoria Mateos[7], Albert Oriol[8], Naresh Bumma[9], Weiying Gong[10], Pourab Roy[11], Karen Rodriguez Lorenc[10], Glenn Kroog[10], Shawn Sarkaria[10]

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Trial in progress: an open-label, multicenter, phase 1 study for IGM-2644 in participants with relapsed and/or refractory multiple myeloma (RRMM)

Roel Funke[1], Henning Schade[2], Jesus Berdeja[3], Keyu Li[1], Maya Kotturi[1], Genevive Hernandez[1], Yinghui Guan[1], Malavika Deodhar[1], Dominique Durant[1], Chris Takimoto[1], Thomas Manley[1], Kevin Hart[1]

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Introduction: IGM-2644 is an engineered high-affinity, high-avidity bispecific anti-CD38 IgM antibody T cell engager (TCE) being developed for the treatment of RRMM. CD38 is a uniformly highly expressed cell surface glycoprotein on neoplastic plasma cells. IGM-2644 is designed to selectively target and kill myeloma cells through both T-cell dependent cellular toxicity (TDCC) and complement dependent cytotoxicity (CDC). In preclinical models, IGM-2644 demonstrates superior CDC and cellular-dependent cytotoxicity compared to daratumumab, especially on low CD38-expressing tumor cells. IGM-2644 may have an improved safety profile compared to bispecific IgGs due to lower cytokine release and

pts will receive salvage therapy. If MRD-negative pts convert to MRD-positive status, they will be treated as MRD-positive pts. The primary endpoint is MRD-complete response rate after tx with tec + dara (intensification). Secondary endpoints include percentage of pts who convert to MRD negativity after ERI; percentage of pts with sustained MRD negativity at pre-defined time points in both tx arms; OS; progression-free survival; event-free survival; time to next tx; duration of response; and safety. Exploratory endpoints are immune profiling and genetic characterization. **Results:** Enrollment is expected to begin in May 2023 (target recruitment N=30). **Conclusions:** This study will provide needed data on the effect of MRD-guided individualized tx approaches in management of pts with HRMM, an underrepresented population with a high unmet need.

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Introduction: Trial in Progress. Despite the increased effectiveness of combination drug therapy, multiple myeloma (MM) remains incurable, and patients eventually succumb to relapsed disease. Therefore, new combination regimens are needed to improve outcomes in MM. Linvoseltamab is a bispecific antibody capable of binding to B-cell maturation antigen (BCMA) on MM cells and CD3 on T cells, inducing targeted T-cell-mediated cytotoxicity of MM cells. Results from a Phase 1/2 first-in-human study of linvoseltamab monotherapy in relapsed/refractory MM (RRMM) showed early, deep, and durable responses with manageable safety and tolerability (NCT03761108; Bumma N, et al. Blood. 2022;140(Suppl 1):10140–1). Given these findings, it is reasonable to explore whether combining linvoseltamab with other drugs can improve the depth and duration of responses. **Methods:** LINKER-MM2 (NCT05137054) is a global, Phase 1b, open-label, multi-cohort study designed to assess the safety, tolerability, and efficacy of linvoseltamab in combination with nine different agents (daratumumab, carfilzomib, lenalidomide, bortezomib, pomalidomide, isatuximab, fianlimab, cemiplimab, or nirogacestat) in separate cohorts of participants with RRMM. Prior exposure to a combination agent is allowed if previously tolerated at the full dose (after a minimum washout period), although some cohorts exclude patients with disease refractory to the cohort-specific combination treatment. The study includes a dose-finding portion to select an appropriate linvoseltamab dose, followed by a dose-expansion portion for each cohort. Linvoseltamab is administered intravenously starting on a weekly basis from initiation of the step-up schedule through the first 15-16 weeks and then transition to every 2-3 weeks. All regimens are given until disease progression or any other reason for discontinuation. Estimated total enrollment is ~315 participants. Eligible patients are 18 years or older with RRMM that progressed after ≥3 lines of therapy, have an Eastern Cooperative Oncology Group performance status ≤1, and have adequate organ function. Key exclusion criteria include the presence of MM brain lesions or meningeal involvement, and previous treatment with certain BCMA-directed therapies depending on the cohort. The primary endpoint is safety and tolerability of each linvoseltamab combination, in terms of dose-limiting toxicities (dose-finding portion only) and treatment-emergent adverse events. Secondary endpoints are objective response rate, duration of response, progression-free survival, minimal residual disease status, pharmacokinetics, immunogenicity, and overall survival. This study is actively recruiting participants and anticipated to open at 50 global sites. **Conclusions:** Analyses from the LINKER-MM2 study will provide important information on the tolerability and preliminary clinical efficacy of linvoseltamab when given in combination with other cancer therapies, aiming to improve care for patients with RRMM.

P-047

Trial in progress: an open-label, multicenter, phase 1 study for IGM-2644 in participants with relapsed and/or refractory multiple myeloma (RRMM)

Roel Funke[1], Henning Schade[2], Jesus Berdeja[3], Keyu Li[1], Maya Kotturi[1], Genevive Hernandez[1], Yinghui Guan[1], Malavika Deodhar[1], Dominique Durant[1], Chris Takimoto[1], Thomas Manley[1], Kevin Hart[1]

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Introduction: IGM-2644 is an engineered high-affinity, high-avidity bispecific anti-CD38 IgM antibody T cell engager (TCE) being developed for the treatment of RRMM. CD38 is a uniformly highly expressed cell surface glycoprotein on neoplastic plasma cells. IGM-2644 is designed to selectively target and kill myeloma cells through both T-cell dependent cellular toxicity (TDCC) and complement dependent cytotoxicity (CDC). In preclinical models, IGM-2644 demonstrates superior CDC and cellular-dependent cytotoxicity compared to daratumumab, especially on low CD38-expressing tumor cells. IGM-2644 may have an improved safety profile compared to bispecific IgGs due to lower cytokine release and

reduced immune cell fratricide with comparable anti-tumor activity in ex vivo and in vivo MM models. **Methods:** This is a first-in-human, Phase 1, multicenter, open-label study to determine the safety and tolerability of IGM-2644 as a single agent in participants (N=30-60) with RRMM. Expansion cohorts will be enrolled to evaluate preliminary efficacy and further define a recommended Phase 2 dose (RP2D). A step-up dosing regimen will be used, with successively higher doses of IGM-2644 administered during a priming cycle. The optimal number and magnitude of steps to reach the plateau RP2D will be determined progressively. At the start of dose escalation, the same dose level will be administered on all dosing days during the priming cycle until a Dose 1 is fixed. Doses 2 and 3 will then be increased in parallel until a Dose 2 maximum tolerated dose (MTD) is defined. The Safety Review Committee may recommend fixing Dose 2 at or below the MTD and continuing escalation of the third priming dose. The highest dose achieved during the priming cycle will represent the plateau dose to be administered once per week in 3-week cycles. Pharmacokinetics, pharmacodynamics, efficacy, and safety data collected throughout the treatment period may be used to support potentially less frequent dosing. A single participant will initially be enrolled into each dose-escalation cohort. Conversion to a standard 3+3 escalation format will be based on the occurrence of one of specified safety events or the achievement of a predetermined dose level, whichever occurs first. Correlative biomarker studies include assessment of blood and tissue biomarkers for association with clinical benefit. **Conclusions:** IGM-2644 is a novel bispecific IgM T cell engager with both CDC and TDCC mechanisms of cytotoxicity and the potential to be active in daratumumab-resistant tumors. This Phase 1 trial is underway, and results will be presented at a future meeting.

P-048

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Introduction: Anti-BCMA chimeric antigen receptor (CAR) T-cell therapy showed excellent efficacy in relapsed/refractory multiple myeloma (R/R MM) patients (pts). Point-of-care (POC) CAR manufacturing abrogates the need for cryopreservation and shipment of cells, thus shortening the manufacturing process and reducing the necessity of bridging therapy. We report outcomes of phase 1b/2 single center clinical trial of autologous POC anti-BCMA CAR T-cell therapy in pts with R/R MM treated with ≥ 3 prior therapies. **Methods:** Pts underwent a single peripheral blood leukapheresis. Fresh T-cells were transduced with retroviral vector encoding the anti-BCMA CAR (based on 11D5-3 ScFv, CD28 costimulatory domain and CD3-ζ signaling domain). Cell dose was 6×10^6/kg (dose level I [n=3]) or 9×10^6/kg (dose level II [n=33]). Primary endpoints were overall response rate (ORR) per IMWG criteria and safety. Secondary endpoints were overall survival (OS) and progression-free survival (PFS). Last follow-up was 05/2023. **Results:** Since 11/2021, 36 pts enrolled (median age 60, IQR 54-67). All pts received CAR T-cell infusion in a median of 11 days (IQR 11-14) after leukapheresis. Only 2 pts received bridging therapy. The median number of prior therapies was 4 (IQR 3-5), with 61% and 33% of the pts being penta and quad-refractory, respectively. 7 (19%) pts had prior exposure to BCMA-targeted therapy (belantamab mafodotin, n=5 [14%]; talqeutamab, n=2 [6%]). At enrollment, 12 (33%) pts had high-risk cytogenetics, 9 (25%) had double-hit myeloma, and 18 (50%) had extramedullary involvement. Only 19 (53%) and 18 (50%) pts were eligible to enroll in the KarMMa (NEJM, 2021) and CARTITUDE-1 (Lancet, 2021) studies, respectively. Only 1 patient (3%) developed grade ≥ 3 cytokine release syndrome, and 1 patient (3%) developed grade ≥ 3 immune effector cell-associated neurotoxicity syndrome. Grade 3-4 neutropenia and thrombocytopenia occurred in 35 (97%) and 19 (53%) pts, respectively. Anemia requiring transfusion occurred in 17 (47%) pts. No grade 3-4 adverse events nor cellular therapy-related deaths were observed. The median follow-up was 6.4 months (IQR 4.9-10.7). Best ORR (PR at least) was 64% (VGPR at least, 50%). Median time to first response was 31 days (95% CI: 26-33). Estimated 6-months OS, PFS and duration of response were 87% (95% CI: 76-100), 46% (95% CI: 31-67), and 61% (95% CI: 41-89), respectively. Pts with prior exposure to BCMA-targeted therapies had an inferior PFS (HR 2.9 [95% CI: 1.1-7.8] p=0.04). **Conclusions:** POC anti-BCMA CAR T-cells induced high response rates with an excellent safety profile in R/R MM pts mostly not eligible to be enrolled in the pivotal trials. The rapid CAR-T production time obviated the need for bridging therapy in most pts. It is noteworthy that prior exposure to BCMA-targeted therapies is associated with dismal PFS, hence those therapies should be carefully considered when CAR T-cell therapy might be intended.

P-049

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reduced immune cell fratricide with comparable anti-tumor activity in ex vivo and in vivo MM models. **Methods:** This is a first-in-human, Phase 1, multicenter, open-label study to determine the safety and tolerability of IGM-2644 as a single agent in participants (N=30-60) with RRMM. Expansion cohorts will be enrolled to evaluate preliminary efficacy and further define a recommended Phase 2 dose (RP2D). A step-up dosing regimen will be used, with successively higher doses of IGM-2644 administered during a priming cycle. The optimal number and magnitude of steps to reach the plateau RP2D will be determined progressively. At the start of dose escalation, the same dose level will be administered on all dosing days during the priming cycle until a Dose 1 is fixed. Doses 2 and 3 will then be increased in parallel until a Dose 2 maximum tolerated dose (MTD) is defined. The Safety Review Committee may recommend fixing Dose 2 at or below the MTD and continuing escalation of the third priming dose. The highest dose achieved during the priming cycle will represent the plateau dose to be administered once per week in 3-week cycles. Pharmacokinetics, pharmacodynamics, efficacy, and safety data collected throughout the treatment period may be used to support potentially less frequent dosing. A single participant will initially be enrolled into each dose-escalation cohort. Conversion to a standard 3+3 escalation format will be based on the occurrence of one of specified safety events or the achievement of a predetermined dose level, whichever occurs first. Correlative biomarker studies include assessment of blood and tissue biomarkers for association with clinical benefit. **Conclusions:** IGM-2644 is a novel bispecific IgM T cell engager with both CDC and TDCC mechanisms of cytotoxicity and the potential to be active in daratumumab-resistant tumors. This Phase 1 trial is underway, and results will be presented at a future meeting.

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San Francisco, San Francisco, CA, USA; [11]Virgina Commonwealth University; [12]City of Hope Comprehensive Cancer Center; [13]Levine Cancer Institute-Atrium Health Wake Forest University School of Medicine; [14]University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA; [15]Taussig Cancer Institute, Cleveland Clinic; *SS, KP, MJ, YL and DH contributed equally

Introduction: In this multi-center study, we evaluated the outcomes of patients treated with intended standard of care cilta-cel. **Methods:** Patients at 14 US academic centers who underwent apheresis with intention to manufacture cilta-cel by 9/15/2022 were included. Data cut-off was April 1, 2023. **Results:** 153 patients underwent apheresis and 143 (94%) received cilta-cel infusion. 10 patients did not get cilta-cel due to progression/death (6), myelodysplastic syndrome (1), manufacturing failure (1), OOS product declined by patient (1) and lost to follow up (1). Amongst patients receiving cilta-cel (N=143), median age was 64 years, with 27% being above age 70; 57% were male, 34% had penta-refractory disease. Compared to CARTITUDE-1 study population, our cohort had higher incidence of extramedullary disease (EMD, 31% vs 13%) and high-risk cytogenetics (41% vs 24%). 57% of the patients would not have met eligibility criteria for CARTITUDE-1. Common reasons for ineligibility were cytopenias (17%), prior BCMA therapy (15%), organ dysfunction (12%), poor performance status (11%) and plasma cell leukemia (7%). 80% of the patients received bridging chemotherapy (overall response rate, ORR: 30%). Lymphodepletion included fludarabine (Flu) + cyclophosphamide (Cy): 84%, bendamustine: 9%, Cy: 3.5%, and cladribine + Cy: 3.5%. Median CAR-T cells infused were 0.6 million/kg, and 22% of patients were treated on expanded access protocol (EAP). Median follow-up was 6 months. Cytokine release syndrome (CRS) was seen in 80% (≥ grade 3: 5%), immune effector cell-associated neurotoxicity syndrome (ICANS) in 18% (≥ grade 3: 6%) and hemophagocytic lymphohistiocytosis (HLH)-like syndrome in 3% of patients. Tocilizumab, steroids, and anakinra were used in 61%, 41%, and 13% of patients, respectively. Delayed neurotoxicity (NT) was seen in 12% (n=17; 7th cranial nerve palsy: 9, Parkinsonism: 2, others: 6), with median time to onset being 25 days. It resolved in 6 patients by last follow-up, while 3 patients died with ongoing delayed NT. Infections were seen in 37% of patients. Day 30 (N=134) and best response rates (N=140) were: ≥ partial response (PR), 81/89%; ≥ very good PR, 51/77%; and ≥ complete response (CR), 29/56%, respectively. In the non-EAP FluCy population (N=92), ORR/≥CR were 94/61%. Median progression free survival was not reached, with 6-month estimate being 79%. 22 patients died by data cut-off, including 14 (10%) due to non-relapse mortality (infection:6, grade 5 CRS:3, CRS/infection:1 grade 5 ICANS:1, delayed NT:2, HLH:1). **Conclusions:** Patients treated with SOC cilta-cel had a favorable ORR (89%) and CR rate (56%) despite a larger proportion of patients having high-risk features relative to trial patients. Response rates were higher in patients receiving conforming products with FluCy conditioning (94%). Delayed NT was seen in 12% and non-relapse mortality in 10% of patients, respectively.

P-050

GEN3014 (HexaBody®-CD38) versus daratumumab in patients with relapsed/refractory multiple myeloma: design of randomized head-to-head expansion cohort of phase 1/2 trial

Sebastian Grosicki[1], Binod Dhakal[2], Ehsan Malek[3], Maria Creignou[4], Wojciech Jurczak[5], Annemiek Broijl[6], Katrine Fladeland Iversen[7], Henrik Gregersen[8], Jakub Radocha[9], Jenny Chen[10], Adeleye Ogunkanmi[10], Andrew Spencer[11]

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Introduction: The approval of CD38-targeted antibodies, such as daratumumab, has changed the treatment landscape for relapsed/refractory multiple myeloma (RRMM). Despite this advancement, patients still progress following daratumumab treatment; therefore, more potent treatment options with higher affinity for CD38 may improve clinical outcomes. GEN3014 (HexaBody®-CD38) is a novel human IgG1 anti-CD38 monoclonal antibody (mAb) that contains the hexamerization enhancing mutation E430G, which facilitates highly efficient complement-dependent cytotoxicity (CDC). In preclinical studies, GEN3014 showed highly potent tumor-cell killing through CDC and was more potent than daratumumab (Hiemstra et al, EHA 2020). Potent antibody dependent cellular cytotoxicity and cellular phagocytosis activity were demonstrated. Preliminary results from the dose-escalation portion of the first-in-human phase 1/2 trial of GEN3014 in patients with RRMM showed a tolerable safety profile and clinical activity, and the recommended phase 2 dose was determined to be 16 mg/kg. Based on these results, the study proceeded with expansion cohorts. Following an interim analysis of 10 anti-CD38 mAb–naive patients with RRMM who had received 16 or 24 mg/kg GEN3014 in the dose-escalation or initial expansion cohorts, an additional 80 anti-CD38 mAb–naive patients with RRMM are to be randomized 1:1 to receive either GEN3014 or daratumumab. Herein we describe the design of the randomized, head-to-head expansion cohort. **Methods:** This is a phase 1/2 open-label, multicenter, multinational trial (NCT04824794) designed to evaluate the safety, tolerability, pharmacokinetics/pharmacodynamics, immunogenicity, and preliminary efficacy of GEN3014 treatment in patients with RRMM or other hematologic malignancies. Patients in the randomized, head-to-head expansion cohort must have documented RRMM based on IMWG criteria and ≥3 prior lines of treatment (including a protease inhibitor [PI] and an immunomodulatory imide drug [IMiD]) or ≥2 prior lines of treatment (including a combination of a PI and an IMiD). Patients

San Francisco, San Francisco, CA, USA; [11]Virgina Commonwealth University; [12]City of Hope Comprehensive Cancer Center; [13]Levine Cancer Institute-Atrium Health Wake Forest University School of Medicine; [14]University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA; [15]Taussig Cancer Institute, Cleveland Clinic; *SS, KP, MJ, YL and DH contributed equally

Introduction: In this multi-center study, we evaluated the outcomes of patients treated with intended standard of care cilta-cel. **Methods:** Patients at 14 US academic centers who underwent apheresis with intention to manufacture cilta-cel by 9/15/2022 were included. Data cut-off was April 1, 2023. **Results:** 153 patients underwent apheresis and 143 (94%) received cilta-cel infusion. 10 patients did not get cilta-cel due to progression/death (6), myelodysplastic syndrome (1), manufacturing failure (1), OOS product declined by patient (1) and lost to follow up (1). Amongst patients receiving cilta-cel (N=143), median age was 64 years, with 27% being above age 70; 57% were male, 34% had penta-refractory disease. Compared to CARTITUDE-1 study population, our cohort had higher incidence of extramedullary disease (EMD, 31% vs 13%) and high-risk cytogenetics (41% vs 24%). 57% of the patients would not have met eligibility criteria for CARTITUDE-1. Common reasons for ineligibility were cytopenias (17%), prior BCMA therapy (15%), organ dysfunction (12%), poor performance status (11%) and plasma cell leukemia (7%). 80% of the patients received bridging chemotherapy (overall response rate, ORR: 30%). Lymphodepletion included fludarabine (Flu) + cyclophosphamide (Cy): 84%, bendamustine: 9%, Cy: 3.5%, and cladribine + Cy: 3.5%. Median CAR-T cells infused were 0.6 million/kg, and 22% of patients were treated on expanded access protocol (EAP). Median follow-up was 6 months. Cytokine release syndrome (CRS) was seen in 80% (≥ grade 3: 5%), immune effector cell-associated neurotoxicity syndrome (ICANS) in 18% (≥ grade 3: 6%) and hemophagocytic lymphohistiocytosis (HLH)-like syndrome in 3% of patients. Tocilizumab, steroids, and anakinra were used in 61%, 41%, and 13% of patients, respectively. Delayed neurotoxicity (NT) was seen in 12% (n=17; 7th cranial nerve palsy: 9, Parkinsonism: 2, others: 6), with median time to onset being 25 days. It resolved in 6 patients by last follow-up, while 3 patients died with ongoing delayed NT. Infections were seen in 37% of patients. Day 30 (N=134) and best response rates (N=140) were: ≥ partial response (PR), 81/89%; ≥ very good PR, 51/77%; and ≥ complete response (CR), 29/56%, respectively. In the non-EAP FluCy population (N=92), ORR/≥CR were 94/61%. Median progression free survival was not reached, with 6-month estimate being 79%. 22 patients died by data cut-off, including 14 (10%) due to non-relapse mortality (infection:6, grade 5 CRS:3, CRS/infection:1 grade 5 ICANS:1, delayed NT:2, HLH:1). **Conclusions:** Patients treated with SOC cilta-cel had a favorable ORR (89%) and CR rate (56%) despite a larger proportion of patients having high-risk features relative to trial patients. Response rates were higher in patients receiving conforming products with FluCy conditioning (94%). Delayed NT was seen in 12% and non-relapse mortality in 10% of patients, respectively.

P-050

GEN3014 (HexaBody®-CD38) versus daratumumab in patients with relapsed/refractory multiple myeloma: design of randomized head-to-head expansion cohort of phase 1/2 trial

Sebastian Grosicki[1], Binod Dhakal[2], Ehsan Malek[3], Maria Creignou[4], Wojciech Jurczak[5], Annemiek Broijl[6], Katrine Fladeland Iversen[7], Henrik Gregersen[8], Jakub Radocha[9], Jenny Chen[10], Adeleye Ogunkanmi[10], Andrew Spencer[11]

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P-051

Safety and efficacy of chimeric antigen receptor T cell therapy in patients with relapse or refractory multiple myeloma and hepatitis B virus-infection

Ying Wang[1], Feng Zhu[1], Jiang Cao[2], Kunming Qi[1], Zhiling Yan[2], Hai Cheng[1], Wei Sang[1], Depeng Li[1], Zhenyu Li[2], Kailin Xu[2]

[1]Xuzhou Medical University; [2]Blood Diseases Institute, Xuzhou Medical University

Introduction: Chimeric antigen receptor (CAR) T-cell therapy has shown encouraging results in patients with relapse or refractory multiple myeloma (RRMM). However, there are certain percentages of patients with RRMM and concomitant hepatitis B virus (HBV) infection, which remains confusion in clinical application of CAR-T cells. This study aimed to explore the safety and efficacy of patients with RRMM and concomitant HBV infection after anti-BCMA and/or anti-CD19 CAR-T cell therapy. **Methods:** Patients with RRMM and concomitant chronic or resolved HBV infection receiving anti-BCMA and/or anti-CD19 CAR T-cell therapy were enrolled. Patients without HBV infection were choosed as control. Clinical and laboratory datda were collected. The occurrence of HBV reactivation was analyzed among the 3 cohorts. The incidence and severity of liver injury and CRS were compared, as were the efficacy and long-term outcomes. The possible role and mechanism of immune status on HBV reactivation were explored by analyzing the changes of lymphocyte subsets among the 3 cohorts. **Results:** Among the 5 patients with chronic HBV infection and 12 patients with resolved HBV infection, only 1 patient with resolved HBV infection experienced HBV reactivation after CAR T-cell infusion, while no patient in no HBV infection cohort developing new HBV-infection. There was no HBV-related hepatitis flare. The incidence of alanine aminotransferase elevation (> 80U/L) was 20% (1/5), 25% (3/12) and 35.71% (5/14) in chronic, resolved, and no HBV infection cohorts, respectively, without statistical difference. After CAR T-cell therapy, the counts of CD4+ and CD8+ lymphocytes decreased, CD4/CD8 inverted. CD19+ lymphocytes decreased significantly and remained depressed up to 2 months post-infusion without difference among the 3 cohorts. The ORRs of patients in the three cohorts after CAR T-cell infusion were 100% (5/5), 91.67 (11/12), 100% (14/14), and the median PFS were 384, 349, and 581 days, respectively, without significant difference. The incidence of CRS in the three cohorts were 80%, 91.67% and 100%, respectively, and there was no significant difference in the incidence and severity of CRS among the three cohorts. **Conclusions:** CAR-T cell therapy could be used in patients with RRMM and concomitant chronic or resolved HBV-infection. HBV serological markers, HBV-DNA, and liver enzymes be closely monitored in these patients during CAR-T cell therapy.

P-052

LINKER-MM3, a phase 3, open-label, randomized study of linvoseltamab versus elotuzumab, pomalidomide, and dexamethasone (EPd) in relapsed/refractory multiple myeloma (RRMM)

Katja Weisel[1], Vania Hungria[2], Hang Quach[3], Sung-Soo Yoon[4], Paula Rodríguez-Otero[5], Arijit Sinha[6], Anita Boyapati[7], Charlotte Lyon[6], Vygngley Moore[7], Tim Inocencio[7], James Harnett[7], Lei Chi[7], Karen Rodriguez Lorenc[7], Glenn Kroog[7], Peter Voorhees[8]

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treatment. Other key eligibility criteria include measurable disease per 2016 IMWG criteria; ≥18 years of age; adequate bone marrow reserves and hepatic, renal, and cardiac function; and no prior treatment with elotuzumab, pomalidomide, or BCMA-directed immunotherapies. Linvoseltamab will be given in 28-day cycles, with step-up dosing to the full dose undertaken during Cycle 1. EPd treatment will also be given in 28-day cycles, according to the package inserts. Both treatment regimens will be given until disease progression or another defined reason for drug discontinuation. The study will take place at ~180 sites globally. A total of ~300 pts will be randomized (1:1) to IV linvoseltamab or EPd, stratified by prior anti-CD38 mAb exposure, International Staging System stage, and extramedullary plasmacytoma status. The primary endpoint is progression-free survival per IMWG criteria, determined by independent review committee (IRC). Key secondary endpoints are objective response rate (including rates of very good partial response or better and complete response or better, determined by IRC); MRD status; overall survival; and change in pain at Week 12 (Brief Pain Inventory-Short Form, Item 3). Incidence/severity of treatment-emergent AEs will also be assessed. Study enrollment is planned to begin in Q3 2023.

P-053

Idecabtagene vicleucel (ide-cel) retreatment response was characterized by poor activation, impaired cellular expansion, and limited cytolytic activity of chimeric antigen receptor (CAR) T cells

Fan Wu[1], Ye Shen[1], Xirong Zheng[1], Manisha Lamba[1], Nathan Martin[1], Shari Kaiser[1], Rashmi Bhatnagar[2], Nikhil Munshi[3], Sagar Lonial[4], Yi Lin[5], Jesús San-Miguel[6], Payal Patel[1], Timothy Campbell[1]

[1]Bristol Myers Squibb, Princeton NJ, USA; [2]Syneos Health, Gurugram, Haryana, India; [3]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/Harvard Medical School; [4]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [5]Mayo Clinic, Rochester, MN, USA; [6]Cancer Center Clinica Universidad de Navarra, Centro Investigacion Medica Aplicada, Instituto de Investigacion de Navarra, Centro Investigacion Biomedica en Red Cancer, Pamplona, Spain

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P-054

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treatment. Other key eligibility criteria include measurable disease per 2016 IMWG criteria; ≥18 years of age; adequate bone marrow reserves and hepatic, renal, and cardiac function; and no prior treatment with elotuzumab, pomalidomide, or BCMA-directed immunotherapies. Linvoseltamab will be given in 28-day cycles, with step-up dosing to the full dose undertaken during Cycle 1. EPd treatment will also be given in 28-day cycles, according to the package inserts. Both treatment regimens will be given until disease progression or another defined reason for drug discontinuation. The study will take place at ~180 sites globally. A total of ~300 pts will be randomized (1:1) to IV linvoseltamab or EPd, stratified by prior anti-CD38 mAb exposure, International Staging System stage, and extramedullary plasmacytoma status. The primary endpoint is progression-free survival per IMWG criteria, determined by independent review committee (IRC). Key secondary endpoints are objective response rate (including rates of very good partial response or better and complete response or better, determined by IRC); MRD status; overall survival; and change in pain at Week 12 (Brief Pain Inventory-Short Form, Item 3). Incidence/severity of treatment-emergent AEs will also be assessed. Study enrollment is planned to begin in Q3 2023.

P-053

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C57BL/6 mice aged 6-8 weeks as recipients. Murine Vk*MYC MM cells of varying concentrations (0.1×10^6 to 1×10^6 cells/mouse) and origins (splenocytes and bone marrow (BM) cells) were transplanted intrafemorally into C57BL/6 mice. PBS-injected C57BL/6 mice were utilized as a control. MM development was monitored through weekly serum protein electrophoresis (SPEP). The hindlimbs and spines were imaged with X-Ray and μ-CT. In addition, MM cells from the spleen and forearm/hip bones were quantified via flow cytometry. **Results:** All mice in this study were successfully engrafted, surviving for 6 to 7 weeks post-injection. Based on the imaging and SPEP results, we observed a direct association between the quantity of injected cells and the severity of bone lesions and tumor burden. Moreover, the cell source (BM cells or splenocytes injected into the femur) played a significant role in the severity of bone lesions. Surprisingly, splenocytes caused more extensive lesions and 25-40% of Vk*MYC cells were present in spleens. In contrast, flow cytometry of BM cells derived from forearms and hip bones showed only 4-10% Vk*MYC cells. Every intrafemorally transplanted mouse developed bone lesions that were enriched in the injected femur (proximal and distal) and occasionally appeared in the tibias and/or non-injected femur, depending on the disease stage. No lesions were detected in the spine of any mice. **Conclusions:** We have observed that upon intrafemoral injection of Vk*MYC cells, the disease progression exhibits a sufficiently slow rate, allowing for the development of bone lesions even when a high cell count (1×10^6) is introduced. Additionally, splenocytes demonstrate a capacity to induce bone lesions similar to those caused by BM cells, even with an increased severity attributed to the heightened disease burden. In conclusion, disease dynamics as well as cell source determine the onset of bone lesions.

P-055

Clinical factors determining the survival of multiple myeloma patients with extramedullary disease: a single-center experience

Arda Bayar[1], Tarik Ercan[1], Asu Fergün Yilmaz[1], Tayfur Toptaş[1], Işik Atagündüz[1], Ayşe Tülin Tuğlular[1]

[1]Marmara University

Introduction: Extramedullary disease (EMD) refers to the involvement of soft tissues due to hematogenous spread or the presence of a tumor mass adjacent to bones originating from focal skeletal lesions in patients with multiple myeloma (MM). Although EMD is generally associated with poor prognosis, survival outcomes can vary depending on the site and stage of involvement, as well as the response to therapy. **Methods:** This retrospective study analyzed the medical records of 419 adult patients with MM treated at a tertiary referral center in Türkiye between 2010 and 2022. Ninety-nine patients with confirmed extramedullary involvement based on pathological and/or radiological findings were included. Data were collected from hospital records and the management information system. The average follow-up time was found to be 40±31.5 months. **Results:** Twenty-seven percent of MM patients were found to have EMD. Extramedullary-extraosseous involvement (EM-E) was observed in 27 (27%) patients. Paraosseous involvement (EM-B) was seen in 72 (72%) patients. PET/CT was the most commonly used imaging modality (76%). Cytogenetic analysis was available for 73 patients, revealing high-risk cytogenetics in 16.4% of cases. Most commonly used induction regimen was bortezomib-cyclophosphamide-dexamethasone (VCD) regimen (36%). Median overall survival (OS) and progression-free survival (PFS) of the patients with EMD were 77 months (range: 58 - 95) and 49 months (range: 39 - 58), respectively. In the univariate analysis; advanced ISS staging (OS HR: 2.42, p = 0.024), high levels of serum Beta-2-Microglobulin (OS HR: 2.46, p = 0.020), and light chain disease (OS median survival 24 months / 78 months, p = 0.049) were associated with a worse OS. Secondary EMD, defined as the detection of EMD during MM follow-up, was associated with a worse PFS (HR: 2.87, p = 0.013). In the multivariate analysis; ASCT (OS HR: 0.26, p = 0.001) and low serum creatinine (OS HR: 1.21 p = 0.025) were independently associated with improved OS. Induction regimen groups showed comparable PFS and OS outcomes. The overall survival analysis for patients with high-risk cytogenetic features showed a decrease in survival (OS HR: 1.9, p = 0.259). **Conclusions:** EMD is an adverse prognostic factor in MM. Establishing standardized imaging methods and reporting systems is crucial for diagnosing EMD and clarifying the definitions of EM-E and EM-B. It is also important to conduct studies on biochemical and cytogenetic markers to identify patients at high risk for EMD, determine appropriate follow-up parameters and reach a consensus on treatment. Our study showed that various clinicals factors including ISS staging, levels of serum Beta-2-Microglobulin and creatinine and EMD subtypes, are associated with inferior outcome. With a median PFS of 79.5 months with ASCT compared to 30.1 months without ASCT, our findings emphasize the importance of ASCT in the management of MM patients with EMD.

P-056

Role the combination of FDG pet plus whole body MRI for staging patients in high risk smoldering myeloma: a prospective trial

Claudio Cerchione[1], Davide Nappi[2], Matteo Marchesini[2], Sonia Ronconi[2], Delia Cangini[2], Michela Ceccolini[2], Giorgia Simonetti[2], Gerardo Musuraca[2], Giovanni Martinelli[2], Alice Rossi[2]

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Introduction: In SMM, it is really important to differentiate high risk SMM (HR-SMM), in which treatment could be available thanks to clinical trials. 2016 IMWG criteria state that detection of bone lesions is mandatory for diagnosis of multiple myeloma (MM) as well as ruling out them is essential for diagnosis of SMM. 18F-FDG PET with CT(FDG PET/TC) or whole body CT are indicated to assess lytic lesions. Magnetic resonance imaging (MRI),especially if the previous two are negative, is a diagnostic tool for identifying extra- or para-skeletal manifestations and complications, namely pathological fractures and spinal cord compression, as well as diagnostic tool for MM when > 1 lytic lesion is detected. Whole-

C57BL/6 mice aged 6-8 weeks as recipients. Murine Vk*MYC MM cells of varying concentrations (0.1×10^6 to 1×10^6 cells/mouse) and origins (splenocytes and bone marrow (BM) cells) were transplanted intrafemorally into C57BL/6 mice. PBS-injected C57BL/6 mice were utilized as a control. MM development was monitored through weekly serum protein electrophoresis (SPEP). The hindlimbs and spines were imaged with X-Ray and μ-CT. In addition, MM cells from the spleen and forearm/hip bones were quantified via flow cytometry. **Results:** All mice in this study were successfully engrafted, surviving for 6 to 7 weeks post-injection. Based on the imaging and SPEP results, we observed a direct association between the quantity of injected cells and the severity of bone lesions and tumor burden. Moreover, the cell source (BM cells or splenocytes injected into the femur) played a significant role in the severity of bone lesions. Surprisingly, splenocytes caused more extensive lesions and 25-40% of Vk*MYC cells were present in spleens. In contrast, flow cytometry of BM cells derived from forearms and hip bones showed only 4-10% Vk*MYC cells. Every intrafemorally transplanted mouse developed bone lesions that were enriched in the injected femur (proximal and distal) and occasionally appeared in the tibias and/or non-injected femur, depending on the disease stage. No lesions were detected in the spine of any mice. **Conclusions:** We have observed that upon intrafemoral injection of Vk*MYC cells, the disease progression exhibits a sufficiently slow rate, allowing for the development of bone lesions even when a high cell count (1×10^6) is introduced. Additionally, splenocytes demonstrate a capacity to induce bone lesions similar to those caused by BM cells, even with an increased severity attributed to the heightened disease burden. In conclusion, disease dynamics as well as cell source determine the onset of bone lesions.

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Introduction: Extramedullary disease (EMD) refers to the involvement of soft tissues due to hematogenous spread or the presence of a tumor mass adjacent to bones originating from focal skeletal lesions in patients with multiple myeloma (MM). Although EMD is generally associated with poor prognosis, survival outcomes can vary depending on the site and stage of involvement, as well as the response to therapy. **Methods:** This retrospective study analyzed the medical records of 419 adult patients with MM treated at a tertiary referral center in Türkiye between 2010 and 2022. Ninety-nine patients with confirmed extramedullary involvement based on pathological and/or radiological findings were included. Data were collected from hospital records and the management information system. The average follow-up time was found to be 40±31.5 months. **Results:** Twenty-seven percent of MM patients were found to have EMD. Extramedullary-extraosseous involvement (EM-E) was observed in 27 (27%) patients. Paraosseous involvement (EM-B) was seen in 72 (72%) patients. PET/CT was the most commonly used imaging modality (76%). Cytogenetic analysis was available for 73 patients, revealing high-risk cytogenetics in 16.4% of cases. Most commonly used induction regimen was bortezomib-cyclophosphamide-dexamethasone (VCD) regimen (36%). Median overall survival (OS) and progression-free survival (PFS) of the patients with EMD were 77 months (range: 58 - 95) and 49 months (range: 39 - 58), respectively. In the univariate analysis; advanced ISS staging (OS HR: 2.42, p = 0.024), high levels of serum Beta-2-Microglobulin (OS HR: 2.46, p = 0.020), and light chain disease (OS median survival 24 months / 78 months, p = 0.049) were associated with a worse OS. Secondary EMD, defined as the detection of EMD during MM follow-up, was associated with a worse PFS (HR: 2.87, p = 0.013). In the multivariate analysis; ASCT (OS HR: 0.26, p = 0.001) and low serum creatinine (OS HR: 1.21 p = 0.025) were independently associated with improved OS. Induction regimen groups showed comparable PFS and OS outcomes. The overall survival analysis for patients with high-risk cytogenetic features showed a decrease in survival (OS HR: 1.9, p = 0.259). **Conclusions:** EMD is an adverse prognostic factor in MM. Establishing standardized imaging methods and reporting systems is crucial for diagnosing EMD and clarifying the definitions of EM-E and EM-B. It is also important to conduct studies on biochemical and cytogenetic markers to identify patients at high risk for EMD, determine appropriate follow-up parameters and reach a consensus on treatment. Our study showed that various clinicals factors including ISS staging, levels of serum Beta-2-Microglobulin and creatinine and EMD subtypes, are associated with inferior outcome. With a median PFS of 79.5 months with ASCT compared to 30.1 months without ASCT, our findings emphasize the importance of ASCT in the management of MM patients with EMD.

P-056

Role the combination of FDG pet plus whole body MRI for staging patients in high risk smoldering myeloma: a prospective trial

Claudio Cerchione[1], Davide Nappi[2], Matteo Marchesini[2], Sonia Ronconi[2], Delia Cangini[2], Michela Ceccolini[2], Giorgia Simonetti[2], Gerardo Musuraca[2], Giovanni Martinelli[2], Alice Rossi[2]

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Introduction: In SMM, it is really important to differentiate high risk SMM (HR-SMM), in which treatment could be available thanks to clinical trials. 2016 IMWG criteria state that detection of bone lesions is mandatory for diagnosis of multiple myeloma (MM) as well as ruling out them is essential for diagnosis of SMM. 18F-FDG PET with CT(FDG PET/TC) or whole body CT are indicated to assess lytic lesions. Magnetic resonance imaging (MRI),especially if the previous two are negative, is a diagnostic tool for identifying extra- or para-skeletal manifestations and complications, namely pathological fractures and spinal cord compression, as well as diagnostic tool for MM when > 1 lytic lesion is detected. Whole-

Body MRI (WB-MRI) is a cross-sectional imaging technique for the entire skeletal study, with high sensitivity in detecting bone lesions, not still widely available because of costs and technical reasons. Moreover, since MRI has a higher sensitivity for detecting higher bone marrow cellularity, which is a clue of plasmacellular infiltration without overt bone lytic lesions, WB-MRI can detect a diffuse pattern of marrow involvement. Nevertheless, the IMWG has not yet defined the MRI diffuse pattern as a criterion for symptomatic disease, then the routine detection of this pattern could be relevant in patients with SMM to possibly suggest a group of patients with higher risk of developing lytic lesions and so progression in MM. **Methods:** In our Institution, from January 2021 to January 2023, we performed a prospective trial enrolling 26 consecutive newly diagnosed HR-SMM, according to IMWG, in which WB-MRI was performed according to MY-RADS criteria in combination with FDG PET-CT(median age 56; range 36-85). **Results:** Interim analysis of the comparison between WB-MRI and FDG PET-CT, showed a discordance in 4/26 (15%). In particular, in 3/26 (12%) WB-MRI showed bone lesions that have lead to symptomatic MM diagnosis according to IMWG, while PET-CT was negative. In one case, PET-CT showed a diffuse uptake, not diagnostic for MM, while WB-MRI was negative. WB-MRI showed a 100% of accuracy in detecting SMM and MM. Therefore, WB-MRI has lead to a modification of the prognosis and treatment (observation in SMM vs treatment in MM) in 3/26 patients (11%) (i.e. Fig. 1). In 5/23 (22%) SMM WB-MRI showed a slight diffuse alteration pattern of bone marrow without any overt lytic bone lesion, which could be a potential prognostic evidence. **Conclusions:** Our preliminary results support a fundamental role of WB-MRI plus FDG PET/CT in newly diagnosed high risk SMM, which could modify prognosis and treatment. In particular, WB-MRI plus FDG PET/CT could be more accurate in the detection of bone lesions than FDG PET/CT alone, being able to anticipate MM diagnosis and its treatment. Moreover, a diffuse pattern of marrow involvement could be detected in some HR-SMM patients without any overt lytic lesions: it is questionable if this group is associated with a rapid progression in lytic lesions and so in symptomatic MM.

P-057

Role of the combination of FDG-PET plus whole body MRI for staging newly diagnosed and relapsed/refractory multiple myeloma: a prospective trial

Claudio Cerchione[1], Davide Nappi[2], Matteo Marchesini[2], Sonia Ronconi[2], Delia Cangini[2], Michela Ceccolini[2], Giorgia Simonetti[2], Gerardo Musuraca[2], Giovanni Martinelli[2], Alice Rossi[2]

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Introduction: The integration of FDG-PET/TC and WB-MRI in the diagnosis of MM may results in higher accuracy to detect bone lesion compared to them alone. This could be translated into better outcomes if early detection of myeloma defining events leads to earlier induction or re-induction treatments. **Methods:** In our Institution, from January 2021 to January 2023, we performed a prospective trial enrolling 73 consecutive newly diagnosed and relapsed/refractory MM (median age 63 years - range 85-35), according to IMWG, in which WB-MRI was performed according to MY-RADS criteria in combination with FDG PET/CT. 31/73 (42%) had a newly diagnosed MM, 25/73 (34%) were in follow-up after autologous stem cell transplantation and 17/73 (23%) patients were affected by relapsed/refractory MM. Subsequently, in 2 cases WB- MRI were aborted and not diagnostic so patients were excluded from the final analysis. In our Institution, from January 2021 to January 2023, we performed a prospective trial enrolling 73 consecutive newly diagnosed and relapsed/refractory MM (median age 63 years - range 85-35), according to IMWG, in which WB-MRI was performed according to MY-RADS criteria in combination with FDG PET/CT. 31/73 (42%) had a newly diagnosed MM, 25/73 (34%) were in follow-up after autologous stem cell transplantation and 17/73 (23%) patients were affected by relapsed/refractory MM. Subsequently, in 2 cases WB- MRI were aborted and not diagnostic so patients were excluded from the final analysis. **Results:** In these 71 patients: 52/71 (73%) cases of concordance of WB-MRI and 18F PET-CT, 18/71 (25%) cases of discordance. In this group 15/18 (83%) cases FDG-PET/CT was negative and WB-MRI showed positive findings according to MYRADS criteria (5 micronodular pattern, 9 diffuse pattern e 1 focal pattern) (Figure 1 Newly diagnosed MM – diffuse pattern in WB-MRI, PET negativity), in 3/18 (17%) FDG-PET/CT was positive for focal lesions and WB-MRI was negative. IMWG criteria showed concordance with WB-MRI data in 16/18 (89 %), in 2/18 (11%) case of follow-up after autologous stem cell transplantation PET-CT showed a relapsed focal lesion while WB-MRI was negative. Accuracy of WB-MRI was 69/71 (97%), whilst PET- CT was 55/71 (77%).These results are in agreement with the literature data about the ability of WB-MRI to depict diffuse and micronodular pattern of bone marrow infiltration. **Conclusions:** Our preliminary results support ta potential complementary role of WB-MRI and FDG PET/CT findings, on the management of patients with MM at both diagnosis and relapse. To date, there is no wide availability of WB-MRI because in concerning about costs and technical issues, but data are consistent with its possible future leading role in MM diagnostic work-up.

P-058

Systematic review and meta-analysis of the symptoms and treatment options of multiple myeloma in sub-Saharan African patients

Dominique Patricia Kingue Tatnou [1], Eveline Ngouadjeu Ndongho[2], Françoise Fidèle Ngo Sack[2,3], Nana Narcisse Nwediwe[1], Guy Roussel Takuissu[4], Sebastien Kenmoe[5], Henri Lucien Kamga[6]

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Introduction: Multiple myeloma (MM) is an incurable blood cancer. It is linked to a variety of symptoms, so mastery would allow for early diagnosis and management, particularly in less developed regions, including Sub-Saharan Africa. The aim of this study was to investigate the clinical and radiological symptoms, outcomes, and management characteristics of MM in sub-Saharan African patients. **Methods:** Four databases (PubMed, Web of Science, Global Index Medicus, and Excerpta Medica Databases) were searched in a systematic database and gray literature search and the design of the study has followed PRISMA standard guidelines. **Results:** This study included 32 articles in total, corresponding to 21172 cases. The overall prevalence of multiple myeloma in sub-Saharan African patients was 10.34% (95% CI: 6.35–15.15). Patients with blood diseases were the most affected, with a prevalence of 18.49% (95% CI: 8.60–31.02). The main radiological symptoms of MM in sub-Saharan Africa were bone lesions (lytic bone lesions, osteolytic lesions, and bone deficiency, essentially) and fractures (long bone fractures, vertebral compression fractures, and vertebral collapse, essentially). The main clinical symptoms at diagnosis of MM in sub-Saharan Africa were musculoskeletal (bone pain and lumbar pain, essentially), haematological (clinical anemia), and constitutional (asthenia). The majority of patients with MM in sub-Saharan Africa were in Stage III. The prevalence of death was 38% (95% CI: 27.31–49.28), with a 5-year survival rate of 16.54% (95% CI: 11.33–22.47) in patients with MM in sub-Saharan Africa. Palliative care was the most commonly used treatment (analgesic), followed by chemotherapy (Alexanian essentially) and combination chemotherapy (Vincristine /Carmustine/ Adriamycin /Prednisone essentially). **Conclusions:** This study has a low risk of bias (100% of studies). The findings suggest that multiple myeloma is a serious health condition in sub-Saharan African patients, and the need to educate the community and clinicians on the characteristics of the disease, for early and optimal management.

P-059

Integrative radiomic and immunological analysis for risk classification and outcome prediction in monoclonal gammopathies

Emilia Gigliotta[1], Andrea Rizzuto[1], Anna Maria Corsale[2,3], Mojtaba Shekarkar Azgomi[2,3], Maria Speciale[2,3], Giulio Giannone[4], Alessandro Fidenco[1], Federica Vernuccio[5], Ada Maria Florena[4], Francesco Dieli[2,3], Serena Meraviglia[2,3], Giuseppe Brancatelli[6], Roberto Cannella[6], Sergio Siragusa[3], Cirino Botta[7]

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Introduction: Multiple myeloma (MM) is a hematologic malignancy characterized by the presence of at least 10% of clonal plasma cells (cPCs) in bone marrow (BM). Bone lytic lesions are common in MM patients, and low-dose whole body CT (LD-CT) is the preferred imaging method for evaluating MM-associated bone disease in individuals with monoclonal gammopathy (MG). In this study, by using innovative radiomic techniques that extract additional information (namely "features") from images, such as tissue density and heterogeneity, we aimed to assess the potential of LD-CT radiomic analysis in differentiating pre-malignant conditions from MM within the MG population and predicting patients' outcomes. **Methods:** We collected data from 106 consecutive suspected MG patients who underwent LD-CT from late 2019 to February 2022. The patient cohort consisted of 10 MGUS, 16 SMM, 59 newly diagnosed MM, 18 MM patients undergoing surveillance CT scans during treatment, and 3 healthy subjects. 35 radiomic features were extracted from texture analysis performed through LifeX software. Additionally, we included CBC count, laboratory tests, disease stage, and percentage of BM cPCs from medical records. Flow cytometry data from 27 BM patient samples were analyzed using FlowCT, a recently developed bioinformatic pipeline, to investigate differences in the BM immune microenvironment. **Results:** Unsupervised hierarchical clustering analysis revealed three distinct patient groups based on the distribution of radiomic features. Interestingly, two of these groups were enriched with SMM (SMM-like) or MGUS (MGUS-like) patients. When focusing exclusively on MM patients, this classification demonstrated prognostic relevance, with patients belonging to MGUS or SMM-like groups experiencing a significantly longer I line progression-free survival (PFS) regardless of treatment used (p=0.01). We also observed a strong correlation between five radiomic features and disease status, with a significant reduction features correlated with tissue skewness and an increase in those associated with tissue uniformity moving from MGUS to SMM or MM (p=0.008), possibly indicating tissue replacement by cPCs (in the absence of evident lytic lesions). Additionally, we found associations between radiomic-identified subgroups and BM immune cell composition. MGUS-like MM patients showed an increase in activated T lymphocytes (p=0.01), while SMM-like MM patients exhibited an increase in activated monocytes (p< 0.01). The MM-exclusive group displayed an intermediate profile between the two. **Conclusions:** Our findings highlight how specific cell types within the MM microenvironment can influence BM density, affecting CT results and, ultimately, patients' prognosis. We provide preliminary evidence of the potential utility of CT, beyond detecting bone lytic lesions, in identifying individuals at a higher risk of disease progression or predicting MM outcomes.

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Introduction: Multiple myeloma (MM) is a hematologic malignancy characterized by the presence of at least 10% of clonal plasma cells (cPCs) in bone marrow (BM). Bone lytic lesions are common in MM patients, and low-dose whole body CT (LD-CT) is the preferred imaging method for evaluating MM-associated bone disease in individuals with monoclonal gammopathy (MG). In this study, by using innovative radiomic techniques that extract additional information (namely "features") from images, such as tissue density and heterogeneity, we aimed to assess the potential of LD-CT radiomic analysis in differentiating pre-malignant conditions from MM within the MG population and predicting patients' outcomes. **Methods:** We collected data from 106 consecutive suspected MG patients who underwent LD-CT from late 2019 to February 2022. The patient cohort consisted of 10 MGUS, 16 SMM, 59 newly diagnosed MM, 18 MM patients undergoing surveillance CT scans during treatment, and 3 healthy subjects. 35 radiomic features were extracted from texture analysis performed through LifeX software. Additionally, we included CBC count, laboratory tests, disease stage, and percentage of BM cPCs from medical records. Flow cytometry data from 27 BM patient samples were analyzed using FlowCT, a recently developed bioinformatic pipeline, to investigate differences in the BM immune microenvironment. **Results:** Unsupervised hierarchical clustering analysis revealed three distinct patient groups based on the distribution of radiomic features. Interestingly, two of these groups were enriched with SMM (SMM-like) or MGUS (MGUS-like) patients. When focusing exclusively on MM patients, this classification demonstrated prognostic relevance, with patients belonging to MGUS or SMM-like groups experiencing a significantly longer I line progression-free survival (PFS) regardless of treatment used (p=0.01). We also observed a strong correlation between five radiomic features and disease status, with a significant reduction features correlated with tissue skewness and an increase in those associated with tissue uniformity moving from MGUS to SMM or MM (p=0.008), possibly indicating tissue replacement by cPCs (in the absence of evident lytic lesions). Additionally, we found associations between radiomic-identified subgroups and BM immune cell composition. MGUS-like MM patients showed an increase in activated T lymphocytes (p=0.01), while SMM-like MM patients exhibited an increase in activated monocytes (p< 0.01). The MM-exclusive group displayed an intermediate profile between the two. **Conclusions:** Our findings highlight how specific cell types within the MM microenvironment can influence BM density, affecting CT results and, ultimately, patients' prognosis. We provide preliminary evidence of the potential utility of CT, beyond detecting bone lytic lesions, in identifying individuals at a higher risk of disease progression or predicting MM outcomes.

P-060

An effective approach using ensemble learning based on a random subspace method in laser-induced breakdown spectroscopy to diagnose blood cancer

Gao Jiajia[1], Zuo Zhiyu[1], Chu Yanwu[2], Chen Feng[2], Guo Lianbo[2], Zhu Guoqing[1], Qi Jianwei[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; [2]Wuhan National Laboratory for Optoelectronics (WNLO), Huazhong University of Science and Technology

Introduction: Blood cancer poses serious threats to human health, and the diagnosis of blood cancer is still facing certain challenges. The chemometrics method combined with laser-induced breakdown spectroscopy (LIBS) can be used for cancer detection. However, it was easily influenced by the spectral feature redundancy and noise, resulting in a low accuracy rate. Thus, it is essential to develop more effective methods for blood cancer diagnosis. **Methods:** We proposed an approach using LIBS combined with the ensemble learning based on the random subspace method (RSM). The blood cancer serum samples including lymphoma, multiple myeloma (MM), chronic myelogenous leukemia (CML) and acute myeloid leukemia (AML) were dripped onto a boric acid substrate for LIBS spectrum collection. **Results:** The results showed that these four cancer types could be distinguished by the RSM-LDA model. Compare with linear discriminant analysis (LDA) and k nearest neighbors (kNN), the RSM-LDA model has the highest average accuracy rate and Area Under Curve (AUC), suggesting the RSM-LDA model has the best classification performance. With the RSM-LDA model, the average accuracy rates for lymphoma vs healthy control (HC), MM vs HC, CML vs HC and AML vs HC were from 94.38%, 94.61%, 94.49% and 94.33% to 96.62%, 98.78%, 96.54% and 98.77%, respectively. For cancerous samples classification, the detectable rate was evaluated with the average detectable rates of lymphoma vs HC, MM vs HC, CML vs HC and AML vs HC and were 89.86%, 92.94%, 89.17% and 93.33%, respectively. Furthermore, the average accuracy rate was improved to 91.00%, and 8% of MM spectra and 6% of lymphoma spectra were misidentified to CML calculated. For blood cancer types identification, the detectable rates of lymphoma, MM, CML and AML were 93.75%, 90.00%, 86.67% and 93.33%, respectively, which means the RSM-LDA model can improve the diagnostic performance. **Conclusions:** In conclusion, the RSM-LDA model provides an effective pattern recognition method for LIBS analysis in blood cancer discrimination.

P-061

Spinal involvement predicts for inferior overall survival (OS), progression free survival (PFS) and higher skeletal related events risk in multiple myeloma (MM) patients: a single center experience

Nikolaos Kanellias[1], Agapi Parcharidou[1], Kate Xu[2], William Wilson[3], Rodothea Americanou[4], Adam Benton[5], Sean Molloy[5], Jan Herzog[5], Rikin Hargunani[5], Rakesh Popat[2], Jonathan Sive[2], Lydia Lee[2], Annabel McMillan[2], Xenofon Papanikolaou[2], Neil Rabin[2], Kwee Yong[2], Charalampia Kyriakou[2]

[1]London Northwest University Healthcare NHS trust; [2]NHS University College London Hospital, London, United Kingdom; [3]Cancer Research UK and UCL Cancer Trials Centre, University College London, London, United Kingdom; [4]University College London Hospitals NHS Foundation Trust; [5]Royal National Orthopaedic Hospital NHS Trust

Introduction: Skeletal related events (SRES) include pathological fractures, radiotherapy (XRT), spinal cord compression (SCC) and surgical interventions (SI) and represent frequent complications of MM osteolytic bone disease (MM OBD) with significant impact on patients' survival. Data from previous studies indicate that spine is the most common site affected by OBD. The aim of this study was to explore the impact of OBD and spinal involvement on survival of MM patients. **Methods:** We retrospectively evaluated the electronic records of 905 newly diagnosed MM (NDMM) patients followed up in a single center between 2018-2023. **Results:** We identified 905 NDMM patients (541 (60%) males, 454 (68%) White, 102 (15%) Black, 61 (9%) Asian, and 43 (8%) of mixed or other ethnic origin. Myeloma subtype was IgG in 509 (78%), IgA in 138 (21%) and light chain in 199 patients. Among patients with known cytogenetics, 118/576 (20%) had high risk (HRC). At diagnosis 692/905 (75%) patients had OBD as per IMWG criteria.405 (45%) patients presented with at least one SRE at diagnosis, 258 with single (186 fractures, 6 SCC, 55 XRT, 11 surgery) and 147 with SREs combinations. Fractures distribution: C1-C7(15), T1-T6 (63), T7-T12 (180), lumbar (131), femora (4), clavicles (5), sacrum (3), pubic rami (4), sternum (9), humeri (8) and ribs (30). 396/905 (44%) patients with OBD, had spinal involvement (vertebral fractures, lytic lesions, and diffuse infiltration of the spinal column). The management of spinal involvement included radiotherapy (87), spinal bracing (157) and 74 surgical interventions (36 cement augmentation, 38 metal spinal operation). On univariable analysis, patients with OBD at diagnosis had significantly worse OS than those without (HR = 2.09, 95% CI 1.11-3.94, p=0.02). This remained significant after adjustment for age, sex, heavy and light chain type (HR 2.54, 95% CI 1.16-5.54, p=0.02). Spinal involvement at diagnosis had significantly worse OS (HR 2.95 95% CI 1.61-5.39 p < 0.001), PFS (HR 1.23 95% CI 1.00-1.52 p=0.05). and remained the only significant independent factor for increased SREs risk (HR 4.19 HR2.09-8.40 p< 0.001). Age (HR 1.04 95% CI 1.00-1.08 p=0.05), application of brace at diagnosis (HR 2.09 95% CI 1.01-4.35p=0.05) and the presence of HRC (HR 2.63 95% CI 1.29-5.38, p=0.008) remained independent prognostic factors

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on overall survival in multivariable analysis in patients with OBD at diagnosis. **Conclusions:** The presence of OBD had a profound impact on OS in NDMM patients. Spinal involvement, that was identified in 44% of the patients, was found to be an independent significant prognostic factor for inferior PFS, OS and higher SREs risk. These findings, warrant focus on optimizing further early spinal disease management, to improve survival outcomes in this subgroup of MM patients.

P-062

Real-world evidence of bisphosphonates and denosumab for multiple myeloma

Nieves Lopez-Muñoz[1], Gema Hernández-Ibarburu[2], Rafael Alonso[1], Jose Maria Sanchez[1], Clara Cuellar[1], M Teresa Cedena[1], Ana Jimenez-Ubieto[1], Maria Calbacho[1], Rosa Ayala[1], Laura Meloni[3], David Perez-Rey[4], Joaquín Martínez-López[5]

[1]Hospital 12 de Octubre; [2]Biomedical Informatics Group, Universidad Politécnica de Madrid; [3]TriNetX, LLC, Cambridge, MA USA; [4]Biomedical Informatics Group, Universidad Politécnica de Madrid, Spain; [5]Hematología Hospital 12 de Octubre, Madrid, Spain

Introduction: Bisphosphonates are widely used in multiple myeloma; but only a randomized clinical have showed that zolendronic acid improved survival as well as reduce the number of bone events. On the other hand, Denosumab, a monoclonal antibody targeting RANKL, appears to reduce skeletal-related events, with no known effect on overall survival in patients with multiple myeloma. The objective of this study is analyze the impact of bisphosphonates treatment and denosumab in a large cohort of patients with multiple myeloma. We used data from TriNetx, a global federated health research platform that includes patients from Europe and US. **Methods:** Patients had symptomatic multiple myeloma (ICD-10-CM code C90.0) diagnosed between 2007 and 2022. Comparator cohorts included 3707 MM patients from US and EMEA Collaborative Networks. Analyses have been performed after propensity scoring matching by age, sex, bone fractures in the 3 months prior to diagnosis, bone disease and previous treatment with corticosteroids, calcium and vitamin D. Patients treated with bisphosphonates included: Pamidronate and Zolendronic acid. Kaplan−Meier analysis was used to estimate survival probabilities, and between-group differences were tested using the log-rank test and hazard ratio. **Results:** First of all, we compared patients treated with bisphosphonates vs no treatment (2310 patients in each cohort). Patients treated with bisphosphonates had a significant longer overall survival (OS) (HR 0.748 (0.665-0.841, p< 0.001). (Figure 1). Thereafter, we compared patients treated with denosumab vs no treatment (968 patients in each cohort). Patients treated with denosumab had a significant longer overall survival (OS) (HR 0.708 (0.597-0.839, p< 0.001). (Figure 2). Finally, we compared patients treated with bisphosphonates vs denosumab (960 patients in each cohort). No difference in overall survival (OS) between the two groups of patients (HR 1.070 (0.907-1.263, p=0.271). (Figure 3). Regarding the increased risk of fractures or the need for orthopedic surgery, no differences were found between the patient groups. **Conclusions:** This large-scale study based on real-world data confirms the bisphosphonates and denosumab prolong survival in MM, with no differences between them.

P-063

Comparison of whole-body imaging in multiple myeloma with respect to lytic involvement and presence of extramedullary disease

Jiri Minarik[1], Michaela Jurinova[2], Vojtech Mahr[2], Eva Buriankova[1], Miroslav Herman[1], Jan Hrbek[1], Vojtech Latal[1], Petra Krhovska[1], Jaroslav Bacovsky[1], Tomas Pika[1]

[1]University Hospital Olomouc; [2]Faculty of Medicine and Dentistry, Palacky University Olomouc

Introduction: The presence of osteolytic involvement in multiple myeloma (MM) is one of the halmarks of the disease. In approximately 5-20% of patients, prognostically negative paramedullary and/or extramedullary disease (EM) is detectable, based on the imaging technique used. Conventional X-ray has only limited sensitivity in the detection of lytic involvement, especially in the spine, and a very low sensitivity for EM. Therefore, more sophisticated whole-body imaging techniques are recommended, such as magnetic resonance imaging (MRI), low dose computed tomography (LD-CT) or positron emission tomography with computed tomography (PET/CT). Each of them has slightly different outcomes and limitations. Our aim was to compare the sensitivity of selected whole-body imaging techniques in the detection of osteolytic involvement and EM. **Methods:** We performed a large retrospective assessment of 411 MRI, 304 PET/CT, 269 Technetium-sestaMIBI and 151 LD-CT findings in 270 patients with MM, smoldering myeloma (SMM) and monoclonal gammopathy of undetermined significance (MGUS). We assessed the presence and number of lytic lesions by each technique and similarly the presence and number of EM. In 80 patients we had concurrent data from PET/CT, MRI and MIBI at the same time, therefore we compared these patients and sensitivity of the three techniques separately. We used statistical software IBM SPSS Statistics, version 23. For the comparison of the techniques, we used Chi-quadrat test, McNemara test, Friedman test and Wilcoxon pair test with Bonferroni correction, the level of statistical significance was $p < 0,05$. **Results:** The imaging techniques had following sensitivity in detection of osteolytic lesions: LD-CT 76,8%, MRI 66,4%, PET/CT 53,6% and MIBI 38,7%. Most examinations detected 3 and more lesions, the presence of only 1 lesion was up to 6% and 2 lesions up to 4% in all techniques. When assessing the presence of EM, the most sensitive technique was PET/CT – 31,3%, followed by LD/CT – 13,9% and MRI – 6,1%, the lowest number of EM were identified by MIBI – 3,0%. Within the assessment of the 80 patients with concurrent imaging by 3 techniques, the most sensitive method for lytic bone assessment was MRI with 81,2%, followed by PET/CT – 58,7% and MIBI – 43,7%. The detection of EM was following: MRI 7,6%, PET/CT 21,2% and MIBI 2,5%; the level of concordance between MRI and PET/CT was 86,3%, between MRI and MIBI 93,8% and between PET/CT and MIBI 80%. **Conclusions:** The whole-body imaging techniques used for

on overall survival in multivariable analysis in patients with OBD at diagnosis. **Conclusions:** The presence of OBD had a profound impact on OS in NDMM patients. Spinal involvement, that was identified in 44% of the patients, was found to be an independent significant prognostic factor for inferior PFS, OS and higher SREs risk. These findings, warrant focus on optimizing further early spinal disease management, to improve survival outcomes in this subgroup of MM patients.

P-062

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Introduction: The presence of osteolytic involvement in multiple myeloma (MM) is one of the halmarks of the disease. In approximately 5-20% of patients, prognostically negative paramedullary and/or extramedullary disease (EM) is detectable, based on the imaging technique used. Conventional X-ray has only limited sensitivity in the detection of lytic involvement, especially in the spine, and a very low sensitivity for EM. Therefore, more sophisticated whole-body imaging techniques are recommended, such as magnetic resonance imaging (MRI), low dose computed tomography (LD-CT) or positron emission tomography with computed tomography (PET/CT). Each of them has slightly different outcomes and limitations. Our aim was to compare the sensitivity of selected whole-body imaging techniques in the detection of osteolytic involvement and EM. **Methods:** We performed a large retrospective assessment of 411 MRI, 304 PET/CT, 269 Technetium-sestaMIBI and 151 LD-CT findings in 270 patients with MM, smoldering myeloma (SMM) and monoclonal gammopathy of undetermined significance (MGUS). We assessed the presence and number of lytic lesions by each technique and similarly the presence and number of EM. In 80 patients we had concurrent data from PET/CT, MRI and MIBI at the same time, therefore we compared these patients and sensitivity of the three techniques separately. We used statistical software IBM SPSS Statistics, version 23. For the comparison of the techniques, we used Chi-quadrat test, McNemara test, Friedman test and Wilcoxon pair test with Bonferroni correction, the level of statistical significance was $p < 0,05$. **Results:** The imaging techniques had following sensitivity in detection of osteolytic lesions: LD-CT 76,8%, MRI 66,4%, PET/CT 53,6% and MIBI 38,7%. Most examinations detected 3 and more lesions, the presence of only 1 lesion was up to 6% and 2 lesions up to 4% in all techniques. When assessing the presence of EM, the most sensitive technique was PET/CT – 31,3%, followed by LD/CT – 13,9% and MRI – 6,1%, the lowest number of EM were identified by MIBI – 3,0%. Within the assessment of the 80 patients with concurrent imaging by 3 techniques, the most sensitive method for lytic bone assessment was MRI with 81,2%, followed by PET/CT – 58,7% and MIBI – 43,7%. The detection of EM was following: MRI 7,6%, PET/CT 21,2% and MIBI 2,5%; the level of concordance between MRI and PET/CT was 86,3%, between MRI and MIBI 93,8% and between PET/CT and MIBI 80%. **Conclusions:** The whole-body imaging techniques used for

the assessment of myeloma bone disease have different sensitivity in the evaluation of lytic lesions as well as extramedullary disease. For the assessment of bone lesions, MRI seems to be most sensitive, still, with very similar outcomes in CT based techniques. For EM, there is high concordance between PET/CT, MRI and MIBI, still PET/CT is able to detect the highest percentage of extramedullary lesions. Supported by MH CZ – DRO (FNOl, 00098892).

P-064

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P-065

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P-065

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P-066

BCMA-CAR-T cells with synthetic circuits of CST6 lyse tumor cells and suppress osteolytic lesions in multiple myeloma

Fumou Sun[1], Yan Cheng[1], Jin-Ran Chen[1], Dongzheng Gai[1], Hongwei Xu[1], Frits van Rhee[2], Guido Tricot[1], John Shaughnessy[2], Fenghuang Zhan[2]

[1]University of Arkansas for Medical Sciences; [2]Myeloma Center, University of Arkansas for Medical Sciences

Introduction: Osteolytic lesions are a hallmark of multiple myeloma (MM). We have previously demonstrated that cystatin E/M (CST6) suppresses MM bone disease by blocking osteoclast differentiation. Recombinant CST6 protein has a short serum half-life in a mouse model. As a therapeutic agent, CST6 protein concentrations should be maintained at relatively high levels. B cell maturation antigen (BCMA)-specific chimeric antigen receptor (CAR)-T cell therapies are associated with high response rates in the treatment of MM. Fourth-generation CARs have been developed and are ideal to deliver CST6, which is a secretory protein, close to nascent focal lesions. Here, we demonstrate that BCMA-CST6-CAR-T cells simultaneously ablate MM cells and suppress osteolytic lesions. **Methods:** The BCMA-CST6-CAR vector contains BCMA-scFv and a 4-1BB co-activation domain with CD3ζ. A P2A self-cleaving peptide was inserted between CAR and CST6. CAR-T cells were incubated with MM1.S cells at a ratio of 5:1 for 24 h. To evaluate the in vivo anti-tumor activity and anti-bone resorption of BCMA-CST6-CAR-T cells, we injected MM1.S cells expressing luciferase into NSG mice. On day 7, MM-bearing mice received CAR-T cells. These mice were sacrificed on day 35, mouse serum CST6 concentrations were evaluated by ELISA, and mouse tibiae were collected for μCT and TRAP staining. **Results:** The percentage of lysed MM1.S cells was 77.2% after 24 h co-culturing with CAR-T cells. No difference in killing was observed between BCMA-CAR-T group and BCMA-CST6-CAR-T group. T cell activation marker CD69 was significantly increased in BCMA-CST6-CAR-T (70.9%) group compared to the MOCK-CAR-T group (9.2%). Bioluminescence imaging of MM-bearing mice revealed that BCMA-CST6-CAR-T cells affected excellent antitumor activity, yielding near-complete tumor clearance by day 21. Again, BCMA-CST6-CAR-T cells and BCAM-CAR-T cells showed very similar effects on inhibiting tumor growth. CST6 serum concentration was significantly higher in the BCAM-CST6-CAR-T group (938.4 ng/ml) compared to the MOCK group (60.9 ng/ml) and BCMA-CAR-T group (64.2 ng/ml) ($P< 0.001$), indicating that BCMA-CST6-CAR-T cells secrete high levels of CST6 protein in vivo. μCT images of mouse tibiae showed that BCMA-CST6-CAR-T cells significantly suppressed osteolytic lesions in MM-bearing mice. TRAP staining of mouse tibia sections demonstrated that the BCMA-CST6-CAR-T cells significantly reduced osteoclast numbers and the proportion of bone surface occupied by osteoclasts. **Conclusions:** This work presents a rational approach to engineering BCMA-CST6-CAR-T cells that can effectively target MM cells and release large amounts of CST6 protein, which efficiently suppresses osteolytic lesions in MM.

P-067

Intestinal nitrogen-recycling bacteria contribute to osteolysis in multiple myeloma

Qin Yang[1], Yinghong Zhu[2], Xingxing Jian[1], Yanjuan He[1], Jing Liu[1], Wen Zhou[3]

[1]Third Xiangya Hospital, Central South University; [2]Cancer Research Institute, School of Basic Medical Sciences, Central South University, Changsha, Hunan, China; [3]State Key Laboratory of Experimental Hematology,Cancer Research Institute, School of Basic Medical Sciences, Central South University, Changsha, Hunan, China

Introduction: Gut microbiota in bone remodeling and regulation has been defined recently. Our previous work has demonstrated that intestinal nitrogen-recycling bacteria enriched in multiple myeloma (MM) and promoted MM progression. However, whether this significantly enriched gut nitrogen-recycling bacteria regulate myeloma bone remodeling remained ill-defined. **Methods:** Shotgun metagenomic sequencing and 16s rRNA qPCR were utilized to screen differential species. Fecal microbiota and single bacteria transplantation were conducted to confirm osteolysis. Further experiments were performed to explore the mechanisms. During the project, the sampling procedure was approved by the Central South University (CSU) Medical Ethics Committee, and animal work was performed under the guidelines of the Institutional Animal Care and local veterinary office and ethics committee of CSU. **Results:** Intestinal nitrogen-recycling bacteria is markedly increased in MM patients with osteolysis. To explore the differential bacteria of MM patients with osteolysis, shotgun metagenomic sequencing was performed and demonstrated the domination of pathological bacteria and the reduced probiotics. Especially, the abundance of E. cloacae was significantly increased, as well as a significant correlation between the severity of osteolysis was defined. Intestinal nitrogen-recycling bacteria promote osteolysis in MM. To further assess the effect of enriched bacteria on osteolysis, fecal microbiota transplantation from MM patients with osteolysis showed more severe osteolysis in MM mice, demonstrating lower BV/TV, Tb.N, and Tb.Th of micro-CT, and higher concentrations of CTX-1 and PINP. Additionally, longitudinal analysis of the colonization demonstrated the gradual domination of E. cloacae. Furthermore, transplantation with E. cloacae confirmed the function of osteolysis in MM mice. NH_4^+ produced by E. cloacae bolsters MM osteoclastogenesis. Finally, to explore the functional mechanisms, a concentration of NH_4^+ was detected and showed a significant increase in MM with osteolysis and a positive correlation withE. cloacae. Meanwhile, analysis of clinical characteristics demonstrated a positive correlation between the concentration of NH_4^+ and osteolysis in MM patients. Furthermore, NH_4^+ was confirmed to promote osteolysis in MM mice, as well as accelerate osteoclastogenesis in vitro with an increased expression of CCL3 detected by WB in MM cells and ELISA in MM mice. Additionally, the higher expression deaminase gene dcd was detected and then a strain of deleted dcd of E. cloacae was testified

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Introduction: Gut microbiota in bone remodeling and regulation has been defined recently. Our previous work has demonstrated that intestinal nitrogen-recycling bacteria enriched in multiple myeloma (MM) and promoted MM progression. However, whether this significantly enriched gut nitrogen-recycling bacteria regulate myeloma bone remodeling remained ill-defined. **Methods:** Shotgun metagenomic sequencing and 16s rRNA qPCR were utilized to screen differential species. Fecal microbiota and single bacteria transplantation were conducted to confirm osteolysis. Further experiments were performed to explore the mechanisms. During the project, the sampling procedure was approved by the Central South University (CSU) Medical Ethics Committee, and animal work was performed under the guidelines of the Institutional Animal Care and local veterinary office and ethics committee of CSU. **Results:** Intestinal nitrogen-recycling bacteria is markedly increased in MM patients with osteolysis. To explore the differential bacteria of MM patients with osteolysis, shotgun metagenomic sequencing was performed and demonstrated the domination of pathological bacteria and the reduced probiotics. Especially, the abundance of E. cloacae was significantly increased, as well as a significant correlation between the severity of osteolysis was defined. Intestinal nitrogen-recycling bacteria promote osteolysis in MM. To further assess the effect of enriched bacteria on osteolysis, fecal microbiota transplantation from MM patients with osteolysis showed more severe osteolysis in MM mice, demonstrating lower BV/TV, Tb.N, and Tb.Th of micro-CT, and higher concentrations of CTX-1 and PINP. Additionally, longitudinal analysis of the colonization demonstrated the gradual domination of E. cloacae. Furthermore, transplantation with E. cloacae confirmed the function of osteolysis in MM mice. NH_4^+ produced by E. cloacae bolsters MM osteoclastogenesis. Finally, to explore the functional mechanisms, a concentration of NH_4^+ was detected and showed a significant increase in MM with osteolysis and a positive correlation withE. cloacae. Meanwhile, analysis of clinical characteristics demonstrated a positive correlation between the concentration of NH_4^+ and osteolysis in MM patients. Furthermore, NH_4^+ was confirmed to promote osteolysis in MM mice, as well as accelerate osteoclastogenesis in vitro with an increased expression of CCL3 detected by WB in MM cells and ELISA in MM mice. Additionally, the higher expression deaminase gene dcd was detected and then a strain of deleted dcd of E. cloacae was testified

small sample size, this is one the first studies describing Whole body low dose whole body CT in myeloma patients in Indian Scenario.

P-066

BCMA-CAR-T cells with synthetic circuits of CST6 lyse tumor cells and suppress osteolytic lesions in multiple myeloma

Fumou Sun[1], Yan Cheng[1], Jin-Ran Chen[1], Dongzheng Gai[1], Hongwei Xu[1], Frits van Rhee[2], Guido Tricot[1], John Shaughnessy[2], Fenghuang Zhan[2]

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Introduction: Osteolytic lesions are a hallmark of multiple myeloma (MM). We have previously demonstrated that cystatin E/M (CST6) suppresses MM bone disease by blocking osteoclast differentiation. Recombinant CST6 protein has a short serum half-life in a mouse model. As a therapeutic agent, CST6 protein concentrations should be maintained at relatively high levels. B cell maturation antigen (BCMA)-specific chimeric antigen receptor (CAR)-T cell therapies are associated with high response rates in the treatment of MM. Fourth-generation CARs have been developed and are ideal to deliver CST6, which is a secretory protein, close to nascent focal lesions. Here, we demonstrate that BCMA-CST6-CAR-T cells simultaneously ablate MM cells and suppress osteolytic lesions. **Methods:** The BCMA-CST6-CAR vector contains BCMA-scFv and a 4-1BB co-activation domain with CD3ζ. A P2A self-cleaving peptide was inserted between CAR and CST6. CAR-T cells were incubated with MM1.S cells at a ratio of 5:1 for 24 h. To evaluate the in vivo anti-tumor activity and anti-bone resorption of BCMA-CST6-CAR-T cells, we injected MM1.S cells expressing luciferase into NSG mice. On day 7, MM-bearing mice received CAR-T cells. These mice were sacrificed on day 35, mouse serum CST6 concentrations were evaluated by ELISA, and mouse tibiae were collected for μCT and TRAP staining. **Results:** The percentage of lysed MM1.S cells was 77.2% after 24 h co-culturing with CAR-T cells. No difference in killing was observed between BCMA-CAR-T group and BCMA-CST6-CAR-T group. T cell activation marker CD69 was significantly increased in BCMA-CST6-CAR-T (70.9%) group compared to the MOCK-CAR-T group (9.2%). Bioluminescence imaging of MM-bearing mice revealed that BCMA-CST6-CAR-T cells affected excellent antitumor activity, yielding near-complete tumor clearance by day 21. Again, BCMA-CST6-CAR-T cells and BCAM-CAR-T cells showed very similar effects on inhibiting tumor growth. CST6 serum concentration was significantly higher in the BCAM-CST6-CAR-T group (938.4 ng/ml) compared to the MOCK group (60.9 ng/ml) and BCMA-CAR-T group (64.2 ng/ml) ($P< 0.001$), indicating that BCMA-CST6-CAR-T cells secrete high levels of CST6 protein in vivo. μCT images of mouse tibiae showed that BCMA-CST6-CAR-T cells significantly suppressed osteolytic lesions in MM-bearing mice. TRAP staining of mouse tibia sections demonstrated that the BCMA-CST6-CAR-T cells significantly reduced osteoclast numbers and the proportion of bone surface occupied by osteoclasts. **Conclusions:** This work presents a rational approach to engineering BCMA-CST6-CAR-T cells that can effectively target MM cells and release large amounts of CST6 protein, which efficiently suppresses osteolytic lesions in MM.

P-067

Intestinal nitrogen-recycling bacteria contribute to osteolysis in multiple myeloma

Qin Yang[1], Yinghong Zhu[2], Xingxing Jian[1], Yanjuan He[1], Jing Liu[1], Wen Zhou[3]

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P-068

Implementation of next generation sequencing as best tool for routine evaluation of minimal residual disease in the daily practice of multiple myeloma patients

Silvia Armuzzi[1,2], Marina Martello[1,2], Barbara Taurisano[1,2], Ilaria Vigliotta[1,2], Ignazia Pistis[2], Vincenza Solli[1,2], Enrica Borsi[2], Gaia Mazzocchetti[1,2], Andrea Poletti[1,2], Ajsi Kanapari[1,2], Elena Zamagni[1,2], Lucia Pantani[1,2], Serena Rocchi[1,2], Paola Tacchetti[1,2], Ilaria Rizzello[2], Michele Cavo[2], Carolina Terragna[2]

[1]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Seràgnoli Institute of Hematology, Bologna

Introduction: In recent years, minimal residual disease (MRD) reduction up to undetectable level has become an independent prognostic factor in Multiple Myeloma (MM) and MRD assessment might become a helpful tool to guide treatment. Here we present the implementation of a highly sensitive Next Generation Sequencing (NGS) workflow for MRD assessment in MM daily clinical practice. **Methods:** 299 newly diagnosed transplant-eligible MM patients (pts) were included in the study between 2016 and 2023, and screened by NGS for clonotype (ID) definition. MRD was assessed pre-maintenance, at the achievement of at least very good partial response, and, thereafter, once a year. A commercial assay covering IgH and IgK genes (Invivoscribe) was employed for ID definition in bone marrow (BM) CD138+ plasma cells (PCs), and for MRD measurement in BM whole blood cells. Data were analyzed by Lymphotrack Dx and MRD software (Invivoscribe). **Results:** ID screening was possible in all pts, by using 70ng of starting DNA and by sequencing firstly IgH-FR1 and Igk and, in cases of no ID identification, also IgH-FR2 and -FR3. Overall, 490 clonal sequences were identified in 281/299 pts (94%). Polyclonal results (6%) were mainly due to low CD138+ PCs percentage in pre (<1.6%) and post (< 84%) enrichments, as well as to low cells number (p-value <.05). MRD trackable sequences were selected thanks to an originality score defined according to V and J regions specificities, CDR3 insertions and/or deletions and clonality percentage. Overall, 246 IgH (177 FR1, 43 FR2 and 26 FR3) and 35 IgK IDs were selected, with a median clonality percentage of 64.5% (2.5%-98.6%). In 10 pts, 2 IDs were identified and used for MRD monitoring, to improve MRD analysis' sensitivity. For MRD detection, 2µg input DNA's triplicates were sequenced with a 1,5 million reads depth. A confidence ≥90% was required to define the sensitivity level. So far, 317 MRD measurements were evaluated in 111/281 pts, (at least one per pts), with an overall median follow-up of 47 months (range 6-83). MRD results were defined negative, with 10-5 sensitivity in 80% of cases, in 146/317 cases; positive in 117/317 cases, with MRD ranging from 1.1x10-5 to 2.3x10-4; low positive (when measurements had < 90% result's confidence) in 54/317 cases, with MRD ranging from 9.9x10-9 to 9,8x10-5. In 50/111 pts, MRD was also measured pre-maintenance (67 evaluations), with 24/67 MRD negative results. **Conclusions:** In conclusion, NGS was successfully implemented as best tool in the daily practice of MM pts. The clonotype was defined in almost all pts, thus allowing MRD molecular monitoring. CD138+ PCs' both quality and amount were critical for successful clonotyping. For MRD assessment, a regular samples' workflow (at least 5 per week) was needed to both limit costs and maintain an acceptable reporting time (7 days). Results confirm the feasibility of MRD assessment by NGS in the daily practice, supporting the upcoming need of MM pts personalized management. **Acknowledgment:** AIRC IG2018-22059.

P-069

Liquid biopsy monitoring is more sensitive than alternative techniques in extramedullary multiple myeloma

Nicholas Bingham[1], Daniel Wong[1], Antonia Reale[1], Tiffany Khong[1], Sridurga Mithraprabhu[1], Andrew Spencer[1]

[1]Alfred Health-Monash University, Melbourne, VIC, Australia

Introduction: Extramedullary disease (EMD) affects 30% of multiple myeloma (MM) patients, predicting poor overall survival due to aggressive disease kinetics and multi-drug resistance. Current methods for detection and monitoring include PET/CT scans; alternatives such as bone marrow (BM) biopsies and consensus response criteria (CRC) are limited as EMD is frequently non-secretory or with minimal BM involvement. EMD is associated with driver mutations (DM) in the MAPK pathway (KRAS, NRAS and BRAF). We have shown DM are detectable in cell free DNA (cfDNA) in EMD patients and now sought to clarify the role of cfDNA characterisation in EMD patients. **Methods:** Plasma was collected in Streck DNA tubes. cfDNA was extracted using QIAGEN QIAamp® Circulating Nucleic Acid Kit. DM were identified by whole genome sequencing or whole exome sequencing. Once identified, droplet digital PCR was used to detect DM in cfDNA at additional timepoints, including prior to EMD development, after treatment and at relapse. **Results:** 13 patients were included. 100% had the EMD DM detected in the blood at the time of EMD diagnosis with variant allele frequency (VAF) ranging from 0.05% to 37.63%. At diagnosis, low cfDNA VAF associated with low disease burden on PET/CT, however high VAFs do not necessarily reflect PET/CT burden and may reflect factors such as tumour necrosis. Eight patients had at least two cfDNA timepoints. Changes in the cfDNA VAF over time mirrored PET-CT-defined response to therapy and relapse. We then compared cfDNA levels after therapy with other response parameters- PET/CT, CRC and EuroFlow minimal residual disease (MRD). Response assessments by cfDNA appeared complementary to PET/CT, with 3 cases showing incongruity between PET/CT and cfDNA; 2 had cfDNA positivity with PET/CT negativity and 1 cfDNA negativity but PET/CT positivity. In patients with secretory

to alleviate osteolysis in MM mice. **Conclusions:** Altogether, our present findings demonstrate that enriched intestinal nitrogen-recycling bacteria contribute to osteolysis by interacting with host metabolism, which reports on the characteristic gut microbiome and offers a new potential therapeutic strategy for the intervention of MM with osteolysis.

P-068

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P-069

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disease, cfDNA was more sensitive compared to CRC, with DM detectable in cfDNA in 3 patients in a CR. cfDNA assessment also outperformed MRD testing, with 40% of MRD negative timepoints demonstrating cfDNA positivity. Importantly, changes in VAF were prognostic. Patients achieving cfDNA negativity had the longest remissions (median 23.5 months) whereas those who did not demonstrated short time to progression (median 6 months). In 2 patients who experienced EMD relapse from cfDNA negativity, cfDNA became positive prior to overt relapse by PET/CT, CRC, or BM MRD. Finally, DM were detectable in cfDNA prior to the initial development of EMD, in one case two years before EMD diagnosis. Liquid biopsies from an additional 24 patients are being analysed. **Conclusions:** In EMD patients MAPK activating DM are detectable in cfDNA. cfDNA is complementary to PET/CT scanning, more sensitive than BM MRD and CRC, and is a predictor of EMD relapse. DM exist in cfDNA prior to EMD, and their detection may allow tailored monitoring strategies and early intervention.

P-070

Failure to clear circulating tumor cells after one week of daratumumab, bortezomib and dexamethasone is associated with a reduced progression-free survival for myeloma patients

Christian Bryant[1], Edward Abadir[1], Nicole Wong Doo[2], Adam Bryant[3], Georgia McCaughan[4], Shihong Yang[1], Vinay Vanguru[1], Tracy King[1], Douglas Joshua[1], Phoebe Joy Ho[1]

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Introduction: Obtaining bone marrow MRD negativity after induction therapy is associated with a superior PFS and OS. Conversely, patients with a high level of circulating tumor cells (CTC) in the peripheral blood prior to commencing front-line therapy have inferior outcomes. Less is known about the impact of CTC level at relapse, and the implications of early changes in CTC levels are not known. In Australia, Bortezomib, Daratumumab and Dexamethasone (BDd) is only available as 2nd line therapy, hence almost all patients receive this combination making them a group who are treated homogeneously and are highly representative of MM patients. We hypothesized that CTC level and their early changes would predict long term outcome in MM patients receiving BDd at 2nd line. **Methods:** Patients receiving BDd at second line were identified. Peripheral blood was collected prior to therapy and on day 8. Blood was analyzed within 24 hours using the Euroflow next-generation flow cytometry platform and the Infinocyte CTC analysis database. **Results:** 28 patients have been analysed with a median follow-up of 232 days (range 46-722). The median limit of detection was 0.00035%, and the median limit of quantification was 0.00081%. CTC were detectable prior to treatment in 27/28 patients (median value 0.0087%, range 0.00081-6.8%). CTC were detectable in 10/28 on Day 8 of cycle 1 (median value 0.0054%, range 0.00028 – 0.33%). There were no differences in age, sex or prior Bortezomib exposure between those who cleared CTC by day 8 and those who did not. Failure to clear CTC was associated with an increased incidence of high risk FISH (50% vs 17%) and gain 1q (50% vs 28%), increased exposure to prior Lenalidomide (60% vs 23%), and a shorter median time from diagnosis (835 vs 1239 days) when compared with those who cleared CTC. Patients who had higher levels of CTC prior to commencing second line (>0.01%) had a shorter PFS than those who did not (median PFS 400 days vs not reached, p=0.0482). The failure to clear CTC by day 8 had a strong correlation with PFS. Patients who failed to clear had a median PFS of 359 days whilst median PFS is not yet reached for those who cleared CTC (p=0.0194). **Conclusions:** This data suggests that failure to clear CTC from the blood within one week of second line BDd predicts patients who are destined for brief remissions. This can be achieved without the need for invasive bone marrow biopsies. Early identification of patients who will have short remissions could allow for a trial of early intensification of therapy to improve outcomes.

P-071

Hevylite in the multiple myeloma patient pathway

Lauren Campbell[1], Ross Sadler[1], Karthik Ramasamy[1], Jaimal Kothari[1]

[1]Oxford University Hospitals NHS Foundation Trust, Oxford, UK

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disease, cfDNA was more sensitive compared to CRC, with DM detectable in cfDNA in 3 patients in a CR. cfDNA assessment also outperformed MRD testing, with 40% of MRD negative timepoints demonstrating cfDNA positivity. Importantly, changes in VAF were prognostic. Patients achieving cfDNA negativity had the longest remissions (median 23.5 months) whereas those who did not demonstrated short time to progression (median 6 months). In 2 patients who experienced EMD relapse from cfDNA negativity, cfDNA became positive prior to overt relapse by PET/CT, CRC, or BM MRD. Finally, DM were detectable in cfDNA prior to the initial development of EMD, in one case two years before EMD diagnosis. Liquid biopsies from an additional 24 patients are being analysed. **Conclusions:** In EMD patients MAPK activating DM are detectable in cfDNA. cfDNA is complementary to PET/CT scanning, more sensitive than BM MRD and CRC, and is a predictor of EMD relapse. DM exist in cfDNA prior to EMD, and their detection may allow tailored monitoring strategies and early intervention.

P-070

Failure to clear circulating tumor cells after one week of daratumumab, bortezomib and dexamethasone is associated with a reduced progression-free survival for myeloma patients

Christian Bryant[1], Edward Abadir[1], Nicole Wong Doo[2], Adam Bryant[3], Georgia McCaughan[4], Shihong Yang[1], Vinay Vanguru[1], Tracy King[1], Douglas Joshua[1], Phoebe Joy Ho[1]

[1]Royal Prince Alfred Hospital; [2]Concord Repatriation and General Hospital; [3]Liverpool Hospital; [4]St Vincents Hospital

Introduction: Obtaining bone marrow MRD negativity after induction therapy is associated with a superior PFS and OS. Conversely, patients with a high level of circulating tumor cells (CTC) in the peripheral blood prior to commencing front-line therapy have inferior outcomes. Less is known about the impact of CTC level at relapse, and the implications of early changes in CTC levels are not known. In Australia, Bortezomib, Daratumumab and Dexamethasone (BDd) is only available as 2nd line therapy, hence almost all patients receive this combination making them a group who are treated homogeneously and are highly representative of MM patients. We hypothesized that CTC level and their early changes would predict long term outcome in MM patients receiving BDd at 2nd line. **Methods:** Patients receiving BDd at second line were identified. Peripheral blood was collected prior to therapy and on day 8. Blood was analyzed within 24 hours using the Euroflow next-generation flow cytometry platform and the Infinocyte CTC analysis database. **Results:** 28 patients have been analysed with a median follow-up of 232 days (range 46-722). The median limit of detection was 0.00035%, and the median limit of quantification was 0.00081%. CTC were detectable prior to treatment in 27/28 patients (median value 0.0087%, range 0.00081-6.8%). CTC were detectable in 10/28 on Day 8 of cycle 1 (median value 0.0054%, range 0.00028 – 0.33%). There were no differences in age, sex or prior Bortezomib exposure between those who cleared CTC by day 8 and those who did not. Failure to clear CTC was associated with an increased incidence of high risk FISH (50% vs 17%) and gain 1q (50% vs 28%), increased exposure to prior Lenalidomide (60% vs 23%), and a shorter median time from diagnosis (835 vs 1239 days) when compared with those who cleared CTC. Patients who had higher levels of CTC prior to commencing second line (>0.01%) had a shorter PFS than those who did not (median PFS 400 days vs not reached, p=0.0482). The failure to clear CTC by day 8 had a strong correlation with PFS. Patients who failed to clear had a median PFS of 359 days whilst median PFS is not yet reached for those who cleared CTC (p=0.0194). **Conclusions:** This data suggests that failure to clear CTC from the blood within one week of second line BDd predicts patients who are destined for brief remissions. This can be achieved without the need for invasive bone marrow biopsies. Early identification of patients who will have short remissions could allow for a trial of early intensification of therapy to improve outcomes.

P-071

Hevylite in the multiple myeloma patient pathway

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P-072

Multiple myeloma patient perceptions of minimal residual disease testing

Jay Hydren[1], Jorge Arturo Hurtado Martinez[1], Felipe Flores Quiroz[1], Patricia Alejandra Flores Pérez[1], Andrea Isabel Robles Espinoza[1], Andrea Jimena Cuevas Vicencio[1], Marilú Nájera Flores[1], Eduardo Franco Hernandez[1], Ana Sahagun Sanchez Aldana[1], Nathan Sweeney[1], Jennifer Ahlstrom[1]

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P-073

Modelling multiple myeloma using best clinical response to treatment to predict overall survival

Adam Irving[1], Dennis Petrie[1], Laura Fanning[1], Anthony Harris[1], Andrew Spencer[2], Erica Wood[1], Cameron Wellard[1], Elizabeth Moore[1], Neil Waters[1], Zoe McQuilten[1]

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In all analyses the HLC assay showed increased sensitivity and utility over the M-protein technique. **Conclusions:** Blood-based assays can be used prior to bone marrow analysis to help influence decisions and improve patient experience. This strategy can also impact patient follow up post initial treatment: 1. At best response, an abnormal uHLC or HLCr suggests a positive MRD status, meaning a possible reduction or delay in the requirement for bone marrow assessment. 2. All patients in ≥VGPR should have HLC performed alongside conventional assays during follow up. 3. If uHLC values become abnormal over follow up then it should be assumed that the patient is about to undergo relapse. The measurement of HLC values increases the sensitivity for detecting MRD, giving further clarification of response status and predicting early relapse.

P-072

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P-073

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versus Stable Disease does not appear to be as strong as the other categories. As expected, predicted OS to all BCR levels decreases with each additional line of therapy. **Conclusions:** Our modelling study suggests that BCR to treatment is able to strongly predict OS in real-world MM clinical practice. Modelling MM in this way will provide clinicians, patients and funders with accurate evidence of the impacts of treatment and policy decisions. Importantly, such modelling could be explored further to facilitate more rapid determinations in regulatory authority drug approval processes so enabling patients earlier access to more effective therapies.

P-074

Personalized mass spectrometry as a tool for minimal residual disease detection in the blood of myeloma patients

Somayya Noori[1], Charissa Wijnands[2], Vincent Bonifay[3], Theo Luider[1], Pierre Sonigo[3], Thomas Dejoie[4], Jolein Gloerich[2], Alain van Gool[2], Martijn van Duijn[1], Joannes Jacobs[2]

[1]Erasmus Medical Center; [2]Radboudumc; [3]Sebia; [4]Centre Hospitalier Universitaire

Introduction: Multiple myeloma (MM) is a clonal plasma cell disorder found in the bone marrow that produces a monoclonal immunoglobulin (M-protein). Blood based M-protein diagnostics allows monitoring of disease activity, but with limited sensitivity. Minimal residual disease (MRD) status is a powerful prognostic biomarker. Lack of sensitivity prevents MRD detection by conventional blood based assays. Bone marrow based assays such as next-generation sequencing (NGS) are highly sensitive in measuring MRD. However, bone marrow biopsies introduce a risk of non-representative sampling and are invasive, which limits repeated testing. Frequent MM monitoring during remission could provide actionable information on disease activity and treatment response. Earlier detection of disease progression could lead to early intervention and, potentially, patient survival benefits. The aim of this study was to perform M-protein monitoring on blood samples of MM patients with sensitive targeted mass spectrometry. **Methods:** We have developed a targeted mass spectrometry-based MRD blood-test (MS-MRD) that detects clonotypic peptides originating from the variable region of the M-protein. Absolute M-protein quantification (g/L) was performed based on the M-protein peptide and an internal standard, and the data were evaluated for early increases in disease activity. MS-MRD was performed on 926 longitudinally collected sera of 41 MM patients from the IFM 2009 trial (ClinicalTrials.gov number: NCT01191060). **Results:** Based on unique patient-specific M-protein peptides, absolute M-protein quantification was feasible in all 41 patients with 1000 times higher sensitivity compared to electrophoretic M-protein quantification. For patients with confirmed progression within the serum sample collection period, MS-MRD revealed the increase of MM disease activity on average 455 days earlier than the progression detected with currently used routine diagnostics ($p \leq 0.0001$). **Conclusions:** MS-MRD blood-testing is feasible in all patients with multiple myeloma and it has similar sensitivity and prognostic value compared to NGS-MRD evaluation performed on bone marrow. The MS-MRD blood-test paves the way for dynamic MRD monitoring to allow detection of early disease relapse. This minimally invasive MRD test may proof to be well suited to facilitate future clinical implementation of MRD-guided therapy.

P-075

Real-world evidence on prognostic value of minimal residual disease in multiple myeloma: Czech experience

Tomas Jelinek[1], Ludmila Muronova[1,2], David Zihala[1], Tereza Sevcikova[1,2], Tereza Popkova[1,2], Hana Plonkova[1], Ondrej Venglar[1,2,3], Ludek Pour[4], Martin Stork[4], Lucie Rihova[5], Renata Bezdekova[1], Jiri Minarik[6], Martin Novak[6], Alexandra Jungova[7], David Chena[7], Jan Straub[8], Martin Spacek[8], Vladimira Rezacova[9], Ondrej Soucek[9], Vladimir Maisnar[10], Jakub Radocha[11], Roman Hájek[12]

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versus Stable Disease does not appear to be as strong as the other categories. As expected, predicted OS to all BCR levels decreases with each additional line of therapy. **Conclusions:** Our modelling study suggests that BCR to treatment is able to strongly predict OS in real-world MM clinical practice. Modelling MM in this way will provide clinicians, patients and funders with accurate evidence of the impacts of treatment and policy decisions. Importantly, such modelling could be explored further to facilitate more rapid determinations in regulatory authority drug approval processes so enabling patients earlier access to more effective therapies.

P-074

Personalized mass spectrometry as a tool for minimal residual disease detection in the blood of myeloma patients

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P-075

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P-076

The impact of heterogeneous disease distribution on MRD detection in patients with relapsed multiple myeloma

Lukas John[1,2], Martin Grözinger[3], Christos Sachpekidis[4], Stefanie Huhn[1], Lilli Sester[1,2], Mirco Friedrich[1,5], Jan Frenking[1,2], Christian Michel[1], Joseph Kauer[1], Barbara Wagner[1], Sabine Quick[1], Schneiders Birgit[1], Ewelina Nickel[1], Ricarda Schwab[1], Calin-Petru Manta[1], Philipp Reichert[1], Stefan Schönland[1], Antonia Dimitrakopolou-Strauß[4,6], Carsten Müller-Tidow[1,7], Uwe Haberkorn[4,6], Michael Hundemer[1], Sandra Sauer[1], Marc Raab[1], Stefan Delorme[3], Niels Weinhold[1,2]

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Introduction: The minimal residual disease (MRD) status is becoming increasingly important as an endpoint for clinical trials in multiple myeloma (MM). For newly diagnosed patients, a strong association between MRD-negativity and long-term survival has been established. However, relapsed MM (RMM) patients often show a short time to next relapse even after having achieved MRD-negativity during salvage therapy. This also holds true for novel immunotherapies, such as bispecific antibodies (BsAb) or CAR-T cells. One explanation could be an increasingly heterogeneous disease distribution with treatment-resistant tumor cells at bone marrow or extramedullary sites other than the iliac crest. We performed a prospective study to address the question if functional imaging complements MRD-diagnostics in RMM patients and at which timepoints residual disease monitoring should be performed. **Methods:** We included 40 patients with at least 2 prior lines of therapy receiving novel agents-based salvage therapy (n=18) or modern immunotherapy (CAR-T or BsAb, n=22). Bone marrow biopsies for MRD detection using the Euroflow-assay (median sensitivity of 3x10-6) and next-generation sequencing (NGS) were taken before initiation of salvage therapy (baseline), and after 3, 6 and 12 months. Whole body MRI including diffusion weighted imaging (DWI) was performed at baseline, and after 1, 3, 6 and 12 months, while 18-F FDG-PET-CT was performed at baseline and after 6 months. **Results:** Here, we present results of an interim analysis at a median follow-up time of 6.4 months (data cutoff May 2023). Notably, at baseline 6 patients (15%) were already Flow-MRD-negative and 5 patients (13%) had very low MRD levels (< 1x10-4). All these patients showed active lesions in both MRI and PET-CT and none of them became MRD-positive during follow-up, demonstrating a highly unbalanced disease distribution. After 3 months, 11/20 patients with at least a VGPR were MRD-negative. Using DWI, active residual lesions were detectable in 4 of the MRD-negative patients (36%). After 6 months, both DWI and PET-CT were applied and the proportion of MRD-negative patients with detectable active lesions increased to 7/11 (64%). PET-CT was more sensitive than DWI in detecting residual disease with 4/7 patients being positive in PET-CT only. Notably, 5/7 patients had received modern immunotherapies, highlighting the prevalence of discrepant findings in this setting. **Conclusions:** Our data suggest that Flow-MRD negativity in RMM patients during salvage therapy needs to be interpreted with caution. The next step will be to test whether NGS can improve the MRD detection rate. Functional imaging also complements MRD-diagnostics after modern immunotherapies. Yet, it remains to be investigated if detected lesions represent active disease or disease remnants and if this combination allows for a better prediction of time to next relapse.

P-077

High sensitivity MRD enumeration using combined size exclusion isolation and immunophenotyping

Sherif Louis[1], Yulia Shifrin[1], Olga Ludkovski[1], Sabine Mai[2]

[1]Telo Genomics Corp.; [2]University of Manitoba

Introduction: Despite the many therapeutic advances in the field of multiple myeloma (MM) that have led to improved outcomes for these patients, MM remains an incurable cancer. Several studies and

6 Czech hematological centers between 2014 and 2022 underwent MRD assessment on D+100 after ASCT using MFC. The most common induction regimen was VTD (bortezomib, thalidomide, dexamethasone) in 70% of pts, the median limit of detection of MFC technique was 0.001%, and the median follow-up was 30.2 months. Overall, 158 (46%) of 342 pts were considered MRD negative which was associated with significantly improved PFS (HR=0.37; 95% CI 0.26 – 0.52; p< 0.001) and OS (HR=0.49; 95% CI 0.3 – 0.81; p=0.004). Median PFS was 49.2 months for pts who were MRD negative vs. 19.0 months for MRD positive pts; median OS was not reached vs. 71.9 months, respectively. In subgroup analysis, MRD negativity was associated with prolonged survival in both high-risk and standard-risk pts by cytogenetics as well as in patients reaching complete remission or better (CR or better) and very good partial response or better (VGPR or better). Finally, in multivariate analysis only MRD positivity and high-risk cytogenetics emerged as independent adverse prognostic factors (HR=2.57; p< 0.001). **Conclusions:** Up to our knowledge, this is the largest real-world study confirming the strong prognostic value of MRD negativity assessed by MFC with median limit of detection to 10e-5 in newly diagnosed transplant-eligible MM. MRD negativity was associated with improved PFS (HR=0.37) and OS (HR=0.49) resembling the results from clinical trials setting. This real-world experience might represent the missing piece of evidence for final approval of MRD as a surrogate for PFS and OS by regulatory authorities.

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Introduction: The minimal residual disease (MRD) status is becoming increasingly important as an endpoint for clinical trials in multiple myeloma (MM). For newly diagnosed patients, a strong association between MRD-negativity and long-term survival has been established. However, relapsed MM (RMM) patients often show a short time to next relapse even after having achieved MRD-negativity during salvage therapy. This also holds true for novel immunotherapies, such as bispecific antibodies (BsAb) or CAR-T cells. One explanation could be an increasingly heterogeneous disease distribution with treatment-resistant tumor cells at bone marrow or extramedullary sites other than the iliac crest. We performed a prospective study to address the question if functional imaging complements MRD-diagnostics in RMM patients and at which timepoints residual disease monitoring should be performed. **Methods:** We included 40 patients with at least 2 prior lines of therapy receiving novel agents-based salvage therapy (n=18) or modern immunotherapy (CAR-T or BsAb, n=22). Bone marrow biopsies for MRD detection using the Euroflow-assay (median sensitivity of 3x10-6) and next-generation sequencing (NGS) were taken before initiation of salvage therapy (baseline), and after 3, 6 and 12 months. Whole body MRI including diffusion weighted imaging (DWI) was performed at baseline, and after 1, 3, 6 and 12 months, while 18-F FDG-PET-CT was performed at baseline and after 6 months. **Results:** Here, we present results of an interim analysis at a median follow-up time of 6.4 months (data cutoff May 2023). Notably, at baseline 6 patients (15%) were already Flow-MRD-negative and 5 patients (13%) had very low MRD levels (< 1x10-4). All these patients showed active lesions in both MRI and PET-CT and none of them became MRD-positive during follow-up, demonstrating a highly unbalanced disease distribution. After 3 months, 11/20 patients with at least a VGPR were MRD-negative. Using DWI, active residual lesions were detectable in 4 of the MRD-negative patients (36%). After 6 months, both DWI and PET-CT were applied and the proportion of MRD-negative patients with detectable active lesions increased to 7/11 (64%). PET-CT was more sensitive than DWI in detecting residual disease with 4/7 patients being positive in PET-CT only. Notably, 5/7 patients had received modern immunotherapies, highlighting the prevalence of discrepant findings in this setting. **Conclusions:** Our data suggest that Flow-MRD negativity in RMM patients during salvage therapy needs to be interpreted with caution. The next step will be to test whether NGS can improve the MRD detection rate. Functional imaging also complements MRD-diagnostics after modern immunotherapies. Yet, it remains to be investigated if detected lesions represent active disease or disease remnants and if this combination allows for a better prediction of time to next relapse.

P-077

High sensitivity MRD enumeration using combined size exclusion isolation and immunophenotyping

Sherif Louis[1], Yulia Shifrin[1], Olga Ludkovski[1], Sabine Mai[2]

[1]Telo Genomics Corp.; [2]University of Manitoba

Introduction: Despite the many therapeutic advances in the field of multiple myeloma (MM) that have led to improved outcomes for these patients, MM remains an incurable cancer. Several studies and

most recently, a large scale, pooled analysis of patients from 4 large randomized controlled studies have demonstrated the prognostic utility of attaining minimal residual disease (MRD) negativity with regards to survival. Given the understanding of how heterogeneous the disease is, there is a need to develop technologies that can identify and enumerate MM MRD plasma cells with superior sensitivity, and further characterize the residual clones, thereby profiling them as high, mid or low risk clones. Currently, ongoing trials that are designed to escalate or de-escalate therapy based on MRD status fail to take into consideration the fact that MRD status carries different significance based on the risk profile of any given patient. Several genomic technologies are currently developing MRD assays for post treatment MM patients. These technologies are predominantly focused on MRD detection, and the enumeration of MRD plasma cells. However, each of these technologies, whether in development or in the clinic, has its own technical limitations that prevent the broad applicability of the technology to all MM patients. Furthermore, these technologies are predominantly applicable to bone marrow specimens, which compromise the main utility of MRD, which is to monitor patients repeatedly over time, due to the invasive nature of bone marrow sample collection procedures. **Methods:** We employed a technology for the enumeration of MRD based on the immunostaining of isolated circulating myeloma plasma cells (CTCs) from peripheral blood. The assay deploys a size-based filtration methodology that recovers CTCs from the patient's blood sample. This is followed by immunostaining, fluorescence three-dimensional (3D) microscopy and automated immunophenotyping detection and enumeration of the MRD plasma cells. **Results:** We report our proof of principle results from spiking experiments where blood samples from consented normal donors were spiked with cells from a characterized and commercially available MM cell line. We report a repeatable achieved sensitivity of up to 10-7 and the confirmed repeatable sensitivity of 10-4-10-7 with accuracy of over 85% across all tested detection levels. **Conclusions:** The technology has the potential to provide a simplified rapid assay for MRD detection and enumeration with satisfactory sensitivity beyond assays in development or currently in the clinic. The assay has the advantages of: 1- a quick turnaround time within 48-72 hours, and 2- applicability to the broader spectrum of MM patients. Furthermore, the isolation of the MM MRD cells with such high sensitivity presents a possibility to accurately profile the level of genomic instability in these cells and provide a prognostic assessment based on the level of aggressiveness of the analyzed MRD cells from the individual patient.

P-078

MRDeep study: measurable residual disease rates in patients with multiple myeloma who achieved complete response in 2nd or 3rd lines of treatment

Manuel Neves[1], Rita Gerivaz[2], Graça Esteves[3], Rui Bergatim[4,5,6,7], Gisela Ferreira[8], Henrique Coelho[9], Celina Afonso[10], Delfim Duarte[11,4], Anabela Neves[12], Helena Matos Silva[13], Joana Caetano[14,15,16], Rita Jaime[17], Catarina Geraldes[18], Paulo Lúcio[1,15]

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Introduction: Measurable Residual Disease (MRD) is rapidly becoming one of the most relevant prognostics indicators for patients with multiple myeloma (MM). The main objective of this cross-sectional, multicenter, non-interventional study was to evaluate the bone marrow MRD status in MM patients in Portugal who had achieved CR and were on their second or third lines of therapy. **Methods:** This study includes relapsed MM (rMM) patients in 2nd or 3rd line of treatment who met the eligibility criteria, including confirmation of the CR defined by negative immunofixation on the serum and urine. Next-Generation Flow (NGF) MRD evaluation of bone marrow aspirate was performed using the standardized 2-tube 8-color EuroFlow approach, with a level of sensitivity of 10^{-5} (0.001%). "Undetectable MRD (uMRD)" was defined as the absence of tumor plasma cells within 100,000 bone marrow cells (10^{-5}). Demographic data, medical history, MM characteristics, treatments and measures of effectiveness were collected, and descriptive statistics were used to summarize data. **Results:** Among the 68 subjects who gave informed consent, 48 were considered eligible for the study, with a median age of 68 (44 to 84 years). Twenty-two (44%) patients had ISS stage III disease, 6 out of 33 patients with available data had a high-risk cytogenetic profile (18.2%) and 7 out of 48 have documented extra-medullary disease (EMD) (14.5%). Of the 48 subjects with confirmed CR, 31 (64.6%) achieved MRD negativity. This incidence was lower in ISS III patients compared with ISS I/II (60% vs. 70.8%, respectively), in patients with high-risk cytogenetics vs. standard risk (33.3% vs. 76%, respectively) and in patients treated without daratumumab-containing regimens compared with those who were treated with daratumumab containing regimens (MRD undetectable in 57.1% and 75%, respectively). The incidence of MRD negativity is higher in daratumumab-containing regimens in

most recently, a large scale, pooled analysis of patients from 4 large randomized controlled studies have demonstrated the prognostic utility of attaining minimal residual disease (MRD) negativity with regards to survival. Given the understanding of how heterogeneous the disease is, there is a need to develop technologies that can identify and enumerate MM MRD plasma cells with superior sensitivity, and further characterize the residual clones, thereby profiling them as high, mid or low risk clones. Currently, ongoing trials that are designed to escalate or de-escalate therapy based on MRD status fail to take into consideration the fact that MRD status carries different significance based on the risk profile of any given patient. Several genomic technologies are currently developing MRD assays for post treatment MM patients. These technologies are predominantly focused on MRD detection, and the enumeration of MRD plasma cells. However, each of these technologies, whether in development or in the clinic, has its own technical limitations that prevent the broad applicability of the technology to all MM patients. Furthermore, these technologies are predominantly applicable to bone marrow specimens, which compromise the main utility of MRD, which is to monitor patients repeatedly over time, due to the invasive nature of bone marrow sample collection procedures. **Methods:** We employed a technology for the enumeration of MRD based on the immunostaining of isolated circulating myeloma plasma cells (CTCs) from peripheral blood. The assay deploys a size-based filtration methodology that recovers CTCs from the patient's blood sample. This is followed by immunostaining, fluorescence three-dimensional (3D) microscopy and automated immunophenotyping detection and enumeration of the MRD plasma cells. **Results:** We report our proof of principle results from spiking experiments where blood samples from consented normal donors were spiked with cells from a characterized and commercially available MM cell line. We report a repeatable achieved sensitivity of up to 10-7 and the confirmed repeatable sensitivity of 10-4-10-7 with accuracy of over 85% across all tested detection levels. **Conclusions:** The technology has the potential to provide a simplified rapid assay for MRD detection and enumeration with satisfactory sensitivity beyond assays in development or currently in the clinic. The assay has the advantages of: 1- a quick turnaround time within 48-72 hours, and 2- applicability to the broader spectrum of MM patients. Furthermore, the isolation of the MM MRD cells with such high sensitivity presents a possibility to accurately profile the level of genomic instability in these cells and provide a prognostic assessment based on the level of aggressiveness of the analyzed MRD cells from the individual patient.

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2nd line of treatment compared to the 3rd line (80% and 60%, respectively). **Conclusions:** With the current treatment protocols it is possible to achieve high quality responses, including uMRD, both in 2nd and 3rd lines of treatment. In our study, better quality of CR response, defined by a higher rate of uMRD, was found in patients treated in 2nd line of treatment, in those patients exposed to daratumumab containing regimens, and in patients with no adverse prognosis factors (defined by ISS III or high-risk cytogenetics). These findings support the relevance of MRD detection in real-world rMM setting. The Euroflow/NGF technique for MRD detection is feasible in clinical practice, enhancing the quality and sensitivity of MM response evaluation. These real-world results endorse the published clinical trials outcomes but further confirmation in larger cohorts is warranted.

P-079

Impact of treatment effect on measurable residual disease (MRD) and progression-free survival (PFS): an aggregate data analysis from randomized clinical trials in multiple myeloma (MM)

Bruno Paiva[1], Anastasiia Zherniakova[2], Jorge Nuñez[3], Paula Rodríguez-Otero[4], Qian Shi[5], Nikhil Munshi[6], Brian Durie[7], Jesús San-Miguel[8]

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Introduction: Novel regimens are needed to increase cure rates in MM, but new studies will not have a (positive or negative) readout for many years due to the unprecedented PFS and overall survival achieved with current therapies. Assessment of MRD is one of the most relevant prognostic factors and outperforms conventional methods of response assessment in MM. However, the role of MRD as a surrogate of treatment efficacy for potential use as an endpoint in clinical trials, remains uncertain. **Methods:** We soughed to analyze the correlation between MRD negative rates defined according to the IMWG response criteria and PFS benefit in randomized clinical trials. For this purpose, we searched for studies describing PFS and MRD data in more than 50 patients in each treatment arm, using next-generation flow cytometry or next-generation sequencing methods with a reported minimum sensitivity of 10-5 until the 2nd of December 2022. MRD negative rates were calculated for the intent-to-treat population and regardless of the depth of response. The strength of the association between the treatment effect on PFS and the treatment effect on MRD negative rates was quantified with the trial-level coefficient of determination (R2trial) and the 95% confidence interval (95% CI). The analyses were weighted by the trial sample size. The criteria for R2trial interpretation was set a priori as poor (0.8). **Results:** The weighted R2trial observed in the aggregated analysis of the 15 clinical trials was 0.70 (95% CI 0.41 - 0.98). Sensitivity analyses using a leave-one-out approach showed consistent R2trial levels ranging from 0.62 to 0.78. Sub analysis according to the inclusion of an autologous transplant in clinical trials showed a similar weighted R2trial in NDTE (0.74, 95% CI 0.24 – 1.00) and NDTI/RRMM (0.83, 95% CI 0.57 – 1.00). Next, we compared the difference in MRD negative rates between experimental vs control arms in clinical trials demonstrating a reduction in the risk of progression and/or death greater than 40% vs those that did not. The median (p25 - p75) difference in MRD negative rates was significantly higher in clinical trials with a hazard ratio < 0.60 vs ≥ 0.60: 21% (17% - 22%) vs 2.5% (0.75% - 5.4%), respectively (P < .001). Interestingly, there was nearly no overlap between p25 vs p75 difference in MRD negative rates observed in the former vs the later studies. Thus, it appears that a cutoff of approximately 10% difference in MRD negative rates between treatment arms may predict a meaningful improvement in PFS. **Conclusions:** The ongoing meta-analyses based on individual patient-level data is mandatory to determine if MRD is a statistically robust surrogate of treatment efficacy, defined according to PFS benefit (i.e. i2TEAMM). Meanwhile, this study suggests moderate value and could provide guidance on the definition of MRD endpoints in MM.

P-080

Clinical implication of MRD measurement by DuraClone in patients with transplant-eligible, real-world-based study, CAREMM-2104

Sung-Soo Park[1,2], Ari Ahn[2], Jung Yeon Lee[2], Yonggoo Kim[2], Myungshin Kim[2], Chang-Ki Min[1]

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Introduction: Because the DuraClone has benefits of shorter time and lower cost to generate minimal residual disease (MRD) measurement compared to EuroFlow which is regarded as standard multiparameter flow cytometry (MFC) method, we explored whether the MRD detection by DuraClone method could be reliable for real-world practice for multiple myeloma (MM). **Methods:** We included 166 patients as the cohort of current study based on following inclusion criteria: (i) patients who have available MRD data at 3±2 months post-autologous stem cell transplantation (ASCT) (ii) Patient who received ASCT as a part of the front-line treatment. Fresh EDTA anticoagulated bone marrow aspirate samples were collected from treated patients with MM. Red blood cells were lysed using Versafix solution (VersaLyse supplemented with 0.25% IOTest Fixative Solution, Beckman Coulter) and cell suspensions containing 5×10^6 nucleated cells were transferred to DuraClone RE PC tubes. DuraClone RE PC antibody panel was composed of CD81-FITC, CD27-PE, CD19-PC5.5, CD200-PC7, CD138-APC, CD56-APC-A750, CD38-Pacific Blue, CD45-Krome Orange. **Results:**

2nd line of treatment compared to the 3rd line (80% and 60%, respectively). **Conclusions:** With the current treatment protocols it is possible to achieve high quality responses, including uMRD, both in 2nd and 3rd lines of treatment. In our study, better quality of CR response, defined by a higher rate of uMRD, was found in patients treated in 2nd line of treatment, in those patients exposed to daratumumab containing regimens, and in patients with no adverse prognosis factors (defined by ISS III or high-risk cytogenetics). These findings support the relevance of MRD detection in real-world rMM setting. The Euroflow/NGF technique for MRD detection is feasible in clinical practice, enhancing the quality and sensitivity of MM response evaluation. These real-world results endorse the published clinical trials outcomes but further confirmation in larger cohorts is warranted.

P-079

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Introduction: Novel regimens are needed to increase cure rates in MM, but new studies will not have a (positive or negative) readout for many years due to the unprecedented PFS and overall survival achieved with current therapies. Assessment of MRD is one of the most relevant prognostic factors and outperforms conventional methods of response assessment in MM. However, the role of MRD as a surrogate of treatment efficacy for potential use as an endpoint in clinical trials, remains uncertain. **Methods:** We soughed to analyze the correlation between MRD negative rates defined according to the IMWG response criteria and PFS benefit in randomized clinical trials. For this purpose, we searched for studies describing PFS and MRD data in more than 50 patients in each treatment arm, using next-generation flow cytometry or next-generation sequencing methods with a reported minimum sensitivity of 10-5 until the 2nd of December 2022. MRD negative rates were calculated for the intent-to-treat population and regardless of the depth of response. The strength of the association between the treatment effect on PFS and the treatment effect on MRD negative rates was quantified with the trial-level coefficient of determination (R2trial) and the 95% confidence interval (95% CI). The analyses were weighted by the trial sample size. The criteria for R2trial interpretation was set a priori as poor (0.8). **Results:** The weighted R2trial observed in the aggregated analysis of the 15 clinical trials was 0.70 (95% CI 0.41 - 0.98). Sensitivity analyses using a leave-one-out approach showed consistent R2trial levels ranging from 0.62 to 0.78. Sub analysis according to the inclusion of an autologous transplant in clinical trials showed a similar weighted R2trial in NDTE (0.74, 95% CI 0.24 – 1.00) and NDTI/RRMM (0.83, 95% CI 0.57 – 1.00). Next, we compared the difference in MRD negative rates between experimental vs control arms in clinical trials demonstrating a reduction in the risk of progression and/or death greater than 40% vs those that did not. The median (p25 - p75) difference in MRD negative rates was significantly higher in clinical trials with a hazard ratio < 0.60 vs ≥ 0.60: 21% (17% - 22%) vs 2.5% (0.75% - 5.4%), respectively (P < .001). Interestingly, there was nearly no overlap between p25 vs p75 difference in MRD negative rates observed in the former vs the later studies. Thus, it appears that a cutoff of approximately 10% difference in MRD negative rates between treatment arms may predict a meaningful improvement in PFS. **Conclusions:** The ongoing meta-analyses based on individual patient-level data is mandatory to determine if MRD is a statistically robust surrogate of treatment efficacy, defined according to PFS benefit (i.e. i2TEAMM). Meanwhile, this study suggests moderate value and could provide guidance on the definition of MRD endpoints in MM.

P-080

Clinical implication of MRD measurement by DuraClone in patients with transplant-eligible, real-world-based study, CAREMM-2104

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Introduction: Because the DuraClone has benefits of shorter time and lower cost to generate minimal residual disease (MRD) measurement compared to EuroFlow which is regarded as standard multiparameter flow cytometry (MFC) method, we explored whether the MRD detection by DuraClone method could be reliable for real-world practice for multiple myeloma (MM). **Methods:** We included 166 patients as the cohort of current study based on following inclusion criteria: (i) patients who have available MRD data at 3±2 months post-autologous stem cell transplantation (ASCT) (ii) Patient who received ASCT as a part of the front-line treatment. Fresh EDTA anticoagulated bone marrow aspirate samples were collected from treated patients with MM. Red blood cells were lysed using Versafix solution (VersaLyse supplemented with 0.25% IOTest Fixative Solution, Beckman Coulter) and cell suspensions containing 5×10^6 nucleated cells were transferred to DuraClone RE PC tubes. DuraClone RE PC antibody panel was composed of CD81-FITC, CD27-PE, CD19-PC5.5, CD200-PC7, CD138-APC, CD56-APC-A750, CD38-Pacific Blue, CD45-Krome Orange. **Results:**

Of 166 patients in our study, there were 113 patients (68.1%) showed MRD-negative (MRD- group) while 53 cases (31.9%) presented MRD-positivity (MRD+ group). With median follow-up of 24.4 months from ASCT, MRD+ group showed poorer survival outcomes compared to MRD- group: 24-months progression-free survival (PFS) rate, 50.6 vs. 72.3%, p< 0.001; 24-months cumulative incidence of MM progression, 46.7 vs. 26.7%, p=0.002. The multivariable analysis showed that MRD status at 3 months was significantly associated with both PFS (Hazard ratio= 2.35, p=0.008) and cumulative incidence of MM progression (Hazard ratio=2.45, p=0.004), even after adjustment for other potential factors. Of MRD- group (n=113), we further analyzed with 67 patients who have data of secondarily measured MRD after 1 year from first measurement of MRD. Patients with conversion of MRD to positivity (n = 24) showed significantly lower outcomes compared to patients achieving sustained MRD negativity (n=43): 24 months-PFS rate, 69.7 vs. 91.9%, p=0.01; 24-months cumulative incidence of MM progression, 30.3% vs. 5.7%, p=0.004. Among 53 patients of MRD+ group, A 24 months-PFS rate in patients who received no further treatment (n=11) showed significantly lower compared to that in patients with subsequent therapy (20.5 vs. 59.8%, p=0.019), we also observed a poor trend of 24 months-cumulative incidence of MM progression in patients who received no further treatment rather than in patients with subsequent therapy (69.3 vs. 40.2%, p=0.07) **Conclusions:** Our data revealed that MRD measurement using DuraClone panel could be applicable with a sensitivity of $1/10^5$ which value is the prerequisite by IMWG recommendation. DuraClone panel-used MRD could be a useful approach regarding both prognostic impact and predictive power for MRD-adopted treatment.

P-081

Sensitive detection of M-proteins and FLC in blood for diagnosis and monitoring of multiple myeloma

Rudolf Kupcik[1], Marie Vajrychova[1], Katerina Hrochova[2], Adela Tomasova[3], Jakub Radocha[4]

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Introduction: Multiple myeloma (MM) is a cancer of plasma cells (myeloma cells) that accumulate in the bone marrow and produce abnormal monoclonal immunoglobulins (mAb, M-proteins). Despite the development of new therapies, MM is still associated with a high likelihood of persistent minimal residual disease (MRD) and thus earlier relapse. Relapse in MM is caused by clonal heterogeneity and evolution, which can lead to selection of drug-resistant malignant plasma cell (PC) clone(s), contributing to treatment failure. Detection of persistent clones, after treatment, is currently limited due to the invasiveness of bone marrow biopsy and the very low frequency of sampling. Therefore, the main goal of our work was to develop a method for sensitive detection of low-abundant PC clones based on the detection of M-proteins and free light chains (FLC) in human serum. **Methods:** The newly developed method combines selective affinity isolation of M-proteins and FLC from a blood sample and their sensitive analysis by high-performance liquid chromatography with UV detection (af-HPLC/UV). Af-HPLC/UV also served as the first step for targeted detection of the variable region (CDR3) of M-proteins by high-resolution mass spectrometry after prior sequencing of the corresponding DNA regions. The reliability and sensitivity of the method were tested on three types of mAb standards added to human sera. Patient samples before and after treatment were also included in this study. **Results:** The af-HPLC/UV workflow was able to detect mAb in serum with high sensitivity (≤100 mg.Le-1). Selective isolation of M-protein and FLC allowed quantitative separation of mAbs by light chain types, which has great potential for the diagnosis of oligoclonality. HPLC with UV detection is then suitable for accurate LC and partial HC classification, as well as for the determination of therapeutic mAbs, which usually complicate analysis by immunofixation electrophoresis. In addition, the sensitivity of the entire workflow can be greatly enhanced when combined with LC-MS/MS of the CDR3 region, which is unique to each antibody clone. These regions can then be monitored in a targeted manner by mass spectrometry based on initial analysis of myeloma cell DNA. The combination of very high sensitivity and the ability to detect multiple clones thus has the potential to sensitively detect resistant and emerging myeloma cell clones in MRD based on M-proteins and FLCs detection directly in the blood. **Conclusions:** With these new MM detection methods, it may be possible in the future to carefully monitor patients at short time intervals and detect not only clones from the time of diagnosis, but also newly formed clones with high sensitivity from blood. The method then has the potential to replace invasive and often problematic bone marrow aspiration.

P-082

Will survival improve by treating multiple myeloma patients at MRD relapse? The REMNANT study

Anne-Marie Rasmussen[1], Frida Askeland[1], Anna Lysen[1], Einar Haukås[2], Anette Eilertsen[3], Galina Tsykunova[4], Anders Vik[5], Birgitte Eiken[6], Vidar Stavseth[7], Jürgen Rolke[8], Eivind Samstad[9], Valdas Peceliunas[10], Randi Fykse Hallstensen[11], Ariane Aasbø Hansen[1], Anita Smith Nilsen[1], Tobias Slørdahl[12], Fredrik Schjesvold[13]

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P-081

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P-082

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P-081

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P-082

Will survival improve by treating multiple myeloma patients at MRD relapse? The REMNANT study

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Introduction: Although many new treatment options have become available, multiple myeloma (MM) is still considered an incurable disease. More recently, the role of achieving minimal residual disease (MRD) negativity has become more clearly defined in patients with MM. Multiple studies show that bone marrow based MRD assessment is one of the strongest prognostic factors, and deeper responses correlate with more favorable outcomes. The REMNANT study will evaluate if treating at MRD relapse after 1st line (1.L) therapy prolongs PFS and OS compared to starting treatment at biochemical relapse/progressive disease (PD) in MM patients **Methods:** The REMNANT study (RElapse from Mrd Negativity As iNdication for Treatment) is an academic, multicenter, open-label, randomized phase II/III study of newly diagnosed (ND) MM patients eligible for autologous stem cell transplant (ASCT). The study has a population-based approach and few exclusion criteria apply, including patients with kidney failure, amyloidosis and other comorbidities. 391 NDMM patients (age 18-75 years) eligible for ASCT will be enrolled in the study and receive 1.L treatment according to Norwegian national guidelines; 4 pre-transplant induction and 4 post-transplant consolidation cycles of bortezomib, lenalidomide and dexamethasone (VRd). After induction patients will undergo tandem or single transplant, depending on toxicity and response to first transplant. Following 1.L treatment 176 patients who are >CR and MRD negative (NGF Euroflow) will be enrolled in part 2 of the study and will be randomized in a 1:1 ratio to receive second line treatment (2.L) at MRD relapse in arm A or at PD in arm B. At loss of MRD negativity (arm A) or at PD in arm B, second line treatment will be daratumumab, carfilzomib, and dexamethasone and patients will be followed for PFS and OS. In part 2 we will compare different methods for measuring MRD; NGF, NGS, mass spectrometry and PET-CT. We want to evaluate how the different methods compare when it comes to sensitivity and outcome (PFS and OS) **Results:** As of May 1st 2023, 276 patients have been enrolled in part 1. 128 patients had reached the post-consolidation step and have been evaluated for MRD status and 66 (52%) were >CR and MRD negative and have been enrolled in part 2 of the study. ORR was 97%. Fifty-two of 276 (17.6%) patients have discontinued treatment during 1.L; 22 due to PD, 11 patients have withdrawn from the study, 6 have died and 5 discontinued due to adverse event. Fifty-two of 276 (17.6%) patients have discontinued treatment during 1.L; 22 due to PD, 11 patients have withdrawn from the study, 6 have died and 5 discontinued due to adverse event. Among patients with PD during 1.L treatment 59% had high-risk cytogenetics (with gain1q and/or del17p and/or t(4;14)). A total of 8 patients have started 2nd line treatment in part 2 due to loss of MRD or PD. **Conclusions:** Data so far show a very good response rate of 97%. The MRD negativity rate among patients who have finished 1.L treatment was 52%.

P-083

The role of minimal residual disease evaluation for patients with multiple myeloma

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Introduction: A new treatment goal for multiple myeloma (MM) is the achievement of minimal residual disease (MRD) negativity, indicating a profound response to therapy. In this study, we present the findings of MRD assessment conducted over three years at our institute, shedding light on its role in managing newly diagnosed (NDMM) or relapsed/refractory MM (RRMM). **Methods:** Since 2019, the institute has initiated a minimal residual disease (MRD) evaluation using next-generation flow (NGF) technology. A minimum of 10^7 cells per sample were acquired to ensure high sensitivity. In addition, the detection limit was set at 20 cells among the total nucleated cells, enabling a sensitivity of 10^5 or higher for all samples. The initial MRD assessment (MRD1) was performed upon achieving VGPR or CR. Subsequently, the second MRD assessment (MRD2) was conducted 12 months after the initial assessment. The progression-free survival 1 (PFS1) was defined from the initiation of front-line chemotherapy until disease progression, death from any cause, or the last follow-up. The PFS2 was determined from the start of second-line chemotherapy. The overall survival (OS) was defined as the period from the commencement of front-line chemotherapy until death or the last follow-up. Statistical analyses were conducted using the IBM PASW version 25.0. **Results:** MRD1 was evaluated in 138 NDMM and 60 RRMM, followed by MRD2 in 53 NDMM and 27 RRMM. The NDMM patients with MRD1-negative seemed to show superior median PFS1 to those without MRD1-negative (67.9 vs. 34.3 months, P=0.123). Although the difference was not statistically significant, patients with MRD2-negative results tended to exhibit a slightly better median PFS1 in a Kaplan-Myer graph than those without MRD2-negative results (not reached vs. not reached, P=0.258). Furthermore, the patients who achieved sustained MRD-negative or converted from MRD1-positive to MRD2-negative seemed to present better PFS than those who did not achieve final MRD2-negative (P=0.337). OS seemed superior in patients with MRD1-negative (P=0.069) but not MRD2-negative (P=0.910). PFS2 between RRMM with MRD1-negative and MRD1-positive was not statistically different (46.0 vs. 34.9 months, P=0.169). Moreover, the patients with MRD2-negative seemed somewhat to present longer median PFS2 than those with MRD2-positive (NR vs. 35.1 months, P=0.058), but not statistically. Moreover, the RRMM patients with sequential MRD-negative or converted from MRD1-positive to MRD2-negative did not show differences in PFS2 compared to other groups (P=0.185). **Conclusions:** We discussed the significance of MRD in the context of both NDMM and RRMM. While the results did not fully demonstrate the critical impact of the sequential acquisition of MRD-negativity following MRD1 due to the small number of patients in each group and short-term follow-up duration, it appeared that patients who maintained MRD-negativity had a notable survival advantage compared to those who tested positive for MRD1 or MRD2 at least once.

Introduction: Although many new treatment options have become available, multiple myeloma (MM) is still considered an incurable disease. More recently, the role of achieving minimal residual disease (MRD) negativity has become more clearly defined in patients with MM. Multiple studies show that bone marrow based MRD assessment is one of the strongest prognostic factors, and deeper responses correlate with more favorable outcomes. The REMNANT study will evaluate if treating at MRD relapse after 1st line (1.L) therapy prolongs PFS and OS compared to starting treatment at biochemical relapse/progressive disease (PD) in MM patients **Methods:** The REMNANT study (RElapse from Mrd Negativity As iNdication for Treatment) is an academic, multicenter, open-label, randomized phase II/III study of newly diagnosed (ND) MM patients eligible for autologous stem cell transplant (ASCT). The study has a population-based approach and few exclusion criteria apply, including patients with kidney failure, amyloidosis and other comorbidities. 391 NDMM patients (age 18-75 years) eligible for ASCT will be enrolled in the study and receive 1.L treatment according to Norwegian national guidelines; 4 pre-transplant induction and 4 post-transplant consolidation cycles of bortezomib, lenalidomide and dexamethasone (VRd). After induction patients will undergo tandem or single transplant, depending on toxicity and response to first transplant. Following 1.L treatment 176 patients who are >CR and MRD negative (NGF Euroflow) will be enrolled in part 2 of the study and will be randomized in a 1:1 ratio to receive second line treatment (2.L) at MRD relapse in arm A or at PD in arm B. At loss of MRD negativity (arm A) or at PD in arm B, second line treatment will be daratumumab, carfilzomib, and dexamethasone and patients will be followed for PFS and OS. In part 2 we will compare different methods for measuring MRD; NGF, NGS, mass spectrometry and PET-CT. We want to evaluate how the different methods compare when it comes to sensitivity and outcome (PFS and OS) **Results:** As of May 1st 2023, 276 patients have been enrolled in part 1. 128 patients had reached the post-consolidation step and have been evaluated for MRD status and 66 (52%) were >CR and MRD negative and have been enrolled in part 2 of the study. ORR was 97%. Fifty-two of 276 (17.6%) patients have discontinued treatment during 1.L; 22 due to PD, 11 patients have withdrawn from the study, 6 have died and 5 discontinued due to adverse event. Fifty-two of 276 (17.6%) patients have discontinued treatment during 1.L; 22 due to PD, 11 patients have withdrawn from the study, 6 have died and 5 discontinued due to adverse event. Among patients with PD during 1.L treatment 59% had high-risk cytogenetics (with gain1q and/or del17p and/or t(4;14)). A total of 8 patients have started 2nd line treatment in part 2 due to loss of MRD or PD. **Conclusions:** Data so far show a very good response rate of 97%. The MRD negativity rate among patients who have finished 1.L treatment was 52%.

P-083

The role of minimal residual disease evaluation for patients with multiple myeloma

Yoon Sang Eun[1], Hyun-Young Kim[2], Duck Cho[2], Seok Jin Kim[1], Kihyun Kim[3]

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Introduction: A new treatment goal for multiple myeloma (MM) is the achievement of minimal residual disease (MRD) negativity, indicating a profound response to therapy. In this study, we present the findings of MRD assessment conducted over three years at our institute, shedding light on its role in managing newly diagnosed (NDMM) or relapsed/refractory MM (RRMM). **Methods:** Since 2019, the institute has initiated a minimal residual disease (MRD) evaluation using next-generation flow (NGF) technology. A minimum of 10^7 cells per sample were acquired to ensure high sensitivity. In addition, the detection limit was set at 20 cells among the total nucleated cells, enabling a sensitivity of 10^5 or higher for all samples. The initial MRD assessment (MRD1) was performed upon achieving VGPR or CR. Subsequently, the second MRD assessment (MRD2) was conducted 12 months after the initial assessment. The progression-free survival 1 (PFS1) was defined from the initiation of front-line chemotherapy until disease progression, death from any cause, or the last follow-up. The PFS2 was determined from the start of second-line chemotherapy. The overall survival (OS) was defined as the period from the commencement of front-line chemotherapy until death or the last follow-up. Statistical analyses were conducted using the IBM PASW version 25.0. **Results:** MRD1 was evaluated in 138 NDMM and 60 RRMM, followed by MRD2 in 53 NDMM and 27 RRMM. The NDMM patients with MRD1-negative seemed to show superior median PFS1 to those without MRD1-negative (67.9 vs. 34.3 months, P=0.123). Although the difference was not statistically significant, patients with MRD2-negative results tended to exhibit a slightly better median PFS1 in a Kaplan-Myer graph than those without MRD2-negative results (not reached vs. not reached, P=0.258). Furthermore, the patients who achieved sustained MRD-negative or converted from MRD1-positive to MRD2-negative seemed to present better PFS than those who did not achieve final MRD2-negative (P=0.337). OS seemed superior in patients with MRD1-negative (P=0.069) but not MRD2-negative (P=0.910). PFS2 between RRMM with MRD1-negative and MRD1-positive was not statistically different (46.0 vs. 34.9 months, P=0.169). Moreover, the patients with MRD2-negative seemed somewhat to present longer median PFS2 than those with MRD2-positive (NR vs. 35.1 months, P=0.058), but not statistically. Moreover, the RRMM patients with sequential MRD-negative or converted from MRD1-positive to MRD2-negative did not show differences in PFS2 compared to other groups (P=0.185). **Conclusions:** We discussed the significance of MRD in the context of both NDMM and RRMM. While the results did not fully demonstrate the critical impact of the sequential acquisition of MRD-negativity following MRD1 due to the small number of patients in each group and short-term follow-up duration, it appeared that patients who maintained MRD-negativity had a notable survival advantage compared to those who tested positive for MRD1 or MRD2 at least once.

P-084

Use of peripheral blood for MRD assessment during maintenance therapy: UTSW experience

Aishwarya Sannareddy[1], Heidi Simmons[2], Ankit Kansagra[3], Adeel Khan[4], Aimaz Afrough[4], Larry Anderson[4], Gurbakhash Kaur[4]

[1]UT Southwestern Medical Center; [2]Adaptive Biotechnologies; [3]The Janssen Pharmaceutical Companies of Johnson & Johnson; [4]Cellular Therapy and Hematologic Malignancies Program, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA

Introduction: Over the years, the treatment modalities for patients diagnosed with Multiple Myeloma (MM) have improved and evolved. Lasting responses and increase in survival outcomes to newer therapies have led to development of advanced tools used to assess the disease pattern. Minimal residual disease (MRD) test is one such tool which detects cancer cells in remission and identifies increasing numbers of tumor cells. This increase in the number of tumor cells may lead to relapse, with a potential to inform clinical decisions on therapy intensification or de-escalation. Bone marrow (BM) biopsies are ideal for MRD assessment in MM patients. There is interest in peripheral blood (PB) use for assessment, which is less invasive, allowing frequent monitoring. In our real-world data set, we studied PB MRD use in patients who were MRD tested by the clonoSEQ® assay (Adaptive Biotechnologies). **Methods:** We performed a retrospective analysis on 49 MM patients with MRD monitored by clonoSEQ at UT Southwestern Medical Center, Dallas, TX. We collected data on demographics; oncology history, treatment history, MRD test and responses. All patients had a initial assessment with BM samples. **Results:** 49 patients underwent both BM and PB MRD at different time points. Analysis of PB MRD use revealed 30 patients tested during maintenance therapy post melphalan autologous stem cell transplant (SCT) and 19 patients who had relapse post SCT. MRD positive(+)PB was concurrent with or preceded clinical relapse in 3 patients. These patients were monitored with MRD in PB between regular BM monitoring. The 1st patient was 1 year post-SCT on Revlimid maintenance with normal light chains, met the criteria for relapse within six months of + PB MRD test. The 2nd patient, 19 months post-SCT on Revlimid maintenance, had elevated Kappa Light chains of 173.30mg/L at the time of the PB MRD test and met the definition of disease relapse, prompting a change in treatment, as the PB MRD results were consistent with the elevated kappa light chains. The 3rd patient, 11 months post-SCT on maintenance therapy, initially had normal light chains at the time of the PB MRD test. However, within a month, their kappa light chains became elevated, indicative of relapsed disease and requiring a change in treatment. All 3 patients had high plasma cell burden (>50%) and high-risk cytogenetics at diagnosis. They all had ≥ 3 lines of chemotherapy and underwent SCT within 19 months from diagnosis. 2 out of 3 patients passed within 2 years of SCT. **Conclusions:** From our small retrospective data analysis, we found evidence that PB MRD monitoring may be informative in certain clinical scenarios such as between BM MRDs during maintenance therapy. MRD+ PB results were concordant or preceded detection of rising disease burden by other clinical measurements. The assessments of MRD in the PB may allow tracking disease in certain clinical settings. Further research with larger patient cohorts is needed to define the utility of PB MRD monitoring in MM patients.

P-085

The use of clonotypic mass spectrometry for post-AHCT blood-based measurable residual disease monitoring in patients with light chain multiple myeloma

Michael Slade[1], Abir Khaled[2], Julie Fortier[1], Mariya Liyasova[2], Mark Fiala[1], Zac McDonald[2], Sarah Kelley[1], Kate Breberina[2], Nisha Owens[2], Zachary Crees[1], Mark Zaydman[1], Mark Schroeder[1], Keith Stockerl-Goldstein[1], Ravi Vij[1]

[1]Washington University School of Medicine in St. Louis; [2]Rapid Novor

Introduction: Given the invasive nature of bone marrow sampling, there is growing interest in blood-based methods of measurable residual disease (MRD) testing for patients with multiple myeloma (MM). We previously reported data utilizing clonotypic mass spectrometry (MS) in patients with intact immunoglobulin M-protein (Slade, ASH 2022). However, 10-20% of patients present with light chain (LC) M-protein and data on the feasibility of clonotypic MS in these patients is limited. **Methods:** Given the invasive nature of bone marrow sampling, there is growing interest in blood-based methods of measurable residual disease (MRD) testing for patients with multiple myeloma (MM). We previously reported data utilizing clonotypic mass spectrometry (MS) in patients with intact immunoglobulin M-protein (Slade, ASH 2022). However, 10-20% of patients present with light chain (LC) M-protein and data on the feasibility of clonotypic MS in these patients is limited. **Results:** Of 17 patients analyzed, 15 had a measurable clonotypic signature at diagnosis while 2 did not and were excluded from further analysis. Fourteen patients were White and 8 were male. Three, 8 and 4 patients were R-ISS stage I, II and III. The median age at AHCT was 59 (range: 45 – 76). The median difference in FLC (dFLC) at diagnosis was 265 mg/dL (range: 43 – 1449) and median EasyM was 5.62 arbitrary units (AU) (range 0.16 – 207.86). The lower limit of quantification varied given the unique clonotypic signature of each M-protein, with a median of 0.0088 AU (range: 0.00094 – 0.033) and median % quantifiable reduction in EasyM of 99.87% (range: 95.86 – 99.99%). At day +100, 14 patients (93%) were in CR. One was in VGPR at day +100. The median dFLC was 0.10 mg/dL (range 0.00 – 0.99). 8 (53%) had no detectable disease by EasyM (MRD-) at day +100; 7 (47%) had residual disease (MRD+). The median % residual EasyM in MRD+ patients was 0.20% of baseline (range 0.02 – 1.12%). Median baseline dFLC (249 vs. 270 mg/dL) and EasyM (0.78 vs. 10.32 AU) were numerically lower in the MRD- group, though these differences did not reach statistical significance. Median follow up was 4.4 years. At last follow up, 4 of 7 patients in the MRD+ group had relapsed and 3 had died. One MRD- patient died in remission from infection on day +619. The remainder of the MRD- patients remain alive and disease-free at a median of 3.9 years (range: 1.0 – 8.3) post-AHCT. **Conclusions:** In

P-084

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Aishwarya Sannareddy[1], Heidi Simmons[2], Ankit Kansagra[3], Adeel Khan[4], Aimaz Afrough[4], Larry Anderson[4], Gurbakhash Kaur[4]

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P-085

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this study, we showed that EasyM generates a trackable clonotype in the vast majority (88%) of patients with LC MM and that relapse was numerically higher in patients with normal dFLC and MRD+ by EasyM at day +100 after AHCT. Defining the clinical application of EasyM requires larger studies with additional time-points, but this series demonstrated that it may be a useful tool for disease monitoring in LC MM.

P-086

Patient and haematologist perspectives of minimal residual disease testing in myeloma

Silene ten Seldam[1], Kate Morgan[1], Katie Joyner[1]

[1]Myeloma Patients Europe

Introduction: Minimal residual disease (MRD) refers to a very small number of cancer cells that remain in the body during or after treatment. Despite growing interest of MRD in clinical practice and clinical trials, little is known regarding the perspectives and experiences of MRD testing from haematologists and myeloma patients. This project captured these perspectives on the current and potential future use of MRD in clinical practice and the psychosocial impact of MRD testing on patients and families. **Methods:** Participants were recruited from across Europe through patient organisations, website and via email. Two focus groups with myeloma patients were held along with individual interviews with haematologists. Focus groups and interviews were online and conducted using semi-structured topic guides, informed by a review of existing literature. Discussions were recorded, transcribed, and thematically analysed. **Results:** The focus group discussions with patients (n=14, from 9 countries) included 3 key themes; awareness of MRD, MRD-informed treatment decision making, and the potential psychosocial burden. Awareness of MRD testing varied amongst patients with some unfamiliar and some having experienced MRD testing themselves. Patients felt optimistic about MRD testing, particularly if it can be used for treatment decision making. Patients expressed willingness to consider more frequent bone marrow tests if MRD results could be used as an indicator for maintenance therapy to be stopped. However, they also highlighted the potential emotional and physical burden of attending hospital for the MRD tests, the invasive biopsies required, and the discomfort of waiting for the results. It was also emphasised that a positive MRD result, in the context of no available further treatments, would be particularly hard for patients. The interviews with haematologists (n=9, from 8 countries) included themes on MRD-informed treatment decision making, and MRD implementation considerations. Haematologists were equally optimistic about the potential for MRD testing in clinical practice and its role in guiding treatment decisions such as maintenance treatment plans. However, they also highlighted multiple challenges in implementing MRD testing in clinical practice, such as laboratory capacity and capability issues, the cost and staff training. **Conclusions:** This research highlighted that patients may be unaware of MRD testing, and there is a need for resources for patients and families to facilitate understanding about what it is and the implications of results. Implementation of MRD testing in future clinical practice would also require training and resources for healthcare professionals and laboratory staff to ensure accuracy and consistency across testing centres. The emotional and physical impact of MRD testing on patients will also need to be considered and healthcare providers need to be mindful of this in their communication and care of myeloma patients.

P-087

Characterization of minimal residual disease (MRD) in patients with relapsed/refractory multiple myeloma treated with elranatamab: analysis of MagnetisMM-3

Cyrille Touzeau[1], Katja Weisel[2], Nizar Bahlis[3], Hang Quach[4], Finn Hamilton[5], Shen-wu Wang[5], Eric Leip[5], Andrea Viqueira[6], Thomas O'Brien[5], Paula Rodríguez-Otero[7]

[1]CHU de Nantes; [2]Universitäres Cancer Center Hamburg; [3]Arnie Charbonneau Cancer Institute, University of Calgary; [4]Vincent's Hospital Melbourne, University of Melbourne, VIC, Australia; [5]Pfizer Inc; [6]Pfizer SLU, Madrid, Spain; [7]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain

Introduction: MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study of elranatamab monotherapy in patients (pts) with multiple myeloma refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody. Achieving MRD negativity has been associated with improved outcomes (PFS, OS). However, successful identification of a baseline diagnostic clone in all relapsed refractory patients remains a challenge. This is the first characterization of baseline calibration success and MRD assessment in pts naïve to B-cell maturation antigen (BCMA)-directed therapy (Cohort A) from MagnetisMM-3. **Methods:** An index/calibration bone marrow aspirate (BMA) was required at screening to identify the dominant rearranged B-cell receptor sequence(s) used to track MRD status during treatment. While a freshly collected BMA sample was preferred to identify the dominant clone, other sample types were permitted and submitted for testing. MRD tracking was performed with BMA samples collected at suspected CR/sCR and after 6 months, 12 months, and yearly after achieving CR. MRD negative status was defined as having a CR or sCR and having less than 1 malignant plasma cell in 10^{-5} nucleated cells as assessed by the clonoSEQ assay. Bulk RNA-seq analysis was performed using BMA samples collected at screening. Clinical data cutoff was March 2023 (~15 months after last patient initial dose) with a median follow up of 14.7 months. **Results:** Successful identification of the dominant clone at baseline for the purpose of NGS MRD assessment was primarily associated with a higher % BM plasma cell content. In all BCMA naïve patients the CR/sCR and MRD negative rate at a sensitivity of 10^{-5} was 21.1% (n=26/123), and in evaluable patients (CR/sCR with an identified clone at baseline and an on-treatment MRD assessment) the MRD-negative rate was 89.7% (n=26/29). MRD-negativity was achieved across subgroups, however, as expected poor prognosis subgroups such as R-ISS 3, high-risk cytogenetics, presence of EMD or patients with penta-refractory disease achieved a lower MRD-negativity rate. Patients

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Introduction: MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study of elranatamab monotherapy in patients (pts) with multiple myeloma refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody. Achieving MRD negativity has been associated with improved outcomes (PFS, OS). However, successful identification of a baseline diagnostic clone in all relapsed refractory patients remains a challenge. This is the first characterization of baseline calibration success and MRD assessment in pts naïve to B-cell maturation antigen (BCMA)-directed therapy (Cohort A) from MagnetisMM-3. **Methods:** An index/calibration bone marrow aspirate (BMA) was required at screening to identify the dominant rearranged B-cell receptor sequence(s) used to track MRD status during treatment. While a freshly collected BMA sample was preferred to identify the dominant clone, other sample types were permitted and submitted for testing. MRD tracking was performed with BMA samples collected at suspected CR/sCR and after 6 months, 12 months, and yearly after achieving CR. MRD negative status was defined as having a CR or sCR and having less than 1 malignant plasma cell in 10^{-5} nucleated cells as assessed by the clonoSEQ assay. Bulk RNA-seq analysis was performed using BMA samples collected at screening. Clinical data cutoff was March 2023 (~15 months after last patient initial dose) with a median follow up of 14.7 months. **Results:** Successful identification of the dominant clone at baseline for the purpose of NGS MRD assessment was primarily associated with a higher % BM plasma cell content. In all BCMA naïve patients the CR/sCR and MRD negative rate at a sensitivity of 10^{-5} was 21.1% (n=26/123), and in evaluable patients (CR/sCR with an identified clone at baseline and an on-treatment MRD assessment) the MRD-negative rate was 89.7% (n=26/29). MRD-negativity was achieved across subgroups, however, as expected poor prognosis subgroups such as R-ISS 3, high-risk cytogenetics, presence of EMD or patients with penta-refractory disease achieved a lower MRD-negativity rate. Patients

this study, we showed that EasyM generates a trackable clonotype in the vast majority (88%) of patients with LC MM and that relapse was numerically higher in patients with normal dFLC and MRD+ by EasyM at day +100 after AHCT. Defining the clinical application of EasyM requires larger studies with additional time-points, but this series demonstrated that it may be a useful tool for disease monitoring in LC MM.

P-086

Patient and haematologist perspectives of minimal residual disease testing in myeloma

Silene ten Seldam[1], Kate Morgan[1], Katie Joyner[1]

[1]Myeloma Patients Europe

Introduction: Minimal residual disease (MRD) refers to a very small number of cancer cells that remain in the body during or after treatment. Despite growing interest of MRD in clinical practice and clinical trials, little is known regarding the perspectives and experiences of MRD testing from haematologists and myeloma patients. This project captured these perspectives on the current and potential future use of MRD in clinical practice and the psychosocial impact of MRD testing on patients and families. **Methods:** Participants were recruited from across Europe through patient organisations, website and via email. Two focus groups with myeloma patients were held along with individual interviews with haematologists. Focus groups and interviews were online and conducted using semi-structured topic guides, informed by a review of existing literature. Discussions were recorded, transcribed, and thematically analysed. **Results:** The focus group discussions with patients (n=14, from 9 countries) included 3 key themes; awareness of MRD, MRD-informed treatment decision making, and the potential psychosocial burden. Awareness of MRD testing varied amongst patients with some unfamiliar and some having experienced MRD testing themselves. Patients felt optimistic about MRD testing, particularly if it can be used for treatment decision making. Patients expressed willingness to consider more frequent bone marrow tests if MRD results could be used as an indicator for maintenance therapy to be stopped. However, they also highlighted the potential emotional and physical burden of attending hospital for the MRD tests, the invasive biopsies required, and the discomfort of waiting for the results. It was also emphasised that a positive MRD result, in the context of no available further treatments, would be particularly hard for patients. The interviews with haematologists (n=9, from 8 countries) included themes on MRD-informed treatment decision making, and MRD implementation considerations. Haematologists were equally optimistic about the potential for MRD testing in clinical practice and its role in guiding treatment decisions such as maintenance treatment plans. However, they also highlighted multiple challenges in implementing MRD testing in clinical practice, such as laboratory capacity and capability issues, the cost and staff training. **Conclusions:** This research highlighted that patients may be unaware of MRD testing, and there is a need for resources for patients and families to facilitate understanding about what it is and the implications of results. Implementation of MRD testing in future clinical practice would also require training and resources for healthcare professionals and laboratory staff to ensure accuracy and consistency across testing centres. The emotional and physical impact of MRD testing on patients will also need to be considered and healthcare providers need to be mindful of this in their communication and care of myeloma patients.

P-087

Characterization of minimal residual disease (MRD) in patients with relapsed/refractory multiple myeloma treated with elranatamab: analysis of MagnetisMM-3

Cyrille Touzeau[1], Katja Weisel[2], Nizar Bahlis[3], Hang Quach[4], Finn Hamilton[5], Shen-wu Wang[5], Eric Leip[5], Andrea Viqueira[6], Thomas O'Brien[5], Paula Rodríguez-Otero[7]

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P-088

High throughput MGUS monitoring program to support incidental MGUS (iMGUS) detection in the community

Gaurav Agarwal[1], Lauren Campbell[2], Oluremi Carty[2], Sally Moore[3], Sarah Gooding[4], Jaimal Kothari[2], Julia Evans[2], Jemma Larham[2], Lisa Ferguson[2], Pamela Roberts[2], Ross Sadler[2], Karthik Ramasamy[2]

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is present in 1-2% of adults older than 50 years. As 1% of patients progress to multiple myeloma (MM) per year, MGUS monitoring has the potential to improve MM outcomes through earlier diagnosis. A variety of monitoring systems have been implemented in the NHS, including hospital, primary care, and nurse-led surveillance. However, most services are inefficient and unsustainable to support population-based monitoring. Here, we setup a risk-adapted monitoring system (OxCOM), in which patients with new incidental MGUS (iMGUS) in Thames Valley were stratified and prospectively monitored. **Methods:** Patients with a new iMGUS were captured over a 24-month period (between 4th March 2021 and 3rd March 2023) in an Immunology Laboratory covering a population of 2.5 million people. Patients were risk-stratified daily by an attending immunologist into high-risk [IgG >30g/L or IgA/IgM >10g/L; or free light chain (FLC) ratio outside 0.1-7.0; or CRAB criteria], intermediate-risk [IgG 15-30g/L or IgA/IgM 5-10g/L; or FLC ratio outside 0.3-3.0; or monoclonal IgD/E or FLC; or band present in urine] or low-risk MGUS [IgG < 15g/L or IgA/IgM < 5g/L]. Low-risk patients were advised for 4-12-monthly remote blood monitoring, run by an OxCOM administrator. Intermediate-risk patients were advised for routine review in a non-Consultant-led telephone or face-to-face (F2F) clinic (primarily nurse-led, supported by physician associate or haematology trainee). High-risk patients were advised for urgent F2F review by a Consultant Haematologist. **Results:** 1,507 patients had new iMGUS detected over a 24-month period [1,014 low-risk, 290 intermediate-risk and 203 high-risk iMGUS), with median age 76.8 years and median 17 months of follow-up. Of 525 low-risk patients with ≥12-months follow-up, 475 (90%) had attended a further monitoring event. Of 88 intermediate-risk patients attending non-Consultant-led review (56 telephone and 32 F2F), 34 (39%) received further imaging and 10 (11%) had bone marrow biopsy. At last follow-up, 17 (19%) intermediate-risk patients had been moved to OxCOM remote monitoring, 65% had ongoing follow-up and 10 (11%) had been diagnosed with malignancy [2 MM, 3 smouldering MM, 2 Waldenström macroglobulinemia (WM), 2 lymphoma and 1 AL amyloidosis). Of 63 high-risk patients attending urgent Consultant-led F2F review, 41 (65%) had been diagnosed with malignancy (17 MM, 9 smouldering MM, 1 plasmacytoma, 9 WM, 2 lymphoma and 3 AL amyloidosis). **Conclusions:** We demonstrate the feasibility of a risk-adapted high-throughput clinical monitoring service for iMGUS. Immunology Laboratory led central oversight by stratifying patients to either OxCOM remote monitoring, routine OxCOM assessment or urgent F2F haematology review. The service therefore establishes a model to enable tailored follow-up and monitoring of iMGUS, which distributes healthcare resource towards higher-risk patients, whilst enabling sustainable monitoring for lower-risk patients.

P-089

Evaluating dynamic changes in the serum free light chain ratio and its effect on risk of progression in smoldering multiple myeloma

Theresia Akhlaghi[1], David Nemirovsky[2], Kylee Maclachlan[2], Neha Korde[2], Sham Mailankody[2], Alexander Lesokhin[2], Hani Hassoun[2], Dhwani Patel[2], Urvi Shah[2], Carlyn Rose Tan[2], Oscar Lahoud[2], Heather Landau[2], Gunjan Shah[2], Michael Scordo[2], David Chung[2], Ola Landgren[3], Sergio Giralt[2], Saad Usmani[2], Andriy Derkach[2], Malin Hultcrantz[2]

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Introduction: Smoldering multiple myeloma (SMM) is a heterogeneous condition comprised of patients with varying risk of progression to multiple myeloma (MM). Existing models to predict the risk of progression to active disease are based on MM markers from a single time point at initial presentation without regard to marker evolution over time. In this study, we assessed the effect of dynamic temporal changes in the free light chain ratio (FLCr) on the risk of progression from SMM to MM. **Methods:** We performed a retrospective analysis of patients diagnosed with SMM between 2002 and 2019 at Memorial Sloan Kettering Cancer Center with follow-up to 2022. Only patients with available FLCs (Freelite, The Binding Site) at diagnosis were included. Baseline laboratory, pathology, and imaging data, as well as date of diagnosis and progression, were manually reviewed. Progression from SMM to active MM was defined according to the diagnostic criteria at the time of progression or initiating treatment for active MM. Serial FLC levels between the date of diagnosis and progression were obtained by computerized extraction. We assessed the time to progression (TTP) using the Kaplan-Meier method, with log-rank tests for comparison between groups. We used Cox regression to estimate the

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P-089

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risk of progression with hazard ratios (HRs) and 95% confidence intervals (CIs). **Results:** A total of 398 patients were included with a median age of 64 years and 55% male. The median baseline FLCr was 9.8 (interquartile range 3.3-34.3). During a median follow-up time of 84 months, 184 patients (46%) progressed to active MM with a median TTP of 94 months. Patients were divided into quintiles based on the baseline FLCr (Q1-Q5). Patients in Q5 had a FLCr from 26.6-94.8 and had an increased risk of a progression (median TTP 36 [95% CI: 29-62] months, HR 3.2 [1.9-5], p< 0.001) when compared to patients in Q1. Patients in Q4 (FLCr 11.3-26.6) had a median TTP of 102 (53-not reached) months and a HR of 1.7 (0.9 -2.9). For patients in Q1-Q3 (FLCr 1-11.2), the median TTP ranged from 128 to 213 months, and HRs were similar for patients in Q3 and Q2 compared to Q1. Patients were further stratified into groups based on the change in the FLCr at 1 year (ΔQ1-ΔQ5). Patients in ΔQ5 had a rise in FLCr (ΔFLCr) of >55% compared to their baseline. After 1 year, they had an increased risk of progression with a median TTP of 48 (21-116) months, and a HR of 2 (1.1-3.8) compared to patients in ΔQ1. Patients in ΔQ4 (ΔFLCr 17-55% increase from baseline) had a median TTP of 67 (39-not reached) months and a HR of 1.8 (0.9-3.3). For patients in ΔQ1-ΔQ3 (ΔFLCr < 17%), the median TTP ranged from 97 to 201 months. There was no significant difference in the HR for progression between patients in ΔQ3 and ΔQ2 compared to ΔQ1. **Conclusions:** In addition to baseline risk stratification based on the FLCr, changes in FLCr within the first year of diagnosis provide additional prognostic information to further guide the management of patients with SMM.

P-090

Clinical characteristics and risk of progression in patients with monoclonal gammopathy of uncertain significance: long-term experience in a single tertiary hospital

Elena Alejo[1], Borja Puertas[1], Cristina Agulló[1], Beatriz Rey-Búa[1], Ramon Garcia-Sanz[2], Noemi Puig[3], María-Victoria Mateos[4], Veronica Gonzalez-Calle[2]

[1]Hospital Universitario de Salamanca; [2]Departamento de Hematología, Hospital Universitario de Salamanca, (HUSA/IBSAL), Centro de Investigación del Cáncer-IBMCC (CSIC/USAL), CIBERONC; [3]Hospital Universitario de Salamanca Hematología. Instituto de investigación biomédica de Salamanca (IBSAL); [4]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain

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P-091

Senescence features in pre-malignant plasma cells and their microenvironment are associated with stable disease in MGUS and SMM

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Introduction: Multiple Myeloma (MM) progresses from monoclonal gammopathy of undetermined significance (MGUS) and/or smoldering MM (SMM). Despite similar primary genetic events as MM, MGUS and SMM are non- or low-proliferative; however, stable MGUS patients are at increased risk for osteoporotic

risk of progression with hazard ratios (HRs) and 95% confidence intervals (CIs). **Results:** A total of 398 patients were included with a median age of 64 years and 55% male. The median baseline FLCr was 9.8 (interquartile range 3.3-34.3). During a median follow-up time of 84 months, 184 patients (46%) progressed to active MM with a median TTP of 94 months. Patients were divided into quintiles based on the baseline FLCr (Q1-Q5). Patients in Q5 had a FLCr from 26.6-94.8 and had an increased risk of a progression (median TTP 36 [95% CI: 29-62] months, HR 3.2 [1.9-5], p< 0.001) when compared to patients in Q1. Patients in Q4 (FLCr 11.3-26.6) had a median TTP of 102 (53-not reached) months and a HR of 1.7 (0.9 -2.9). For patients in Q1-Q3 (FLCr 1-11.2), the median TTP ranged from 128 to 213 months, and HRs were similar for patients in Q3 and Q2 compared to Q1. Patients were further stratified into groups based on the change in the FLCr at 1 year (ΔQ1-ΔQ5). Patients in ΔQ5 had a rise in FLCr (ΔFLCr) of >55% compared to their baseline. After 1 year, they had an increased risk of progression with a median TTP of 48 (21-116) months, and a HR of 2 (1.1-3.8) compared to patients in ΔQ1. Patients in ΔQ4 (ΔFLCr 17-55% increase from baseline) had a median TTP of 67 (39-not reached) months and a HR of 1.8 (0.9-3.3). For patients in ΔQ1-ΔQ3 (ΔFLCr < 17%), the median TTP ranged from 97 to 201 months. There was no significant difference in the HR for progression between patients in ΔQ3 and ΔQ2 compared to ΔQ1. **Conclusions:** In addition to baseline risk stratification based on the FLCr, changes in FLCr within the first year of diagnosis provide additional prognostic information to further guide the management of patients with SMM.

P-090

Clinical characteristics and risk of progression in patients with monoclonal gammopathy of uncertain significance: long-term experience in a single tertiary hospital

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P-091

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fracture and show reduced overall survival due to aging co-morbidities. Since oncogenes and DNA damage drive senescent growth arrest, we hypothesize that stable MGUS and SMM pre-malignant PCs exhibit senescence features. **Methods:** We performed gene set enrichment analysis (GSEA) of a published human PC gene array dataset (GSE5900). Immunostaining and fluorescent in situ hybridization were performed to evaluate senescence in MGUS, SMM and MM patient PCs and trephine bone biopsies from MGUS and SMM patients that progressed or not to MM. Lastly, quantitative PCR was used to validate senescence gene expression changes in MGUS, SMM, and MM PCs. **Results:** MGUS and SMM PCs exhibited significant enrichment for senescence phenotyping gene sets that were distinct from aging. PCs from bone marrow aspirates were identified as senescent based on the Loss of LMNB1 (LoL, < 50%) and senescence associated distension of satellites (SADS, ≥3/cell). PCs from patients with stable MGUS (N=4) exhibited increased percentage of senescent PCs compared to SMM and MM, while stable vs progressing SMM PCs (stable vs progressed ≤5 years, n=6-8) were unchanged. However, PCs from stable, but not progressing SMM, had increased expression of senescence genes (CDKN2A, TP53, BCL2, and IL1B). Both stable MGUS and SMM PCs showed a significant increase in the expression of the retrotransposable element, L1HS, which is increased with senescence, compared to PCs from SMM progressors. Trephine biopsy cells were scored as senescent based on LoL and loss of nuclear HMGB1. Stable MGUS patients exhibited increased percentage of senescent PCs compared to MM and MGUS patients that progressed ≤10 years (n=20-40). Senescent PCs in trephine biopsies correlated with senescence in the bone marrow microenvironment (BMME). Of interest, MGUS and SMM PCs from patients that progressed ≤10 years both exhibited a significant loss in neighboring senescent BMME compared to stable MGUS and SMM PCs. **Conclusions:** Overall, we demonstrate the presence of stage-specific senescence features in PCs from stable MGUS and SMM patients; these features are decreased in PCs from SMM progressors and MM, consistent with the protective effect of senescence against tumorigenesis. Thus, evaluating PC senescence in MGUS and SMM may have prognostic value to identify patients that will progress to MM. Importantly, given the increased risk for osteoporotic fracture and reduced overall survival in stable MGUS patients, the senescence-related protection against MM may come at the expense of premature aging. Ongoing studies are evaluating the safety and therapeutic utility of ablating pre-malignant senescent cells in MGUS and SMM.

P-092

High serum free light chains levels in African ancestry population screened for monoclonal gammopathy: implication for definition of FLC reference range accounting for renal function and race

Luca Bertamini[1], Jean-Baptiste Alberge[1], Habib El-Khoury[1], David Lee[1], Grace Fleming[1], Ciara Murphy[1], Maya Davis[1], Jacqueline Perry[1], Christian Cea-Curry[1], Audrey Pentz[2], Thulisile Hlubi[2], Natalie Smyth[3], Dhananjay Sakrikar[4], Mark Perkins[5], Stephen Harding[5], Derek Troske[4], Gad Getz[6], Timothy Rebbeck[1], Maureen Joffe[2], Catherine Marinac[1], Nelson Leung[7], Wenlong Carl Chen[8], Irene Ghobrial[1]

[1]Dana-Farber Cancer Institute; [2]Noncommunicable Diseases Research Division, Wits Health Consortium (PTY) Ltd, Johannesburg, South Africa; [3]Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [4]The Binding Site Inc., Rochester, MN, USA; [5]The Binding Site Group Ltd., Birmingham, UK; [6]Broad Institute of MIT and Harvard, Cambridge, MA; [7]Mayo Clinic; [8]Sydney Brenner Institute for Molecular Science, University of the Witwatersrand

Introduction: Serum free light chains (sFLC) are important for diagnosis and prognosis of plasma cell dyscrasias and are known to be affected by kidney function and inflammation. In a biobanked population, African Americans (AA) were reported to have significantly higher Kappa (κ) and Lambda (λ) sFLC after adjusting for kidney function. We hypothesize that adjusted sFLC reference ranges are needed for individuals of African and European descent. **Methods:** We analyzed serum from 738 healthy Black South African (SA) and 3402 US individuals (AA+EA) as part of a study screening individuals at high risk of multiple myeloma (MM) and precursors (self-identify as Black or with family history of blood cancer). sFLC levels were measured using the Optilite® Freelite assay (The Biding Site). Participants were screened for Monoclonal Gammopathy of Undetermined Significance (MGUS; M protein ≥ 0.2 g/L) by MALDI-TOF mass spectrometry. Serum Cystatin C (Optilite®) was used to calculate estimated Glomerular Filtration Rate (eGFR) with CKD-EPI Cystatin C Equation (2012) formula for 752 individuals. Group medians were compared with Wilcoxon tests. Abnormal sFLCr was defined as a value outside the reference range with involved sFLC above the manufacturer's reference range. We used the 95% central interval (CI) for new sFLCr reference ranges. **Results:** After excluding individuals with Heavy Chain-MGUS, we included 654 SA, 326 AA, and 2,551 EA. Median age was 52, 56 and 58 respectively. Females were more common in the AA (74%) and EA (73%) vs SA (52%). Calculated median eGFR was 118 ml/min for SA and 112 for AA. HIV positivity was higher in SA (23%) than other groups (< 1%), 99% of whom were under treatment (Tenofovir 92%). The median free κ was higher in SA (32 mg/l,) than AA (18.1 mg/l,, +80%, p60 ml/min), excluding those with free κ and λ outside the 95% CI, we identified a new FLCr reference range of 0.80-2.38. **Conclusions:** We observed a significantly higher sFLC for Black (SA and AA) than White individuals (EA), independent of renal function. This could be due to genetic background and social and environmental factors, like HIV infection. While further validation is needed, we propose a new sFLC range for African ancestry populations with normal renal function.

P-093

Solitary plasmacytoma: single institution experience and systematic review and meta-analysis of clinical outcomes

Charalampos Charalampous[1], Jean-Sebastien Claveau[1], Prashant Kapoor[1], Moritz Binder[1], Francis Buadi[1],

fracture and show reduced overall survival due to aging co-morbidities. Since oncogenes and DNA damage drive senescent growth arrest, we hypothesize that stable MGUS and SMM pre-malignant PCs exhibit senescence features. **Methods:** We performed gene set enrichment analysis (GSEA) of a published human PC gene array dataset (GSE5900). Immunostaining and fluorescent in situ hybridization were performed to evaluate senescence in MGUS, SMM and MM patient PCs and trephine bone biopsies from MGUS and SMM patients that progressed or not to MM. Lastly, quantitative PCR was used to validate senescence gene expression changes in MGUS, SMM, and MM PCs. **Results:** MGUS and SMM PCs exhibited significant enrichment for senescence phenotyping gene sets that were distinct from aging. PCs from bone marrow aspirates were identified as senescent based on the Loss of LMNB1 (LoL, < 50%) and senescence associated distension of satellites (SADS, ≥3/cell). PCs from patients with stable MGUS (N=4) exhibited increased percentage of senescent PCs compared to SMM and MM, while stable vs progressing SMM PCs (stable vs progressed ≤5 years, n=6-8) were unchanged. However, PCs from stable, but not progressing SMM, had increased expression of senescence genes (CDKN2A, TP53, BCL2, and IL1B). Both stable MGUS and SMM PCs showed a significant increase in the expression of the retrotransposable element, L1HS, which is increased with senescence, compared to PCs from SMM progressors. Trephine biopsy cells were scored as senescent based on LoL and loss of nuclear HMGB1. Stable MGUS patients exhibited increased percentage of senescent PCs compared to MM and MGUS patients that progressed ≤10 years (n=20-40). Senescent PCs in trephine biopsies correlated with senescence in the bone marrow microenvironment (BMME). Of interest, MGUS and SMM PCs from patients that progressed ≤10 years both exhibited a significant loss in neighboring senescent BMME compared to stable MGUS and SMM PCs. **Conclusions:** Overall, we demonstrate the presence of stage-specific senescence features in PCs from stable MGUS and SMM patients; these features are decreased in PCs from SMM progressors and MM, consistent with the protective effect of senescence against tumorigenesis. Thus, evaluating PC senescence in MGUS and SMM may have prognostic value to identify patients that will progress to MM. Importantly, given the increased risk for osteoporotic fracture and reduced overall survival in stable MGUS patients, the senescence-related protection against MM may come at the expense of premature aging. Ongoing studies are evaluating the safety and therapeutic utility of ablating pre-malignant senescent cells in MGUS and SMM.

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fracture and show reduced overall survival due to aging co-morbidities. Since oncogenes and DNA damage drive senescent growth arrest, we hypothesize that stable MGUS and SMM pre-malignant PCs exhibit senescence features. **Methods:** We performed gene set enrichment analysis (GSEA) of a published human PC gene array dataset (GSE5900). Immunostaining and fluorescent in situ hybridization were performed to evaluate senescence in MGUS, SMM and MM patient PCs and trephine bone biopsies from MGUS and SMM patients that progressed or not to MM. Lastly, quantitative PCR was used to validate senescence gene expression changes in MGUS, SMM, and MM PCs. **Results:** MGUS and SMM PCs exhibited significant enrichment for senescence phenotyping gene sets that were distinct from aging. PCs from bone marrow aspirates were identified as senescent based on the Loss of LMNB1 (LoL, < 50%) and senescence associated distension of satellites (SADS, ≥3/cell). PCs from patients with stable MGUS (N=4) exhibited increased percentage of senescent PCs compared to SMM and MM, while stable vs progressing SMM PCs (stable vs progressed ≤5 years, n=6-8) were unchanged. However, PCs from stable, but not progressing SMM, had increased expression of senescence genes (CDKN2A, TP53, BCL2, and IL1B). Both stable MGUS and SMM PCs showed a significant increase in the expression of the retrotransposable element, L1HS, which is increased with senescence, compared to PCs from SMM progressors. Trephine biopsy cells were scored as senescent based on LoL and loss of nuclear HMGB1. Stable MGUS patients exhibited increased percentage of senescent PCs compared to MM and MGUS patients that progressed ≤10 years (n=20-40). Senescent PCs in trephine biopsies correlated with senescence in the bone marrow microenvironment (BMME). Of interest, MGUS and SMM PCs from patients that progressed ≤10 years both exhibited a significant loss in neighboring senescent BMME compared to stable MGUS and SMM PCs. **Conclusions:** Overall, we demonstrate the presence of stage-specific senescence features in PCs from stable MGUS and SMM patients; these features are decreased in PCs from SMM progressors and MM, consistent with the protective effect of senescence against tumorigenesis. Thus, evaluating PC senescence in MGUS and SMM may have prognostic value to identify patients that will progress to MM. Importantly, given the increased risk for osteoporotic fracture and reduced overall survival in stable MGUS patients, the senescence-related protection against MM may come at the expense of premature aging. Ongoing studies are evaluating the safety and therapeutic utility of ablating pre-malignant senescent cells in MGUS and SMM.

P-092

High serum free light chains levels in African ancestry population screened for monoclonal gammopathy: implication for definition of FLC reference range accounting for renal function and race

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Introduction: Serum free light chains (sFLC) are important for diagnosis and prognosis of plasma cell dyscrasias and are known to be affected by kidney function and inflammation. In a biobanked population, African Americans (AA) were reported to have significantly higher Kappa (κ) and Lambda (λ) sFLC after adjusting for kidney function. We hypothesize that adjusted sFLC reference ranges are needed for individuals of African and European descent. **Methods:** We analyzed serum from 738 healthy Black South African (SA) and 3402 US individuals (AA+EA) as part of a study screening individuals at high risk of multiple myeloma (MM) and precursors (self-identify as Black or with family history of blood cancer). sFLC levels were measured using the Optilite® Freelite assay (The Biding Site). Participants were screened for Monoclonal Gammopathy of Undetermined Significance (MGUS; M protein ≥ 0.2 g/L) by MALDI-TOF mass spectrometry. Serum Cystatin C (Optilite®) was used to calculate estimated Glomerular Filtration Rate (eGFR) with CKD-EPI Cystatin C Equation (2012) formula for 752 individuals. Group medians were compared with Wilcoxon tests. Abnormal sFLCr was defined as a value outside the reference range with involved sFLC above the manufacturer's reference range. We used the 95% central interval (CI) for new sFLCr reference ranges. **Results:** After excluding individuals with Heavy Chain-MGUS, we included 654 SA, 326 AA, and 2,551 EA. Median age was 52, 56 and 58 respectively. Females were more common in the AA (74%) and EA (73%) vs SA (52%). Calculated median eGFR was 118 ml/min for SA and 112 for AA. HIV positivity was higher in SA (23%) than other groups (< 1%), 99% of whom were under treatment (Tenofovir 92%). The median free κ was higher in SA (32 mg/l,) than AA (18.1 mg/l,, +80%, p60 ml/min), excluding those with free κ and λ outside the 95% CI, we identified a new FLCr reference range of 0.80-2.38. **Conclusions:** We observed a significantly higher sFLC for Black (SA and AA) than White individuals (EA), independent of renal function. This could be due to genetic background and social and environmental factors, like HIV infection. While further validation is needed, we propose a new sFLC range for African ancestry populations with normal renal function.

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[1]Mayo Clinic

Introduction: Solitary plasmacytomas are rare plasma cell neoplasms located in bone or extramedullary sites. Information on risk factors affecting disease-free survival (DFS) and survival outcomes is lacking. **Methods:** We conducted a retrospective study on 147 patients with plasmacytoma seen at the Mayo Clinic (January 1st, 2005 – June 30th, 2022). Our primary outcome was DFS, measured from the date of diagnosis to plasmacytoma recurrence or progression to multiple myeloma. We also performed a systematic review (1960 - 2022) and meta-analysis of 62 studies and 3487 patients with solitary plasmacytomas. Forest plots were constructed for each meta-analysis to examine and display study-level data using the random-effects model. **Results:** The median age at diagnosis was 60.7 years (range: 15.4 - 83.6). Patients with up to 10% clonal plasma cells in the bone marrow (plasmacytoma +, N=72) were older than those with a true solitary (N=75) plasmacytoma (63.5 vs. 56.2 years, p 5 mg/dl (HR= 1.9) and a positive urine immunofixation (HR= 3.4) were the only significant risk factors for earlier progression. In contrast, for solitary plasmacytoma, only a DFLC>5 mg/dl (HR= 2.7) retained significance. In the meta-analysis, most patients were male (66.1%) with a median age of 58 years and a tumor size of 4.9 cm. Radiation therapy was the main treatment, with 90.6% receiving it alone or in combination with other therapies. The objective response rate was 92.6%, with a 3-year DFS rate of 66.9%, 5-year DFS of 55%, and 10-year DFS of 42.1%. The 5-year overall survival (OS) rate was 79.6%, and the 10-year OS rate was 64.7%. There was a significant difference in the 5-year DFS rate between patients with bone plasmacytomas (51.1%) and extramedullary locations (69.8%), p< 0.01. The OS was numerically shorter in patients with bone plasmacytoma than with extramedullary plasmacytoma, respectively (76.7% vs. 81% at 5 years and 61% vs. 70.1% at 10 years, p=NS). **Conclusions:** The study provides important insight into survival outcomes and risk factors for plasmacytoma patients and highlights the importance of comprehensive disease staging at diagnosis.

P-094

Characterising risk and biology of smouldering myeloma for early detection of symptomatic myeloma: data from the UK cosmos study

Daniel Hughes[1], Louise Ainley[1], Elise Rees[1], Kane Foster[1], Catherine SY. Lecat[2], Eileen Boyle[1], Dylan Jankovic[1], Grant Vallance[3], Sayeh Foroughi[1], Ceri Bygrave[4], Hannah Hunter[5], Jindriska Lindsay[6], Agapi Parcharidou[7], Firas Al-Kaisi[8], Dean Smith[9], Fenella Willis[10], Charlotte Kallmeyer[11], Jonathan Ashcroft[12], H Ahmad[3], Jackie Ruell[13], Linda Barton[14], Moez Dungarwalla[15], Karthik Ramasamy[3], Kwee Yong[1]

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Introduction: Smouldering myeloma(SMM) risk models are largely based on genetics and disease bulk at a single timepoint. Improved understanding of disease dynamics and the influence of immunity on progression will help refine models and design of interventional trials. COSMOS is a prospective multi-centre observational study running in the UK since 2021, examining tumour dynamics, immune function, and serial biopsies to track disease longitudinally. **Methods:** COSMOS enrols patients with previous history, newly diagnosed or suspected SMM. Clinical, radiological and laboratory features are recorded with regular blood and bone marrow(BM) sampling. All samples undergo initial flow cytometry for tumour and immune subsets with downstream bulk and single cell sequencing and deep immune profiling. **Results:** We recruited 167 patients, median age 69yr (range 27-85), 47.3% male. At entry 82% were SMM, 10.5% MGUS and 7.5% myeloma by CRAB criteria(excluded from subsequent results). Median (range) paraprotein, light chain ratio(LCr) and BM plasma cell percentage(BMPC%) were 18.5g/L(1-77), 8.28(1.04-638.9), and 15(5-60). 43.8% had one or more high-risk cytogenetic lesions. 30%, 28%, 25%, 17% were low, low-intermediate, intermediate, and high-risk(IMWG). 7(4.2%) had ultra high-risk(UHR) disease(SLiM criteria). Median follow-up 10months(range 1-24) with low rate of withdrawal (3.6%). At entry there was negative correlation between BMPC%/paraprotein and albumin(p=0.02 and p< 0.001). Paraprotein negatively correlated with haemoglobin(p=0.04) and LDH(p=0.04). BMPC% negatively correlated with CD11b+ myeloid cells(p=0.019). CD4/8+ T-cells, Tregs, and NK-cells did not correlate with disease bulk or other immune cell frequencies. In total 21 patients progressed at median 11m(range 1-130) from diagnosis, 12 within 3 months of study entry and were excluded from our analysis of risk factors based on registration parameters. 12(57%) had bone disease. Of the 9 progressing on study at median 28m(4-130) from diagnosis. 66% were high-risk with paraprotein, LCr, and BMPC% significantly higher than non-progressors. No significantly different alterations in routine biochemical parameters or immune cells by 12m from entry were seen between progressors and non-progressors. 6/7 UHR patients have not progressed. Our laboratory pipeline includes scRNAseq on BM cells. For one progressing patient, we observed longitudinal clonal expansion of CD8+ T cell TCR clones alongside accumulation of proliferating(MKI67+TYMS+) tumour cells consistent with anti-tumour response. **Conclusions:** COSMOS has good and steady recruitment of UK SMM patients. BMPC% at entry correlates with decreasing haematopoietic reserve

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and decreasing albumin. In SMM, LDH does not appear to correlate with disease bulk. Broad immune cell subsets does not inform on risk or progression, indicating the need for our ongoing in-depth immune analysis. Longitudinal scRNA seq may give insight into immune processes associated with progression.

P-095

Evolving M-spike and risk of progression in smoldering multiple myeloma

Malin Hultcrantz[1], David Nemirovsky[2], Theresia Akhlaghi[3], Kylee Maclachlan[1], Neha Korde[1], Sham Mailankody[1], Alexander Lesokhin[4], Hani Hassoun[1], Dhwani Patel[4], Urvi Shah[1], Carlyn Rose Tan[4], Oscar Lahoud[4], Heather Landau[5], Gunjan Shah[4], Michael Scordo[4], David Chung[5], Ola Landgren[6], Sergio Giralt[4], Saad Usmani[4], Andriy Derkach[4]

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Introduction: Current risk scoring systems for smoldering multiple myeloma (SMM) are based on disease burden where patients with M-spike >2 g/dL, bone marrow plasma cells >20%, and free light chain ratio >20 are deemed at high risk for progression. Here, we assessed information on the dynamics of the M-spike concentration for predicting progression to multiple myeloma (MM). **Methods:** We analyzed all patients with SMM managed at Memorial Sloan Kettering Cancer Center between 2002-2019 with follow up to 2022. Descriptive statistics, Kaplan Meier curves, and Cox regression were used to analyze the risk of progression in relation to baseline M-spike and change in M-spike concentration. Disease progression was defined as fulfilling CRAB criteria and/or starting treatment for MM. Patient who progressed within the first 3 months of SMM diagnosis were excluded. **Results:** We included 398 patients with SMM, 55% men and median age was 63.6 years. The median baseline M-spike level was 1.3 g/dL. Patients were stratified into quintiles with the highest risk of progression seen in quintile 5 (Q5), i.e. baseline M-spike of >=2.2 g/dL, where the median time to progression (TTP) was 29 months (95% confidence interval [CI] 24-64 months). The TTP for patients in Q4, i.e. M-spike of 1.6-2.2 g/dL, was 67 months (95% CI 51-115 months). The TTP was longer for patients with lower M-spike and was similar in Q1-3 (M-spike 0-1.6 g/dL) where the TTP ranged from 112-138 months. During the first year of follow up, 11% of SMM patients progressed to MM. The rate of change (delta) in M-spike during year 1 of follow up translated into a higher risk of progression. In patients in the highest quintile of change (deltaQ5), delta M-spike of 0.3 g/dL or more during the first year, the median TTP was 22 months. For SMM patients with baseline M-spike concentrations in Q5, the hazard ratio (HR) for progression to MM was 3 times higher (HR=2.9, 95% CI 1.8-4.6) compared to patients in Q1. Similarly, in SMM patients with the highest rate of change (deltaQ5), the HR was 2.9, (95% CI 1.6-5.4) compared to patients in deltaQ1 after year 1. Interestingly, of the 11% (n=44) of patients who progressed during the first year, only 45% were in M-spike Q5 (n=20) at baseline. Of the remaining patients who progressed to MM during the first year of follow up, 9 were from baseline Q4 while 12 were from Q1-3, and 3 had no baseline M-spike. **Conclusions:** In summary, we confirmed that a higher baseline M-spike was associated with a higher risk of progression from SMM to MM. However, among patients who progressed at year 1 of follow up, 55% were not in the baseline Q5 M-spike group. Furthermore, we found that patients with a high rate of change in M-spike during the first year had a similar rate of progression to MM compared to SMM patients with a high baseline M-spike. Thus, both burden of disease and disease biology reflected in a rapid change in M-spike should be considered when predicting the risk of progression in patients with SMM.

P-096

Real world evidence of suboptimal humoral and cellular immune response to vaccination in ostensibly asymptomatic patients with precursor stage of multiple myeloma

Yoshinobu Konishi[1], Romanos Sklavenitis-Pistofidis[1], Michelle Aranha[1], Ting Wu[2], Hong Yue[1], Elizabeth Lightbody[1], Mahshid Rahmat[1], Michael Timonian[1], Shohreh Varmeh[1], Daniel Heilpern-Mallory[1], Michael Agius[1], Nang Su[1], Jacqueline Perry[1], Erica Horowitz[1], Maya Davis[1], Anna Justis[1], Radosław Nowak[1], Mark Hamilton[3], Daniel Auclair[4], Catherine Marinac[1], Eric Fischer[1], Gad Getz[2,5], Irene Ghobrial[1]

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Introduction: Patients with hematological malignancies, including multiple myeloma (MM), experience sub-optimal responses to SARS-CoV-2 vaccination. Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM) are precursors to MM and exhibit altered immune cell composition and function. The SARS-CoV-2 pandemic and the subsequent population-wide vaccination represent an opportunity to study the real-life immune response to a common antigen. Here, we present updated results from the IMPACT study, a study we launched in November 2020 to characterize the effect of plasma cell premalignancy on response to SARS-CoV-2 vaccination (vx). **Methods:** We performed: (i) ELISA for SARS-CoV-2-specific antibodies on 1,887 peripheral blood (PB) samples (237 healthy donors (HD), and 550 MGUS, 947 SMM, and 153 MM patients) drawn pre- and post-vx; (ii) single-cell RNA, T cell receptor (TCR), and B cell receptor (BCR) sequencing (10x Genomics) on 224 PB samples (26 HD, and 20 MGUS, 48 SMM, and 24 MM patients) drawn pre- and post-vx; (iii) plasma cytokine profiling (Olink) on

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Introduction: Patients with hematological malignancies, including multiple myeloma (MM), experience sub-optimal responses to SARS-CoV-2 vaccination. Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM) are precursors to MM and exhibit altered immune cell composition and function. The SARS-CoV-2 pandemic and the subsequent population-wide vaccination represent an opportunity to study the real-life immune response to a common antigen. Here, we present updated results from the IMPACT study, a study we launched in November 2020 to characterize the effect of plasma cell premalignancy on response to SARS-CoV-2 vaccination (vx). **Methods:** We performed: (i) ELISA for SARS-CoV-2-specific antibodies on 1,887 peripheral blood (PB) samples (237 healthy donors (HD), and 550 MGUS, 947 SMM, and 153 MM patients) drawn pre- and post-vx; (ii) single-cell RNA, T cell receptor (TCR), and B cell receptor (BCR) sequencing (10x Genomics) on 224 PB samples (26 HD, and 20 MGUS, 48 SMM, and 24 MM patients) drawn pre- and post-vx; (iii) plasma cytokine profiling (Olink) on

and decreasing albumin. In SMM, LDH does not appear to correlate with disease bulk. Broad immune cell subsets does not inform on risk or progression, indicating the need for our ongoing in-depth immune analysis. Longitudinal scRNA seq may give insight into immune processes associated with progression.

P-095

Evolving M-spike and risk of progression in smoldering multiple myeloma

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Introduction: Current risk scoring systems for smoldering multiple myeloma (SMM) are based on disease burden where patients with M-spike >2 g/dL, bone marrow plasma cells >20%, and free light chain ratio >20 are deemed at high risk for progression. Here, we assessed information on the dynamics of the M-spike concentration for predicting progression to multiple myeloma (MM). **Methods:** We analyzed all patients with SMM managed at Memorial Sloan Kettering Cancer Center between 2002-2019 with follow up to 2022. Descriptive statistics, Kaplan Meier curves, and Cox regression were used to analyze the risk of progression in relation to baseline M-spike and change in M-spike concentration. Disease progression was defined as fulfilling CRAB criteria and/or starting treatment for MM. Patient who progressed within the first 3 months of SMM diagnosis were excluded. **Results:** We included 398 patients with SMM, 55% men and median age was 63.6 years. The median baseline M-spike level was 1.3 g/dL. Patients were stratified into quintiles with the highest risk of progression seen in quintile 5 (Q5), i.e. baseline M-spike of >=2.2 g/dL, where the median time to progression (TTP) was 29 months (95% confidence interval [CI] 24-64 months). The TTP for patients in Q4, i.e. M-spike of 1.6-2.2 g/dL, was 67 months (95% CI 51-115 months). The TTP was longer for patients with lower M-spike and was similar in Q1-3 (M-spike 0-1.6 g/dL) where the TTP ranged from 112-138 months. During the first year of follow up, 11% of SMM patients progressed to MM. The rate of change (delta) in M-spike during year 1 of follow up translated into a higher risk of progression. In patients in the highest quintile of change (deltaQ5), delta M-spike of 0.3 g/dL or more during the first year, the median TTP was 22 months. For SMM patients with baseline M-spike concentrations in Q5, the hazard ratio (HR) for progression to MM was 3 times higher (HR=2.9, 95% CI 1.8-4.6) compared to patients in Q1. Similarly, in SMM patients with the highest rate of change (deltaQ5), the HR was 2.9, (95% CI 1.6-5.4) compared to patients in deltaQ1 after year 1. Interestingly, of the 11% (n=44) of patients who progressed during the first year, only 45% were in M-spike Q5 (n=20) at baseline. Of the remaining patients who progressed to MM during the first year of follow up, 9 were from baseline Q4 while 12 were from Q1-3, and 3 had no baseline M-spike. **Conclusions:** In summary, we confirmed that a higher baseline M-spike was associated with a higher risk of progression from SMM to MM. However, among patients who progressed at year 1 of follow up, 55% were not in the baseline Q5 M-spike group. Furthermore, we found that patients with a high rate of change in M-spike during the first year had a similar rate of progression to MM compared to SMM patients with a high baseline M-spike. Thus, both burden of disease and disease biology reflected in a rapid change in M-spike should be considered when predicting the risk of progression in patients with SMM.

P-096

Real world evidence of suboptimal humoral and cellular immune response to vaccination in ostensibly asymptomatic patients with precursor stage of multiple myeloma

Yoshinobu Konishi[1], Romanos Sklavenitis-Pistofidis[1], Michelle Aranha[1], Ting Wu[2], Hong Yue[1], Elizabeth Lightbody[1], Mahshid Rahmat[1], Michael Timonian[1], Shohreh Varmeh[1], Daniel Heilpern-Mallory[1], Michael Agius[1], Nang Su[1], Jacqueline Perry[1], Erica Horowitz[1], Maya Davis[1], Anna Justis[1], Radosław Nowak[1], Mark Hamilton[3], Daniel Auclair[4], Catherine Marinac[1], Eric Fischer[1], Gad Getz[2,5], Irene Ghobrial[1]

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106 PB samples (32 HD, and 38 MGUS and 36 SMM patients) drawn pre- and post-vx; and (iv) bulk TCR sequencing (Adaptive Biotechnologies) on 8 PB samples from 4 patients (2 MGUS, 2 SMM) drawn pre- and post-vx. **Results:** Patients with MGUS and SMM achieved comparable antibody titers to HD two months post-vx. However, patient titers waned significantly faster, and 4 months post-vx we observed significantly lower titers in both MGUS (Wilcoxon rank-sum, p=0.030) and SMM (p=0.010). These results indicate impaired humoral immune response in patients with MGUS and SMM. At baseline, the TCR repertoire was significantly less diverse in patients with SMM compared to HD (Wilcoxon rank-sum, p=0.039), while no significant difference was observed in the BCR repertoire (p=0.095). Interestingly, a significant increase in TCR repertoire diversity was observed post-vx in patients with SMM (paired t-test, p=0.014), indicating rare T cell clone recruitment in response to vaccination. In both HD and patients, recruited clones showed upregulation of genes associated with CD4+ naïve and memory T cells, suggesting at least partial preservation of the T cell response in SMM, which was confirmed by bulk TCR-sequencing in 4 patients. Lastly, by cytokine profiling, we observed a defect in IL-1β and IL-18 induction post-vx in patients with SMM compared to HD (Wilcoxon rank-sum, p=0.047 and p=0.015, respectively), two key monocyte-derived mediators of acute inflammation, suggesting an altered innate immune response as well. **Conclusions:** Taken together, our findings highlight that despite the absence of clinical manifestations, plasma cell premalignancy is associated with defects in both innate and adaptive immune responses. Therefore, patients with plasma cell premalignancy may require adjusted vaccination strategies for optimal immunization.

P-097

Single-cell RNA sequencing of circulating tumor cells in precursor myeloma patients reveals early mechanisms of disease dissemination

Elizabeth Lightbody[1], Danielle Firer[2], Romanos Sklavenitis-Pistofidis[1], Junko Tsuji[2], Michael Agius[1], Ankit Dutta[1], Ting Wu[2], Hadley Barr[1], Mahshid Rahmat[1], Yoshinobu Konishi[1], Michelle Aranha[1], Jean-Baptiste Alberge[1], Nang Kham Su[1], Cody Boehner[1], Laura Hevenor[1], Habib El-Khoury[1], Katherine Towle[1], Christian Cea-Curry[1], Erica Horowitz[1], Jacqueline Perry[1], Anna Cowan[1], Daniel Auclair[3], Catherine Marinac[1], Gad Getz[2], Irene Ghobrial[1]

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P-098

Prevalence of metabolic comorbidities and viral co-infections in monoclonal gammopathy: a retrospective analysis

Tinatin Muradashvili[1], Mansen Yu[1], Natalia Neparidze[1]

[1]Yale University

Introduction: Monoclonal gammopathy (MG) encompasses a spectrum of related diseases, with monoclonal gammopathy of undetermined significance (MGUS) being the most prevalent, serving as a precursor of smoldering and clinical multiple myeloma. While the association between gammopathies, metabolic conditions and antigenic stimulation has long been recognized, the precise etiopathogenic mechanism remains to be elucidated. The aim of this study is to assess the prevalence of metabolic comorbidities and

106 PB samples (32 HD, and 38 MGUS and 36 SMM patients) drawn pre- and post-vx; and (iv) bulk TCR sequencing (Adaptive Biotechnologies) on 8 PB samples from 4 patients (2 MGUS, 2 SMM) drawn pre- and post-vx. **Results:** Patients with MGUS and SMM achieved comparable antibody titers to HD two months post-vx. However, patient titers waned significantly faster, and 4 months post-vx we observed significantly lower titers in both MGUS (Wilcoxon rank-sum, p=0.030) and SMM (p=0.010). These results indicate impaired humoral immune response in patients with MGUS and SMM. At baseline, the TCR repertoire was significantly less diverse in patients with SMM compared to HD (Wilcoxon rank-sum, p=0.039), while no significant difference was observed in the BCR repertoire (p=0.095). Interestingly, a significant increase in TCR repertoire diversity was observed post-vx in patients with SMM (paired t-test, p=0.014), indicating rare T cell clone recruitment in response to vaccination. In both HD and patients, recruited clones showed upregulation of genes associated with CD4+ naïve and memory T cells, suggesting at least partial preservation of the T cell response in SMM, which was confirmed by bulk TCR-sequencing in 4 patients. Lastly, by cytokine profiling, we observed a defect in IL-1β and IL-18 induction post-vx in patients with SMM compared to HD (Wilcoxon rank-sum, p=0.047 and p=0.015, respectively), two key monocyte-derived mediators of acute inflammation, suggesting an altered innate immune response as well. **Conclusions:** Taken together, our findings highlight that despite the absence of clinical manifestations, plasma cell premalignancy is associated with defects in both innate and adaptive immune responses. Therefore, patients with plasma cell premalignancy may require adjusted vaccination strategies for optimal immunization.

P-097

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P-098

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Tinatin Muradashvili[1], Mansen Yu[1], Natalia Neparidze[1]

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P-098

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viral infections in a large population with monoclonal gammopathy, providing insights into the disease's pathophysiology. **Methods:** We conducted a retrospective chart review at a single center for patients aged 18 years and older, diagnosed with monoclonal gammopathy between 2014 and 2020. We excluded patients without documented immunofixation or serum protein electrophoresis studies, as well as those with "faint" or "extremely faint" monoclonal components, resulting in a final data set of 1515 patients. Variables of interest including age, race, ethnicity, gender, hyperlipidemia, diabetes, BMI, HIV, human papillomavirus (HPV), hepatitis C (HCV) and hepatitis B (HBV) status were identified by a combination of direct extraction from the EMR by the Joint Data Analytics Team and manual review of laboratory values, provider notes and scanned documents. **Results:** Among the 1515 patients diagnosed with monoclonal gammopathy, the average age was 76.36 (±11.3) years. The majority of patients (79.4%) self-identified as White, while 238 (15.7%) as Black/African American and 10 (0.7%) as Asian. Non-Hispanic individuals accounted for 1428 (94.3%) of the patients. The mean body mass index (BMI) was 27.5 (±6.73) years. Diabetes mellitus was reported in 614 (40.5%) cases, and hyperlipidemia was observed in 1362 (89.9%) cases. A total of 1236 (81.6%) patients used a statin at some point. Dyslipidemia and diabetes are estimated to affect 53% and 11.3% of the U.S. population, respectively. Among individuals aged 65 and older, the prevalence of dyslipidemia and diabetes is reported to be 60.3% and 21.2%, respectively. In our cohort, viral comorbidities included HIV in 20 (1.3%) patients and HPV in 14 (0.9 %) patients. In comparison, 12.6 per 100,000 people in the U.S. had HIV in 2019. Additionally, 49 out of 812 (6%) patients had positive HCV antibodies, compared to 1.7% of US adults. There were 56 of 711 (7.9%) patients with HBV infections. As of May 2023, out of the total 1515 patients, 485 (32%) deaths were reported. **Conclusions:** Patients with MG demonstrate significantly higher rates of dyslipidemia, diabetes, HIV, and positive HCV antibodies compared to the general US adult population. These findings highlight the importance of metabolic and viral infections in MG and emphasize the need for additional research on biologic drivers to guide preventative strategies.

P-099

Phase II trial of daratumumab, bortezomib, lenalidomide and dexamethasone in high-risk smoldering multiple myeloma

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[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Introduction: Lenalidomide has shown to delay progression in patients with high-risk smoldering multiple myeloma (HR-SMM). Curative intent trials with carfilzomib-based therapy and stem cell transplantation are under investigation in HR-SMM, leading to deep responses but with concern for treatment-related toxicities (Mateos ASH 2022). Daratumumab, bortezomib, lenalidomide and dexamethasone (D-RVD) has shown high rates of minimal residual disease (MRD) negativity in MM (Voorhees Blood 2020). Thus, we proposed to examine the activity and safety of D-RVD in patients with HR-SMM. **Methods:** This is a phase II, open label study evaluating D-RVD in HR-SMM. Eligibility criteria included HR-SMM per Mayo 2018 "20-2-20" model and other previously established criteria including Mayo 2008 criteria, presence of immunoparesis, evolving type of SMM, and high risk FISH. Treatment with D-RVD is 2 years (24 cycles) with daratumumab subcutaneous (SQ) per standard dose and schedule, bortezomib SQ on days 1, 8, 15 for cycles 1-6 and then biweekly until completion of cycle 24 and lenalidomide on days 1-21 with weekly dexamethasone. All eligible patients undergo stem cell collection after 6 cycles of therapy. The primary objective is rate of MRD-negativity at 2 years. Secondary objectives include PFS, ORR, and safety. The trial has been amended to include part 2, which will randomize patients that are MRD positive after 2 years to observation vs continued therapy with daratumumab and lenalidomide for an additional 24 months. The primary objective of part 2 is rate of MRD conversion from positive to negative. **Results:** At the time of data cut off, 30 patients have been enrolled to part 1 with a median follow up of 14 months. The median age is 60 years old (range 36-77). Ninety percent of patients were classified as either high (18, 60%) or intermediate risk (9, 30%) per Mayo 2018 criteria with median plasmacytosis of 20%, median M protein of 2.17 g/dl and median FLC ratio of 8.1. Twelve patients (40%) had high-risk FISH results (10 with 1q gain, 2 with t(4;14), 1 with t(14;16) and 1 with del 17p). Most common grade 3 toxicities included neutropenia (17%), ALT increased (10%), hypertension (7%) and diarrhea (7%). Upper respiratory infections occurred in 66% of patients (COVID 19 infection in 10 patients, only 1 grade 3). No patients discontinued therapy due to toxicity. The overall response rate is 87% with 40% CR, 23% VGPR and 23% PR. Sixty-three percent of patients achieved VGPR or greater. MRD was evaluable in 24 patients with at least 6 months of follow up and MRD negativity rate is 58% (14/24) and 38% (9/24) at thresholds of 10-5 and 10-6, respectively. No patients have progressed on treatment. Stem cell collection was successful in all eligible patients with average stem cell yield of 5.57 x 10-6 CD34+ cells/kg. **Conclusions:** D-RVD in HR-SMM demonstrates significant activity, including high rates of MRD-negative disease, and has a similar toxicity profile to MM.

P-100

Prevalence of monoclonal gammopathies in adult Uruguayan population

Eloísa Riva[1], Lucia Pérez Baliero[1], David Garrido[1], Alicia Olascoaga[1], Gabriela Villanueva[1], Raquel Ballesté[1], Cecilia Guillermo[2], Nicolas Marchetti[2], Andrea Urbin[2], Nadia Krul[1]

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viral infections in a large population with monoclonal gammopathy, providing insights into the disease's pathophysiology. **Methods:** We conducted a retrospective chart review at a single center for patients aged 18 years and older, diagnosed with monoclonal gammopathy between 2014 and 2020. We excluded patients without documented immunofixation or serum protein electrophoresis studies, as well as those with "faint" or "extremely faint" monoclonal components, resulting in a final data set of 1515 patients. Variables of interest including age, race, ethnicity, gender, hyperlipidemia, diabetes, BMI, HIV, human papillomavirus (HPV), hepatitis C (HCV) and hepatitis B (HBV) status were identified by a combination of direct extraction from the EMR by the Joint Data Analytics Team and manual review of laboratory values, provider notes and scanned documents. **Results:** Among the 1515 patients diagnosed with monoclonal gammopathy, the average age was 76.36 (±11.3) years. The majority of patients (79.4%) self-identified as White, while 238 (15.7%) as Black/African American and 10 (0.7%) as Asian. Non-Hispanic individuals accounted for 1428 (94.3%) of the patients. The mean body mass index (BMI) was 27.5 (±6.73) years. Diabetes mellitus was reported in 614 (40.5%) cases, and hyperlipidemia was observed in 1362 (89.9%) cases. A total of 1236 (81.6%) patients used a statin at some point. Dyslipidemia and diabetes are estimated to affect 53% and 11.3% of the U.S. population, respectively. Among individuals aged 65 and older, the prevalence of dyslipidemia and diabetes is reported to be 60.3% and 21.2%, respectively. In our cohort, viral comorbidities included HIV in 20 (1.3%) patients and HPV in 14 (0.9 %) patients. In comparison, 12.6 per 100,000 people in the U.S. had HIV in 2019. Additionally, 49 out of 812 (6%) patients had positive HCV antibodies, compared to 1.7% of US adults. There were 56 of 711 (7.9%) patients with HBV infections. As of May 2023, out of the total 1515 patients, 485 (32%) deaths were reported. **Conclusions:** Patients with MG demonstrate significantly higher rates of dyslipidemia, diabetes, HIV, and positive HCV antibodies compared to the general US adult population. These findings highlight the importance of metabolic and viral infections in MG and emphasize the need for additional research on biologic drivers to guide preventative strategies.

P-099

Phase II trial of daratumumab, bortezomib, lenalidomide and dexamethasone in high-risk smoldering multiple myeloma

Omar Nadeem[1], Robert Redd[1], Clifton Mo[1], Jacob Laubach[1], Paul G. Richardson[1], Julia Prescott[1], Marjorie Marto[1], Christine Davie[1], Caroline Ricciardi[1], Elizabeth Murphy[1], Meredith Bertoni[1], Dechen Choden[1], Sophie Magidson[1], Brian Sheehan[1], Hira Shrestha[1], Adam S. Sperling[1], Elizabeth K. O'Donnell[2], Irene M. Ghobrial[1]

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Introduction: Lenalidomide has shown to delay progression in patients with high-risk smoldering multiple myeloma (HR-SMM). Curative intent trials with carfilzomib-based therapy and stem cell transplantation are under investigation in HR-SMM, leading to deep responses but with concern for treatment-related toxicities (Mateos ASH 2022). Daratumumab, bortezomib, lenalidomide and dexamethasone (D-RVD) has shown high rates of minimal residual disease (MRD) negativity in MM (Voorhees Blood 2020). Thus, we proposed to examine the activity and safety of D-RVD in patients with HR-SMM. **Methods:** This is a phase II, open label study evaluating D-RVD in HR-SMM. Eligibility criteria included HR-SMM per Mayo 2018 "20-2-20" model and other previously established criteria including Mayo 2008 criteria, presence of immunoparesis, evolving type of SMM, and high risk FISH. Treatment with D-RVD is 2 years (24 cycles) with daratumumab subcutaneous (SQ) per standard dose and schedule, bortezomib SQ on days 1, 8, 15 for cycles 1-6 and then biweekly until completion of cycle 24 and lenalidomide on days 1-21 with weekly dexamethasone. All eligible patients undergo stem cell collection after 6 cycles of therapy. The primary objective is rate of MRD-negativity at 2 years. Secondary objectives include PFS, ORR, and safety. The trial has been amended to include part 2, which will randomize patients that are MRD positive after 2 years to observation vs continued therapy with daratumumab and lenalidomide for an additional 24 months. The primary objective of part 2 is rate of MRD conversion from positive to negative. **Results:** At the time of data cut off, 30 patients have been enrolled to part 1 with a median follow up of 14 months. The median age is 60 years old (range 36-77). Ninety percent of patients were classified as either high (18, 60%) or intermediate risk (9, 30%) per Mayo 2018 criteria with median plasmacytosis of 20%, median M protein of 2.17 g/dl and median FLC ratio of 8.1. Twelve patients (40%) had high-risk FISH results (10 with 1q gain, 2 with t(4;14), 1 with t(14;16) and 1 with del 17p). Most common grade 3 toxicities included neutropenia (17%), ALT increased (10%), hypertension (7%) and diarrhea (7%). Upper respiratory infections occurred in 66% of patients (COVID 19 infection in 10 patients, only 1 grade 3). No patients discontinued therapy due to toxicity. The overall response rate is 87% with 40% CR, 23% VGPR and 23% PR. Sixty-three percent of patients achieved VGPR or greater. MRD was evaluable in 24 patients with at least 6 months of follow up and MRD negativity rate is 58% (14/24) and 38% (9/24) at thresholds of 10-5 and 10-6, respectively. No patients have progressed on treatment. Stem cell collection was successful in all eligible patients with average stem cell yield of 5.57 x 10-6 CD34+ cells/kg. **Conclusions:** D-RVD in HR-SMM demonstrates significant activity, including high rates of MRD-negative disease, and has a similar toxicity profile to MM.

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Introduction: Lenalidomide has shown to delay progression in patients with high-risk smoldering multiple myeloma (HR-SMM). Curative intent trials with carfilzomib-based therapy and stem cell transplantation are under investigation in HR-SMM, leading to deep responses but with concern for treatment-related toxicities (Mateos ASH 2022). Daratumumab, bortezomib, lenalidomide and dexamethasone (D-RVD) has shown high rates of minimal residual disease (MRD) negativity in MM (Voorhees Blood 2020). Thus, we proposed to examine the activity and safety of D-RVD in patients with HR-SMM. **Methods:** This is a phase II, open label study evaluating D-RVD in HR-SMM. Eligibility criteria included HR-SMM per Mayo 2018 "20-2-20" model and other previously established criteria including Mayo 2008 criteria, presence of immunoparesis, evolving type of SMM, and high risk FISH. Treatment with D-RVD is 2 years (24 cycles) with daratumumab subcutaneous (SQ) per standard dose and schedule, bortezomib SQ on days 1, 8, 15 for cycles 1-6 and then biweekly until completion of cycle 24 and lenalidomide on days 1-21 with weekly dexamethasone. All eligible patients undergo stem cell collection after 6 cycles of therapy. The primary objective is rate of MRD-negativity at 2 years. Secondary objectives include PFS, ORR, and safety. The trial has been amended to include part 2, which will randomize patients that are MRD positive after 2 years to observation vs continued therapy with daratumumab and lenalidomide for an additional 24 months. The primary objective of part 2 is rate of MRD conversion from positive to negative. **Results:** At the time of data cut off, 30 patients have been enrolled to part 1 with a median follow up of 14 months. The median age is 60 years old (range 36-77). Ninety percent of patients were classified as either high (18, 60%) or intermediate risk (9, 30%) per Mayo 2018 criteria with median plasmacytosis of 20%, median M protein of 2.17 g/dl and median FLC ratio of 8.1. Twelve patients (40%) had high-risk FISH results (10 with 1q gain, 2 with t(4;14), 1 with t(14;16) and 1 with del 17p). Most common grade 3 toxicities included neutropenia (17%), ALT increased (10%), hypertension (7%) and diarrhea (7%). Upper respiratory infections occurred in 66% of patients (COVID 19 infection in 10 patients, only 1 grade 3). No patients discontinued therapy due to toxicity. The overall response rate is 87% with 40% CR, 23% VGPR and 23% PR. Sixty-three percent of patients achieved VGPR or greater. MRD was evaluable in 24 patients with at least 6 months of follow up and MRD negativity rate is 58% (14/24) and 38% (9/24) at thresholds of 10-5 and 10-6, respectively. No patients have progressed on treatment. Stem cell collection was successful in all eligible patients with average stem cell yield of 5.57 x 10-6 CD34+ cells/kg. **Conclusions:** D-RVD in HR-SMM demonstrates significant activity, including high rates of MRD-negative disease, and has a similar toxicity profile to MM.

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Introduction: Multiple myeloma (MM) is usually diagnosed in an advanced stage, which is associated with end-organ failure, inferior quality of life and survival, and increased costs for healthcare institutions. MM precursor stages (MGUS and SMM) can be detected easily through blood protein tests. A prospective, nationwide, screening study performed in Iceland, has detected MGUS in 4.9% and SMM in 0.5% of adults >49 years. However, there is still no recommendation regarding the benefits of population screening for MM precursor diseases. The objective of this research is to assess the prevalence of monoclonal plasma cell disorders in the adult population in Uruguay and evaluate the progression to active disease. **Methods:** A prospective, single-cohort, nationwide descriptive study conducted at Hospital de Clínicas, Montevideo, Uruguay. Residents ≥ 40 years were invited to participate. Recruitment started in October 2021 and ended in October 2022. Patients with a previously known plasma cell disorder were excluded. Medical history was obtained in all cases. CAPILLARYS 2 Flex Piercing was used for Protein and Immunotyping analyses, Hydrasys 2 for immunofixation, and Freelite (The Binding Site) for serum-free light chains. If a monoclonal component (MC) was detected, patients were evaluated according to current IMWG recommendations. Patients diagnosed or progressed to active disease were offered early treatment. **Results:** 3905 patients were included; the median age was 56 years (40-104) IQR 17, and 58.4% were females. A MC was found in 104 patients (prevalence 2.7%), with a median age of 63 years (40-88) IQR 17, 54.8% were females. Patients without MC had a median age of 55 years (40-104) IQR 17. The median value of the MC was 0.5 g/dl, (0.1-2 g/dl) IQR 0.5. 10.6% had a non-quantifiable MC. 3.8% had a bi-clonal MC. MC was IgG 76%, IgA 13.4%, IgM 7.7%, Kappa 1.9%, Lambda 1%. The median value of sFLC kappa, lambda, and ratio (rFLC) were 23.5 mg/L (IQR 24), 18.5 mg/L (IQR 17), and 1.3 (IQR 0.83) respectively. An abnormal rFLC was found in 32% (33/102). Out of 102 patients, 54 were low-risk MGUS, 34 intermediate-low-risk MGUS, 8 intermediate-high-risk MGUS, 1 SMM, 3 active MM, and 2 asymptomatic Waldenstrom Macroglobulinemia. The patients with active MM had no end-organ failure, and treatment started within 1 month from diagnosis. No significant association was found between MC and gender or comorbidities. 1% of patients had a family history of MM. The prevalence of MC according to age subgroups was 1.26% in 40-49 years, 1.92% in 50-59 years, 3.11% in 60-69 years, 6.78% in 70-79 years, and 7.14% in >80 years. Age >55 years was associated with a significant risk of monoclonal gammopathy (OR 2.9; IC 95% 1.87-4.5, p< 0.01). **Conclusions:** The prevalence of MGUS was 2.45% and SMM was 0.03%. Age >50 years increases significantly the risk of MC. 3 patients were diagnosed with asymptomatic active disease.

P-101

Single-cell RNA sequencing of 1.3 million plasma cells from patients with MGUS and SMM

Romanos Sklavenitis-Pistofidis[1], Elizabeth Lightbody[1], Junko Tsuji[2], Michael Agius[1], Mahshid Rahmat[1], Yoshinobu Konishi[1], Ting Wu[2], Michelle Aranha[1], Danielle Firer[2], Nicholas Haradhvala[2], Gad Getz[2,3], Irene Ghobrial[1]

[1]Dana-Farber Cancer Institute; [2]Broad Institute of MIT & Harvard; [3]Massachusetts General Hospital Cancer Center

Introduction: Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM) exhibit variable risk of progression to full-blown Multiple Myeloma (MM), which cannot be fully explained by differences in tumor burden or genetic alterations. Therefore, characterizing non-genetic changes in malignant plasma cells may help to identify novel mechanisms of disease progression and improve prognostication. **Methods:** Here, we performed single-cell RNA and V(D)J-sequencing on 245 samples from 36 patients with MGUS, 136 patients with SMM, 37 patients with MM, and 25 healthy donors. Libraries were prepared with the Chromium Single-cell 5' Gene Expression and V(D)J enrichment kit by 10X Genomics and sequenced at the Genomics Platform of the Broad Institute of MIT and Harvard (Cambridge, MA). **Results:** Overall, we sequenced 1,318,218 plasma cells, including 960,998 malignant and 357,220 normal plasma cells. By comparing tumor cells between patients and healthy donors, as well as between patients from different risk stages, we derived an expression signature that captures both the presence of malignancy and the tumor's stage. This signature includes known culprits, such as IL6, as well as genes related to bone biology, hypoxia, metabolic activity, and cytomobility. We validated the capacity of this signature to identify disease and measure risk of progression in an independent gene expression profiling dataset (GSE6477) and showed a significant association with both progression-free survival (PFS) and overall survival (OS) in the CoMMpass dataset. Notably, this association remained significant when we accounted for the patient's ISS stage and the tumor's proliferative index, suggesting that this signature captures orthogonal aspects of the tumor's aggressiveness. Furthermore, by comparing malignant and normal plasma cells within each patient, we were able to identify differentially expressed genes per tumor and assess how frequently each gene is dysregulated at scale. The most common upregulated genes were the oncogene MLLT3 (rank 1), the growth factor IGF1 (rank 2), and the proteasome regulator TJP1 (rank 3). This approach provides a rationale for the prioritization of novel targets, based on their rank, and can potentially uncover clinically meaningful differences between disease stages. **Conclusions:** Our current understanding of transcriptomic alterations in patients with MGUS and SMM is based on bulk RNA-sequencing or microarray studies, which cannot distinguish between malignant and normal plasma cells, whose proportions vary across patients. This large single-cell RNA-sequencing cohort of patients with MGUS and SMM can help us gain novel insights into malignant plasma cell biology and nominate therapeutic targets for interception of progression.

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P-102

Thrombotic significance in plasma cell disorders: do associated clonal hematopoiesis of indeterminate potential (CHIP) mutations increase the risk?

Ritika Vankina[1], Kaylyn Kirk[1], Katharine Hooper[1], Aswanth Reddy[2], Swarup Kumar[1]

[1]UConn Health; [2]Mercy Health

Introduction: The exact mechanisms of elevated thrombo-embolic risk in plasma cell disorders remain unclear. Whilst several factors such as therapeutic regimens, comorbid medical conditions and concurrent use of antiplatelet/anticoagulants can affect thrombotic propensity in these disease states have been reported; genomic alterations, particularly that of clonal hematopoiesis of indeterminate potential (CHIP) mutations which are somatic mutations noted to affect hematopoiesis is not well understood. Several have been linked to qualitative and quantitative platelet traits in previously described studies (Veninga et al Hematologica 2020, Vannuchhi et al, Semin Thromb Hemost 2013). We report genomic data and known thrombo-embolic events from 64 patients with plasma cell disorders within a year of their disease diagnosis or later. **Methods:** In this retrospective analysis, clinical and bone marrow based genomic data (Tempus xT® 684 gene DNA-based NGS platform) was gathered on 64 patients with a diagnosis of Monoclonal gammopathy of undetermined significance (MGUS), Multiple Myeloma (MM), Smoldering Myeloma (SM), AL amyloidosis (AMY) and Waldenstrom's Macroglobulinemia (WM). CHIP mutations with a predilection for thrombo-embolic events (12 with increased platelet count and 4 with function) were collected as described in Veninga et al 2020. Venous thrombotic events (VTE), ischemic coronary events (ICE), and cerebrovascular accidents (CVA) within one year or after disease diagnosis were also abstracted. **Results:** Twenty-two CHIP mutations were identified amongst all 64 patients. 11 being in MM, followed by WM (6), MGUS (4), SM (1), SP (0), and AMY (0). 18 of these CHIP mutations were known to increase platelet count and/or function, the most frequent ones being DNMT3A LOF (7,38.9%) and JAK2 GOF (3,16.7%). In 24 MM patients, 9 patients had a CHIP mutation which increase platelet count/function, of whom, 4 (44.4%) had a thrombo-embolic event (3 VTE and 1 ICD) whilst the frequency of thrombo-embolic events in the patients without CHIP mutations was 33.3% (5/15; 4 VTE and 1 CVA); (p 0.68, Fischer's exact test). No thrombotic events were reported in MGUS, SM, and WM patients with identified CHIP mutations and increased platelet count/function. Of all the patients in the data set regardless of the presence of a CHIP mutation, a total of 9(14%) suffered a VTE, 3 (4.7%) CVA, and 4 (6.3%) an ICE within a year of disease diagnosis. **Conclusions:** In this analysis of 64 patients, we identified a proportion of patients with CHIP mutations that affect platelet function and/or count as well as thrombo-embolic events around the time of their diagnosis or later however a clear association could not be established between them. Further studies are needed to inform of the thrombotic risk and the initiation of prophylactic anticoagulation in these disorders.

P-103

Albumin: globulin reversal as a screening tool for MGUS (targeted screening) in hospitalized setting

Uday Yanamandra[1], Abhinav Kumar[1], Anurodh Gupta[1], Bhushan Asthana[1], J Muthu Krishnan[1]

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Introduction: There is an unmet need to discover novel targeted screening guidelines for monoclonal gammopathy of undetermined clinical significance (MGUS) in the Indian scenario which can help in early detection and diagnosis. Liver function tests (LFTs) are routinely performed in hospital settings for a variety of indications, with many having albumin-globulin (A:G) ratio reversals. We have designed this study to gauge the prevalence of MGUS in individuals above the age of 50 years with A: G ratio reversal in hospitalized settings. The objectives of the study were to measure the incidence of A: G ratio reversal in total LFT samples run in the hospital for various indications and to determine whether targeted screening of unexplained A: G ratio reversal in hospitalized patients is a fruitful strategy. **Methods:** This is a single-center, prospective observational study carried out from 01 May 2022 to 30 May 2023 at tertiary care center in Western India. All the LFTs of the admitted patients over the study period to the medical wards were included in the study. Patients with A:G reversal were subjected to detailed clinical examination and investigations to rule out non-myelomatous causes for the reversal of the ratio. Samples with unexplained A:G ratio reversal and unresolving A:G reversal despite of three months of observation were subjected to Serum Protein Electrophoresis (SPEP). Data was analysed using JMP ver. 16.0.0. **Results:** A total of 5148 LFTs were screened during the study period, of which 300 (5.82%) had A:G reversal. The median age of the study population with A:G reversal was 59 years (IQR - 14.3) with a male preponderance (59%). Etiologically amongst patients with A:G reversal 54% had infection, 15% had inflammation, 13% suffer from Chronic Liver Disease and 9% have Chronic Kidney Disease. Only 9% of patients (n-27) had no evident secondary causes, and of these 11% (n-3) have an M-spike on SPEP. Of all patients with A:G reversal, 1.1% have evidence of MGUS, all being IgG Lambda variants and none having any features of smoldering or multiple myeloma based on IMWG guidelines. **Conclusions:** A:G reversal compounded with good clinical history and examination can be an effective tool for targeted screening of MGUS. A majority of A:G reversals in hospital settings are due to secondary causes, requiring deliberate effort for exclusion.

P-104

Prevalence of MGUS in rural Indian population: Results of SIMPLe (IMAGe-002) study

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P-102

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Ritika Vankina[1], Kaylyn Kirk[1], Katharine Hooper[1], Aswanth Reddy[2], Swarup Kumar[1]

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Introduction: The exact mechanisms of elevated thrombo-embolic risk in plasma cell disorders remain unclear. Whilst several factors such as therapeutic regimens, comorbid medical conditions and concurrent use of antiplatelet/anticoagulants can affect thrombotic propensity in these disease states have been reported; genomic alterations, particularly that of clonal hematopoiesis of indeterminate potential (CHIP) mutations which are somatic mutations noted to affect hematopoiesis is not well understood. Several have been linked to qualitative and quantitative platelet traits in previously described studies (Veninga et al Hematologica 2020, Vannuchhi et al, Semin Thromb Hemost 2013). We report genomic data and known thrombo-embolic events from 64 patients with plasma cell disorders within a year of their disease diagnosis or later. **Methods:** In this retrospective analysis, clinical and bone marrow based genomic data (Tempus xT® 684 gene DNA-based NGS platform) was gathered on 64 patients with a diagnosis of Monoclonal gammopathy of undetermined significance (MGUS), Multiple Myeloma (MM), Smoldering Myeloma (SM), AL amyloidosis (AMY) and Waldenstrom's Macroglobulinemia (WM). CHIP mutations with a predilection for thrombo-embolic events (12 with increased platelet count and 4 with function) were collected as described in Veninga et al 2020. Venous thrombotic events (VTE), ischemic coronary events (ICE), and cerebrovascular accidents (CVA) within one year or after disease diagnosis were also abstracted. **Results:** Twenty-two CHIP mutations were identified amongst all 64 patients. 11 being in MM, followed by WM (6), MGUS (4), SM (1), SP (0), and AMY (0). 18 of these CHIP mutations were known to increase platelet count and/or function, the most frequent ones being DNMT3A LOF (7,38.9%) and JAK2 GOF (3,16.7%). In 24 MM patients, 9 patients had a CHIP mutation which increase platelet count/function, of whom, 4 (44.4%) had a thrombo-embolic event (3 VTE and 1 ICD) whilst the frequency of thrombo-embolic events in the patients without CHIP mutations was 33.3% (5/15; 4 VTE and 1 CVA); (p 0.68, Fischer's exact test). No thrombotic events were reported in MGUS, SM, and WM patients with identified CHIP mutations and increased platelet count/function. Of all the patients in the data set regardless of the presence of a CHIP mutation, a total of 9(14%) suffered a VTE, 3 (4.7%) CVA, and 4 (6.3%) an ICE within a year of disease diagnosis. **Conclusions:** In this analysis of 64 patients, we identified a proportion of patients with CHIP mutations that affect platelet function and/or count as well as thrombo-embolic events around the time of their diagnosis or later however a clear association could not be established between them. Further studies are needed to inform of the thrombotic risk and the initiation of prophylactic anticoagulation in these disorders.

P-103

Albumin: globulin reversal as a screening tool for MGUS (targeted screening) in hospitalized setting

Uday Yanamandra[1], Abhinav Kumar[1], Anurodh Gupta[1], Bhushan Asthana[1], J Muthu Krishnan[1]

[1]Armed Forces Medical College

Introduction: There is an unmet need to discover novel targeted screening guidelines for monoclonal gammopathy of undetermined clinical significance (MGUS) in the Indian scenario which can help in early detection and diagnosis. Liver function tests (LFTs) are routinely performed in hospital settings for a variety of indications, with many having albumin-globulin (A:G) ratio reversals. We have designed this study to gauge the prevalence of MGUS in individuals above the age of 50 years with A: G ratio reversal in hospitalized settings. The objectives of the study were to measure the incidence of A: G ratio reversal in total LFT samples run in the hospital for various indications and to determine whether targeted screening of unexplained A: G ratio reversal in hospitalized patients is a fruitful strategy. **Methods:** This is a single-center, prospective observational study carried out from 01 May 2022 to 30 May 2023 at tertiary care center in Western India. All the LFTs of the admitted patients over the study period to the medical wards were included in the study. Patients with A:G reversal were subjected to detailed clinical examination and investigations to rule out non-myelomatous causes for the reversal of the ratio. Samples with unexplained A:G ratio reversal and unresolving A:G reversal despite of three months of observation were subjected to Serum Protein Electrophoresis (SPEP). Data was analysed using JMP ver. 16.0.0. **Results:** A total of 5148 LFTs were screened during the study period, of which 300 (5.82%) had A:G reversal. The median age of the study population with A:G reversal was 59 years (IQR - 14.3) with a male preponderance (59%). Etiologically amongst patients with A:G reversal 54% had infection, 15% had inflammation, 13% suffer from Chronic Liver Disease and 9% have Chronic Kidney Disease. Only 9% of patients (n-27) had no evident secondary causes, and of these 11% (n-3) have an M-spike on SPEP. Of all patients with A:G reversal, 1.1% have evidence of MGUS, all being IgG Lambda variants and none having any features of smoldering or multiple myeloma based on IMWG guidelines. **Conclusions:** A:G reversal compounded with good clinical history and examination can be an effective tool for targeted screening of MGUS. A majority of A:G reversals in hospital settings are due to secondary causes, requiring deliberate effort for exclusion.

P-104

Prevalence of MGUS in rural Indian population: Results of SIMPLe (IMAGe-002) study

Uday Yanamandra[1], Saurabh Bobdey[1], Celine Raphael[1], Junah Hassan[1], VK Bhatti[1], J Muthu Krishnan[1], SMILe Study Group[1]

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P-102

Thrombotic significance in plasma cell disorders: do associated clonal hematopoiesis of indeterminate potential (CHIP) mutations increase the risk?

Ritika Vankina[1], Kaylyn Kirk[1], Katharine Hooper[1], Aswanth Reddy[2], Swarup Kumar[1]

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P-105

Multiple myeloma therapy in Tawam hospital: first report from United Arab Emirates

Arif Alam[1]

[1]SEHA

Introduction: Plasma cell disorders are a heterogeneous group of disease ranging from Monocloncal gammopathy of unknown significance to Multiple myeloma (MM) and the highly lethal plasma cell leukemia. The standard of care for induction has been become a triplet regimen lately. Here we describe our experience with the management of MM patients **Methods:** This is a retrospective analysis of Thirty-five patients who were seen with diagnosis with plasma cell disorders from January 1, 2016 till June 30th 2018 at our center in the UAE. Patients with solitary plasmacytoma and plasma cell leukemia were excluded from further analysis (N=3). Thirty-two patients were included in the analysis. **Results:** The median age was 58 years (range 26 to 94 years). Male to female ratio was 3:1. Biochemical classification showed ten patients with light chain disease only. Twelve patients had IgG kappa disease, eight had IgG lambda while there was one with IgA lambda disease and one was non-secretory with diffuse plasmacytomas. ISS staging (based on albumin and Beta 2 microglobulin) showed ISS stage 1=7, ISS stage 2= 13, ISS stage 3=8 and data was not available for four patients (diagnosed elsewhere). Cytogenetic risk stratification was not possible due to lack of access to interphase FISH. Seven patients did not receive any therapy either due to refusal for further investigation and therapy or poor performance status and comorbidities. Four of these seven have expired while the other three have been lost to follow-up. Twenty-four patients were given induction therapy with a Bortezomib (V)-based regimen while one received IMIDs-based treatment. Regimens and patient numbers are as follows: RVd (Lenalidomide/V/ dexamethasone) (N=16), PVd (pomalidomide instead of R due to renal insufficiency) (N=1), V/thalidomide (T) (N=1), VCd (N=2; one for secondary amyloidosis) and Vd (N=4) (poor performance status and/or comorbidities). All patients were given zoledronic acid as well as herpes zoster prophylaxis. Venous thromboembolism (VTE) prophylaxis was prescribed based on published guidelines. Response evaluation was performed in patients receiving at least four cycles of therapy: CR(N=7); Very Good Partial Remission (VGPR) (N=6); Partial Response (PR) (N=5) and not evaluable for response due to lack of data (N=7). Five patients were documented to have received autologous stem cell transplant (autoSCT). Seven patients, lost to follow up after induction presumably received an autoSCT. **Conclusions:** This is the first report on the management of MM patients in UAE. With a median follow-up of 216 days (range 3 to 839 days) the response rate to induction therapy was 72% (CR+ VGPR). We are unable to report progression free survival due to short follow-up. This response rate of 72% (VGPR or better) is less than the reported in the literature. This may partly be due to lack of patient data regarding induction therapy elsewhere, the use of double over triplet regimens and the absence of autoSCT facilities.

P-106

Clinical outcomes of older patients aged 80 and over with newly diagnosed multiple myeloma

Sung Hwa Bae[1], Sang Hwan Lee[2], Hee Jeong Cho[3], Joon Ho Moon[4], Min Kyoung kim[5], Mi Hwa Heo[6], Young Rok Do[7]

[1]Daegu Catholic University Hospital; [2]Daegu Fatima Hospital; [3]Department of Hematology-Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, South Korea; [4]Kyungpook National University Hospital; [5]Yeungnam University Hospital; [6]Dongsan Medical Center; [7]Department of Hemato-Oncology, Keimyung University Dongsan Medical Center, Daegu, South Korea

Introduction: Multiple myeloma (MM) is primarily a disease of elderly patients. Although effective novel agents and supportive care have substantially improved outcomes, geriatric patients with MM have a higher risk of early mortality and lower survival rates. In this study, we retrospectively analyzed the clinical features and survival outcomes of MM patients aged ≥80 years. **Methods:** MM patients

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P-106

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aged ≥80 years from 2010 to 2019 at 5 hospitals in Daegu, Korea were eligible for inclusion were enrolled. The primary endpoints of this study were overall survival and prognostic factors for overall survival. **Results:** A total of 127 patients, with a median age of 83 years (range, 80-93 years) were included in this analysis. Of these, 52 patients (40.9%) had a poor performance status (ECOG 3-4), 84 (66.1%) had an International Staging System (ISS) stage III disease, and 69 (54.3%) had a Charlson comorbidity index score of 2 or more. Chemotherapy was given to 86 patients (67.7%). The median overall survival of all patients was 13.8 months. Thirty-four patients (26.8%) died within 3 months of MM diagnosis. In the univariate analysis, prognostic factors for overall survival were age (80-83 vs. >83, p=0.017), ECOG performance status (0-2 vs. 3,4, p< 0.001), ISS stage (I, II vs. III, p=0.005), hypercalcemia (p=0.007), thrombocytopenia (p=0.007) and treatment (chemotherapy vs. best supportive care, p< 0.001). In multivariate analyses, overall survival was affected by ECOG performance status, ISS stage, and chemotherapy treatment. **Conclusions:** Some elderly MM patients aged ≥80 years exhibit very poor prognosis, highlighting the need to effectively distinguish such patients and develop appropriate best supportive care for them.

P-107

The second revision of international staging system (R2-ISS) in newly diagnosed multiple myeloma patients: RWE settings

Aleksandra Sretenovic[1,2], Marko Mitrovic[1], Nikola Vukosavljevic[3], Natalija Kecman[1], Jelica Jovanovic[1], Zoran Bukumiric[4], Jelena Bila[1,2]

[1]Clinic of Hematology University Clinical Centre of Serbia; [2]Medical faculty, Univeristy of Belgrade; [3]Clinical Hospital Center "Zvezdara"; [4]Institute for Medical Statistics and Informatics, Medical faculty, Univeristy of Belgrade

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P-108

Unravelling transplant-ineligible newly diagnosed multiple myeloma treatment in real-world practice in Spain: CARINAE study

Maria Casanova Espinosa[1], Miguel Teodoro Hernandez Garcia[2], Juan Alfons Soler Campos[3], Susana Herráez Rodriguez[4], Maria José Moreno Belmonte[5], Miriam González-Pardo[6], Mercedes Gironella Mesa[7], Felipe de Arriba de la Fuente[8]

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aged ≥80 years from 2010 to 2019 at 5 hospitals in Daegu, Korea were eligible for inclusion were enrolled. The primary endpoints of this study were overall survival and prognostic factors for overall survival. **Results:** A total of 127 patients, with a median age of 83 years (range, 80-93 years) were included in this analysis. Of these, 52 patients (40.9%) had a poor performance status (ECOG 3-4), 84 (66.1%) had an International Staging System (ISS) stage III disease, and 69 (54.3%) had a Charlson comorbidity index score of 2 or more. Chemotherapy was given to 86 patients (67.7%). The median overall survival of all patients was 13.8 months. Thirty-four patients (26.8%) died within 3 months of MM diagnosis. In the univariate analysis, prognostic factors for overall survival were age (80-83 vs. >83, p=0.017), ECOG performance status (0-2 vs. 3,4, p< 0.001), ISS stage (I, II vs. III, p=0.005), hypercalcemia (p=0.007), thrombocytopenia (p=0.007) and treatment (chemotherapy vs. best supportive care, p< 0.001). In multivariate analyses, overall survival was affected by ECOG performance status, ISS stage, and chemotherapy treatment. **Conclusions:** Some elderly MM patients aged ≥80 years exhibit very poor prognosis, highlighting the need to effectively distinguish such patients and develop appropriate best supportive care for them.

P-107

The second revision of international staging system (R2-ISS) in newly diagnosed multiple myeloma patients: RWE settings

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with bortezomib, melphalan and prednisone (DVMP group), between Sep/01/19 and Nov/30/20. Here, we present the efficacy and safety outcomes obtained in the second interim analysis after ≈24-month study initiation. **Results:** 117 patients recruited, 108 evaluable for efficacy in this interim analysis (group A n=51; group B n=57). No significant differences were observed in basal clinical and demographics characteristics between groups: mean age 76.9 years; male (53.7%); cardiopathy 28.7%; renal failure 25%; pulmonary obstructive disease 8.3%; peripheral neuropathy 2.8%; median ECOG PS 1; most common myeloma type was IgG (49.5%); 13.9% had a high risk cytogenetic profile, defined by one of the following alterations: t(4;14), t(14;16) and del 17p13; plasmacytoma 24.3 %. More than 90% of the patients in group A started treatment with schemes based on bortezomib, lenalidomide, or both. Median follow-up was 36.3 versus 23.3 months for group A and B, respectively, since initiation of first-line treatment (p< 0,0001). Probably in relation to the different follow-up, the median PFS for Group A was 32.78 months and not reached for Group B (p=0,1129). The progression rate at 18-months was 27.5% and 10.5% for Group A and B respectively (p=0,0238). Rates of ≥VGPR and ≥CR, were 60% and 30% in Group A whilst 75.4% and 33.3% in Group B. 36.9% of the patients showed adverse drug reactions (ADR) related to the first-line treatment during the prospective period. 10.6% of the reported ADRs were serious with no significant differences between groups. No unexpected ADRs were observed. Additional data will be presented at the Congress. **Conclusions:** In this interim analysis, a significant clinical benefit has been identified in patients treated with DVMP, with improved PFS indicators vs. other treatment alternatives. Along with the deeper hematological responses observed, we expect this benefit to be consolidated in the final PFS analysis of the Carinae study. These real-world practice data continue to support the choice of daratumumab regimens in frontline TIE-NDMM patients.

P-109

Carfilzomib-lenalidomide-dexamethasone Vs. lenalidomide-dexamethasone in non-frail transplant-ineligible patients with newly diagnosed multiple myeloma: the EMN20 trial

Mattia D'Agostino[1,2], Elisabetta Antonioli[3], Barbara Gamberi[4], Benedetto Bruno[1,2], Daniele Derudas[5], Patrizia Tosi[6], Francesca Fazio[7], Carmelo Carlo-Stella[8], Sonia Ronconi[9], Paolo Corradini[10], Stelvio Ballanti[11], Claudia Cellini[12], Antonietta Pia Falcone[13], Sara Bringhen[14], Massimo Offidani[15], Alessandro Rambaldi[16], Delia Rota-Scalabrini[17], Alberto Agazzi[18], Gloria Margiotta Casaluci[19], Giuseppe Pietrantuono[20], Francesca Patriarca[21], Alessandra Larocca[2,14], Mario Boccadoro[22]

[1]Division of Hematology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino [2]Division of Hematology, Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy; [3]UO Ematologia, AOU Careggi, Firenze, Italy; [4]Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Italy; [5]SC di Ematologia e CTMO, Ospedale Oncologico di Riferimento Regionale "A. Businco", ARNAS "G. Brozu", Cagliari, Italy; [6]UO Ematologia, Ospedale di Rimini, Rimini, Italy; [7]Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; [8]Department of Oncology and Hematology, Humanitas Cancer Center, Humanitas Clinical and Research Center and Department of Biomedical Sciences, Humanitas University, Rozzano, Italy; [9]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [10]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano MI, Italy; [11]Sezione di Ematologia e Immunologia Clinica, Ospedale Santa Maria della Misericordia, località Sant'Andrea delle Fratte, Perugia, Italy; [12]AUSL Romagna, U.O.C. Ematologia, Ospedale Santa Maria delle Croci, Ravenna, Italy; [13]Hematology, IRCCS "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Italy; [14]SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Department of Oncology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; [15]Clinica di Ematologia, Azienda Ospedaliero-Universitaria delle Marche, Ancona, Italy; [16]UO Ematologia, ASST Papa Giovanni XXIII, Bergamo, Italy; [17]Medical Oncology Department, Candiolo Cancer Institute, FPO-IRCCS, Torino, Italy; [18]Hematoncology Division, European Institute of Oncology, Milan, Italy; [19]A.O.U. Maggiore della Carità, Novara, Italy; [20]Hematology and Stem Cell Transplantation Unit, IRCCS Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture, Italy; [21]Clinica Ematologica e Unità di Terapie Cellulari, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Dipartimento di Area Medica (DAME), Università di Udine, Udine, Italia; [22]European Myeloma Network, Italy

Introduction: Trial in Progress (TiP). Prior to the recent introduction of daratumumab (Dara) in the frontline setting, lenalidomide-dexamethasone (Rd) has represented a standard of care for transplant-ineligible (NTE) patients (pts) with newly diagnosed multiple myeloma (NDMM). Nonetheless, median progression-free survival (PFS) with Rd was still limited, as compared with 3/4-drug regimens, also including carfilzomib (K). The randomized, multicenter phase III EMN20 trial (NCT04096066) compares KRd vs Rd in fit/intermediate-fit NDMM pts according to the International Myeloma Working Group frailty score. **Methods:** NTE NDMM pts were randomized to KRd (28-day cycles, once-weekly K 56 mg/m² on days 1,8,15 for 12 cycles and on days 1,15 from cycle 13 onwards, R 25 mg orally on days 1-21 and d 40 mg on days 1,8,15,22) or continuous Rd (28-day cycles, R 25 mg on days 1-21, d 40 mg on days 1,8,15,22). Pt stratification was based on International Staging System (ISS) stage and fitness status. After 5 years, pts in the KRd arm will stop K administration and continue Rd, except for pts achieving sustained minimal residual disease (MRD) negativity after 2 years, who will stop K administration after 2 years and continue Rd. The primary endpoints were MRD after 2 years of treatment and PFS. For MRD assessment, the clonoSEQ® assay was used at the sensitivity of $\geq 10^{-5}$. The MRD negativity rate was the proportion of MRD-negative pts (sensitivity $\geq 10^{-5}$) at 2 years of treatment. Key secondary endpoints included response rates, overall survival and safety. On Nov 23, 2021, the protocol was prematurely stopped after the introduction of frontline Dara-Rd. Here we report the demographics of the enrolled pts. **Results:** A total of 101 pts were enrolled and 82 were randomized (KRd 42

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Carfilzomib-lenalidomide-dexamethasone Vs. lenalidomide-dexamethasone in non-frail transplant-ineligible patients with newly diagnosed multiple myeloma: the EMN20 trial

Mattia D'Agostino[1,2], Elisabetta Antonioli[3], Barbara Gamberi[4], Benedetto Bruno[1,2], Daniele Derudas[5], Patrizia Tosi[6], Francesca Fazio[7], Carmelo Carlo-Stella[8], Sonia Ronconi[9], Paolo Corradini[10], Stelvio Ballanti[11], Claudia Cellini[12], Antonietta Pia Falcone[13], Sara Bringhen[14], Massimo Offidani[15], Alessandro Rambaldi[16], Delia Rota-Scalabrini[17], Alberto Agazzi[18], Gloria Margiotta Casaluci[19], Giuseppe Pietrantuono[20], Francesca Patriarca[21], Alessandra Larocca[2,14], Mario Boccadoro[22]

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Introduction: Trial in Progress (TiP). Prior to the recent introduction of daratumumab (Dara) in the frontline setting, lenalidomide-dexamethasone (Rd) has represented a standard of care for transplant-ineligible (NTE) patients (pts) with newly diagnosed multiple myeloma (NDMM). Nonetheless, median progression-free survival (PFS) with Rd was still limited, as compared with 3/4-drug regimens, also including carfilzomib (K). The randomized, multicenter phase III EMN20 trial (NCT04096066) compares KRd vs Rd in fit/intermediate-fit NDMM pts according to the International Myeloma Working Group frailty score. **Methods:** NTE NDMM pts were randomized to KRd (28-day cycles, once-weekly K 56 mg/m² on days 1,8,15 for 12 cycles and on days 1,15 from cycle 13 onwards, R 25 mg orally on days 1-21 and d 40 mg on days 1,8,15,22) or continuous Rd (28-day cycles, R 25 mg on days 1-21, d 40 mg on days 1,8,15,22). Pt stratification was based on International Staging System (ISS) stage and fitness status. After 5 years, pts in the KRd arm will stop K administration and continue Rd, except for pts achieving sustained minimal residual disease (MRD) negativity after 2 years, who will stop K administration after 2 years and continue Rd. The primary endpoints were MRD after 2 years of treatment and PFS. For MRD assessment, the clonoSEQ® assay was used at the sensitivity of $\geq 10^{-5}$. The MRD negativity rate was the proportion of MRD-negative pts (sensitivity $\geq 10^{-5}$) at 2 years of treatment. Key secondary endpoints included response rates, overall survival and safety. On Nov 23, 2021, the protocol was prematurely stopped after the introduction of frontline Dara-Rd. Here we report the demographics of the enrolled pts. **Results:** A total of 101 pts were enrolled and 82 were randomized (KRd 42

vs Rd 40); 19 pts were not randomized due to screening failure (17) and withdrawal of consent (2). Pt characteristics were well balanced between the KRd and Rd arms: median age was 73 (interquartile range [IQR] 70–76) and 74 years (IQR 72–76), 60% vs 58% of pts were fit, 40% vs 42% were intermediate fit, 33% vs 30% had ISS stage III disease, 17% vs 8% had Revised ISS III, 10% vs 3% had Eastern Cooperative Oncology Group (ECOG) Performance Status 2 and 22% vs 22% had high-risk cytogenetics, respectively. Median follow-up was 23 months (IQR 19–28). In the KRd vs Rd arms, 33/42 (78.6%) vs 19/40 (47.5%) pts are still under treatment; reasons for discontinuation were medical decision (1 vs 4), death (2 vs 4), adverse events (2 vs 1), progressive disease (3 vs 10), lost to follow-up (1 vs 0) and consent withdrawal (0 vs 2). The analysis of the primary MRD endpoint is planned for Q4 of 2023, after all pts have received 2 years of treatment. **Conclusions:** Data about MRD will be presented at the meeting.

P-110

Ixazomib maintenance in transplant-ineligible patients with newly diagnosed multiple myeloma: final overall survival analysis from the TOURMALINE-MM4 study

Meletios Dimopoulos[1], Wee Joo Chng[2], Shinsuke Iida[3], María-Victoria Mateos[4], Gareth Morgan[5], Sagar Lonial[6], Ivan Špička[7,8], Hang Quach[9], Albert Oriol[10], Roman Hájek[11], Mamta Garg[12], Nicola Giuliani[13], Meral Beksac[14], Eirini Katodritou[15], Sara Bringhen[16], Cong Li[17], Xiaoquan Zhang[17], Richard Labotka[17], Vincent Rajkumar[18]

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Introduction: The double-blind TOURMALINE-MM4 study (NCT02312258) included patients (pts) with newly diagnosed multiple myeloma (NDMM) who were ineligible for autologous stem cell transplantation (ASCT; Dimopoulos, J Clin Oncol 2020). The study previously demonstrated a statistically significant and clinically meaningful improvement in its primary endpoint of progression-free survival (PFS) for ixazomib (ixa) vs placebo (pbo) maintenance. An interim analysis showed no statistically significant difference in the key secondary endpoint of overall survival (OS; Dimopoulos, ASH 2021). We present the final OS analysis. **Methods:** Full methods have been published previously (Dimopoulos, J Clin Oncol 2020). Eligible pts were randomized to receive single agent ixa (n=425) or pbo maintenance (n=281) for up to twenty-six 28-day cycles, or until progressive disease (PD) or unacceptable toxicity. **Results:** At data cut (Oct 29, 2022), median follow-up for ixa vs pbo was 57 vs 58 months, OS events had occurred in 43 vs 41% of pts, and median OS was 65 vs 70 months (not statistically significant; hazard ratio [HR] 1.090; 95% confidence interval [CI] 0.861–1.381). There were no significant differences in median OS for ixa vs pbo among pts aged ≥75 years at randomization (55 vs 70 months; HR 1.317; 95% CI 0.909–1.909), frail pts (56 vs 44 months; HR 0.975; 95% CI 0.613–1.549), and pts with baseline high-risk cytogenetics [del(17p) and/or t(4;14) and/or t(14;16); 37 vs 48 months; HR 1.357; 95% CI 0.799–2.306]. Median PFS2 (PFS on next-line therapy) for ixa vs pbo was 51 vs 50 months (not significant; HR 0.984; 95% CI 0.777–1.246); median time to next therapy was 22 vs 17 months (not significant; HR 0.881; 95% CI 0.734–1.058). For ixa vs pbo, 72% of pts in each arm received ≥1 subsequent anti-cancer therapy, including: corticosteroids (67 vs 67%); immunomodulatory drugs (60 vs 61%); proteasome inhibitors (PI; 34 vs 36%); and monoclonal antibodies (26 vs 26%). The incidence of new primary malignancies (NPMs) in each treatment arm was 3%, with < 1% incidence of hematological NPMs in either arm; no new safety signals were identified. **Conclusions:** The final OS analysis for TOURMALINE-MM4 showed no statistically significant difference between ixa and pbo, including among high-risk pts, despite the study meeting its primary endpoint. However, showing an OS advantage in myeloma trials is becoming increasingly difficult due to confounding effects of expanding numbers of effective treatment options with novel mechanisms of action for subsequent therapies, and imbalances in these therapies between treatment arms. Notably, due to the double-blind study design, following progression, 34% of pts who received ixa received another PI to which they were likely already refractory. Ixa had a tolerable safety profile and NPM incidence remained low. In the appropriate setting, ixa could be a viable alternative for non-ASCT NDMM pts who are refractory to common maintenance options such as lenalidomide.

P-111

Overall survival trends in young (<55 years) transplant-inaccessible multiple myeloma patients treated at a safety net hospital system

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P-111

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P-111

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Introduction: Multiple myeloma (MM) typically affects older adults, with a median age of diagnosis of 70 years, but 10-15% of MM patients are diagnosed at 55 years or younger. Stem cell transplant (SCT) is generally considered the standard of care for young patients with good functional status. However, little is known about the outcomes for young and fit MM patients who are unable to receive transplant due to financial status or insurance coverage. This study assesses the clinical characteristics of young transplant-eligible (TE) MM patients and compares outcomes between those who are transplant accessible (TE/TA) and transplant inaccessible (TE/TI). **Methods:** This retrospective study includes 186 patients diagnosed with MM between 18-55 years from 1997-2022 at a safety net hospital in Dallas, TX. A total of 450 patients of all ages were diagnosed with MM during this period. Patients with smoldering MM, MGUS and solitary plasmacytoma were excluded. Demographics, baseline myeloma markers, comorbidities and treatments were collected from the EHR. Outcomes were analyzed by transplant status and overall survival (OS). **Results:** Our cohort showed a high percentage of young multiple myeloma patients (41.3%) diagnosed at 55 years or younger. The median age of diagnosis was 49 years. This population consisted of 48.4% Hispanics and 33.9% African Americans as well 24.2% undocumented immigrants. There were 22 patients with ISS/R-ISS stage I disease at diagnosis (11.8%), 37 with stage II (19.9%) and 55 with stage III (29.6%). Approximately 72% of the cohort had lytic lesions. The most common first line therapies were VD (21.5%), VRD (19.4%), and CyBorD (9.7%). Other regimens such as RD, TD, and DRD made up the remainder. There was a total of 46 patients who received SCT (24.7%) (TE/TA). Both TE/TA and TE/TI relied on taxpayer funded charity assistance programs, with 75.0% and 62.5% respectively who cited this as their primary insurance coverage. Median OS, including TE/TA and TE/TI, was 7.83 years. There was a significant association with SCT access and OS (HR 0.24, 95% CI 0.11 to 0.50, p< 0.001). The mOS for TE/TA was 18.5 years with a 5-year OS rate of 94.4% (CI 86.7% to 100%), while the mOS for TE/TI was 6.60 years with a 5-year OS rate of 55.8% (CI 45.7% to 65.9%). In stage 3 disease, mOS for TE/TA and TE/TI was 7.82 versus 3.80 (HR 0.27, CI 0.10 to 0.73, p=0.002). Of the entire cohort, 36.6% were deceased at the time of data collection and 21.5% were lost to follow up at the time of data analysis. **Conclusions:** Accessibility to stem cell transplant remains a significant barrier in patients with hematologic malignancies who face financial and healthcare disparities. Our results show that MM patients who are transplant eligible but inaccessible (TE/TI) have worse OS compared to transplant accessible (TE/TA) patients.

P-112

Determining the impact of multimorbidity in older patients initiating treatment for newly-diagnosed multiple myeloma using artificial intelligence/ machine learning methods

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Introduction: Older patients with multiple myeloma (MM) often present with multiple other comorbid conditions (multimorbidity) in addition to their MM. Due to the strict exclusion criteria of clinical trials, the nature and impact of these chronic conditions alongside myeloma treatment and measures of disease risk are not well-understood. Here, we used artificial intelligence and machine learning (AI/ML) methods to understand the incremental impact of multimorbidity on overall survival of MM patients as compared to MM disease characteristics alone. **Methods:** We analyzed the impact of multimorbidity on prognosis using U.S. Veterans Affairs (VA) electronic health record and cancer registry data from the 132 VA Medical Centers that treat veterans with cancer. We included all veterans aged 65+ with newly diagnosed MM initiating treatment at VA between 2004 and 2020. We measured pretreatment predictors including sociodemographic variables, MM disease parameters, labs, and treatment. We further measured 33 comorbidities tracked by the CMS Chronic Conditions Data Warehouse, as well as the prescription of 15 clinically-important classes of chronic medication. We trained random forest AI/ML models to predict three-year mortality using 3/4 of the population and validated the best-performing model on the remaining 1/4. Model performance was evaluated using area under the receiver operating characteristic curve (AUC, higher numbers = better discrimination) to measure discrimination and the Brier score to measure calibration (lower numbers = better calibration). Final model performance was compared between models containing MM-specific predictors and models containing all comorbidities and medications in addition to MM-specific predictors. **Results:** We identified 4416 patients with a median age of 74 years (interquartile range [IQR] 69-80) meeting the inclusion criteria. Median number of chronic conditions per patient was 8 (IQR 6-10), and median number of different drug classes per patient was 5 (IQR 3-7). The final model built using only MM-specific predictors demonstrated poor predictive performance (AUC 0.65, Brier score 0.23). The final model built using comorbidities and medications in addition

Adeel Khan[2], Aimaz Afrough[2], Heather Wolfe[2], Yazan Madanat[2], Praveen Ramakrishnan Geethakumari[2], Elif Yilmaz[2], Farrukh Awan[2], Robert Collins[2], Larry Anderson[2], Jenny Li[1], Gurbakhash Kaur[2]

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Introduction: Multiple myeloma (MM) typically affects older adults, with a median age of diagnosis of 70 years, but 10-15% of MM patients are diagnosed at 55 years or younger. Stem cell transplant (SCT) is generally considered the standard of care for young patients with good functional status. However, little is known about the outcomes for young and fit MM patients who are unable to receive transplant due to financial status or insurance coverage. This study assesses the clinical characteristics of young transplant-eligible (TE) MM patients and compares outcomes between those who are transplant accessible (TE/TA) and transplant inaccessible (TE/TI). **Methods:** This retrospective study includes 186 patients diagnosed with MM between 18-55 years from 1997-2022 at a safety net hospital in Dallas, TX. A total of 450 patients of all ages were diagnosed with MM during this period. Patients with smoldering MM, MGUS and solitary plasmacytoma were excluded. Demographics, baseline myeloma markers, comorbidities and treatments were collected from the EHR. Outcomes were analyzed by transplant status and overall survival (OS). **Results:** Our cohort showed a high percentage of young multiple myeloma patients (41.3%) diagnosed at 55 years or younger. The median age of diagnosis was 49 years. This population consisted of 48.4% Hispanics and 33.9% African Americans as well 24.2% undocumented immigrants. There were 22 patients with ISS/R-ISS stage I disease at diagnosis (11.8%), 37 with stage II (19.9%) and 55 with stage III (29.6%). Approximately 72% of the cohort had lytic lesions. The most common first line therapies were VD (21.5%), VRD (19.4%), and CyBorD (9.7%). Other regimens such as RD, TD, and DRD made up the remainder. There was a total of 46 patients who received SCT (24.7%) (TE/TA). Both TE/TA and TE/TI relied on taxpayer funded charity assistance programs, with 75.0% and 62.5% respectively who cited this as their primary insurance coverage. Median OS, including TE/TA and TE/TI, was 7.83 years. There was a significant association with SCT access and OS (HR 0.24, 95% CI 0.11 to 0.50, p< 0.001). The mOS for TE/TA was 18.5 years with a 5-year OS rate of 94.4% (CI 86.7% to 100%), while the mOS for TE/TI was 6.60 years with a 5-year OS rate of 55.8% (CI 45.7% to 65.9%). In stage 3 disease, mOS for TE/TA and TE/TI was 7.82 versus 3.80 (HR 0.27, CI 0.10 to 0.73, p=0.002). Of the entire cohort, 36.6% were deceased at the time of data collection and 21.5% were lost to follow up at the time of data analysis. **Conclusions:** Accessibility to stem cell transplant remains a significant barrier in patients with hematologic malignancies who face financial and healthcare disparities. Our results show that MM patients who are transplant eligible but inaccessible (TE/TI) have worse OS compared to transplant accessible (TE/TA) patients.

P-112

Determining the impact of multimorbidity in older patients initiating treatment for newly-diagnosed multiple myeloma using artificial intelligence/ machine learning methods

Nathanael Fillmore[1], Clark DuMontier[2], Hannah Tosi[3], Chunlei Zheng[4], June Corrigan[3], Jennifer La[5], Cenk Yilidrim[3], Mayuri Dharne[3], Danne Elbers[5], Gregory Abel[6], Camille Edwards[4], J Michael Gaziano[2], Nhan Do[4], Mary Brophy[4], Dae Kim[6], Jane Driver[2], Nikhil Munshi[7]

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Introduction: Older patients with multiple myeloma (MM) often present with multiple other comorbid conditions (multimorbidity) in addition to their MM. Due to the strict exclusion criteria of clinical trials, the nature and impact of these chronic conditions alongside myeloma treatment and measures of disease risk are not well-understood. Here, we used artificial intelligence and machine learning (AI/ML) methods to understand the incremental impact of multimorbidity on overall survival of MM patients as compared to MM disease characteristics alone. **Methods:** We analyzed the impact of multimorbidity on prognosis using U.S. Veterans Affairs (VA) electronic health record and cancer registry data from the 132 VA Medical Centers that treat veterans with cancer. We included all veterans aged 65+ with newly diagnosed MM initiating treatment at VA between 2004 and 2020. We measured pretreatment predictors including sociodemographic variables, MM disease parameters, labs, and treatment. We further measured 33 comorbidities tracked by the CMS Chronic Conditions Data Warehouse, as well as the prescription of 15 clinically-important classes of chronic medication. We trained random forest AI/ML models to predict three-year mortality using 3/4 of the population and validated the best-performing model on the remaining 1/4. Model performance was evaluated using area under the receiver operating characteristic curve (AUC, higher numbers = better discrimination) to measure discrimination and the Brier score to measure calibration (lower numbers = better calibration). Final model performance was compared between models containing MM-specific predictors and models containing all comorbidities and medications in addition to MM-specific predictors. **Results:** We identified 4416 patients with a median age of 74 years (interquartile range [IQR] 69-80) meeting the inclusion criteria. Median number of chronic conditions per patient was 8 (IQR 6-10), and median number of different drug classes per patient was 5 (IQR 3-7). The final model built using only MM-specific predictors demonstrated poor predictive performance (AUC 0.65, Brier score 0.23). The final model built using comorbidities and medications in addition

to MM-specific predictors demonstrated superior predictive performance (AUC 0.87, Brier score 0.15). Being prescribed a diuretic, a beta-blocker, an opioid, or having chronic kidney disease were among the top predictors contributing to mortality risk. **Conclusions:** Our findings in a real-world population of older adults with MM initiating treatment highlight that including information on multimorbidity alongside MM-specific information yields far superior prediction of mortality compared to a focus only on MM-specific information. Further investigation into the disease-disease, disease-drug, and drug-drug interactions that mediate this risk will yield important clinical insights into the mechanisms of mortality in patients treated outside of clinical trials.

P-113

Clinical consensus on first-line (1L) treatments for transplant-ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM): delphi panel of US hematologists and oncologists

Rafael Fonseca[1], Adriana Rossi[2], Jennifer Voelker[3], Trevor Homan[3], Shuchita Kaila[3], Rohan Medhekar[3], Jessica Wilcock[4], Anna Karakusevic[4], James Cochrane[4], Daisy Bridge[4], Richard Perry[4], Faith Davies[5]

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Introduction: In the past decade, the treatment of transplant ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM) has evolved significantly. However, despite established guidelines there is a lack of uniformity in prescribing patterns. Triplets are still reserved for later lines, while monotherapy and doublets with inferior efficacy are routinely prescribed as 1L therapy, leading to a missed opportunity to attain the best long-term outcomes. Moreover, guidelines do not offer definitive recommendations on anti–CD38- vs proteasome inhibitor-based triplets in 1L, and there are no head-to-head (H2H) trials comparing these regimens which could aid in decision making. To address this knowledge gap, this study sought to gather clinical consensus from a panel of multiple myeloma (MM) experts on factors impacting 1L prescribing, challenges with existing therapies, optimal duration of therapy (DoT), and treatment decision making for TIE NDMM. **Methods:** A modified Delphi Panel with 2 online survey rounds and a virtual consensus meeting was used. US-based hematologists/oncologists who treat TIE NDMM patients were selected as expert panelists. To reach consensus, ≥80% of panelists had to rate their agreement/disagreement within a 3-point range on either end of 9-point Likert scale. The panel was double blinded to maintain the validity of the study and to prevent bias. **Results:** Eighteen experts with an average of 18.8 years in practice (119.7 MM appointments/month; 104.7 patients with MM/month) completed both surveys; 9 of them participated in the consensus meeting. Consensus was reached that, in addition to the treatment's effects on progression-free survival (PFS), overall survival (OS), and its adverse event profile, frailty (89%), poor ECOG score (83%), and comorbidities (89%) have a strong impact on treatment selection. All panelists concurred that it is important to always or in most cases use the most effective regimen (one that best improved PFS and OS) as 1L therapy. Sixteen (89%) panelists considered one regimen to be more efficacious than other regimens; of these, 88% considered daratumumab (D), lenalidomide (R), dexamethasone(d) (DRd) or D-containing quadruplet (quad) regimens as most efficacious for use as 1L therapy for TIE NDMM. Neuropathy was cited as the greatest challenge in treating TIE NDMM with bortezomib (V; 94%), with 89% of panelists stating that it has prevented them from prescribing V. Regarding optimal DoT, panelists agreed that the treatment should be continued until progression as long as benefits outweigh risk (89%). **Conclusions:** A panel of MM experts reached clinical consensus that it was important to utilize the most effective regimen as 1L therapy for TIE NDMM. Most panelists agreed that DRd or D-containing quad regimens were the most effective 1L treatment for TIE NDMM. In the absence of absence of H2H trials among current triplet and quad regimens, these findings may help physicians with decision making.

P-114

In-class transition (*i*CT) from parenteral bortezomib (V) to oral ixazomib in multiple myeloma (MM) by age and frailty status: updated subgroup analysis from the fully accrued US MM-6 study

Saulius Girnius[1], Joshua Richter[2], Roger Lyons[3], Kimberly Bogard[4], Sudhir Manda[5], Ruemu Birhiray[6], Habte Yimer[3], Kim Tran[4], Suman Kambhampati[7], Jyoti Arora[4], Stephen Noga[4], Robert Rifkin[8]

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Introduction: Long-term proteasome inhibitor (PI) therapy can improve outcomes for patients (pts) with MM, but is challenging in routine practice. This is due to PI-related toxicity and administration burden, particularly for elderly/frail pts who are often transplant ineligible. For such pts, it is important to prolong progression-free survival (PFS) and to improve depth/duration of response. The prospective, community-based, phase 4 US MM-6 study investigated *in*-class transition (*i*CT) from parenteral V-based induction to all-oral ixazomib-lenalidomide-dexamethasone (IRd) in pts with newly diagnosed MM (NDMM; NCT03173092). **Methods:** Following 3 cycles of V-based induction, eligible pts with NDMM were enrolled to receive up to 39 cycles of IRd. The primary endpoint was 2-year PFS. Secondary endpoints included treatment duration, overall response rate (ORR), overall survival (OS), and

to MM-specific predictors demonstrated superior predictive performance (AUC 0.87, Brier score 0.15). Being prescribed a diuretic, a beta-blocker, an opioid, or having chronic kidney disease were among the top predictors contributing to mortality risk. **Conclusions:** Our findings in a real-world population of older adults with MM initiating treatment highlight that including information on multimorbidity alongside MM-specific information yields far superior prediction of mortality compared to a focus only on MM-specific information. Further investigation into the disease-disease, disease-drug, and drug-drug interactions that mediate this risk will yield important clinical insights into the mechanisms of mortality in patients treated outside of clinical trials.

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safety. Endpoints were assessed by age (<75 vs ≥75 years [yrs]) and frailty status (non-frail vs frail). **Results:** At datacut (Oct 17, 2022), 140 pts had received IRd; 42% were aged ≥75 yrs (median age: 73 yrs) and 61% were frail. Overall median follow-up was 27 months (mos). For pts aged <75 vs ≥75 yrs and for non-frail vs frail pts, 12 vs 7% and 13 vs 8% were ongoing on IRd, respectively. Median duration of IRd was 11 mos overall, 14 vs 9 mos in pts aged <75 vs ≥75 yrs, and 12 vs 10 mos in non-frail vs frail pts. Overall median duration of all PI-based therapy was 14 mos, 18 vs 12 mos in pts aged <75 vs ≥75 yrs, and 15 vs 13 mos in non-frail vs frail pts. ORR increased from 62% at the end of induction (including complete response [CR]: 8%) to 80% (including CR: 37%) following *i*CT to IRd; for pts aged <75 vs ≥75 yrs, ORR increased from 60 to 80% vs 64 to 80%; and in non-frail vs frail subgroups, ORR increased from 70 to 81% vs 57 to 79%. The overall 2-year PFS rate was 71% (95% confidence interval [CI]: 61–78), 72% (95% CI: 60–81) vs 67% (95% CI: 50–80) in pts aged <75 vs ≥75 yrs, and 74% (95% CI: 58–85) vs 68% (95% CI: 55–78) in non-frail vs frail pts; differences were not significant. Median PFS and OS were not reached overall, nor in any subgroup. Overall, 98% of pts experienced ≥1 treatment-emergent adverse event (TEAE; 69% grade ≥3; 44% serious TEAEs). For pts aged <75 vs ≥75 yrs, 69 vs 68% experienced a grade ≥3 TEAE; serious TEAEs occurred in 42 vs 47%; TEAEs leading to dose modification occurred in 67 vs 66%; and 2 pts died in each subgroup. For non-frail vs frail subgroups, 61 vs 73% experienced a grade ≥3 TEAE; serious TEAEs occurred in 39 vs 48%; TEAEs leading to dose modification occurred in 61 vs 70%; and 1 vs 3 pts died, respectively. **Conclusions:** *i*CT from V-based induction to all-oral IRd permits prolonged PI-based therapy and improves depth of response, with a tolerable safety profile, including in elderly/frail pts. For such pts, IRd may be an alternative to induction/maintenance.

P-115

Progression-free survival of daratumumab vs. bortezomib triplet combination with lenalidomide and dexamethasone in transplant ineligible newly diagnosed multiple myeloma patients: a chart review study

Lucio Gordan[1], Carlyn Rose Tan[2], Robert Vescio[3], Jing Christine Ye[4,5], Carolina Schinke[6], Rohan Medhekar[7], Alex Fu[8,9], Marie-Hélène Lafeuille[10], Philippe Thompson-Leduc[10], Vipin Khare[7], John Reitan[11], Gary Milkovich[12], Shuchita Kaila[7], Faith Davies[13], Saad Usmani[2]

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Introduction: Daratumumab, lenalidomide and dexamethasone (DRd) and bortezomib, lenalidomide and dexamethasone (VRd) are the only guideline recommended preferred regimens for the treatment of transplant ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM). Both DRd and VRd have demonstrated superior efficacy vs. Rd in the MAIA and SWOG S0777 trials, respectively, but there is no head-to-head (H2H) clinical trial comparing their efficacy. Differing populations in MAIA (TIE [99% patients aged ≥65 years]) and S0777 (transplant not-intended [43% patients aged ≥65 years]) trials, make a naïve unadjusted comparison of outcomes across these trials challenging and biased. The current TAURUS chart review study is the first H2H study comparing the progression-free survival (PFS) among TIE NDMM patients treated with DRd or VRd as first-line of therapy (1L) in similar clinical settings. **Methods:** A multicenter chart review study was conducted at 9 academic and community cancer centers across the US. Patients ≥65 years with NDMM, considered TIE by the treating physician were included if they initiated DRd/VRd as 1L between January 2019 and September 2021. The sample included all eligible patients treated with DRd and a random sample of VRd patients. PFS was defined as the time from DRd/VRd initiation until disease progression (per physician assessment and guided by the IMWG criteria) or death. Comparability of baseline characteristics between cohorts was assessed using standardized differences (std.diff.). Characteristics with std.diff. ≥10% were considered imbalanced. The Inverse Probability of Treatment Weighting (IPTW) method was used to balance characteristics. A doubly robust Cox regression model, adjusting for clinically relevant baseline characteristics which remained imbalanced after weighting, was used to compare PFS between cohorts. **Results:** Charts of 99 DRd and 78 VRd patients were abstracted. After weighting (DRd weighted n=91, VRd weighted n=87), mean age of patients (DRd: 76.2 years, VRd: 75.9 years) and gender distribution (female; DRd: 51%, VRd: 52%) were similar between cohorts. ECOG categories, 1q21 gain/amplification, and other high-risk cytogenetics (t-[4;14], t-[14;16], del [17p]) were also well balanced. Small differences were observed in year of index date and ISS staging, which were added as regressors to the Cox model. At data cut-off, 13 DRd (14.5%) and 24 VRd (28.2%) patients experienced disease progression or death. Patients treated with 1L DRd had a 65% lower risk of disease progression or death compared to 1L VRd (adjusted hazard ratio=0.35, 95% CI: 0.17-0.73, p< 0.01). **Conclusions:** DRd is associated with a significantly lower risk of disease progression or death compared to VRd as 1L treatment for TIE NDMM patients. Results from the current TAURUS chart review study could help inform the selection of optimal 1L treatment for these patients in the absence of H2H trial comparing these two guideline recommended regimens.

safety. Endpoints were assessed by age (<75 vs ≥75 years [yrs]) and frailty status (non-frail vs frail). **Results:** At datacut (Oct 17, 2022), 140 pts had received IRd; 42% were aged ≥75 yrs (median age: 73 yrs) and 61% were frail. Overall median follow-up was 27 months (mos). For pts aged <75 vs ≥75 yrs and for non-frail vs frail pts, 12 vs 7% and 13 vs 8% were ongoing on IRd, respectively. Median duration of IRd was 11 mos overall, 14 vs 9 mos in pts aged <75 vs ≥75 yrs, and 12 vs 10 mos in non-frail vs frail pts. Overall median duration of all PI-based therapy was 14 mos, 18 vs 12 mos in pts aged <75 vs ≥75 yrs, and 15 vs 13 mos in non-frail vs frail pts. ORR increased from 62% at the end of induction (including complete response [CR]: 8%) to 80% (including CR: 37%) following *i*CT to IRd; for pts aged <75 vs ≥75 yrs, ORR increased from 60 to 80% vs 64 to 80%; and in non-frail vs frail subgroups, ORR increased from 70 to 81% vs 57 to 79%. The overall 2-year PFS rate was 71% (95% confidence interval [CI]: 61–78), 72% (95% CI: 60–81) vs 67% (95% CI: 50–80) in pts aged <75 vs ≥75 yrs, and 74% (95% CI: 58–85) vs 68% (95% CI: 55–78) in non-frail vs frail pts; differences were not significant. Median PFS and OS were not reached overall, nor in any subgroup. Overall, 98% of pts experienced ≥1 treatment-emergent adverse event (TEAE; 69% grade ≥3; 44% serious TEAEs). For pts aged <75 vs ≥75 yrs, 69 vs 68% experienced a grade ≥3 TEAE; serious TEAEs occurred in 42 vs 47%; TEAEs leading to dose modification occurred in 67 vs 66%; and 2 pts died in each subgroup. For non-frail vs frail subgroups, 61 vs 73% experienced a grade ≥3 TEAE; serious TEAEs occurred in 39 vs 48%; TEAEs leading to dose modification occurred in 61 vs 70%; and 1 vs 3 pts died, respectively. **Conclusions:** *i*CT from V-based induction to all-oral IRd permits prolonged PI-based therapy and improves depth of response, with a tolerable safety profile, including in elderly/frail pts. For such pts, IRd may be an alternative to induction/maintenance.

P-115

Progression-free survival of daratumumab vs. bortezomib triplet combination with lenalidomide and dexamethasone in transplant ineligible newly diagnosed multiple myeloma patients: a chart review study

Lucio Gordan[1], Carlyn Rose Tan[2], Robert Vescio[3], Jing Christine Ye[4,5], Carolina Schinke[6], Rohan Medhekar[7], Alex Fu[8,9], Marie-Hélène Lafeuille[10], Philippe Thompson-Leduc[10], Vipin Khare[7], John Reitan[11], Gary Milkovich[12], Shuchita Kaila[7], Faith Davies[13], Saad Usmani[2]

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P-116

The simplified frailty index (S-FI) identifies a less vulnerable population of frail patients than patients who are defined frail using the International Myeloma working Group Frailty index (IMWG-FI)

Kaz Groen[1], Febe Smits[2], Kazem Nasserinejad[3], Mark-David Levin[4], Josien Regelink[5], Gert-Jan Timmers[6], Esther de Waal[7], Matthijs Westerman[8], Gerjo Velders[9], Koen de Heer[10], Rineke Leys[11], Roel van Kampen[12], Claudia Stege[13], Maarten Seefat[1], Inger Nijhof[14], Ellen van der Spek[15], Saskia Klein[16], Niels van de Donk[17], Paula Ypma[18], Sonja Zweegman[19]

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Introduction: The International Myeloma working Group introduced a frailty index (IMWG-FI), which classifies patients as either fit, intermediate-fit or frail, based on age, comorbidities and dependency in (instrumental) activities of daily living ((I)ADL). A simplified frailty index (S-FI) has been introduced, replacing (I)ADL by the WHO performance score (WHO-PS). Even though both scores predict outcome, it is currently unknown whether the level of frailty is identical between the 2 scores. **Methods:** This is a pooled analysis of the HOVON 123 and HOVON 143 studies. In the HOVON 123 study, 238 non-transplant eligible newly diagnosed multiple myeloma patients, were treated with 9 cycles of melphalan, prednisone and bortezomib. In the HOVON 143 study, 65 frail and 65 intermediate fit NTE-NDMM patients, according to the IMWG-FI, were treated with 9 cycles of ixazomib, daratumumab and low dose dexamethasone (Ixa-Dara-dex), followed by maintenance until progression with a maximum of 2 years. Patients with unknown frailty score, either according to the IMWG-FI or S-FI, were excluded from analysis. Patients were classified as fit, intermediate fit and frail, using both indexes to determine the concordance rates and to investigate patient characteristics and clinical outcome of the different frailty groups. **Results:** The IMWG-FI and S-FI were missing in 19 patients. As fit patients were underrepresented (n=8) we excluded this subgroup, leaving 341 patients. Of the 67 patients who were intermediate-fit according to the S-FI, 61 patients (91%) remained intermediate-fit and 6 (9%) patients were reclassified to frail when using the IMWG-FI. Of the 272 patients who were frail based on the S-FI, 202 patients (74%) remained frail, however, 70 patients (26%) were reclassified to intermediate-fit when using the IMWG-FI. These 70 frail patients who would be classified as intermediate-fit when using the IMWG-FI had favorable patient- and disease characteristics, compared to the 202 patients who were frail according to both scores. They were younger (>80 years: 0% versus 56%), more often ADL independent (100% vs 69%) and IADL independent (93% vs 40%), had less comorbidities (CCI ≤1: 80% vs 49%) and a more favorable ISS stage (ISS 3: 27% vs 48%). In addition, PFS2 and OS were significantly longer in these 70 reclassified patients (median PFS2 40.0 versus 29.1m, HR 0.66 (95% CI: 0.47-0.91), p=0.01 and median OS 50.6m versus 24.1m, HR 0.55 (95% CI: 0.39-0.80), p=0.0014), as compared to the 202 patients who were frail based on both scores. **Conclusions:** We here show that the S-FI identifies more patients as frail, including patients that would have been classified as intermediate fit when the gold standard, the IMWG-FI, was used. These reclassified frail patients have favorable patient- and disease characteristics, translating in a superior PFS2 and OS as compared to the subgroup of frail patients who were defined frail in both classifications. This hampers comparisons between studies using the S-FI versus the IMWG-FI.

P-117

A prognostic score based on age, eGFR (CKD-EPI), performance status and ultra-high-risk disease outperforms R2-ISS for elderly myeloma patients: an analysis of the Greek myeloma study group registry

Eirini Katodritou[1], Efstathios Kastritis[2], Dimitra Dalampira[1], Aggeliki Sevastoudi[1], Foteini Theodorakakou[2], Sosana Delimpasi[3], Emmanouil Spanoudakis[4], Ioannis Ntanasis-Stathopoulos[2], Theodora Triantafyllou[1], Aikaterini Daiou[1], Anastasia Pouli[5], Maria Gavriatopoulou[2], Evgenia Verrou[1], Meletios Dimopoulos[2], Evangelos Terpos[2]

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Introduction: Second revision of ISS (R2-ISS) enhanced the prognostic value of R-ISS; however, its impact on transplant ineligible (TI) Multiple Myeloma (MM) patients was not clearly defined. We aimed to evaluate prognostication of R2-ISS in TI population in the real-world in comparison with other well-known prognostic factors for OS i.e., age, performance status, renal function, and ultra-high-risk MM (UHR). **Methods:** We analyzed 780 newly diagnosed TI MM patients with complete data for R2-ISS diagnosed between 2003-2022 (median age 74 years, range 65-91; M/F: 384/396; IgG: 475, IgA: 209, light chain: 75, IgD: 7, non-secretory: 11, IgM: 3). **Results:** Forty-seven percent were ≥75 years, 52% had ECOG ≥2, 27% had CKD-EPI eGFR < 40mL/min/1.73m^2, 46% had anemia (Hb < 10g/dL), and 29%/12% had ISS-3/R-ISS-3, respectively. Per R2-ISS, 128 patients were classified in low (I), 254 in low-intermediate (II), 355 in intermediate-high (III) and 43 in high risk (IV) group; UHR MM [including two of the following: del17p, t(4;14), t(14;16) and +1q21] was found in 68/780 (8.7%) patients. Regarding therapy, 215 patients received upfront either lenalidomide-based triplets (LBT; n=135) or daratumumab-based regimens (DBR; n=80) (28%). The rest received mostly bortezomib combinations or Rd (389; 50%); ORR was 83% (CR: 18%). After a median follow up of 72 months (mo) (95% CI: 65-79), 478 patients died (61%); median PFS and OS was 24 mo (95% CI: 22-26) and 50 mo (95% CI: 44-56), respectively; 2nd line therapy was given in 369/780 patients; median post-progression OS was 17 mo (95% CI: 13-20). In the univariate cox regression analysis age ≥75 vs. 65-74, R-ISS, R2-ISS, UHR MM, ECOG ≥2, CKD-EPI < 40 vs. ≥40 mL/min/1.73m, anemia and treatment with LBT/DBR were significant predictors for OS. Age ≥75, CKD-EPI < 40 mL/min/1.73m^2, ECOG ≥2 and UHR MM maintained their negative prognostication in the multivariate analysis [HzRs: age ≥75: 1.4, CKD-EPI < 40 mL/min/1.73m^2: 1.57, ECOG ≥2: 1.76 and UHR MM: 1.6; p< 0.05); prognostic significance of R2-ISS was marginal (p=0.05). Median OS for R2-ISS I-IV was, 72.6 mo (95% CI: 59-86), 66 mo (95%CI: 53-82), 43 mo (95% CI: 37-49) and 15 mo, respectively (p< 0.001). Age ≥75, CKD-EPI < 40, mL/min/1.73m^2, ECOG ≥2 and UHR MM, scoring 1 point each, composed a model that recognized 4 prognostic risk groups: low: 0 points, low-intermediate: 1 point, intermediate-high 2 points and high ≥3 points. Median OS for patients classified as low risk (n=185), low-intermediate (n=298), intermediate-high (n=203) and high (n=94) was 79 mo (95% CI: 65-92), 60 mo (95% CI: 52-68), 42 mo (95% CI: 36-48) and 15 mo (95% CI:9-20), respectively (HzR: low vs. high: 0.21, low-intermediate vs. high: 0.32 and intermediate-high vs. high: 0.46; p< 0.001). **Conclusions:** In conclusion, age ≥75 years, CKD-EPI < 40mL/min/1.73m^2, ECOG≥2 and UHR MM were the strongest negative predictors for OS, building up a 4-group prognostic score for TI MM patients. Prognostic impact of R2-ISS was marginal. Further validation is warranted.

P-118

Machine learning assisted risk stratification of newly diagnosed multiple myeloma with respect to the VRd treatment

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Introduction: Bortezomib plus lenalidomide plus dexamethasone (VRd) regimen has been administered as the first-line treatment for newly diagnosed multiple myeloma (NDMM). While the regimen generally offers a high response rate and improved survival, as much as 15% of the patients suffered from early death and/or disease progression in our retrospective analysis. We thus developed the machine learning (ML) models predicting survival of the NDMM patients following the VRd treatment so as to assist personalized treatment selection. **Methods:** We used the Multiple Myeloma Research Foundation's dataset (IA17) and identified 254 transplant ineligible NDMM treated by the VRd regimen as the first-line therapy. ML models were developed using the XGBoost (eXtreme Gradient Boosting) method. From the total of 148 demographic and clinical variables, a minimal set was chosen via sequential forward feature selection. The overall survival (OS) model was trained to compute the time-course of changes in the probability of being alive using accelerated failure time. The MMRF cohort was divided into the training and validation set during 5-fold cross-validation via the StratifiedKFold that minimizes the differences in the composition of classes such as international staging system (ISS) across the folds. The predictive performance of the trained ML models was assessed with respect to the ROC–AUC recorded during validation. We used the computed probability of survival (t = 36 months) during validation for the VRd-specific risk stratification. **Results:** Clinical characteristics of the VRd treatment group within the MMRF dataset were as follows. The median age was 68 years, with 63% of the patients being male. IgG isotype was the most dominant (38%), and the majority belonged to the ISS stage I (38%) and II (40%). The median progression-free survival (PFS) and OS of the group were 49 and 94 months, respectively. The ML models achieved the ROC-AUC of up to 0.886 when predicting OS by the three years (36 months) following the first administration of VRd regimen. The median OS of the high and low risk groups were significantly different (29 months vs not reached, P < 0.0001), recording the hazard ratio of 7.14 (95% CI, 4.48-11.38). The following covariates were identified as being the most important when predicting the risk of early death following the VRd treatment: UAMS 70 gene index, CD56 expression, serum lambda level, white blood cell counts, FISH results with respect to 8p22 and CYLD. **Conclusions:** In conclusion, we used the ML method to stratify the transplant ineligible NDMM into the high and low risk subgroups with respect to administration of the VRd regimen as the first-line treatment. Together with the previously developed ML models predicting response and survival following the VMP or Rd treatment, the proposed ML model can

Introduction: Second revision of ISS (R2-ISS) enhanced the prognostic value of R-ISS; however, its impact on transplant ineligible (TI) Multiple Myeloma (MM) patients was not clearly defined. We aimed to evaluate prognostication of R2-ISS in TI population in the real-world in comparison with other well-known prognostic factors for OS i.e., age, performance status, renal function, and ultra-high-risk MM (UHR). **Methods:** We analyzed 780 newly diagnosed TI MM patients with complete data for R2-ISS diagnosed between 2003-2022 (median age 74 years, range 65-91; M/F: 384/396; IgG: 475, IgA: 209, light chain: 75, IgD: 7, non-secretory: 11, IgM: 3). **Results:** Forty-seven percent were ≥75 years, 52% had ECOG ≥2, 27% had CKD-EPI eGFR < 40mL/min/1.73m^2, 46% had anemia (Hb < 10g/dL), and 29%/12% had ISS-3/R-ISS-3, respectively. Per R2-ISS, 128 patients were classified in low (I), 254 in low-intermediate (II), 355 in intermediate-high (III) and 43 in high risk (IV) group; UHR MM [including two of the following: del17p, t(4;14), t(14;16) and +1q21] was found in 68/780 (8.7%) patients. Regarding therapy, 215 patients received upfront either lenalidomide-based triplets (LBT; n=135) or daratumumab-based regimens (DBR; n=80) (28%). The rest received mostly bortezomib combinations or Rd (389; 50%); ORR was 83% (CR: 18%). After a median follow up of 72 months (mo) (95% CI: 65-79), 478 patients died (61%); median PFS and OS was 24 mo (95% CI: 22-26) and 50 mo (95% CI: 44-56), respectively; 2nd line therapy was given in 369/780 patients; median post-progression OS was 17 mo (95% CI: 13-20). In the univariate cox regression analysis age ≥75 vs. 65-74, R-ISS, R2-ISS, UHR MM, ECOG ≥2, CKD-EPI < 40 vs. ≥40 mL/min/1.73m, anemia and treatment with LBT/DBR were significant predictors for OS. Age ≥75, CKD-EPI < 40 mL/min/1.73m^2, ECOG ≥2 and UHR MM maintained their negative prognostication in the multivariate analysis [HzRs: age ≥75: 1.4, CKD-EPI < 40 mL/min/1.73m^2: 1.57, ECOG ≥2: 1.76 and UHR MM: 1.6; p< 0.05); prognostic significance of R2-ISS was marginal (p=0.05). Median OS for R2-ISS I-IV was, 72.6 mo (95% CI: 59-86), 66 mo (95%CI: 53-82), 43 mo (95% CI: 37-49) and 15 mo, respectively (p< 0.001). Age ≥75, CKD-EPI < 40, mL/min/1.73m^2, ECOG ≥2 and UHR MM, scoring 1 point each, composed a model that recognized 4 prognostic risk groups: low: 0 points, low-intermediate: 1 point, intermediate-high 2 points and high ≥3 points. Median OS for patients classified as low risk (n=185), low-intermediate (n=298), intermediate-high (n=203) and high (n=94) was 79 mo (95% CI: 65-92), 60 mo (95% CI: 52-68), 42 mo (95% CI: 36-48) and 15 mo (95% CI:9-20), respectively (HzR: low vs. high: 0.21, low-intermediate vs. high: 0.32 and intermediate-high vs. high: 0.46; p< 0.001). **Conclusions:** In conclusion, age ≥75 years, CKD-EPI < 40mL/min/1.73m^2, ECOG≥2 and UHR MM were the strongest negative predictors for OS, building up a 4-group prognostic score for TI MM patients. Prognostic impact of R2-ISS was marginal. Further validation is warranted.

P-118

Machine learning assisted risk stratification of newly diagnosed multiple myeloma with respect to the VRd treatment

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assist personalized treatment selection for the transplant ineligible NDMM.

P-119

The role of lenalidomide-dexamethasone therapy in elderly patients with multiple myeloma in clinical practice: comparison with bortezomib-based therapy

Jihyun Kwon[1], Yong-Pyo Lee[2], Hee Sue Park[1]

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Introduction: No clinical trials have directly compared the continuous use of lenalidomide plus dexamethasone (Rd) with a fixed-duration treatment using proteasome inhibitors. In this study, we aimed to identify the role of Rd and proteasome inhibitor-based therapies as frontline treatments for elderly patients with multiple myeloma (MM). **Methods:** We collected and retrospectively analyzed the clinical data of 78 patients with MM who were ineligible for autologous hematopoietic stem cell transplantation (Auto-HSCT). Patients who received Rd as the first treatment were defined as group R and those who received bortezomib-based treatment were defined as group V. The primary endpoints of this study were overall survival and progression-free survival after first-line treatment. **Results:** The median age was 77.1 years (range 64.4–88.7). High-risk cytogenetics were confirmed in 11 patients. Thirty-nine patients (50.0%) received bortezomib-based therapy as the first treatment and 32 (41.0%) received Rd therapy. Patients in group R were older than those in group V (median age 79.3 vs 75.2 years, P=0.003). Three patients in group V had del(17p13) with none in group R. There was no significant difference between the two groups in the distribution of risk groups according to the International Staging System (ISS) and the Revised-ISS. The overall response rate was 74.2% in group R and 74.4% in group V (P=0.987). The time to best response was significantly shorter in group V than in group R. (6.8 vs 9.2 months, P=0.043). The median progression-free survival was 28.8 months in group R and 20.2 months in group V (P=0.042). The most common reason for treatment discontinuation in group R was treatment-related complications (15 patients, 55.6%). In group V, 15 patients (38.5%) terminated treatment according to the plan, followed by complications (12 patients, 30.8%). Twenty-five (64.1%) patients in group V received second-line lenalidomide-based therapy, whereas only seven (21.9%) patients in group R received secondary treatment. The period from the completion of the first treatment to the start of the second treatment was 1.0 months in group R and 3.7 months in group V (P=0.042). The median progression-free survival of the second-line treatment was significantly longer in group V (22.6 months) than in group R (5.4 months) (P=0.001). The median overall survival was 26.6 months in group R and 48.7 months in group V (P=0.010). In the multivariate analysis, significant prognostic factors were age >76 years (hazard ratio 3.398, P< 0.001) and ISS III risk group (hazard ratio 8.367, P=0.043). **Conclusions:** The type of primary treatment did not affect overall survival. Rd therapy showed superior progression-free survival compared with bortezomib-based regimens, despite the relatively older age of the patients. However, it is necessary to consider the high early termination rate due to complications and disadvantages caused by short drug holiday periods.

P-120

Impact of exclusion from clinical trials in non-candidate transplant patients with newly diagnosed multiple myeloma

Luis Gerardo Rodríguez-Lobato[1], Anna de Daniel i Bisbe[1], Natalia Tovar[1], Carlos Fernández de Larrea[1], Maria Teresa Cibeira[1], Raquel Jiménez-Segura[1], David Moreno[1], Aina Oliver-Caldés[1], Joan Bladé[1], Laura Rosinol[1]

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Introduction: Medical societies recommend the inclusion of newly diagnosed multiple myeloma (NDMM) patients in clinical trials (CTs), but the actual number of patients who cannot be included and the associated prognosis remains unknown. Furthermore, there are concerns about the generalization of CT results to real-world clinical practice due to strict patient recruitment criteria. Our objective was to analyze the main causes of exclusion of non-transplant-eligible NDMM patients from CTs and to evaluate the outcomes of patients treated within or outside of CTs. **Methods:** We included 211 NDMM patients between 2003 and 2017. The above-mentioned interval was divided into three time periods (period 1: 03-07, period 2: 08-12, and period 3: 13-17). 106 (50%) received treatment outside of CTs (OCT), while 105 patients (50%) were included in a CT (89% in a phase III CT); among the included patients, 43 (40%) were randomized to the control group (CG), and 62 (60%) were assigned to the experimental group (EG). CT inclusion was analyzed as a time-dependent covariate. **Results:** Patients included in CTs were younger, had better renal function, and had a better ECOG performance status. The main causes for non-inclusion in CTs were comorbidities (41%), ECOG>2 (30%), renal insufficiency (14%), very advanced age (12.3%), and patient refusal (10%). The number of days between diagnosis and treatment initiation was longer for patients included in CTs (CT=27.5 vs. OCT=17; P=0.002). The complete response rate was similar in the first two analyzed periods regardless of the type of treatment received, while in the last period, the EG group showed an improvement (period 3: EG=28% vs. CG=18% vs. OCT=3%; P< 0.001). The median follow-up for the entire population was 46 months. The median progression-free survival (PFS) was similar in the first two periods (03-12; P=NS), showing only a benefit in the EG in the last period (EG=32 vs. CG=17.5 vs. OCT=15 months; P< 0.001). The median overall survival (OS) was longer in patients included in CTs (EG and CG) compared to the OCT group in the two last studied periods (period 2: EG=75 vs. CG=57 vs. OCT=26 months; period 3: EG=not reached vs. CG=71 vs. OCT=36; P< 0.001). **Conclusions:** Half of the non-transplant candidate NDMM patients cannot be included in CTs because they do not meet the inclusion criteria, primarily due to the presence of comorbidities. Patients included in CTs, even those randomized to the control group, have a longer OS than non-included patients. This OS benefit is due to a selection

assist personalized treatment selection for the transplant ineligible NDMM.

P-119

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P-120

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P-119

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P-120

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bias, which hinders the extrapolation of CT results to real clinical practice and should be considered when selecting treatment for patients who usually do not meet the inclusion criteria.

P-121

Real world outcomes of undocumented multiple myeloma patients: a safety net hospital experience

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Introduction: There are approximately 16-29 million undocumented immigrants (UI) in United States (US). UIs face more 2-fold problems in seeking medical care compared to the general population due to various financial and social burdens which include fear of deportation, language barriers, and low socioeconomic status. Most UIs are not eligible for Medicaid, state-based or employer-sponsored coverage plans, and rely on safety net hospital systems. UIs diagnosed with hematological malignancies, such as multiple myeloma (MM), face additional burdens of financially prohibitive therapies and the need for frequent provider and infusion visits. Studies have shown that immigration status can lead to disparate health outcomes, but these outcomes are poorly defined. In this study, we aim to highlight the real-world outcomes of a unique population of UIs diagnosed with MM. **Methods:** We performed a retrospective analysis on 450 patients (pts) treated for MM at Parkland Health from 1997 to 2022. Pts were considered undocumented if a valid social security number was unavailable in their electronic health record or did not qualify for a state-based insurance plan. All pts were "transplant-ineligible" due to financial constraints and lack of insurance coverage. Most pts were able to access reduced cost MM therapies through Parkland's financial assistance program. We performed a survival analysis to assess the overall survival outcomes. **Results:** Of the 450 pts, 45 UIs were identified. 99% of UIs were Hispanic and 78% were < 55 years at diagnosis. 35 pts (77%) were enrolled in financial assistance programs and 10 pts had no insurance on file. The average distance travelled to access treatment was 12.68 miles. 25 (55%) had cytogenetic abnormalities such as gain in chromosome 1q, 17 p deletion, and t (4;14) found in 7 (16%), 4 (9%) and 5 (11%). 27 (60%) had ≥50% plasma cell burden. 18 received 1st line therapy, 13 received 2nd line, 5 received 3rd line, 3 received 4th line, and 3 received 5th line therapy. Most commonly used 1st line therapies were VRD (28%), VD (15.5%), Dara-RD (13%), and Dara-VRD (8%). 2nd line therapies were Dara-RD (8.8%), IRD (8.8%) and KRD (6.6%); and 3rd line therapies were Dara-RD (4.4%) and KPD (2.2%). 1 pt underwent a stem cell transplant. 23 pts expired or were lost to follow-up (51%). The median overall survival (OS) was 4.92 years and 1 year OS (95% CI), 96% (74.8% to 98.9%), 5 year OS 48% (23.4% to 72.6%) and 10 year OS - 0%. **Conclusions:** Our study highlights key demographic characteristics in a unique cohort of UIs and reflects the challenges they face in accessing cancer care in the US. These pts frequently present with advanced and symptomatic disease at diagnosis and often require multiple lines of subsequent therapy; however, due to early death and frequent loss to follow up, less than half are alive and in follow up at 5 years, suggesting inferior outcomes compared to documented patients. Further research is warranted regarding the healthcare needs and experiences of UIs.

P-122

Ocular adverse events and functional impact in transplant ineligible, newly diagnosed multiple myeloma patients treated with belantamab mafodotin, lenalidomide and dexamethasone in BelaRd trial

Evangelos Terpos[1], Ioannis Ntanasis-Stathopoulos[1], Maria Gavriatopoulou[1], Panagiotis Malandrakis[1], Despina Fotiou[1], Magdalini Migkou[1], Foteini Theodorakakou[1], Vassiliki Spiliopoulou[1], Rodanthi Syrigou[1], Evangelos Eleutherakis-Papaiakovou[1], Stavros Gkolfinopoulos[2], Kyriaki Manousou[2], Efstathios Kastritis[1], Meletios Dimopoulos[1]

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Introduction: Ocular adverse events (OAEs), manifesting as visual acuity changes, ocular symptoms, and corneal findings, are common with belantamab mafodotin (belamaf; GSK2857916) and the main reason for dose modifications. Here, we present the OAEs and the associated functional impairment in transplant-ineligible (TI), newly diagnosed multiple myeloma (NDMM) patients (pts) treated with an extended dose schedule of belamaf in the phase 1/2 BelaRd study. **Methods:** BelaRd (NCT04808037) is an open-label, phase 1/2 study conducted in Greece, aiming to enroll 66 TI NDMM pts. In Part 1, which investigates the safety/clinical activity of belamaf plus Rd, 36 pts are randomized (1:1:1) to receive belamaf at doses of 2.5, 1.9 or 1.4 mg/kg. In this part, belamaf is initially administered q8w and, depending on toxicity, dosing may be rescheduled to q12w. Ocular exams include Snellen best corrected visual acuity (BCVA) and slit lamp corneal evaluation. Ocular symptoms are classified by CTCAE v5.0, while the Ocular Surface Disease Index (OSDI) captures dry eye disease and activities of daily living (ADL). This descriptive analysis included all Part 1 pts (cut-off date 15/04/23). **Results:** Among 201/227/192 BCVA assessments in cohorts 2.5/1.9/1.4, a worse than 20/50 result (in the better seeing eye) was observed in 21 (10%)/23 (10%)/18 (9%), while BCVA ≤ 20/200 was noted in 2 (1%)/3 (1%)/11 (6%), with a median time to resolution of 1 month. Across all cohorts, the most frequently reported ocular symptom ≥Gr 2 was dry eye (174/618, 28%), while ≥Gr3 keratopathy was noted in <

bias, which hinders the extrapolation of CT results to real clinical practice and should be considered when selecting treatment for patients who usually do not meet the inclusion criteria.

P-121

Real world outcomes of undocumented multiple myeloma patients: a safety net hospital experience

Aishwarya Sannareddy[1], Sharlene Dong[1], Ramya Sankarasubramanian[1], Umar Khan[1], Heather Reves[1], Shifa Kanjwal[1], Navid Sadeghi[1], Radhika Kainthla[1], Heather Wolfe[2], Elif Yilmaz[2], Farrukh Awan[2], Praveen Ramakrishnan Geethakumari[2], Yazan Madanat[2], Adeel Khan[2], Aimaz Afrough[2], Robert Collins[2], Larry Anderson[2], Jenny Li[1], Gurbakhash Kaur[2]

[1]UT Southwestern Medical Center; [2]Cellular Therapy and Hematologic Malignancies Program, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA

Introduction: There are approximately 16-29 million undocumented immigrants (UI) in United States (US). UIs face more 2-fold problems in seeking medical care compared to the general population due to various financial and social burdens which include fear of deportation, language barriers, and low socioeconomic status. Most UIs are not eligible for Medicaid, state-based or employer-sponsored coverage plans, and rely on safety net hospital systems. UIs diagnosed with hematological malignancies, such as multiple myeloma (MM), face additional burdens of financially prohibitive therapies and the need for frequent provider and infusion visits. Studies have shown that immigration status can lead to disparate health outcomes, but these outcomes are poorly defined. In this study, we aim to highlight the real-world outcomes of a unique population of UIs diagnosed with MM. **Methods:** We performed a retrospective analysis on 450 patients (pts) treated for MM at Parkland Health from 1997 to 2022. Pts were considered undocumented if a valid social security number was unavailable in their electronic health record or did not qualify for a state-based insurance plan. All pts were "transplant-ineligible" due to financial constraints and lack of insurance coverage. Most pts were able to access reduced cost MM therapies through Parkland's financial assistance program. We performed a survival analysis to assess the overall survival outcomes. **Results:** Of the 450 pts, 45 UIs were identified. 99% of UIs were Hispanic and 78% were < 55 years at diagnosis. 35 pts (77%) were enrolled in financial assistance programs and 10 pts had no insurance on file. The average distance travelled to access treatment was 12.68 miles. 25 (55%) had cytogenetic abnormalities such as gain in chromosome 1q, 17 p deletion, and t (4;14) found in 7 (16%), 4 (9%) and 5 (11%). 27 (60%) had ≥50% plasma cell burden. 18 received 1st line therapy, 13 received 2nd line, 5 received 3rd line, 3 received 4th line, and 3 received 5th line therapy. Most commonly used 1st line therapies were VRD (28%), VD (15.5%), Dara-RD (13%), and Dara-VRD (8%). 2nd line therapies were Dara-RD (8.8%), IRD (8.8%) and KRD (6.6%); and 3rd line therapies were Dara-RD (4.4%) and KPD (2.2%). 1 pt underwent a stem cell transplant. 23 pts expired or were lost to follow-up (51%). The median overall survival (OS) was 4.92 years and 1 year OS (95% CI), 96% (74.8% to 98.9%), 5 year OS 48% (23.4% to 72.6%) and 10 year OS - 0%. **Conclusions:** Our study highlights key demographic characteristics in a unique cohort of UIs and reflects the challenges they face in accessing cancer care in the US. These pts frequently present with advanced and symptomatic disease at diagnosis and often require multiple lines of subsequent therapy; however, due to early death and frequent loss to follow up, less than half are alive and in follow up at 5 years, suggesting inferior outcomes compared to documented patients. Further research is warranted regarding the healthcare needs and experiences of UIs.

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P-123

Safety and clinical activity of belantamab mafodotin plus lenalidomide and dexamethasone in transplant ineligible patients with newly diagnosed multiple myeloma: the phase 1/2 BelaRd study

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Introduction: The combination of lenalidomide and dexamethasone (Rd) is preferred in the treatment of transplant ineligible (TI) patients (pts) with newly diagnosed multiple myeloma (NDMM). Belantamab mafodotin (belamaf; GSK2857916) is an antibody-drug conjugate targeting BCMA, which has shown efficacy in pretreated MM pts. Preclinical data demonstrate synergy between belamaf and lenalidomide, while these drugs do not have overlapping toxicities. Thus, there is a strong rationale for investigating the belamaf-Rd combination in TI NDMM pts. **Methods:** BelaRd (NCT04808037) is an open-label, phase 1/2 study conducted in Greece, aiming to enroll 66 TI NDMM pts. Here we report results from Part 1 which evaluates the safety/tolerability of three belamaf doses (2.5/1.9/1.4 mg/kg) plus Rd in 36 pts and establishes the recommended phase 2 dose (cut-off date 15/04/2023). In this part, belamaf is initially administered q8w and, depending on toxicity, dosing may be rescheduled to q12w. **Results:** Of the 36 pts [median age: 72.5 years; male: 19 (53%)] in Part 1, 29 (81%) are still on treatment, while 7 (19%) have discontinued [6 pts due to belamaf-unrelated fatal events: (COVID-19 infection: 1/1/2; Pneumonia: 1/1/0, for cohorts 2.5/1.9/1.4 respectively); 1 pt withdrew consent]. The median belamaf administrations and number of cycles reached were 6/7/7 and 18.5/21.5/18.5, for the respective cohorts. The most common (≥10% of pts) non-ocular ≥ Gr3 treatment-emergent adverse events were fatigue (21 pts, 58%; [7 (58%)/7 (58%)/7 (58%)]), rash (6 pts, 17%; [2 (17%)/2 (17%)/2 (17%)]), diarrhoea (8 pts, 22%; 2 (17%)/3 (25%)/3 (25%)]), insomnia (4 pts, 11%; 0/4 (33%)/0]) and COVID-19 infection (5 pts, 14%; [2 (17%)/1 (8%)/2 (17%)]), while no ≥Gr3 thrombocytopenias and infusion-related reactions were reported. Regarding ≥Gr3 infections other than COVID, pneumonia was reported for 3 (8%) pts [1 (8%)/1 (8%)/1 (8%)]. Among 201/227/192 best corrected visual acuity (BCVA) assessments in cohorts 2.5/1.9/1.4, a worse than 20/50 result (in the better seeing eye) was observed in 21 (10%)/23 (10%)/18 (9%), while BCVA ≤20/200 was noted in 2 (1%)/3 (1%)/11 (6%). The overall response rate was 100% across all cohorts. More specifically, CR or better was achieved in 6 (50%)/4 (33%)/5 (42%), VGPR in 3 (25%)/7 (58%)/4 (33%) and PR in 3 (25%)/1 (8%)/3 (25%) of the pts in cohorts 2.5/1.9/1.4, with a median time to first response of 1 month. Finally, over a median follow-up of 18.7 months no disease progression was observed. **Conclusions:** Belamaf-Rd, with the extended schedule for belamaf, has shown a very manageable safety profile with minimal impact in vision-related functioning in an elderly, non-fit pt population. Meanwhile, a very promising clinical activity is observed with rapid, deep and durable responses across all dose levels. Consequently, after validation with bigger pt numbers, this novel combination may well be a very attractive frontline option for this vulnerable TI-NDMM population.

P-124

Therapeutic efficacy of ixazomib-based regimen in frail patients with newly diagnosed multiple myeloma based on the dynamic assessment of frailty

Hua Xue[1], Mei Jian Xu[1]

[1]Affiliated Hospital of Hebei University

Introduction: The treatment of multiple myeloma in the elderly is challenging with a high heterogeneity, and most of clinical trial findings about MM are not suitable to elderly frail patients (10-20%). More real-world studies are urgently needed to seek for effective, highly tolerable regimens to elderly frail patients with MM based on the dynamic assessment of frailty, thus guiding clinical management. To explore the efficacy and safety of the oral proteasome inhibitor ixazomib-based regimen in frail patients with newly diagnosed MM based on the dynamic assessment of frailty in the real world. **Methods:** A total of 17 elderly patients (NDMM) who were managed by a minimal of 2 cycles of oral proteasome inhibitor ixazomib-based regimen and assessed as Frail by the geriatric assessment scoring system of IMWG-GA in Affiliated Hospital of Hebei University from January 1, 2018 to June 30, 2022 were recruited. The objective ORR, PFS, OS, and AEs were recorded. **Results:** A total of 17

2% of assessments. Regarding OSDI, from 186/217/181 responses received, the number of "all/most' of the time worst responses in the ocular symptoms category were 5 (3%)/6 (3%)/8 (4%), while the respective proportions in the ADL category were 6 (3%)/4 (2%)/3 (2%). In terms of missed doses, among 122/129/112 planned belamaf infusions across cohorts, the number of skipped doses due to OAEs were 48 (39%)/41 (32%)/30 (27%). The overall response rate was 100%, no disease progression was observed over a median follow-up of 18.7 months, and 29 (81%) patients achieved at least VGPR while 15 (42%) achieved at least CR, with a median time to first response of 1 month. **Conclusions:** Belamaf-Rd, with the extended schedule for belamaf, had a minimal impact in vision-related functioning, as the 'all/most' of the time worst answers in the ADL category of OSDI was < 3% across cohorts. Furthermore, the frequency of clinically relevant impairment in vision was low, as a meaningful BCVA decline was observed in ≤10% of assessments, with a rapid time to resolution. Finally, the treatment combination induced rapid, deep and durable responses across all dose levels. In conclusion, this novel extended belamaf schedule nearly eradicates the risk for clinically relevant ocular toxicity and impact on ADL, without any compromise in clinical activity.

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Introduction: The combination of lenalidomide and dexamethasone (Rd) is preferred in the treatment of transplant ineligible (TI) patients (pts) with newly diagnosed multiple myeloma (NDMM). Belantamab mafodotin (belamaf; GSK2857916) is an antibody-drug conjugate targeting BCMA, which has shown efficacy in pretreated MM pts. Preclinical data demonstrate synergy between belamaf and lenalidomide, while these drugs do not have overlapping toxicities. Thus, there is a strong rationale for investigating the belamaf-Rd combination in TI NDMM pts. **Methods:** BelaRd (NCT04808037) is an open-label, phase 1/2 study conducted in Greece, aiming to enroll 66 TI NDMM pts. Here we report results from Part 1 which evaluates the safety/tolerability of three belamaf doses (2.5/1.9/1.4 mg/kg) plus Rd in 36 pts and establishes the recommended phase 2 dose (cut-off date 15/04/2023). In this part, belamaf is initially administered q8w and, depending on toxicity, dosing may be rescheduled to q12w. **Results:** Of the 36 pts [median age: 72.5 years; male: 19 (53%)] in Part 1, 29 (81%) are still on treatment, while 7 (19%) have discontinued [6 pts due to belamaf-unrelated fatal events: (COVID-19 infection: 1/1/2; Pneumonia: 1/1/0, for cohorts 2.5/1.9/1.4 respectively); 1 pt withdrew consent]. The median belamaf administrations and number of cycles reached were 6/7/7 and 18.5/21.5/18.5, for the respective cohorts. The most common (≥10% of pts) non-ocular ≥ Gr3 treatment-emergent adverse events were fatigue (21 pts, 58%; [7 (58%)/7 (58%)/7 (58%)]), rash (6 pts, 17%; [2 (17%)/2 (17%)/2 (17%)]), diarrhoea (8 pts, 22%; 2 (17%)/3 (25%)/3 (25%)]), insomnia (4 pts, 11%; 0/4 (33%)/0]) and COVID-19 infection (5 pts, 14%; [2 (17%)/1 (8%)/2 (17%)]), while no ≥Gr3 thrombocytopenias and infusion-related reactions were reported. Regarding ≥Gr3 infections other than COVID, pneumonia was reported for 3 (8%) pts [1 (8%)/1 (8%)/1 (8%)]. Among 201/227/192 best corrected visual acuity (BCVA) assessments in cohorts 2.5/1.9/1.4, a worse than 20/50 result (in the better seeing eye) was observed in 21 (10%)/23 (10%)/18 (9%), while BCVA ≤20/200 was noted in 2 (1%)/3 (1%)/11 (6%). The overall response rate was 100% across all cohorts. More specifically, CR or better was achieved in 6 (50%)/4 (33%)/5 (42%), VGPR in 3 (25%)/7 (58%)/4 (33%) and PR in 3 (25%)/1 (8%)/3 (25%) of the pts in cohorts 2.5/1.9/1.4, with a median time to first response of 1 month. Finally, over a median follow-up of 18.7 months no disease progression was observed. **Conclusions:** Belamaf-Rd, with the extended schedule for belamaf, has shown a very manageable safety profile with minimal impact in vision-related functioning in an elderly, non-fit pt population. Meanwhile, a very promising clinical activity is observed with rapid, deep and durable responses across all dose levels. Consequently, after validation with bigger pt numbers, this novel combination may well be a very attractive frontline option for this vulnerable TI-NDMM population.

P-124

Therapeutic efficacy of ixazomib-based regimen in frail patients with newly diagnosed multiple myeloma based on the dynamic assessment of frailty

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Introduction: The treatment of multiple myeloma in the elderly is challenging with a high heterogeneity, and most of clinical trial findings about MM are not suitable to elderly frail patients (10-20%). More real-world studies are urgently needed to seek for effective, highly tolerable regimens to elderly frail patients with MM based on the dynamic assessment of frailty, thus guiding clinical management. To explore the efficacy and safety of the oral proteasome inhibitor ixazomib-based regimen in frail patients with newly diagnosed MM based on the dynamic assessment of frailty in the real world. **Methods:** A total of 17 elderly patients (NDMM) who were managed by a minimal of 2 cycles of oral proteasome inhibitor ixazomib-based regimen and assessed as Frail by the geriatric assessment scoring system of IMWG-GA in Affiliated Hospital of Hebei University from January 1, 2018 to June 30, 2022 were recruited. The objective ORR, PFS, OS, and AEs were recorded. **Results:** A total of 17

eligible elderly patients with NDMM were recruited, and their baseline characteristics were listed in Table 1. Among them, there were 11 (64.7%) patients aged 75 years and older, and 15 (88.2%) patients with a minimal of Eastern Cooperative Oncology Group (ECOG) score of 2 points. All recruited patients were initially given ixazomib and dexamethasone (ID regimen). After 2-3 cycles of ID regimen, the frailty and therapeutic efficacy were dynamically assessed. After the improvement of frailty, those who had a worse efficacy than partial response (PR) or high risk assessed by the Revised Multiple Myeloma International Staging System (R-ISS) were additionally given cyclophosphamide (n=5), or lenalidomide (n=1) or daratumumab(n=1). The detailed treatment regimens were shown in Table 2. The median number of cycles of treatment for all patients was 7 (3-11), and the median ORR was 82.3% (14/17), and 16/17 (94.1%) achieving minimal response (MR) and above. Two deaths were reported, both of whom were older than 80 years and combined with multiple comorbidities. One patient died of treatment discontinuation at 17 months, and the other died of gastrointestinal bleeding at 2 years. Early deaths were not reported. Four patients experienced disease progression after self-withdrawal, and 11 patients were still managed by ixazomib-based regimen. The median follow-up period was 9.0 (2.6-37.0) months. The median PFS and median OS were not reached. All 17 patients were assessed for safety, and the overall tolerance was acceptable. Most of AEs were grade 1-2. None of them withdrew due to AEs. **Conclusions:** For frail patients with MM, an initial treatment of ID regimen is effective and safe based on the dynamic assessment of IMWG-GA, suggesting that the oral ID regimen is a first-line treatment to elderly frail patients with NDMM. Clinical benefits and the optimal regimen for elderly frail patients with MM adjusted based on the stratification of the frailty still needs evidence-based medical data.

P-125

Ixazomib versus lenalidomide or ixazomib and lenalidomide combination as maintenance regimen for transplant-ineligible multiple myeloma: update of a multi-center prospective study in China

Zhe Zhuang[1], Ying Tian[2], Hong Yu[3], Lei Shi[4], Wei-wei Tian[5], Qinhua Liu[6], Dongmei Zou[7], Fei Dong[8], Ru Feng[9], Yanping Ma[10], Shuangjiao Liu[1], Hui Liu[9], Hongmei Jing[8], Wanling Sun[7], Liang-Ming Ma[5], Li Bao[4], Rong Fu[3], Yin Wu[2], Wenming Chen[2], Junling Zhuang[1]

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Introduction: Maintenance therapy (MT) deepens response and prolongs progression free survival (PFS) in patients with newly diagnosed multiple myeloma (NDMM) after frontline regimens. Ixazomib, a 2nd generation oral proteasome inhibitor (PI), has been approved for MT due to convenience and tolerability. We conducted this prospective multi-center study to compare the efficacy and safety of Ixazomib (I-MT) or Ixazomib plus Lenalidomide (IL-MT) to Lenalidomide (L-MT) as maintenance regimen in transplant-ineligible NDMM patients. **Methods:** This study was approved by the Institutional Review Board of Peking Union Medical College Hospital and registered (NCT04217967). NDMM patients were enrolled from 10 centers of North China MM Registry, since September 2019. Patients receiving up to 5-9 cycles of front-line regimens and reaching at least partial response (PR) started MT. If PR was not reached after 4 cycles, 2nd-line induction for 2-5 cycles would be conducted till PR was reached. Ixazomib 4mg was given on day 1,8,15. Lenalidomide 25mg was given every other day on days 1–21 in a 28-day cycle. Patients in dual-drug group were administrated with both Ixazomib and Lenalidomide, dose as listed above. The primary endpoint was progression free survival (PFS) from MT. **Results:** A total of 200 patients were enrolled, including 74 in I-MT, 76 in L-MT and 50 in IL-MT. Patients in L-MT group was younger than those in I-MT and IL-MT group (median age of 61.0±8.1ys, vs 65.2±8.5ys and 63.5±8.3ys, respectively, p=0.03). The proportion of deletion 17p was slightly higher in IL-MT group. While other baseline characteristics, including gender ratio, paraprotein isotype, international staging system (ISS), revised-ISS (R-ISS), were comparable among different MT regimen groups. The median follow-up duration since maintenance was 27, 28 and 23 months in I-MT, L-MT and IL-MT, respectively. There were 75.6%, 80.3% and 80% of the patients reached very good remission (VGPR) or better before MT, while the rates of deep responses improved to 85.1%, 87.1% and 88% during follow-up. Progressive disease (PD) was recorded in 46.7% (N=32) of patients on I-MT, 31.6% (N=24) on L-MT and 36% (N=18) on IL-MT, respectively. The median PFS was 29.3m, not reached (NR) and 22.9m, while OS was not reached in all groups. Cox model multivariate analysis suggested that I-MT and IL-MT provided similar PFS to that of L-MT (HR 95% CI 0.57-1.95, p=0.87; and HR 95% CI 0.56-1.96, p=0.87; respectively). The main reason of MT withdrawal was disease progression. Adverse event related discontinuation was 8.3%, 0% and 20%, respectively. **Conclusions:** We design this multi-centered prospective study to evaluate whether dual drug maintenance will further strengthen response in non-transplant NDMM patients. Our preliminary data suggest that more clinicians in the real practice are inclined to prescribe IL-MT for high-risk patients. Whether dual-drug maintenance will provide better survival still needs to be defined.

P-126

Adding value of serum-free light chain in assessing response and progression in multiple myeloma with measurable disease

Elham Askari[1], Vincent Rajkumar[1], David Murray[1], Angela Dispenzieri[1], Prashant Kapoor[1], Moritz Binder[1], Francis Baudi[1], Joselle Cook[1], David Dingli[1], Amie Fonder[1], Morie Gertz[1], Wilson Gonsalves[1],

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P-126

Adding value of serum-free light chain in assessing response and progression in multiple myeloma with measurable disease

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Suzanne Hayman[1], Miriam Hobbs[1], Yi Hwa[1], Taxiarchis Kourelis[1], Martha Lacy[1], Nelson Leung[1], Yi Lin[1], Rahma Warsame[1], Robert Kyle[1], Shaji Kumar[1]
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Introduction: Highly effective therapies in multiple myeloma (MM), highlights the need for more sensitive biomarkers for response and progression assessments. Serum-free light chain (s-FLC) has a high specificity /sensitivity for detecting monoclonal paraprotein. The difference between Involved and uninvolved FLC (d-FLC) is used by the International Myeloma Working Group (IMWG) for assessing the response/progression in non secretory MM. We attempt to validate if the serial measurement of s-FLC, adds value in monitoring MM with measurable disease. **Methods:** This retrospective study included newly diagnosed (MM), evaluated at mayo clinic (Rochester) between 2011-2021. All patients had s-FLC measurable (Involved FLC level ≥ 10 mg/dL, with abnormal ratio) at baseline plus measurable serum and/or urine with serial matched data available. All 3 biomarkers were measured at baseline, after each cycle, and at the time of best response and disease progression. We performed a direct comparison of response categories between 3 markers at each time point. **Results:** A total of 841 patients were included, 52% IgMM, 20% light chain (MM) and 28% with measurable M-protein in both serum and urine. After the first cycle of treatment, the major response rates (VGPR, PR) by FLC were (42%,40%), sPEP (11%,47%), and uPEP (51%,17%) (Figure 1). MRRs> 90%, observed earlier by s-FLC (2nd cycle) than by s/u M-protein (4th cycle). Among 81% of patients who achieved ≥VGPR at best response, 90% had response by FLC and urine.In patients with paraprotein response < VGPR, achieving FLC response ≥ VGPR, was associated with better PFS (HR 0.65, P < 0.03). Median d-FLC was reduced by 86% after cycle 1, compared to urine M-protein of 91% (Figure 2). The correlation coefficients between the percentage change of d-FLC and urine M-protein after each cycle, showed a moderate relationship, (r 0.562-0.607,p < .001). A higher degree of correlation was detected in LCCM (r 0.607-0.771,P < .001). After a median follow-up of 51 months, 56% had progression disease (PD): 62% by s-FLC, 56% by serum M-protein and 24% by urine. (Figure 3). Among the 48% of patients with measurable urine M-protein at baseline, 58% developed PD, however only 19.5% had progression by urine M-protein and 68%, presented PD by s-FLC. All patients with PD by urine, had PD by s-FLC. Among 13% (60) of total patients with PD, s-FLC was the only tumor marker detectable. **Conclusions:** In this study, a similar response rate between serum FLC and urine paraprotein confirms the current cutoffs used for response categories for s-FLC. Serum FLC changes closely paralleled the changes in measurable urine protein and suggest that 24-hour urine can be replaced by serum FLC for response and progression. With direct comparison, we detected the effect of treatment response earlier with FLC in multiple time points.We also detected in 13% of patients with progression, the serum FLC as the only marker of progression, suggesting value of FLC in monitoring for relapse/progression.

P-127

Bone marrow plasmacytosis >5% at time of autologous transplant influences survival outcomes in patients with standard risk cytogenetics

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[1]Translational Hematology and Oncology, Tuassig Cancer Institute, Cleveland Clinic; [2]Heart, Vascular & Thoracic Institute, Cleveland Clinic; [3]Division of Medical Oncology, Mayo Clinic; [4]Cleveland Clinic Taussig Cancer Institute; [5]Division of Medical Oncology, University of Washington

Introduction: Autologous hematopoietic cell transplant (AHCT) remains the standard consolidation in multiple myeloma (MM) patients who achieve at least partial response to induction chemotherapy. Indeed, AHCT aims to deepen response in MM patients while also prolonging remission in a disease of known eventual relapse. Here, we explored our internal cohort of MM patients undergoing AHCT to test whether a BMPC cut off of 5% provides survival advantages in patient who responded to a single line of modern induction therapy. **Methods:** We screened all MM patients who underwent AHCT between 2011 and 2021. Inclusion criteria included transplant within 12 months of diagnosis, receiving a single line of modern induction chemotherapy, and absence of relapse prior to AHCT. Patients were subsequently stratified into BMPC < 5% and ≥5% pre-AHCT. Kaplan-Meier analysis determined median overall survival (mOS) and median progression free survival (mPFS) post-AHCT with subgroup analysis according to the cytogenetic risk categories as well. **Results:** A total of 311 patients with available data were included in our study. On further BMPC stratification, we identified 233 (74.9%) patients with BMPC < 5% and 78 (25.1%) patients with BMPC ≥5% at AHCT, respectively. Both groups had similar baseline characteristics, including age at diagnosis (median 61.5 vs 60.4 years; P=0.86), age at transplant (62.0 vs 61.0 years; P=0.87), smoking history (65.9 vs 64.8%, 30.2 vs 33.8%, 3.9 vs 1.4% for never, prior, and current smokers; P=0.54), sex (Males 59.2 vs 61.1%; P=0.78), ethnicity (White 84.5 vs 91.7%; P=0.31); Eastern Cooperative Oncology Group (ECOG) performance status (P=0.81), International Scoring System stages (33.7 vs 38.7%, 42.7 vs 32.3%, 23.6 vs 29%, for stage I, II, and III; P=0.34), cytogenetic risk (High-risk 41.4 vs 37.7%; P=0.61), Immunoglobulin subtype (IgG 69.2 vs 66.1%; P=0.65), Melphalan dose (high dose 200 mg/m^2 97.0 vs 98.6%; P=0.45), and Mobilization regimen (G-CSF + Plerixafor 87.1 vs 88.7%; P=0.71) for BMPC < 5% and BMPC ≥5% at AHCT, respectively. Patients with < 5% BMPC had better probability of OS (median 88.8 vs 68.1 months; HR 0.6 95% CI 0.3-1.2; P=0.07), but it did not reach statistical significance. There was no difference in PFS (median 35.5 vs 33.1 months; HR 0.8 95% CI 0.5-1.2; P=0.2), for the BMPC < 5% and BMPC ≥5% groups. On subgroups analysis, no differences were noted in OS (median 70.1 vs 68.1 months; HR 0.4 95% CI 0.1-1.3; P=0.13) and PFS (median 22.6 vs 22.4 months; HR 0.9 95% CI 0.5-1.7; P=0.72) for

Suzanne Hayman[1], Miriam Hobbs[1], Yi Hwa[1], Taxiarchis Kourelis[1], Martha Lacy[1], Nelson Leung[1], Yi Lin[1], Rahma Warsame[1], Robert Kyle[1], Shaji Kumar[1]
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Introduction: Highly effective therapies in multiple myeloma (MM), highlights the need for more sensitive biomarkers for response and progression assessments. Serum-free light chain (s-FLC) has a high specificity /sensitivity for detecting monoclonal paraprotein. The difference between Involved and uninvolved FLC (d-FLC) is used by the International Myeloma Working Group (IMWG) for assessing the response/progression in non secretory MM. We attempt to validate if the serial measurement of s-FLC, adds value in monitoring MM with measurable disease. **Methods:** This retrospective study included newly diagnosed (MM), evaluated at mayo clinic (Rochester) between 2011-2021. All patients had s-FLC measurable (Involved FLC level ≥ 10 mg/dL, with abnormal ratio) at baseline plus measurable serum and/or urine with serial matched data available. All 3 biomarkers were measured at baseline, after each cycle, and at the time of best response and disease progression. We performed a direct comparison of response categories between 3 markers at each time point. **Results:** A total of 841 patients were included, 52% IgMM, 20% light chain (MM) and 28% with measurable M-protein in both serum and urine. After the first cycle of treatment, the major response rates (VGPR, PR) by FLC were (42%,40%), sPEP (11%,47%), and uPEP (51%,17%) (Figure 1). MRRs> 90%, observed earlier by s-FLC (2nd cycle) than by s/u M-protein (4th cycle). Among 81% of patients who achieved ≥VGPR at best response, 90% had response by FLC and urine.In patients with paraprotein response < VGPR, achieving FLC response ≥ VGPR, was associated with better PFS (HR 0.65, P < 0.03). Median d-FLC was reduced by 86% after cycle 1, compared to urine M-protein of 91% (Figure 2). The correlation coefficients between the percentage change of d-FLC and urine M-protein after each cycle, showed a moderate relationship, (r 0.562-0.607,p < .001). A higher degree of correlation was detected in LCCM (r 0.607-0.771,P < .001). After a median follow-up of 51 months, 56% had progression disease (PD): 62% by s-FLC, 56% by serum M-protein and 24% by urine. (Figure 3). Among the 48% of patients with measurable urine M-protein at baseline, 58% developed PD, however only 19.5% had progression by urine M-protein and 68%, presented PD by s-FLC. All patients with PD by urine, had PD by s-FLC. Among 13% (60) of total patients with PD, s-FLC was the only tumor marker detectable. **Conclusions:** In this study, a similar response rate between serum FLC and urine paraprotein confirms the current cutoffs used for response categories for s-FLC. Serum FLC changes closely paralleled the changes in measurable urine protein and suggest that 24-hour urine can be replaced by serum FLC for response and progression. With direct comparison, we detected the effect of treatment response earlier with FLC in multiple time points.We also detected in 13% of patients with progression, the serum FLC as the only marker of progression, suggesting value of FLC in monitoring for relapse/progression.

P-127

Bone marrow plasmacytosis >5% at time of autologous transplant influences survival outcomes in patients with standard risk cytogenetics

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P-128

Daratumumab – VTD vs VTD: peri-transplant evaluation

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[1]University Hospital of Leon

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P-129

Real world evidence of prognostic impact of t(14;16) translocation in multiple myeloma: a report of the myeloma triveneto working group

Gregorio Barilà[1], Laura Bonaldi[2], Laura Pavan[3], Annalisa Martines[2], Anna Pascarella[4], Susanna Vedovato[1], Cristina Clissa[5], Chiara Marcon[6], Anna Furlan[7], Omar Perbellini[1], Massimiliano Arangio Febbo[8], Edoardo Scomazzon[1], Tamara Berno[3], Martina Tinelli[5], Luca Massarotti[3], Angela Bonalumi[5], Livio Trentin[3], Mauro Krampera[5], Francesca Patriarca[6], Alberto Tosetto[1], Renato Zambello[3]

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t(14;16) subgroup with a cohort of 227 SR patients, including 78 t(11;14) cases and 81 hyperdiploid (HRD) cases. Overall, t(14;16) patients showed a reduced, although non statistically significant, OS as compared to SR patients (75 vs 105 months, p=0.1104); however, after the exclusion of del17p cases, the outcome of the two subgroups was superimposable (not reached vs 105 months, p=0.9948). Of notice, t(14;16) alone cases displayed reduced OS with respect of SR cases without +1q abnormalities (38.5 vs 105 months, p=0.0231). The t(14;16) alone dismal outcome was maintained when compared with defined cytogenetic subgroups of patients, notably t(11;14) alone patients (p=0.0875) and HRD alone patients (p=0.0016). **Conclusions:** The data herein presented showed that within t(14;16) patients, the presence of del17p conferred inferior survival while +1q abnormalities did not affect the outcome. Of notice t(14;16) alone patients showed reduced survival with respect to SR patients overall and in cytogenetically defined subsets, thus confirming the negative prognostic impact of this alteration.

P-130

Retrospective assessment of outcomes with autologous bone marrow transplant in multiple myeloma - Real world data of 23 years

Tasneem Bharmal[1], Reetu Jain[1], S. H. Advani[1], Ganpati Bhatt[1], Samir Shah[1], Fahad Afzal[1], Neal Joseph[1], Asha Ojha[1], Elvis Alex[1], Payal Bhatt[1], Mamta Yargop[1], Poonam Nuingare[1], Tapan Saikia[1]

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P-131

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t(14;16) subgroup with a cohort of 227 SR patients, including 78 t(11;14) cases and 81 hyperdiploid (HRD) cases. Overall, t(14;16) patients showed a reduced, although non statistically significant, OS as compared to SR patients (75 vs 105 months, p=0.1104); however, after the exclusion of del17p cases, the outcome of the two subgroups was superimposable (not reached vs 105 months, p=0.9948). Of notice, t(14;16) alone cases displayed reduced OS with respect of SR cases without +1q abnormalities (38.5 vs 105 months, p=0.0231). The t(14;16) alone dismal outcome was maintained when compared with defined cytogenetic subgroups of patients, notably t(11;14) alone patients (p=0.0875) and HRD alone patients (p=0.0016). **Conclusions:** The data herein presented showed that within t(14;16) patients, the presence of del17p conferred inferior survival while +1q abnormalities did not affect the outcome. Of notice t(14;16) alone patients showed reduced survival with respect to SR patients overall and in cytogenetically defined subsets, thus confirming the negative prognostic impact of this alteration.

P-130

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P-132

Post-induction undetectable flow minimal residual disease ameliorates the high risk determined by FISH among newly diagnosed multiple myeloma

Guldane Cengiz Seval[1], Klara Dalva[1], Sule Mine Bakanay[1], Ender Soydan[1], Osman Ilhan[1], Meral Beksac[1], Gulcin Miyase Sonmez[1]

[1]Ankara University School of Medicine, Department of Hematology

Introduction: Post-induction minimal residual disease(MRD) within marrow is currently recognized as poor-prognostic among transplant-eligible patients with multiple myeloma(MM). An emerging number of studies are evaluating MRD within the context of cytogenetic risk. In this study, we aimed to quantify clonal plasma cells (PCs) by flow both in apheresis products(gMRD) and marrow(mMRD) to evaluate the impact on the outcome according to risk determined by FISH cytogenetics. **Methods:** Four hundred fifty-four subsequent newly diagnosed MM patients transplanted between 2007-2022 were included prospectively. Standard-risk cytogenetics(SR) is defined as t(11;14) or a normal karyotype, whereas del(17p13), t(4;14), t(14;16), + 1q21 and complex findings are high-risk cytogenetics(HR).Results were reported in the intention-to-treat(ITT) population for mMRD. **Results:** Median follow-up after AHCT was 32.4 mos(range:3.2-168). The induction regimen consisted of bortezomib without or with immunomodulatory drugs 77.5% and 11.9%. Consolidation 19%(n=83/437), and maintenance 27.4%(n=118/431) were administered based on the guidelines and regulations. Cytogenetically HR, standard or missing were observed in 18.5%(n=84), 77.5%(n=352) and 4%(n=18) of the total cohort. Post-induction complete response(CR) was achieved in 18.7% of patients(n=85). Following mobilization(n=453), gMRD and mMRD were undetectable in 48.9%(181/370) and 13.5%(41/303) of patients. There was a correlation between gMRD and mMRD(SE: 0.318, p< 0.001). Having undetectable mMRD estimates a 5 years-PFS of 71.3% (p< 0.001). Among 40 mMRD(-) patients, only six (two with HR) have relapsed. Likewise, 5 years-PFS according to undetectable gMRD 44.8% (p=0.02) or according to HR vs SR is 31.3% vs 37.8% (p=0.19). Distribution of patients divided into four groups according to mMRD status and cytogenetic risk are as follows: mMRD(-)SR (n=30; 10.3%), MRD(-)HR (n=9; 3.1%), MRD(+)SR (n=207; 71.4%), MRD(+)HR (n=44;15.2%). Kaplan-Meier curves revealed significant differences in median PFS among these groups; mMRD(-)SR: NR, MRD(-)HR: 50 mos, MRD(+)SR: 23.3 mos, MRD(+)HR: 18.6 mos (p=0.006). In a MVA model (age, ISS, FISH, post-induction CR or MRD) post-induction mMRD (HR:0.26 (95% CI:0.11-0.59),p< 0.001) and post-induction CR (HR:0.19 (95% CI:0.07-0.51),p< 0.001) appeared to determine PFS independently. **Conclusions:** Our real-world triplet drug induction-based and majority unmaintained experience among AHCT-eligible myeloma patients, shows post-induction mMRD to be correlated with PFS. Although observed less frequently, achieving post-induction MRD(-) marrow may ameliorate the poor prognosis of HR determined by FISH. Combined analysis of the depth of response and FISH appears to increase the significance of risk assessment. In the future, more intensive induction regimens may allow better recognition of cytogenetic and molecular sub-groups versus depth of response in the prediction of long-term outcomes.

P-133

Validation of two international myeloma staging systems: second revision of ISS and mayo additive staging sytems (MASS) in an external cohort of Ankara University

Guldane Cengiz Seval[1], Merve Aydogan[1], Mehmet Hakan Akbulut[1], Bulent Karakaya[1], Gul Yavuz[1], Hulya Yilmaz[1], Meral Beksac[1]

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risk cytogenetics. Induction regimens included lenalidomide(R)-VD in 14 pts, carfilzomib(K)-RD in 4 pts, and a combination of RVD, KRD and cyclophosphamide-VD in 5 pts. Five pts received dara prior to ASCT. Median treatment duration was 24 cycles (range 4-27) and 19 pts completed 2yrs of therapy. At a median follow-up of 22mos, 1-yr and 2-yr PFS were 85% (95% CI, 73-99%), and 74% (58-92%) respectively. One-yr PFS was 80% (59-100%) and 91% (75%-100%) in the high and standard-risk pts, respectively. During maintenance, 8 pts had a deepening of response. No grade ≥4 toxicities were observed. Four pts had grade 3 toxicity, including respiratory infection, weight gain, hypertension and back pain. Ten pts had dose delays for toxicity, predominantly infections. CyTOF data from peripheral blood of 12 pts show profound changes in the frequencies of different immune populations including terminally differentiated T cells (TEMRA), activated monocytes, and NK cells. Dara treatment rapidly induced depletion in NK cell populations, which persisted until treatment discontinuation; no association with progression was noted. Four of the 12 pts evaluated progressed within the treatment period (< 24mos) and had increased CD4 suppressive T cell populations including TIGIT, PD-1, PDL-1 and TIM3-expressing T reg cells and bulk NKT cells. Preliminary scRNA sequencing data in 4 pts showed that upon dara discontinuation, pts had an increase in CD8+ cytotoxic T cell and B regulatory cell populations carrying unique genetic features. Specifically, we found a significant deregulation in the T cell and B cell activation markers including Granulysin, Granzyme A, IFG2R, CXCR4, CXCR5, NFKBID, among others. MRD, scRNA and CyTOF analysis from the rest of the pts will be presented. **Conclusions:** Single-agent dara maintenance post-ASCT is safe and demonstrates promising PFS in high-risk and standard-risk MM. In pts progressing on dara, unique changes in the distribution of immune cell populations and increased expression of T cell immune suppressive markers were seen. **Acknowledgments:** MMRC.

P-132

Post-induction undetectable flow minimal residual disease ameliorates the high risk determined by FISH among newly diagnosed multiple myeloma

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Introduction: Post-induction minimal residual disease(MRD) within marrow is currently recognized as poor-prognostic among transplant-eligible patients with multiple myeloma(MM). An emerging number of studies are evaluating MRD within the context of cytogenetic risk. In this study, we aimed to quantify clonal plasma cells (PCs) by flow both in apheresis products(gMRD) and marrow(mMRD) to evaluate the impact on the outcome according to risk determined by FISH cytogenetics. **Methods:** Four hundred fifty-four subsequent newly diagnosed MM patients transplanted between 2007-2022 were included prospectively. Standard-risk cytogenetics(SR) is defined as t(11;14) or a normal karyotype, whereas del(17p13), t(4;14), t(14;16), + 1q21 and complex findings are high-risk cytogenetics(HR).Results were reported in the intention-to-treat(ITT) population for mMRD. **Results:** Median follow-up after AHCT was 32.4 mos(range:3.2-168). The induction regimen consisted of bortezomib without or with immunomodulatory drugs 77.5% and 11.9%. Consolidation 19%(n=83/437), and maintenance 27.4%(n=118/431) were administered based on the guidelines and regulations. Cytogenetically HR, standard or missing were observed in 18.5%(n=84), 77.5%(n=352) and 4%(n=18) of the total cohort. Post-induction complete response(CR) was achieved in 18.7% of patients(n=85). Following mobilization(n=453), gMRD and mMRD were undetectable in 48.9%(181/370) and 13.5%(41/303) of patients. There was a correlation between gMRD and mMRD(SE: 0.318, p< 0.001). Having undetectable mMRD estimates a 5 years-PFS of 71.3% (p< 0.001). Among 40 mMRD(-) patients, only six (two with HR) have relapsed. Likewise, 5 years-PFS according to undetectable gMRD 44.8% (p=0.02) or according to HR vs SR is 31.3% vs 37.8% (p=0.19). Distribution of patients divided into four groups according to mMRD status and cytogenetic risk are as follows: mMRD(-)SR (n=30; 10.3%), MRD(-)HR (n=9; 3.1%), MRD(+)SR (n=207; 71.4%), MRD(+)HR (n=44;15.2%). Kaplan-Meier curves revealed significant differences in median PFS among these groups; mMRD(-)SR: NR, MRD(-)HR: 50 mos, MRD(+)SR: 23.3 mos, MRD(+)HR: 18.6 mos (p=0.006). In a MVA model (age, ISS, FISH, post-induction CR or MRD) post-induction mMRD (HR:0.26 (95% CI:0.11-0.59),p< 0.001) and post-induction CR (HR:0.19 (95% CI:0.07-0.51),p< 0.001) appeared to determine PFS independently. **Conclusions:** Our real-world triplet drug induction-based and majority unmaintained experience among AHCT-eligible myeloma patients, shows post-induction mMRD to be correlated with PFS. Although observed less frequently, achieving post-induction MRD(-) marrow may ameliorate the poor prognosis of HR determined by FISH. Combined analysis of the depth of response and FISH appears to increase the significance of risk assessment. In the future, more intensive induction regimens may allow better recognition of cytogenetic and molecular sub-groups versus depth of response in the prediction of long-term outcomes.

P-133

Validation of two international myeloma staging systems: second revision of ISS and mayo additive staging sytems (MASS) in an external cohort of Ankara University

Guldane Cengiz Seval[1], Merve Aydogan[1], Mehmet Hakan Akbulut[1], Bulent Karakaya[1], Gul Yavuz[1], Hulya Yilmaz[1], Meral Beksac[1]

[1]Ankara University School of Medicine, Department of Hematology

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novel scores in an independent external cohort from our Institution. **Methods:** This retrospective study is performed on a database of 524 consecutive majority transplant eligible NDMM patients treated in our center between September 2007- March 2022. As 1q amplification has been added to our FISH panels lately, 208 consecutive patients met the criteria for R2-ISS or MASS score parameters, and analysis was performed in this cohort. High-risk cytogenetics (HCR) was defined accordingly. Progression eligible for analysis-free survival (PFS) was defined as the time from the diagnosis until disease progression, relapse, or death due to any cause. **Results:** Patients (median age 61 years (33-88 years); (female/male: 47.1%/52.9%) received either bortezomib-based triplet (96.7%) without (n:142) or with an immunomodulatory drug (28.4%) as induction therapy. Out of the 208 patients, 169 patients underwent autologous hematopoietic stem cell transplantation (AHCT). As a post-ASCT treatment, consolidation (20.2%) and maintenance (38.9%) were given to patients. The median follow-up for all patients is 19.8 months (range: 3-237 mos). HCR was detected in 42 patients (20.2%) with an additional +1q identified among 96 cases, accounting for 46.2% of 208 patients. Based on the calculation of risk score in MASS; 42 patients (20.2%) ranked as score 0 (MASS I), 67 patients (32.2%) score 1 (MASS II) and 99 patients (47.6%) score +2 (MASS III). The cross-tabulation of MASS with R2-ISS will be presented late depicting a further sub-grouping of MASS scores within R2-ISS. With a median follow-up of 26.2 months, patients with +1q had significantly shorter PFS (95% CI: 18.9%-43.9%, p< 0.001) than those without +1q. The 2 years-PFS was 92.7% vs 81.1% vs 63.4% in the MASS I, II, and III groups, respectively (p< 0.001) and 95% vs 87.2% vs 73.6% vs 40.3% in the R2-ISS I, II, III, and IV groups, respectively (p< 0.001). **Conclusions:** Our single-center uniform real World data-based study confirms the prognostic role +1q as a poor prognostic parameter. The MASS-based PFS analysis shows a distinct separation of PFS curves ranging between 92.7% and 63.4%. With R2-ISS the distinctive power is expanded with PFS-2 years values ranging between 95% and 40.3%. Based on our analysis either MASS or preferably R2-ISS are both reliable and reproducible methods to powerfully predict the prognosis of patients with NDMM.

P-134

Clonal isotype switch predicts long-term survival in multiple myeloma after autologous stem cell transplantation

Hanwool Cho[1], Jinhang Kim[2], Nanyoung Yun[2], Jeong-A Kim[2]

[1]Department of Laboratory Medicine, St. Vincent Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; [2]Division of Hematology, Department of Internal Medicine, St. Vincent Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

Introduction: Clonal isotype switch (CIS) results in emergence of new oligoclonal immunoglobin bands that are different from the original bands identified at the time of diagnosis. CIS has been reported in patients with multiple myeloma (MM) who received a high dose melphalan chemotherapy followed by autologous stem cell transplantation (ASCT). However, clinical relevance of CIS after ASCT is still unclear. **Methods:** The retrospective analysis included 82 patients with MM who had undergone ASCT. 27 patients (38%) received a vincristine, doxorubicin and dexamethasone (VAD) as an induction treatment (IT), while 54 patients (62%) were initially treated with the bortezomib-containing IT. A CIS was observed in 26 patients (31%) of the 82 patients with a higher prevalence with the use of novel agents versus VAD in induction (40% vs. 15%; P=0.061). **Results:** In prognostic terms, revised international scoring system (R-ISS) and post-ASCT CIS status remained at a significant predictor in OS and PFS in the multivariate analysis. Interestingly, patients with CIS after ASCT had a significantly longer 10-year overall survival (OS; with CIS vs. without CIS; 56% vs. 25%, respectively; p=0.002) and 10-year progression-free survival (PFS; with CIS vs. without CIS; 52% vs. 32%, respectively; p=0.02). Among 26 patients with CIS, 11 patients had only one monoclonal band and 15 patients had developed oligoclonal bands (>2 monoclonal bands) throughout the post-ASCT follow-up period. Oligoclonal CIS was observed about 18% of patients in total 82 patients. Interestingly, the estimated 10-year OS and PFS of CIS patients with oligoclonal bands were 75.0% and 68.6%, respectively. **Conclusions:** CIS after ASCT is a favorable prognostic indicator based on its positive correlation with OS and PFS after transplantation in patients with MM. In addition, a higher frequency of CIS after ASCT was associated with the bortezomib-containing IT. The use of bortezomib-containing IT may contribute to a higher anti-tumor effect or a stronger immune reconstitution.

P-135

Evaluation of the R2-ISS in real-world patients with newly diagnosed multiple myeloma: a nationwide cohort study by the Korean multiple myeloma working party (KMM 2202)

Hyungwoo Cho[1], Kihyun Kim[2], Sang Eun Yoon[3], Sung-Hoon Jung[4], Je-Jung Lee[5], Joon Ho Moon[5], Hee Jeong Cho[5], Ho Sup Lee[6], Ka-Won Kang[7], Sung-Yong Kim[8], Hyeon-Seok Eom[9], Yeung-Chul Mun[10], Young Hoon Park[10], Sung-Soo Yoon[11], Young Rok Do[12], Won Sik Lee[13], Chang-Ki Min[14], Dok Hyun Yoon[1]

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P-134

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Introduction: The second revision of the International Staging System (R2-ISS) has recently been developed to improve the risk stratification of newly diagnosed multiple myeloma (NDMM) patients over the Revised-ISS (R-ISS). We aimed to evaluate its effectiveness in real-world clinical practice and compare its performance with the R-ISS **Methods:** We collected clinical and laboratory data from newly diagnosed MM patients treated between January 2010 and July 2019 at 13 hospitals participating in the Korean Multiple Myeloma Working Party (KMMWP) in South Korea. A total of 572 newly diagnosed MM patients who received IMiDs and/or PIs as part of their first-line treatment and had complete information on R2-ISS and R-ISS were included in the study. **Results:** The median age was 63 years (range: 36–88), with 245 patients (42.8%) being 65 years or older. According to the R2-ISS, 69 (12.0%), 163 (28.5%), 283 (49.5%), and 57 (10.0%) patients were classified as stages I, II, III, and IV, respectively. We observed a significant difference in median overall survival (OS) among the four stages of R2-ISS (111.7, 82.8, 49.1, and 26.1 months for stages I, II, III, and IV, respectively; $P < 0.001$). In addition, significant differences in OS were observed among the R2-ISS stages within the R-ISS II patients (n = 389). Median OS was not reached in R2-ISS I (n = 2), 82.8 months (95% CI: 67.3–125.9) in R2-ISS II (n = 152), 49.6 months (95% CI: 40.2–62.4) in R2-ISS III (n = 105), and 14.9 months (95% CI: 5.7–NA) in R2-ISS IV patients (n = 44) ($P < 0.001$). Notably, the R2-ISS demonstrated a significantly higher C-statistic for OS compared to the R-ISS (0.613 vs. 0.567; $P = 0.003$), along with a substantial difference in Akaike's information criterion between the two models (3709.2 vs. 3727.2). Furthermore, the R2-ISS successfully stratified patients with different survival outcomes based on age (elderly or young), treatment (PIs, IMiDs, or IMiDs plus PIs), eligibility for upfront autologous stem cell transplantation, and eligibility for clinical trial participation. **Conclusions:** In conclusion, the R2-ISS was successfully validated in real-world MM patients who received primary therapy with IMiDs and/or PIs. It showed a significant improvement in discriminatory power and model fitness compared to the R-ISS, mainly by effectively reclassifying R-ISS II patients into different risk groups. While the R2-ISS does not consider all potential risk factors, its additive nature allows for the inclusion of new prognostic variables in the future.

P-136

Phase I open-label single-arm study of dual targeting BCMA and CD19 FasTCAR-T cells (GC012F) as first-line therapy for transplant-eligible newly diagnosed high-risk multiple myeloma

Juan Du[1], Wanting Qiang[1], Jing Lu[1], Yanchun Jia[1], Haiyan He[1], Jin Liu[1], Pei Guo[1], Ying Yang[1], Zhongyuan Feng[1], Lina Jin[1], Xiaoqiang Fan[1], Jia Liu[2], Qi Zhang[2], Lianjun Shen[2], Lihong Weng[2], Wenling Li[2], Wei Cao[2]

[1]Department of Hematology, Shanghai Changzheng Hospital; [2]Gracell Biotechnologies Ltd.

Introduction: High-risk (HR) newly-diagnosed multiple myeloma (NDMM) has poor outcomes with standard first-line therapy, even in transplant-eligible (TE) patients (pts). A CAR-T therapy with high efficacy and manageable safety profile would be a potential solution to this significant unmet need. GC012F is an autologous B cell maturation antigen (BCMA) and CD19 dual-targeting CAR-T cells therapy developed on the novel FasTCAR-T enabling next-day manufacturing platform. A single arm, open-label phase I investigator-initiated study (NCT04935580) was conducted in a frontline setting for TE HR NDMM pts to assess the safety and feasibility of GC012F CAR-T cell therapy. Data was presented at ASH 2022 for initial 16 pts. Here we present updated data for study with longer follow-up and 3 additional pts treated (total n=19). **Methods:** From June 2022 to April 2023, 19 pts with median age 59 (range 43-69) were treated and evaluated with a single infusion of GC012F at 3 doses levels (DL) of 1E5/kg (n=1), 2E5/kg (n=4), or 3E5/kg (n=14), after a 3-day lymphodepletion consisting of cyclophosphamide and fludarabine. The primary objective of this study was safety; the secondary were pharmacokinetics and efficacy. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by ASTCT 2019. Efficacy assessment was referred to the IMWG 2016 criteria. Expansion of CAR-T cells and CAR copy numbers were analyzed by flow cytometry and qPCR, respectively. **Results:** As of April 12, 2023, the median follow-up time was 14.3 months (range 1.8-21.8 months). All pts had one or more high-risk features including 89% R-ISS stage II or III and 63% with EM. All pts received 2 cycles of induction therapy prior to the infusion. The overall response rate (ORR) was100% and 100% of pts achieved stringent complete response (sCR). All pts achieved minimal residual disease (MRD) negativity assessed by Euroflow with the sensitivity of 10-6. Median duration of response (DOR) and progression-free survival (PFS) were not reached. Only 6 pts (32%) experienced low-grade cytokine release syndrome (CRS), among them 26% was grade 1 (n=5) and 5% grade 2 (n=1). No any grade CRS occurred in other 68% pts. No ICANS or deaths occurred during the study. Robust CAR T-cell expansion was observed in all pts: median Cmax was 62131 (range 8754 - 331159) copies /μg gDNA and the median Tmax was 10 days (range 9-14 days). **Conclusions:** Consistent with the previous RRMM cohort treated with GC012F, initial data from this phase I study demonstrated that BCMA-CD19 dual FasTCAR-T GC012F resulted in a deep and durable remission in TE HR NDMM pts with

of Korea, Goyang, South Korea; [10]Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, South Korea; [11]Seoul National University College of Medicine, Seoul, South Korea; [12]Department of Hemato-Oncology, Keimyung University Dongsan Medical Center, Daegu, South Korea; [13]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, South Korea; [14]Seoul St. Mary's Hospital, Seoul, South Korea

Introduction: The second revision of the International Staging System (R2-ISS) has recently been developed to improve the risk stratification of newly diagnosed multiple myeloma (NDMM) patients over the Revised-ISS (R-ISS). We aimed to evaluate its effectiveness in real-world clinical practice and compare its performance with the R-ISS **Methods:** We collected clinical and laboratory data from newly diagnosed MM patients treated between January 2010 and July 2019 at 13 hospitals participating in the Korean Multiple Myeloma Working Party (KMMWP) in South Korea. A total of 572 newly diagnosed MM patients who received IMiDs and/or PIs as part of their first-line treatment and had complete information on R2-ISS and R-ISS were included in the study. **Results:** The median age was 63 years (range: 36–88), with 245 patients (42.8%) being 65 years or older. According to the R2-ISS, 69 (12.0%), 163 (28.5%), 283 (49.5%), and 57 (10.0%) patients were classified as stages I, II, III, and IV, respectively. We observed a significant difference in median overall survival (OS) among the four stages of R2-ISS (111.7, 82.8, 49.1, and 26.1 months for stages I, II, III, and IV, respectively; $P < 0.001$). In addition, significant differences in OS were observed among the R2-ISS stages within the R-ISS II patients (n = 389). Median OS was not reached in R2-ISS I (n = 2), 82.8 months (95% CI: 67.3–125.9) in R2-ISS II (n = 152), 49.6 months (95% CI: 40.2–62.4) in R2-ISS III (n = 105), and 14.9 months (95% CI: 5.7–NA) in R2-ISS IV patients (n = 44) ($P < 0.001$). Notably, the R2-ISS demonstrated a significantly higher C-statistic for OS compared to the R-ISS (0.613 vs. 0.567; $P = 0.003$), along with a substantial difference in Akaike's information criterion between the two models (3709.2 vs. 3727.2). Furthermore, the R2-ISS successfully stratified patients with different survival outcomes based on age (elderly or young), treatment (PIs, IMiDs, or IMiDs plus PIs), eligibility for upfront autologous stem cell transplantation, and eligibility for clinical trial participation. **Conclusions:** In conclusion, the R2-ISS was successfully validated in real-world MM patients who received primary therapy with IMiDs and/or PIs. It showed a significant improvement in discriminatory power and model fitness compared to the R-ISS, mainly by effectively reclassifying R-ISS II patients into different risk groups. While the R2-ISS does not consider all potential risk factors, its additive nature allows for the inclusion of new prognostic variables in the future.

P-136

Phase I open-label single-arm study of dual targeting BCMA and CD19 FasTCAR-T cells (GC012F) as first-line therapy for transplant-eligible newly diagnosed high-risk multiple myeloma

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a very favorable safety profile. These preliminary results emphasize the potential of CAR-T treatment in newly-diagnosed MM pts. Additional studies with larger cohorts and longer follow-ups will further show the significance and benefits of earlier line application of CAR-T therapy for MM pts.

P-137

A phase 3, two-stage, randomized study of iberdomide maintenance versus lenalidomide maintenance post autologous stem cell transplantation in newly diagnosed multiple myeloma: EXCALIBER-maintenance

Francesca Gay[1], Meletios Dimopoulos[2], Xiaojun Huang[3], Sagar Lonial[4], Karthik Ramasamy[5], Michael Amatangelo[6], Abdallah Abouihia[7], Mark Masin[7], Hina Maniar[6], Jorge Acosta[7], Paulo Maciag[6], Niels van de Donk[8]

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P-138

Online CME improves clinical decision-making in the management of patients with multiple myeloma

Victoria Harvey-Jones[1], Sanneke Koekkoek[1], Caroline Phillips[1]

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P-138

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treatment strategy for newly diagnosed MM (morphine sulfate slow release, 57%, P<.001; VRd, 19%, P<.001; daraVTd IV, 15%, P<.001; daraVTd sub-cut, 12%, P<.01; zoledronic acid, 60%, P<.001). 3. Counselling patients regarding potential outcomes and treatment-related adverse events (TrAEs) (order patient education, 25%, P<.01; order AE monitoring, 26%, P<.001). 4. Case 2 (n=335 hem/oncs) 75-yr-old man with a history of type 2 diabetes, atrial fibrillation, hypertension, and MM. Routine lab work 2 weeks ago returned abnormal; patient asked to come in to discuss the results. Significant changes observed for: 1. Ordering appropriate tests to evaluate the patient (SPEP/SIFE, 13%, P<.01; serum FLC assay, 10%, P<.05; PET-CT, 17%, P<.01; FBC, 8%, P<.05; FISH analysis, 10%, P<.05; chemistry panel, 9%, P<.05; bone marrow aspirate, 11%, P<.05; diagnosis of relapsed/refractory (R/R) MM, 34%, P<.001). 2. Selecting an appropriate treatment strategy for R/R MM (PomVd, 43%, P<.001; zoledronic acid, 51%, P<.001). 3. Counselling patients regarding potential outcomes and TrAEs (order patient education, 14%, P<.01; order AE monitoring, 15%, P<.01; at home blood sugar monitoring, 10%, P<.05) **Conclusions:** These results demonstrate the success of immersive, online VPS education that engages physicians in a practical learning experience in improving their performance in managing patients with MM.

P-139

Impact of melphalan staggered dosing prior to autologous hematopoietic cell transplantation for multiple myeloma patients

Catherine Hoang[1], Candido Chacon[1], Brendon Cornett[2], Tara Gregory[3], Danielle Smidt[1]

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P-140

Multiple myeloma in Latin America cancer registry: the MYLACRE study

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treatment strategy for newly diagnosed MM (morphine sulfate slow release, 57%, P<.001; VRd, 19%, P<.001; daraVTd IV, 15%, P<.001; daraVTd sub-cut, 12%, P<.01; zoledronic acid, 60%, P<.001). 3. Counselling patients regarding potential outcomes and treatment-related adverse events (TrAEs) (order patient education, 25%, P<.01; order AE monitoring, 26%, P<.001). 4. Case 2 (n=335 hem/oncs) 75-yr-old man with a history of type 2 diabetes, atrial fibrillation, hypertension, and MM. Routine lab work 2 weeks ago returned abnormal; patient asked to come in to discuss the results. Significant changes observed for: 1. Ordering appropriate tests to evaluate the patient (SPEP/SIFE, 13%, P<.01; serum FLC assay, 10%, P<.05; PET-CT, 17%, P<.01; FBC, 8%, P<.05; FISH analysis, 10%, P<.05; chemistry panel, 9%, P<.05; bone marrow aspirate, 11%, P<.05; diagnosis of relapsed/refractory (R/R) MM, 34%, P<.001). 2. Selecting an appropriate treatment strategy for R/R MM (PomVd, 43%, P<.001; zoledronic acid, 51%, P<.001). 3. Counselling patients regarding potential outcomes and TrAEs (order patient education, 14%, P<.01; order AE monitoring, 15%, P<.01; at home blood sugar monitoring, 10%, P<.05) **Conclusions:** These results demonstrate the success of immersive, online VPS education that engages physicians in a practical learning experience in improving their performance in managing patients with MM.

P-139

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P-140

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to profile the treatment landscape of LA MM patients. **Methods:** This was a retrospective and prospective non-interventional, multicenter study of MM patients from 5 LA countries. Patients aged ≥ 18 diagnosed with MM between January 1, 2016 and June 30, 2021 were included. Data were extracted from medical charts between August 2019 and June 2022 and a descriptive analysis was conducted. **Results:** A total of 1,029 patients from 22 reference centers were enrolled, with a median follow-up of 26.8 months. Two thirds (66.8%) had private health insurance coverage. The median age at diagnosis was 64 years and most patients were diagnosed as International Staging System (ISS) stage III (44%). End-organ damage signs and symptoms at diagnosis were reported in most of the patients, with half of them (45.2%) presenting anemia, 12.7% hypercalcemia, 22% renal disfunction and 80.2% bone lesions. Approximately 60% of the patients underwent a cytogenetic test and, of these, one-third (27%) had a cytogenetic abnormality. From the enrolled patients, 1,003 started the first line of therapy (LOT), 405 LOT2, 168 LOT3, 74 LOT4 and 20 LOT5, resulting in an attrition rate of approximately 23-34% from one LOT to the subsequent LOT. Most patients (69.9%) were eligible for stem cell transplant (SCT) upfront, but, of those, 26.8% did not receive it. The main reason was insufficient response, disease progression or death before SCT. Considering patients who underwent SCT, the majority in both private and public settings received a proteasome inhibitor (PI)-based therapy (60.6%, 40.8% respectively) and considering those who did not undergo SCT, the majority in the private setting received a PI-based therapy (58.6%), while in the public setting the majority received an immunomodulatory drug (IMiD) based therapy (53.7%). For LOT2, anti-CD38 based regimens were the most received in the private setting (31.9%) and PI-based regimens for the public setting (40.2%). The median progression-free survival (PFS) of LOT1 was 40 months, LOT2 15.9 months, LOT3 8.9 months, and later LOT 4.6 months. The median overall survival (OS) for all patients was 48.9 months. **Conclusions:** The attrition rate between subsequent LOTs is high and the pattern of treatment differs between private and public settings. The adoption of novel therapies in LA is still low compared with other regions in the world, and the unmet need is higher in earlier LOTs and for patients with no health insurance.

P-141

Response and survival outcomes of daratumumab, lenalidomide, bortezomib and dexamethasone (D-RVD) induction in transplant-eligible newly diagnosed multiple myeloma (NDMM) patients

Nisha Joseph[1], Jonathan Kaufman[1], Sagar Lonial[1], Craig Hofmeister[1], Madhav Dhodapkar[1], Vikas Gupta[1], Sara DiCamillo[1], Danielle Roberts[1], Lawrence Boise[1], Ajay Nooka[1]

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Introduction: The combination of lenalidomide, bortezomib, and dexamethasone (RVD) has been shown to be highly effective for both transplantation-eligible and -ineligible patients with newly diagnosed myeloma (NDMM). More recently, the addition of daratumumab (D) to RVd (D-RVd) in transplant-eligible NDMM patients was evaluated in the GRIFFIN trial (Voorhees et al) showing that sCR rates improved for D-RVd vs RVd. We present the largest cohort of patients consecutively treated with D-RVd induction therapy and the impact of D-RVd on long-term outcomes. **Methods:** 326 consecutive patients with newly diagnosed myeloma treated with D-RVd induction therapy from April 2018 until August 2022 were included in this analysis. Demographic and clinical characteristics and outcomes data were obtained from our institutional review board-approved myeloma database, and manual extraction. Responses and progression were evaluated per International Myeloma Working Group Uniform Response Criteria. **Results:** The cohort consisted of 181 (55.5%) males, 133 (41%) black. The median age was 64.3 (23.5-79.3) vs 59 (34.7-76.7) years, p< 0.05 for whites vs. black, respectively. 199 (65.2%) had IgG isotype, 64 (21.4%) had t(11;14), 17 (5.2%) had del 17p, 13 (4%) had t(4;14) 3 (1%) had t(14;16) and 5 (1.5%) had t(14;20). Altogether, 45 (13.8%) had high-risk disease, 52 (16%) had ISS stage 3 disease and 15 (4.6%) had R-ISS stage 3 disease. 84.6% received single agent maintenance with lenalidomide. The overall response rate was 99.7% after induction therapy [86.5% achieving a very good partial response or better (≥VGPR), 21.5% achieving complete response or better (≥CR)] and 99.3% after transplantation (95.6% achieving ≥VGPR and 42.8% achieving complete response or better (≥CR) after transplantation. The estimated 3-year progression-free survival was 91% at a median follow up of 17.1 months. This compares favorably to our historical cohort of RVD patients, where the 3-year PFS rate was 70%. The estimated 4-year overall survival was 92% at a median follow up of 17.3 months, again comparing favorably to our historical cohort of RVD patients with a 4-year OS of 79%. **Conclusions:** D-RVd is a highly effective induction regimen that delivers high quality response rates (≥VGPR) in close to 95% of patients after transplantation. In the absence of phase 3 data supporting D-RVd as induction regimen, this study provides the evidence of benefit of adding daratumumab to RVd in increasing depth of response, and provides an early glimpse of the promising PFS and OS particularly when compared to our historical cohort. This is the largest cohort of patients treated with D-RVd reported to date, and demonstrates the superiority of quadruplets in treating newly diagnosed multiple myeloma.

P-142

Stem cell collection after isatuximab or elotuzumab plus lenalidomide, bortezomib and dexamethasone in transplant-eligible multiple myeloma: single center data from the GMMG-HD6 and -HD7 trials

Joseph Kauer[1], Emma Freundt[2], Anita Schmitt[1], Niels Weinhold[1,3], Elias Mai[1,4], Carsten Müller-Tidow[1,5], Hartmut Goldschmidt[6], Marc Raab[1], Katharina Kriegsmann[1], Sandra Sauer[1]

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to profile the treatment landscape of LA MM patients. **Methods:** This was a retrospective and prospective non-interventional, multicenter study of MM patients from 5 LA countries. Patients aged ≥ 18 diagnosed with MM between January 1, 2016 and June 30, 2021 were included. Data were extracted from medical charts between August 2019 and June 2022 and a descriptive analysis was conducted. **Results:** A total of 1,029 patients from 22 reference centers were enrolled, with a median follow-up of 26.8 months. Two thirds (66.8%) had private health insurance coverage. The median age at diagnosis was 64 years and most patients were diagnosed as International Staging System (ISS) stage III (44%). End-organ damage signs and symptoms at diagnosis were reported in most of the patients, with half of them (45.2%) presenting anemia, 12.7% hypercalcemia, 22% renal disfunction and 80.2% bone lesions. Approximately 60% of the patients underwent a cytogenetic test and, of these, one-third (27%) had a cytogenetic abnormality. From the enrolled patients, 1,003 started the first line of therapy (LOT), 405 LOT2, 168 LOT3, 74 LOT4 and 20 LOT5, resulting in an attrition rate of approximately 23-34% from one LOT to the subsequent LOT. Most patients (69.9%) were eligible for stem cell transplant (SCT) upfront, but, of those, 26.8% did not receive it. The main reason was insufficient response, disease progression or death before SCT. Considering patients who underwent SCT, the majority in both private and public settings received a proteasome inhibitor (PI)-based therapy (60.6%, 40.8% respectively) and considering those who did not undergo SCT, the majority in the private setting received a PI-based therapy (58.6%), while in the public setting the majority received an immunomodulatory drug (IMiD) based therapy (53.7%). For LOT2, anti-CD38 based regimens were the most received in the private setting (31.9%) and PI-based regimens for the public setting (40.2%). The median progression-free survival (PFS) of LOT1 was 40 months, LOT2 15.9 months, LOT3 8.9 months, and later LOT 4.6 months. The median overall survival (OS) for all patients was 48.9 months. **Conclusions:** The attrition rate between subsequent LOTs is high and the pattern of treatment differs between private and public settings. The adoption of novel therapies in LA is still low compared with other regions in the world, and the unmet need is higher in earlier LOTs and for patients with no health insurance.

P-141

Response and survival outcomes of daratumumab, lenalidomide, bortezomib and dexamethasone (D-RVD) induction in transplant-eligible newly diagnosed multiple myeloma (NDMM) patients

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Introduction: The combination of lenalidomide, bortezomib, and dexamethasone (RVD) has been shown to be highly effective for both transplantation-eligible and -ineligible patients with newly diagnosed myeloma (NDMM). More recently, the addition of daratumumab (D) to RVd (D-RVd) in transplant-eligible NDMM patients was evaluated in the GRIFFIN trial (Voorhees et al) showing that sCR rates improved for D-RVd vs RVd. We present the largest cohort of patients consecutively treated with D-RVd induction therapy and the impact of D-RVd on long-term outcomes. **Methods:** 326 consecutive patients with newly diagnosed myeloma treated with D-RVd induction therapy from April 2018 until August 2022 were included in this analysis. Demographic and clinical characteristics and outcomes data were obtained from our institutional review board-approved myeloma database, and manual extraction. Responses and progression were evaluated per International Myeloma Working Group Uniform Response Criteria. **Results:** The cohort consisted of 181 (55.5%) males, 133 (41%) black. The median age was 64.3 (23.5-79.3) vs 59 (34.7-76.7) years, p< 0.05 for whites vs. black, respectively. 199 (65.2%) had IgG isotype, 64 (21.4%) had t(11;14), 17 (5.2%) had del 17p, 13 (4%) had t(4;14) 3 (1%) had t(14;16) and 5 (1.5%) had t(14;20). Altogether, 45 (13.8%) had high-risk disease, 52 (16%) had ISS stage 3 disease and 15 (4.6%) had R-ISS stage 3 disease. 84.6% received single agent maintenance with lenalidomide. The overall response rate was 99.7% after induction therapy [86.5% achieving a very good partial response or better (≥VGPR), 21.5% achieving complete response or better (≥CR)] and 99.3% after transplantation (95.6% achieving ≥VGPR and 42.8% achieving complete response or better (≥CR) after transplantation. The estimated 3-year progression-free survival was 91% at a median follow up of 17.1 months. This compares favorably to our historical cohort of RVD patients, where the 3-year PFS rate was 70%. The estimated 4-year overall survival was 92% at a median follow up of 17.3 months, again comparing favorably to our historical cohort of RVD patients with a 4-year OS of 79%. **Conclusions:** D-RVd is a highly effective induction regimen that delivers high quality response rates (≥VGPR) in close to 95% of patients after transplantation. In the absence of phase 3 data supporting D-RVd as induction regimen, this study provides the evidence of benefit of adding daratumumab to RVd in increasing depth of response, and provides an early glimpse of the promising PFS and OS particularly when compared to our historical cohort. This is the largest cohort of patients treated with D-RVd reported to date, and demonstrates the superiority of quadruplets in treating newly diagnosed multiple myeloma.

P-142

Stem cell collection after isatuximab or elotuzumab plus lenalidomide, bortezomib and dexamethasone in transplant-eligible multiple myeloma: single center data from the GMMG-HD6 and -HD7 trials

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Introduction: In transplant-eligible patients with newly diagnosed multiple myeloma (MM), induction therapy followed by high-dose chemotherapy (HDCT) and peripheral blood stem cell (PBSC) transplantation is standard-of-care. Modern triplet and quadruplet regimen are commonly used as induction therapy, but their impact on PBSC mobilization and collection outcomes remain incompletely understood. This study evaluates the impact of prolonged lenalidomide induction and isatuximab- or elotuzumab-containing quadruplet induction therapies on PBSC mobilization and collection. **Methods:** 179 transplant-eligible patients with newly diagnosed MM treated within the randomized phase III clinical trials GMMG-HD6 (NCT02495922) and GMMG-HD7 (NCT03617731) at a single academic center were included. The median age at diagnosis was 59 (range 26-71). 62% of patients were male, 65% showed IgG myeloma, 64% kappa light chain restriction, and 28% presented with high-risk cytogenetics. Patients were evaluated according to PBSC mobilization and collection parameters such as overall collection result, CD34+ cell levels in peripheral blood, leukapheresis (LP) delays and overall number of LP sessions as well as the rate of rescue mobilization with plerixafor. Patients underwent four different induction regimen: Lenalidomide, bortezomib, and dexamethasone (RVd, six 21-day cycles, n=44), isatuximab-RVd (six 21-day cycles, n=35), RVd (four 21-day cycles, n=51), or elotuzumab-RVd (four 21-day cycles, n=49). **Results:** Patients' characteristics were well balanced among groups. Collection failures, defined by the inability to collect three sufficient PBSC transplants, were rare (n=3, 2%) with no occurence in the isatuximab-RVd and elotuzumab-RVd groups. Intensified induction with six 21-day cycles of RVd in comparison to four 21-day cycles of RVd did not hamper overall numbers of collected PBSC (9.7 x10^6/kg bw, IQR 3.1, versus 10.5 x10^6/kg bw, IQR 3.9, p=0.331). Plerixafor was more commonly used after six cycles versus four cycles of RVd (16% versus 8%). No negative impact on overall PBSC collection was observed upon addition of elotuzumab to RVd (10.9 x10^6/kg bw, IQR 3.8 versus 10.5 x10^6/kg bw, IQR 3.9, p=0.915). Patients treated with isatuximab-RVd (six cycles) had overall lower numbers of collected stem cells as compared to patients receiving RVd (six cycles) induction (8.8 x10^6/kg bw, IQR 1.8 versus 9.7 x10^6/kg bw, IQR 3.1, p=0.801), without experiencing more LP delay or significantly increased numbers of LP sessions in a multivariable logistic regression analysis. Plerixafor use was more common after isatuximab plus RVd versus RVd alone (34% versus 16%). **Conclusions:** We provide the first detailed data on stem cell collection after induction with isatuximab plus RVd. These data demonstrate that stem cell collection is feasible after prolonged induction with isatuximab-RVd without collection failures. Addition of elotuzumab to RVD as well as prolonged induction with RVd did not affect stem cell yield.

P-143

Treatment access among Black and White older adults with multiple myeloma: A SEER-Medicare analysis

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Introduction: Multiple myeloma (MM) is an incurable cancer of the plasma cells that has seen incredible treatment innovation over the past two decades though not all groups have benefited equally from these improvements. This study explores trends in MM treatment access among Black and White older adults in the United States. **Methods:** Black and White older adults diagnosed with MM (2007-2017) were identified in the SEER-Medicare database. Individuals were required to have continuous Medicare Parts A and B coverage 12 months prior to and following diagnosis (or until death), and Part D coverage 12 months following diagnosis (or until death). Primary outcomes were receipt of any MM treatment (TX) within 12 months of diagnosis, and receipt of any MM care at an NCI cancer center (NCI CC) within 12 months of diagnosis (a proxy for early access to MM specialists). Patients were categorized by year of diagnosis into 3 roughly equal time periods; 2007-10, 2011-14, 2015-17. We used standardized mortality ratio weighting to standardize the distribution of age, sex, and pre-diagnosis Charlson comorbidity score across racial groups with White race as reference. Modified Poisson regression was used to estimate change (risk difference) across time periods stratified by race, and differences by race within time periods. **Results:** Our cohort consisted of 1,649 Black and 9,017 White older adults with MM. The percentage of White individuals receiving any TX increased from 62.8 to 71.0% (2011-14 vs 2007-10, RD = 8.3, [95% CI: 5.9, 10.6]) to 73.4% (2015-17 vs 2011-14, RD = 2.4 [0.2, 4.6]). The percentage of Black individuals receiving any TX increased from 56.9 to 59.4%, (2011-14 vs 2007-10, RD= 2.5, [-4.4, 9.4]) to 64.7%, (2015-17 vs 2011-14, RD = 5.3, [-1.4, 1.2]). A lower percentage of Black individuals received treatment compared with White individuals in all time periods; 2007-10: RD = 5.9 (0.3, 11.5), 2011-14: RD = 11.6 (6.9, 16.4), 2015-17: RD 8.8 (3.7, 13.9). The percentage of White individuals receiving any care at an NCI CC increased from 21.5 to 28.1% (2011-14 vs 2007-10, RD = 6.6, [4.4, 8.8]) to 34.9% (2015-17 vs 2011-14, RD = 6.8 [4.6, 9.1]). The percentage of Black individuals receiving any care at an NCI CC increased from 16.4 to 19.2%, (2011-14 vs 2007-10, RD= 2.8, [-2.3, 7.9]) to 22.1%, (2015-17 vs 2011-14, RD = 3.0, [-2.5, 8.4]). A lower percentage of Black individuals received care at NCI CC compared with White individuals in all time periods; 2007-10: RD = 5.0 (0.9, 9.1), 2011-14: RD = 8.8 (5.0, 12.6), 2015-17: RD 12.7 (8.2, 17.2). **Conclusions:** Overtime more people are enjoying access to MM TX and care at NCI CC, but these increases have not been experienced

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P-143

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by all race groups equally. Black/White disparities were noted at each time period and while the percentage of White individuals receiving TX and care at an NCI CC saw significant increases over time, Black individuals, already disadvantaged compared to White individuals, have seen more modest nonsignificant increases over time.

P-144

Busulfan plus melphalan versus high-dose melphalan as a conditioning regimen for autologous stem cell transplantation in multiple myeloma with high-risk features (KMM 2015)

Sung-Hoon Jung[1], Je-Jung Lee[2], Mihee Kim[3], Chang-Ki Min[4], Ji Yun Lee[5], Jae-Cheol Jo[6], Sung-Soo Yoon[7], Sung-Nam Lim[8], Young Rok Do[9], Kihyun Kim[10], Jae Hoon Lee[11], Kwai Han Yoo[11], Sung Hwa Bae[12], Jun Ho Yi[13], Jongheon Jung[14], Hyeon-Seok Eom[15]

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Introduction: Despite the development of effective agents for multiple myeloma (MM), managing patients with high-risk MM (HRMM) remains challenging. High-dose treatment followed by autologous stem cell transplantation (ASCT) is considered the frontline treatment for transplant-eligible patients with HRMM. This study aimed to compare the efficacy of two conditioning regimens, high-dose melphalan (HDMEL; 200 mg/m^2) and busulfan plus melphalan (BUMEL), for upfront ASCT in newly diagnosed patients with MM and high-risk features. **Methods:** This study retrospectively collected the data of patients diagnosed with MM between May 2005 and June 2021 who received ASCT with BUMEL or HDMEL conditioning from 12 institutions that participated in the KMM 2015 trial. **Results:** A total of 221 patients underwent ASCT between May 2005 and June 2021, and among them, 79 had high-risk cytogenetic abnormalities. In patients with high-risk cytogenetics, BUMEL showed a tendency toward longer overall survival (OS) and progression-free survival (PFS) compared to HDMEL (median OS: not reached vs. 53.2 months; P = 0.091; median PFS: not reached vs. 31.7 months; P = 0.062). Furthermore, multivariate analysis revealed that BUMEL was significantly associated with improved PFS (hazard ratio = 0.37, 95% confidence interval = 0.15–0.89, P = 0.026). Additionally, we compared BUMEL with HDMEL in patients with other high-risk features, such as high lactate dehydrogenase level, extramedullary disease, and poor response to frontline therapy. Notably, among patients with less than a very good partial response (VGPR) to frontline therapy, the BUMEL group had a significantly longer median PFS compared to the HDMEL group (55.1 vs. 17.3 months, respectively; P = 0.011). **Conclusions:** These findings suggest that BUMEL is an effective conditioning regimen for upfront ASCT in MM patients with high-risk cytogenetics, and it may be more suitable than HDMEL for patients with less than a VGPR to frontline therapy.

P-145

Early M protein immune reconstitution is a good prognostic marker for patients with high-risk cytogenetic multiple myeloma after autologous hematopoietic stem cell transplantation

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Introduction: The presence of transient monoclonal immunoglobulins (i.e. M-protein immune reconstitution) in serum immunofixation electrophoresis after autologous hematopoietic stem cell transplantation in patients with multiple myeloma has been reported, and patients with high-risk cytogenetics tend to have poor prognosis; the purpose of this paper is to investigate the impact of post-transplant M-protein immune reconstitution on the prognosis of patients with high-risk cytogenetic multiple myeloma **Methods:** To retrospectively analyze the clinical data of 290 newly diagnosed multiple myeloma patients from August 1, 2008 to July 31, 2021 at the First Affiliated Hospital of Sun Yat-sen University, all of whom underwent sequential autologous hematopoietic stem cell transplantation after induction therapy, and to analyze and compare the clinical characteristics and prognostic survival of patients with and without M-protein immune reconstitution **Results:** M protein immune reconstitution was observed in 25.9% (75/290 patients), the most common type of immunoglobulin was IgG-λ. The median time to obtain reconstruction was 3 months (1-38 months) and the median duration was 4 months (1-39 months) after transplantation, and there were no statistical differences in disease stage, tumor load and cytogenetics between the immune reconstituted and unreconstructed groups. The CR rate and MRD negativity were higher in the M protein immune reconstitution group (P=0.019, 85.3% vs 69.3%, P=0.014, 81.9% vs 66.5%), and although there were no statistical differences in PFS and OS between the M protein immune reconstitution group and the group without immune reconstruction, the overall median survival time was longer in the M protein immune reconstruction group (P=0.137, 80m vs 72m; P=0.800, 49m vs 33m).Among patients in the cytogenetic high-risk group, access to M protein immune reconstitution predicted better PFS and OS (P=0.011, 80m vs 31m; P=0.079, 54m vs 16m).Also in R-ISS stage III patients, PFS and OS were better in patients who obtained M protein immune reconstitution than in those who did not (P=0.008, 80m vs 20m; P=0.044, 52m vs 26m). **Conclusions:** Better prognosis in immune reconstructed patients may be associated

by all race groups equally. Black/White disparities were noted at each time period and while the percentage of White individuals receiving TX and care at an NCI CC saw significant increases over time, Black individuals, already disadvantaged compared to White individuals, have seen more modest nonsignificant increases over time.

P-144

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P-145

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Introduction: The presence of transient monoclonal immunoglobulins (i.e. M-protein immune reconstitution) in serum immunofixation electrophoresis after autologous hematopoietic stem cell transplantation in patients with multiple myeloma has been reported, and patients with high-risk cytogenetics tend to have poor prognosis; the purpose of this paper is to investigate the impact of post-transplant M-protein immune reconstitution on the prognosis of patients with high-risk cytogenetic multiple myeloma **Methods:** To retrospectively analyze the clinical data of 290 newly diagnosed multiple myeloma patients from August 1, 2008 to July 31, 2021 at the First Affiliated Hospital of Sun Yat-sen University, all of whom underwent sequential autologous hematopoietic stem cell transplantation after induction therapy, and to analyze and compare the clinical characteristics and prognostic survival of patients with and without M-protein immune reconstitution **Results:** M protein immune reconstitution was observed in 25.9% (75/290 patients), the most common type of immunoglobulin was IgG-λ. The median time to obtain reconstruction was 3 months (1-38 months) and the median duration was 4 months (1-39 months) after transplantation, and there were no statistical differences in disease stage, tumor load and cytogenetics between the immune reconstituted and unreconstructed groups. The CR rate and MRD negativity were higher in the M protein immune reconstitution group (P=0.019, 85.3% vs 69.3%, P=0.014, 81.9% vs 66.5%), and although there were no statistical differences in PFS and OS between the M protein immune reconstitution group and the group without immune reconstruction, the overall median survival time was longer in the M protein immune reconstruction group (P=0.137, 80m vs 72m; P=0.800, 49m vs 33m).Among patients in the cytogenetic high-risk group, access to M protein immune reconstitution predicted better PFS and OS (P=0.011, 80m vs 31m; P=0.079, 54m vs 16m).Also in R-ISS stage III patients, PFS and OS were better in patients who obtained M protein immune reconstitution than in those who did not (P=0.008, 80m vs 20m; P=0.044, 52m vs 26m). **Conclusions:** Better prognosis in immune reconstructed patients may be associated

by all race groups equally. Black/White disparities were noted at each time period and while the percentage of White individuals receiving TX and care at an NCI CC saw significant increases over time, Black individuals, already disadvantaged compared to White individuals, have seen more modest nonsignificant increases over time.

P-144

Busulfan plus melphalan versus high-dose melphalan as a conditioning regimen for autologous stem cell transplantation in multiple myeloma with high-risk features (KMM 2015)

Sung-Hoon Jung[1], Je-Jung Lee[2], Mihee Kim[3], Chang-Ki Min[4], Ji Yun Lee[5], Jae-Cheol Jo[6], Sung-Soo Yoon[7], Sung-Nam Lim[8], Young Rok Do[9], Kihyun Kim[10], Jae Hoon Lee[11], Kwai Han Yoo[11], Sung Hwa Bae[12], Jun Ho Yi[13], Jongheon Jung[14], Hyeon-Seok Eom[15]

[1]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Hwasun, South Korea; [2]Department of Hematology-Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, South Korea; [3]Chonnam National University Hwasun Hospital; [4]Seoul St. Mary's Hospital, Seoul, South Korea; [5]Seoul National University Bundang Hospital; [6]Ulsan University Hospital; [7]Seoul National University College of Medicine, Seoul, South Korea; [8]Inje University College of Medicine, Haeundae Paik Hospital; [9]Department of Hemato-Oncology, Keimyung University Dongsan Medical Center, Daegu, South Korea; [10]Sungkyunkwan University Samsung Medical Center, Seoul, South Korea; [11]Gachon University Gil Medical Center; [12]Daegu Catholic University Hospital; [13]Chung-ang University Hospital; [14]National Cancer Center; [15]Department of Internal Medicine, National Cancer Center of Korea, Goyang, South Korea

Introduction: Despite the development of effective agents for multiple myeloma (MM), managing patients with high-risk MM (HRMM) remains challenging. High-dose treatment followed by autologous stem cell transplantation (ASCT) is considered the frontline treatment for transplant-eligible patients with HRMM. This study aimed to compare the efficacy of two conditioning regimens, high-dose melphalan (HDMEL; 200 mg/m^2) and busulfan plus melphalan (BUMEL), for upfront ASCT in newly diagnosed patients with MM and high-risk features. **Methods:** This study retrospectively collected the data of patients diagnosed with MM between May 2005 and June 2021 who received ASCT with BUMEL or HDMEL conditioning from 12 institutions that participated in the KMM 2015 trial. **Results:** A total of 221 patients underwent ASCT between May 2005 and June 2021, and among them, 79 had high-risk cytogenetic abnormalities. In patients with high-risk cytogenetics, BUMEL showed a tendency toward longer overall survival (OS) and progression-free survival (PFS) compared to HDMEL (median OS: not reached vs. 53.2 months; P = 0.091; median PFS: not reached vs. 31.7 months; P = 0.062). Furthermore, multivariate analysis revealed that BUMEL was significantly associated with improved PFS (hazard ratio = 0.37, 95% confidence interval = 0.15–0.89, P = 0.026). Additionally, we compared BUMEL with HDMEL in patients with other high-risk features, such as high lactate dehydrogenase level, extramedullary disease, and poor response to frontline therapy. Notably, among patients with less than a very good partial response (VGPR) to frontline therapy, the BUMEL group had a significantly longer median PFS compared to the HDMEL group (55.1 vs. 17.3 months, respectively; P = 0.011). **Conclusions:** These findings suggest that BUMEL is an effective conditioning regimen for upfront ASCT in MM patients with high-risk cytogenetics, and it may be more suitable than HDMEL for patients with less than a VGPR to frontline therapy.

P-145

Early M protein immune reconstitution is a good prognostic marker for patients with high-risk cytogenetic multiple myeloma after autologous hematopoietic stem cell transplantation

Huihui Zhu[1], Juan Li[1]

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with the acquisition of a deeper response, but in high-risk patients, early acquisition of immune reconstitution may suggest a better prognosis.

P-146

MASS-4 is more suitable than MASS-3 for prognostic stratification in transplant-eligible patients with newly diagnosed multiple myeloma

Juan Li[1], Fan Yang[1]

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Introduction: In 2022, Mayo Clinic proposed the Mayo Additive Staging System (MASS), a new staging system for patients with newly diagnosed multiple myeloma (NDMM). Based on the number of risk factors (ISS III, elevated lactate dehydrogenase, 1q gain/ amplification, high-risk IgH translocations, chromosome 17 abnormalities), they were divided into the 3-tier MASS (MASS-3) (no, 1, ≥2 high-risk factors for stage I, II, III, respectively) and 4-tier MASS (MASS-4) (no, 1, 2, ≥3 high-risk factors for stage I, II, III, IV, respectively). Real-world studies have shown that MASS-3 and MASS-4 are suitable for prognostic stratification in Chinese patients with NDMM, but there is no clear evidence of their utility in transplant-eligible patients with NDMM. **Methods:** A retrospective analysis of the clinical data of 215 NDMM patients who received "induction therapy-autologous hematopoietic stem cell transplantation (ASCT)" in our center was performed. **Results:** The median progression-free survival (PFS) of MASS-3 I, II, and III was 77.7, 87.7, and 50.5 months, respectively(P=0.011), and the median overall survival (OS) was not reached, 109.6, and 69.7 months, respectively(P=0.003). The PFS and OS of patients with MASS-3 III were significantly shorter than those of stage I (P< 0.05). The median PFS of MASS-4 I, II, III, and IV was 77.7, 87.7, 52.6, and 34.5 months, respectively (P=0.004), and the median OS was not reached, 109.6, 106.0, and 40.6 months, respectively (P< 0.001). The PFS and OS of patients with MASS-4 III were significantly shorter than those of stage I (P< 0.05). The PFS of patients with MASS-4 IV was significantly shorter than that of stage I, II, or III (P < 0.001). The OS of stage IV was significantly shorter than that of stage I or II (P < 0.01), and tended to be shorter than that of III (P =0.06). In patients with single ASCT, different ages, and different induction regimens, the prognostic stratification of MASS-4 was also better than that of MASS-3. However, there was no significant difference in PFS and OS between different MASS-3 or MASS-4 stages in patients with tandem ASCT. **Conclusions:** Among transplant-eligible patients with NDMM, the prognostic stratification value of MASS-4 was better than that of MASS-3, particularly distinguishing high-risk patients with poor prognosis. Compared with single ASCT, tandem ASCT may overcome the poor prognosis of high-risk MASS patients.

P-147

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P-148

On-demand plerixafor added to high-dose cyclophosphamide and pegfilgrastim in the mobilization of patients with multiple myeloma: high effectiveness and affordable cost

Liqiong Hou[1], Juan Li[1]

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effective method as mobilization regimen, but FIL requires daily, multi-injection administration.We adopted a mobilization regimen with CTX combination pegfilgrastim (PEG) and on-demand plerixafor, allowing for a single injection given the long half-life and slow elimination of PEG. Here, we performed a real-world analysis to evaluate the efficacy and cost of high-dose CTX combination PEG and on-demand plerixafor for mobilization in MM patients. **Methods:** We retrospectively compared 340 patients whith MM mobilized between August 2008 and December 2022 using the following mobilization strategies:CTX+PEG+/-Plerixafor(n=60), CTX+ PEG (n=91), CTX+ FIL(n=169), FIL+Plerixafor(n=20). Then the stem cell mobilization and collection results of the four groups were compared **Results:** Mobilization with CTX+PEG+/-Plerixafor resulted in a significantly higher total CD34+ cells collected (8.81×10^6/kg) compared to patients mobilized with other mobilization regimens: CTX+PEG(5.47×10^6/kg; p<0.001), CTX+FIL (4.65×10^6/kg; p<0.001), FIL+Plerixafor(2.73×10^6/kg; p<0.001). Day1+Day 2 CD34+ cells collected were higher in CTX+PEG+/- Plerixafor group too.(CTX+PEG+/- Plerixafor, 7.87×10^6/kg vs. CTX+PEG, 4.96×10^6/kg vs. CTX+ FIL, 3.92×10^6/kg vs FIL+Plerixafor, 2.425×10^6/kg) (p<0.001).The percentage of patients who achieved $>6\times10^6$/kg in CTX+PEG+/- Plerixafor group are significantly higher in CTX+PEG+/- Plerixafor group (74.6%) than other mobilization regimens: CTX+ PEG (44.9%; p<0.001), CTX+FIL (37.3%; p<0.001) , FIL+Plerixafor (15%; p<0.00) . Apheresis sessions were fewer in CTX+PEG+/- Plerixafor group (CTX+PEG+/- Plerixafor 2 vs CTX+PEG 3 vs CTX+FIL 3 vs FIL+Plerixafor 4) (p<0.001). Patients proceeded to ASCT with a mean of 2.94 (2.25, 4.77) $\times10^6$/kg CD34+cell infused for CTX+PEG+/- Plerixafor, 2.94 (2.37, 4.24) infused for CTX+PEG, 2.61 (2.31, 2.88) infused for FIL+Plerixafor, 3.17 (2.11, 4.90) infused for CTX+PEG (p=0.057). The median time to neutrophil and platelet engraftment not different in the four groups. Total costs of a mobilizing strategy using CTX+PEG+/- Plerixafor was significant lower ($5670.64) compared to G-CSF+Plerixafor group($11098.61), and significant higher than CTX+PEG group ($3842.23)and CTX+G-CSF group($3727.82) (p<0.001) . The incidence of neutropenic fever not different in the CTX+PEG+/-Plerixafor group(4%), CTX+PEG group (10%) and CTX+ FIL group (18%) (p=0.051). There was no patients suffered with neutropenic fever in FIL+Plerixafor **Conclusions:** Given higher rates of successful mobilization, affordable cost and toxicity, on-demand plerixafor added to high-dose CTX and PEG may be preferable in myeloma patients.

P-149

Follow-up of transplant-eligible multiple myeloma received Busulfan-based conditioing versus high-dose melphalan

Sung-Nam Lim[1], Beyong-Sok Sohn[2]

[1]Inje University College of Medicine, Haeundae Paik Hospital;
[2]Sanggye Paik Hospital, Inje University College of Medicine

Introduction: We previously reported that there was no difference in PFS between the two groups receiving conditioning using busulfan-based and high-dose melphalan. These results showed that busulfan-based conditioning has high efficacy with manageable adverse events. So, we followed up on the previously published data and conducted additional analyses focusing on biochemical and clinical relapse-related events. This retrospective study was performed to investigate the effectiveness and safety of busulfan, cyclophosphamide, and etoposide (BuCyE) versus high-dose melphalan, followed by ASCT. **Methods:** A total of 35 patients who had been treated with remission induction for bortezomib, thalidomide, and dexamethasone (VTD) were enrolled between March 2016 and September 2021. The median age of enrolled patients was 57 years, ranging from 47 to 67 years. The conditioning regimens were as follows, the busulfan-based regimen was composed of busulfan 3.2 mg/kg from days -7 to days -5, etoposide 200 mg/m^2 from days -5 to days -4, cyclophosphamide 50 mg/m^2 from days -3 to days -2 and HEMEL conditioning regimen consisted of melphalan from 140 mg/m^2 to 200 mg/m^2. **Results:** Revised international staging system (R-ISS) was shown as follows; stage I with 0 in BuCyE vs. 27.2% in HD-MEL, stage II with 84.6% in BuCyE vs. 68.1% in HD-MEL, and 15.4% in BuCyE vs. 4.5%, respectively. The overall response rate before ASCT was 100% in both groups, including 76.9% in BuCyE and 63.6% in HDMEL with more than very good partial response, and 30.8% in BuCyE versus 40.9% in HDMEL with complete response, respectively. The median follow-up for the group was 38 months. The 3-year progression-free survival (PFS) was 51.2% for the HDMEL group versus 61.5% for the BuCyE group. PFS was analyzed by dividing it into biochemical relapse and clinical relapse. When disease progression is limited to clinical relapse, the median PFS was 56.8 months in HDMEL (95% CI, 26.1 to 87.4 months) and 38.3 months in BuCyE (95% CI, 27.9 to 48.6 months) (P=0.611). If an event of PFS contained both biochemical relapse and clinical relapse the median PFS was 31.3 months in HDMEL (95% CI, 26.8 to 62.8 months) and 38.3 months in BuCyE (95% CI, 27.9 to 48.6 months) (P=0.877). Five-year overall survival rate was 76.1% in HDMEL versus 100% in BuCyE (P=0.168). The average time from ASCT to leukocyte recovery (≥ 1,000/mm^3 of absolute neutrophil count) and platelet recovery (≥50,000/mm^3 of platelet count) is as follows: 11 days in HDMEL versus 12 days in BuCyE (P=0.101) and 39 days in HDMEL versus 34 days in BuCyE (P=0.840), respectively. Among the patients who did not achieve complete remission (CR) before ASCT, the proportion of patients who achieved CR after ASCT was 46% (6/13) in HDMEL versus 50% (4/8) in BuCyE. **Conclusions:** Our results of the follow-up study showed that a busulfan-based conditioning regimen of BuCyE could be expected to prolong PFS and survival through secondary treatment compared to the high-dose melphalan conditioning regimen.

P-150

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P-150

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P-150

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Introduction: Attaining undetectable minimal residual disease (MRD) is the current therapeutic goal for multiple myeloma (MM). But there is a current lack of data regarding the clinical benefit of autologous stem cell transplantation (ASCT) for myeloma patients achieving early MRD-negative status after induction treatment, in addition to the interaction of longitudinal MRD status with ASCT. **Methods:** The present study included 407 transplant-eligible MM patients with available MRD status from the National Longitudinal Cohort of Hematological Diseases in China (NCT04645199), of whom 147 (34.4%) achieved early undetectable MRD and 182 (44.7%) received ASCT. **Results:** Early MRD-negative status was associated with a lower risk of disease progression (HR=0.447; 95%CI, 0.333-0.600; P< 0.001) and death (HR=0.473; 95%CI, 0.320-0.700; P< 0.001). Of note, patients who achieved undetectable MRD early still benefitted from ASCT, with a remarkable improvement in the median MRD-negative duration (33.5 to 58.0 months, P< 0.001), progression-free survival (PFS; 46.0 to 88.3 months, P< 0.001), and overall survival (OS; 76.4 months to not reached, P=0.003). These clinical benefits were more pronounced in patients with aggressive features (high-risk cytogenetic abnormalities or high tumor burden) other than in standard-risk patients. Similar results were observed in patients with detectable MRD after induction treatment. Additionally, we identified four MRD-status transformation patterns following ASCT, which were strongly correlated with diverse survival outcomes (P< 0.001). **Conclusions:** These findings emphasize the crucial role of ASCT in myeloma patients regardless of early MRD status, especially for high-risk patients. Longitudinal MRD conversion after ASCT also has a significant impact on risk stratification.

P-151

Demographic and clinical characteristics of multiple myeloma patients in a tertiary cancer institute of India

Dhyey Rajkumar Mishra[1], Aditya Ranjithkumar Nair[1], Jash Yogesh Shah[1], Bhausaheb Bagal[2], Lingaraj Nayak[2], Hasmukh Jain[2], Saswata Saha[2], Alok Shetty[2], Nishant Jindal[2], Sumeet Mirgh[2], Anant Gokarn[2], Sachin Punatar[2], Prashant Tembhare[3], Dhanlaxmi Shetty[4], Vasundhara Patil[5], Manju Sengar[2], Navin Khattry[6]

[1]Seth GS Medical College and Kem Hospital, Mumbai; [2]Department of Medical Oncology, Tata Memorial Centre; [3]Department of Hemato-pathology, ACTREC, Tata Memorial Centre; [4]Department of Cancer Cytogenetics, Avdanced Centre for Training, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Kharghar, Navi Mumbai, India; [5]Department of Radiodiagnosis, Tata Memorial Centre; [6]Advanced Centre for Training, Research and Education in Cancer (ACTREC), Tata Memorial Centre

Introduction: Multiple myeloma is a relapsing remitting type of hematological cancer with no long term cure and heterogeneous outcomes. Presenting features impacts outcomes and varies across different ethnic and geographic regions. Differences with respect to incidence and outcomes in the African American population are well documented. Earlier studies from India have reported young age, late stages of the diseases and high incidence of myeloma defining events. We looked at consecutive cohort of patients with newly diagnosed myeloma over a year at a tertiary cancer institute to see the demographic and presenting characteristics. **Methods:** We did a retrospective analysis of all consecutive newly diagnosed patients with Multiple myeloma between January 2017 and December 2017. Data was collected from the electronic medical record. SPSSV22 was used for descriptive analysis. **Results:** A total of 254 newly diagnosed patients were registered at our hospital in the specified study period. Median age of study population was 57.2 years (range 26 to 79) and 168 (66.1%) were male. Comorbidities were reported in 109(42.9%) patients, mainly hypertension in 66 (60%),diabetes in 43 (39.4%). ECOG performance status was 2 or more in 143 (56.4%) patients. Most common symptom at diagnosis was bone pain, mostly backache, seen in 61.4% patients and 11 (4.4%) patients presented with paraparesis due to cord compression. Bone lesions were detected on imaging in 220 (86.6%), renal involvement in 74 (29.4%), anemia in 142 (55.9%) and hypercalcemia in 42 (16.5%). Fifteen (6%) presented with severe renal failure requiring dialysis. Median Hb was 9.6gm/dl (range 2.8 to 15.8), Median calcium was 9.45mg/dl (range 5.5 to 16.18) and median creatinine was 1.2mg/dl (range 0.6 to 21). The Imaging modality used was skeleton survey in 25.1%, low dose CT in 18.1%, MRI in 38.7% and PET-CT in 18.1%. 62(24.4%) patients had evidence of paramedullary soft tissue plasmacytoma. ISS stage was I in only 44 (17.7%) while ISS-III was present in 115 (46.4%) patients. LDH was elevated in 96 (37.8%) patients. Cytogenetics revealed hyperdiploidy in 98 out of 234 tested for same (38.5%) and high risk IgH translocation (t(4;14), (14;16), (14;20)) was reported in 42 (17.9%) patients while 1q gain was present in 30 (12.7%) patients. 17p/TP53 del was detected in 7(2.8%) patients. R-ISS was available for 199 patients with 19 (9.5%),134 (67.3%), and 46 (23.1%) having R-ISS I, II and III respectively. **Conclusions:** Our study highlights earlier age of presentation, higher incidence of end organ damage due to myeloma. A low incidence of high risk cytogenetic abnormalities was detected which resulted in a maximum number of patients in R-ISS II category. Though limited by retrospective nature and patient population from a tertiary care institute, the study suggests the need for prospective registry studies to document the potential difference in presentation among Indian patients and need for awareness about myeloma for early diagnosis.

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P-151

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Introduction: Multiple myeloma is a relapsing remitting type of hematological cancer with no long term cure and heterogeneous outcomes. Presenting features impacts outcomes and varies across different ethnic and geographic regions. Differences with respect to incidence and outcomes in the African American population are well documented. Earlier studies from India have reported young age, late stages of the diseases and high incidence of myeloma defining events. We looked at consecutive cohort of patients with newly diagnosed myeloma over a year at a tertiary cancer institute to see the demographic and presenting characteristics. **Methods:** We did a retrospective analysis of all consecutive newly diagnosed patients with Multiple myeloma between January 2017 and December 2017. Data was collected from the electronic medical record. SPSSV22 was used for descriptive analysis. **Results:** A total of 254 newly diagnosed patients were registered at our hospital in the specified study period. Median age of study population was 57.2 years (range 26 to 79) and 168 (66.1%) were male. Comorbidities were reported in 109(42.9%) patients, mainly hypertension in 66 (60%),diabetes in 43 (39.4%). ECOG performance status was 2 or more in 143 (56.4%) patients. Most common symptom at diagnosis was bone pain, mostly backache, seen in 61.4% patients and 11 (4.4%) patients presented with paraparesis due to cord compression. Bone lesions were detected on imaging in 220 (86.6%), renal involvement in 74 (29.4%), anemia in 142 (55.9%) and hypercalcemia in 42 (16.5%). Fifteen (6%) presented with severe renal failure requiring dialysis. Median Hb was 9.6gm/dl (range 2.8 to 15.8), Median calcium was 9.45mg/dl (range 5.5 to 16.18) and median creatinine was 1.2mg/dl (range 0.6 to 21). The Imaging modality used was skeleton survey in 25.1%, low dose CT in 18.1%, MRI in 38.7% and PET-CT in 18.1%. 62(24.4%) patients had evidence of paramedullary soft tissue plasmacytoma. ISS stage was I in only 44 (17.7%) while ISS-III was present in 115 (46.4%) patients. LDH was elevated in 96 (37.8%) patients. Cytogenetics revealed hyperdiploidy in 98 out of 234 tested for same (38.5%) and high risk IgH translocation (t(4;14), (14;16), (14;20)) was reported in 42 (17.9%) patients while 1q gain was present in 30 (12.7%) patients. 17p/TP53 del was detected in 7(2.8%) patients. R-ISS was available for 199 patients with 19 (9.5%),134 (67.3%), and 46 (23.1%) having R-ISS I, II and III respectively. **Conclusions:** Our study highlights earlier age of presentation, higher incidence of end organ damage due to myeloma. A low incidence of high risk cytogenetic abnormalities was detected which resulted in a maximum number of patients in R-ISS II category. Though limited by retrospective nature and patient population from a tertiary care institute, the study suggests the need for prospective registry studies to document the potential difference in presentation among Indian patients and need for awareness about myeloma for early diagnosis.

P-152

Attrition rates in multiple myeloma and factors influencing patient dropouts at a tertiary referral center in India

Aditya Ranjithkumar Nair[1], Jash Yogesh Shah[1], Dhyey Rajkumar Mishra[1], Bhausaheb Bagal[2], Hasmukh Jain[2], Lingaraj Nayak[2], Prashant Tembhare[3], Saswata Saha[4], Alok Shetty[2], Anant Gokarn[2], Sachin Punatar[2], Dhanlaxmi Shetty[5], Sumeet Mirgh[2], Nishant Jindal[2], Vasundhara Patil[6], Manju Sengar[2], Navin Khattry[7]

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Introduction: Because of its relapsing-remitting nature and no long-term cure, patients with multiple myeloma require extended therapy with chemotherapy, novel agents, monoclonal antibodies, and autologous stem cell transplants (ASCT) for optimal outcomes. Attrition during treatment can negatively impact long-term outcomes and factors influencing the same may be important to focus on to achieve optimal patient outcomes. This study aims to examine attrition rates and the factors influencing them. **Methods:** This retrospective study analyzed data from 224 newly diagnosed patients of multiple myeloma from January 2017 to December 2017 at TMH, Mumbai. The patients included had received or were started on at least one line of therapy. The patient factors such as age, co-morbidities, clinical and laboratory evaluations were recorded along with the lines of therapy (LOTs) received, best response, and therapies received including ASCT. Factors predicting attrition were analyzed using a chi-squared test in two groups using SPSS version 22. **Results:** Among the newly diagnosed patients during the study period, the median age was 57 years, with 67.1 % being male. The most common 1st line therapy given was Bortezomib, cyclophosphamide, and dexamethasone combination (76.4% of patients). The attrition rates among the patients were 28.6% for the second LOT, 33.8 % for the 3rd LOT, and 45.3% for the subsequent LOTs. Among the people who dropped out for the second LOT, only 3% of patients had received ASCT, 18.8% of patients had received maintenance post 1st LOT, 2% had associated co-morbidities, 37.5% had renal dysfunction, 46.9% patients were ISS stage III at diagnosis and 28.1% patients had high-risk cytogenetics at presentation. In the group who received second LOT or higher, 11.2% of the patients received ASCT, 27.3 % had received maintenance post 1st LOT, 68.3% had received Radiotherapy, 34.2 % had associated co-morbidities, renal dysfunction was present in 25.5% of the patients, 46% of the patients were ISS stage III at diagnosis and 25.5% patients had high-risk cytogenetics at presentation. Among the factor analyzed, doublet therapy, ECOG scores of 2 or more, and having Del17p at presentation showed a significantly higher likelihood of attrition (p-value of 0.042, 0.011, and 0.014 respectively). The median Overall Survival (OS) was 3.9 years (95% Confidence Interval 3.3 years – 4.6 years). The median Overall Survival (OS) for people who dropped out after first-line of therapy was 1 year (95% Confidence Interval 0.6 years – 1.5 years) compared to an OS of 5.6 years (95% Confidence Interval 5.1 years – 6.0 years) in patients who did receive second-line therapy. **Conclusions:** Our study shows a significant proportion of patients did not receive subsequent lines of therapy in our clinical setting and have inferior survival. Most effective therapies should be used in earlier lines to benefit patients from all available treatment modalities.

P-153

Maintenance therapy with carfilzomib, pomalidomide and dexamethasone (KPd) in high-risk myeloma patients (pts): a Phase 2 study with a safety run-in

Ajay Nooka[1], Nisha Joseph[1], Madhav Dhodapkar[1], Craig Hofmeister[1], Vikas Gupta[1], Joel Andrews[1], Charise Gleason[1], Bryan James Burton[1], Manali Rupji[1], Ian McFadden[2], Rani Najdi[2], Lawrence Boise[1], Jonathan Kaufman[1], Sagar Lonial[1]

[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]Amgen

Introduction: High-risk pts derive survival benefit from combination maintenance (PI and IMiD) strategies. We have evaluated the safety and efficacy of the next generation PI (carfilzomib) and IMiD (pomalidomide) in combination with dexamethasone in high-risk myeloma (NCT03756896) **Methods:** Newly diagnosed high-risk myeloma pts that have achieved ≥PR post-ASCT were included. High-risk myeloma was defined by the presence of t(4;14) in 31%, t(14;16) in 17.2%, del17p in 58.6% pts by FISH or CTG or presence of ≥20% circulating cells (pPCL) in 6.9%. Double-hit myeloma (as defined by presence of ≥2 high-risk cytogenetic abnormalities including gain of 1q) was seen in 58.6% of pts. Each cycle is 28 days. Carfilzomib 20/56 mg/m^2 IV was given on days 1,8,15 and pomalidomide 2 mg PO on days 1 to 21 and dexamethasone 40 mg PO was administered on days of carfilzomib. Statistical analysis was conducted using SAS Version 9.4. **Results:** After the safety run in the first 3 pts, 26 additional pts were enrolled. Median age was 60 years (range, 46–75); 58.6% male and 58.6% black. At diagnosis, 65.5% had RISS stage 3 disease. 54.5% of whites and 64.7% of blacks had double-hit disease. Median time from diagnosis and from transplant to study entry was 9.3 (range, 6.08-12.42) and 2.89 (range, 2-8.51) months, respectively. At study entry, ≥CR and ≥VGPR rates were 24.1% and 68.9%, respectively, which deepened to 89.7% and 100% while on study. The median time to best response was 1.84 months (range, 0-13.34). Of the 15 pts with available MRD data, MRD (10-5) and (10-6) were achieved in 86.7% and 66.7%, respectively. After a median follow-up of 30.5 months, 48 month PFS was 54% and 48 month OS was 67%. Interestingly, all pts that have progressed and/or died had double-hit disease expect 1 patient. There was no PFS or OS difference by RISS. At data cut-off as of May 1st 2023, 27.6% of pts were still receiving treatment; most common reason for permanent

P-152

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P-153

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treatment discontinuation was progressive disease (34.5%). Among the 6 pt deaths, the most common cause of death was progressive disease (83.3%). Most common hematological treatment-emergent adverse events (TEAEs) reported in the cohort included neutropenia [55.2% (Grade 3/4: 55.2%)], anemia [13.8% (Grade 3/4: 0%)] and thrombocytopenia [10.3% (Grade 3/4: 3.4%)]. Non-hematological TEAEs include hypophosphatemia [69% (Grade 3/4: 27.6%)], muscle cramps [38.8% (Grade 3/4: 3.4%)], hypomagnesemia [27.5% (Grade 3/4: 0%)], head ache [24.1% (Grade 3/4: 3.42%)], agitation [20.7% (Grade 3/4: 0%)] and acneiform rash [(20.7% (Grade 3/4: 0%)]. The TEAEs of interest included cardiac [13.8% (Grade 3/4: 3.4%)], cataracts [17.2% (Grade 3/4: 17.2%)] and CVA [3.4% (Grade 3/4: 3.4%)] **Conclusions:** In pts with high-risk myeloma, KPd combination maintenance is safe, well-tolerated and efficacious. Presence of double-hit disease is a predictor for progression. These results support further exploration of combination maintenance strategies among high-risk pts.

P-154

Biomarker utility of circRNAs in multiple myeloma: the exemplary cases of ciRS-7 and circCCT3 as surrogate prognostic molecular biomarkers combined with the R-ISS staging system

Maria Papatsirou[1], Ioannis Ntanasis-Stathopoulos[2], Paraskevi Karousi[1], Panagiotis Malandrakis[2], Despina Fotiou[2], Christine-Ivy Liacos[1], Maria Gavriatopoulou[1], Efstathios Kastritis[2], Andreas Scorilas[1], Meletios Dimopoulos[1], Christos Kontos[1], Evangelos Terpos[2]

[1]National and Kapodistrian University of Athens; [2]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Greece

Introduction: Circular RNAs (circRNAs) are a non-coding RNA type with potential as molecular biomarkers in multiple myeloma (MM). Recently, ciRS-7 was found to be downregulated in MM patients' cells that have acquired resistance to therapy, and circCCT3 has been linked to MM progression. Our goal was to study the expression of these circRNAs in MM, smoldering myeloma (SMM), and monoclonal gammopathy of undetermined significance (MGUS), and to evaluate their clinical significance. **Methods:** 175 patients with plasma cell dyscrasias provided sample. All bone marrow aspirates were immediately processed for CD138+ selection of plasma cells. For the classification of MM patients, the ISS and revised ISS (R-ISS) staging methods were used. L-363, H929, and U266 MM cell lines were also propagated. Total RNA was extracted from the samples and cell lines before reverse transcription and pre-amplification of ciRS-7, circCCT3, and GAPDH (reference gene). Then, utilizing divergent PCR primers, an in-house methodology for the quantification of circRNAs by nested real-time qPCR was developed. The expression of ciRS-7 and circCCT3 was quantified in relative quantification units (RQU). **Results:** The study included 110 newly diagnosed MM patients, 35 with SMM, and 30 with MGUS. The median age of all patients at diagnosis was 70 years; 106 (60.6%) cases were male, while 69 (39.4%) were female. Furthermore, 23 (20.9%) of MM patients were in R-ISS stage I, 62 (56.4%) in R-ISS stage II, and 25 (22.7%) in R-ISS stage III. The intracellular levels of ciRS-7 were significantly different among the 3 patient subgroups (median RQU: 0.40 for MM vs. 1.74 for SMM vs. 2.79for MGUS; P< 0.001), while circCCT3 was upregulated in MM compared to SMM patients (median value: 16.24 RQU in MM vs. 3.07 RQU in SMM; P=0.022). Regarding the survival analysis, ciRS-7 and circCCT3 seem to have opposite effects on the overall (OS) and progression-free survival (PFS) of MM patients. Patients with high levels of ciRS-7 have lower OS (P=0.008) and PFS (P=0.046) probabilities. In contrast, MM patients with high circCCT3 expression had greater OS time intervals (P=0.006); this favorable prognostic significance extends to PFS (P=0.015) as well. Bootstrap multivariate Cox regression analysis showed that the prognostic value of ciRS-7 and circCCT3 expression is independent of R-ISS stage and age of MM patients, both regarding OS (HR=3.69, BCa 95% CI=1.52-14.26, bootstrap P=0.004 for ciRS-7, HR=0.23, BCa 95% CI=0.043-0.57, bootstrap P=0.003 for circCCT3) and PFS (HR=2.01, BCa 95% CI=1.07-3.93, bootstrap P=0.022 for ciRS-7, HR=0.41, BCa 95% CI=0.21-0.74, bootstrap P=0.004 for circCCT3). **Conclusions:** Our study revealed that ciRS-7 and circCCT3 levels differ significantly between patients with MM, SMM, and MGUS. Moreover, both circRNAs have a prognostic value independent of R-ISS staging and age of MM patients; these molecules may be able to serve as additional prognostic biomarkers in MM, integrated with R-ISS.

P-155

Comparative analysis of outcomes in patients with CRAB versus SLiM criteria at diagnosis of multiple myeloma

Benjamin Patrick[1], Farid Azadian[2], Hyra S. Sapru[2], Christopher Cipkar[2], Hira Mian[3], Arleigh McCurdy[4], Alissa Visram[2]

[1]Ottawa Hospital Research Institute; [2]The Ottawa Hospital; [3]McMaster University, Hamilton, Ontario, Canada; [4]University of Ottawa

Introduction: In 2014 the International Myeloma Working Group (IMWG) redefined the multiple myeloma (MM) diagnostic criteria to include ultra-high risk smoldering MM patients (those with "SLiM" criteria of bone marrow plasma cell burden (BM PC) >60%, >1 focal lesion on MRI, or a free light chain (FLC) ratio ≥100 with involved FLC >100 mg/L). However, there is a paucity of data to examine the real-world health outcomes of patients initially presenting with end-organ damage ("CRAB": hypercalcemia, anemia, renal failure, or osteolytic bone lesions) versus SLiM criteria. Therefore, this study aimed to compare the progression-free survival (PFS) and overall survival (OS) between patients with only SLiM versus CRAB criteria at MM diagnosis. **Methods:** This retrospective study included patients diagnosed with MM between January 2016 to December 2022 at the Ottawa Hospital. Time to event analyses using the Kaplan-Meier method were used to evaluate the median PFS (primary endpoint) and median OS (secondary endpoint), defined from the time of initiating first line therapy for MM. Overall

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P-154

Biomarker utility of circRNAs in multiple myeloma: the exemplary cases of ciRS-7 and circCCT3 as surrogate prognostic molecular biomarkers combined with the R-ISS staging system

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Introduction: Circular RNAs (circRNAs) are a non-coding RNA type with potential as molecular biomarkers in multiple myeloma (MM). Recently, ciRS-7 was found to be downregulated in MM patients' cells that have acquired resistance to therapy, and circCCT3 has been linked to MM progression. Our goal was to study the expression of these circRNAs in MM, smoldering myeloma (SMM), and monoclonal gammopathy of undetermined significance (MGUS), and to evaluate their clinical significance. **Methods:** 175 patients with plasma cell dyscrasias provided sample. All bone marrow aspirates were immediately processed for CD138+ selection of plasma cells. For the classification of MM patients, the ISS and revised ISS (R-ISS) staging methods were used. L-363, H929, and U266 MM cell lines were also propagated. Total RNA was extracted from the samples and cell lines before reverse transcription and pre-amplification of ciRS-7, circCCT3, and GAPDH (reference gene). Then, utilizing divergent PCR primers, an in-house methodology for the quantification of circRNAs by nested real-time qPCR was developed. The expression of ciRS-7 and circCCT3 was quantified in relative quantification units (RQU). **Results:** The study included 110 newly diagnosed MM patients, 35 with SMM, and 30 with MGUS. The median age of all patients at diagnosis was 70 years; 106 (60.6%) cases were male, while 69 (39.4%) were female. Furthermore, 23 (20.9%) of MM patients were in R-ISS stage I, 62 (56.4%) in R-ISS stage II, and 25 (22.7%) in R-ISS stage III. The intracellular levels of ciRS-7 were significantly different among the 3 patient subgroups (median RQU: 0.40 for MM vs. 1.74 for SMM vs. 2.79for MGUS; P< 0.001), while circCCT3 was upregulated in MM compared to SMM patients (median value: 16.24 RQU in MM vs. 3.07 RQU in SMM; P=0.022). Regarding the survival analysis, ciRS-7 and circCCT3 seem to have opposite effects on the overall (OS) and progression-free survival (PFS) of MM patients. Patients with high levels of ciRS-7 have lower OS (P=0.008) and PFS (P=0.046) probabilities. In contrast, MM patients with high circCCT3 expression had greater OS time intervals (P=0.006); this favorable prognostic significance extends to PFS (P=0.015) as well. Bootstrap multivariate Cox regression analysis showed that the prognostic value of ciRS-7 and circCCT3 expression is independent of R-ISS stage and age of MM patients, both regarding OS (HR=3.69, BCa 95% CI=1.52-14.26, bootstrap P=0.004 for ciRS-7, HR=0.23, BCa 95% CI=0.043-0.57, bootstrap P=0.003 for circCCT3) and PFS (HR=2.01, BCa 95% CI=1.07-3.93, bootstrap P=0.022 for ciRS-7, HR=0.41, BCa 95% CI=0.21-0.74, bootstrap P=0.004 for circCCT3). **Conclusions:** Our study revealed that ciRS-7 and circCCT3 levels differ significantly between patients with MM, SMM, and MGUS. Moreover, both circRNAs have a prognostic value independent of R-ISS staging and age of MM patients; these molecules may be able to serve as additional prognostic biomarkers in MM, integrated with R-ISS.

P-155

Comparative analysis of outcomes in patients with CRAB versus SLiM criteria at diagnosis of multiple myeloma

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[1]Ottawa Hospital Research Institute; [2]The Ottawa Hospital; [3]McMaster University, Hamilton, Ontario, Canada; [4]University of Ottawa

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response rate (ORR) was defined as achieving a partial response or better. Nonparametric methods were used to compare baseline demographic and treatment characteristics of SLiM versus CRAB patients. **Results:** Overall, 617 MM patients were included in the study (49 [8%] with SLiM MM and 567 [92%] with CRAB MM). Among patients with CRAB MM, the most common presentation was osteolytic lesions (n=340, 60%), anemia (n=269, 47%), renal failure (n=118, 21%), then hypercalcemia (n=63, 11%), as defined by the IMWG (Rajkumar et al. Lancet Oncol. 2014). Among SLiM MM patients, the most common treatment indications were BM PC >60% (n=21, 42.9%), FLC ratio ≥100 (n=13, 26.5%), followed by focal lesions on MRI (n=13, 26.5%). SLiM versus CRAB MM patients had similar ages at diagnosis (median age 67.3 versus 67.5 years, respectively, p=0.889) and similar proportions of patients with ISS stage 3 disease at diagnosis (33% versus 26.5%, respectively, p=0.076). Treatment of SLiM versus CRAB patients was similar; immunomodulatory drugs or proteosome inhibitors were used in first line treatment in 90% versus 92% of patients (p=0.578), and 49% versus 44% of patients received an upfront transplant (p=0.553). SLiM versus CRAB MM patients had a similar PFS (median PFS 36.9 versus 31.8 months, respectively, p=0.365) and ORR (89% in both groups, p=0.964). However, there was a trend towards longer OS among patients presenting with SLiM versus CRAB MM (median PFS 99.5 versus 66.7 months, respectively, p=0.070). **Conclusions:** Despite similar baseline demographics and treatments, we found a trend towards improved survival among patients treated for SLiM MM. Further work is needed to identify whether survival benefits are due to persistence of less resistant clones leading to longer PFS at relapse. However, these real-world data support the current practice of early intervention in patients with SLiM MM.

P-156

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Introduction: The association of lenalidomide to bortezomib and dexamethasone (VRd) as induction therapy (IT) in newly diagnosed multiple myeloma (NDMM) patients (pts) eligible for autologous stem-cell transplantation (ASCT) has demonstrated excellent response rates and survival outcomes with manageable toxicities. Urgent treatment is often required in this setting and lenalidomide may not be immediately available for upfront use. **Methods:** Single center retrospective study, including NDMM pts treated between Jan/2018-Jun/2022, who received IT with VRd, using a sequential regimen (sVRd) (bi-weekly Vd for 1-2 cycles followed by association of lenalidomide in the remaining cycles) or a 28-day VRd regimen upfront (uVRd), for 6 cycles. This study aims to evaluate clinical characteristics, efficacy, toxicities and survival outcomes with VRd and to compare the sVRd versus uVRd. High risk cytogenetic abnormalities (HRCAs) defined by the Revised-International Staging System (R-ISS): del17p, t(4;14) and/or t(14;16). CRAB criteria and response evaluation according to the IMWG criteria. Toxicities graded according to CTCAE v5.0. **Results:** 62 pts; median age of 62.5 years (range 42-70); 53.2% male. Clinical characteristics at diagnosis: 80.6% lytic bone lesions, 43.5% anemia, 25.8% kidney failure and 9.7% hypercalcemia. 10% had HRCAs and 38% amp1q21 (FISH available in 79%). ISS stage III present in 37.3% and R-ISS stage III in 10.6%. All pts were treated with VRd (median 8 cycles), of which 66.1% (n=41) received sVRd (group 1) and 32.3% (n=20) received uVRd (group 2). 58.1% underwent single ASCT, 3.2% tandem ASCT and 9.7% salvage-ASCT (after ≥2nd line therapy). 77.3% of ASCT pts received maintenance therapy (76.5% including lenalidomide). 69.4% experienced grade ≥2 treatment-related toxicities: 32.3% peripheral neuropathy, 30.6% infection, 17.7% hematologic toxicity, 9.7% lenalidomide-related rash and 4.8% thrombotic events. Overall response rate at the end of IT was 85.5% (complete response 40.3%; very good partial response 30.6%; partial response [PR] 14.5%), with no differences between groups. 14.5% of the pts had treatment failure (< PR). At median follow-up (MFU) of 22.0 months (mo), progression-free survival (PFS) was 77.7% and overall survival (OS) 85.4%. Median PFS was 52.8 mo (95% CI 33.55-71.98) and median OS was not reached. There were no differences between groups in PFS (at MFU: gr1 82.7% vs. gr2 75%; p=0.783) or OS (at MFU: gr1 87.3% vs. gr2 89.7%; p=0.736). **Conclusions:** The use of VRd as 1st line therapy has shown great efficacy in this real-word population, with outcomes consistent with recent published data. Our results also prove non-inferiority of a sequential strategy versus the use of a triplet-regimen upfront. This treatment approach may benefit pts requiring urgent treatment (e.g. kidney failure) or with poor performance-status at diagnosis. Furthermore, it can be useful to test disease sensitivity to different treatment classes.

P-157

How public policies have improved the overall survival of transplant eligible newly diagnosed multiple myeloma patients in the Chilean public health system

Patricia Graffigna[1], Moises Russo[2], Claudia Gajardo[3], Daniela Zambrano[3], Verónica Lizama[3], Macarena Roa[3], Karen Lopez[3], Gabriela Espinoza[3], Ximena Valladares[3], Camila Peña[3]

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Introduction: In Chile, particularly in the public system, treatment of patients with transplant eligible NDMM has evolved, being divided into 4 treatment periods endorsed and financed by the Ministry of Health, since 2000. The main aim of this study was to evaluate the overall survival (OS) of these patients in the different periods. **Methods:** Ambispective observational cohort study. A total of 213 ≤65 years patients from our institutional registry were analyzed.

response rate (ORR) was defined as achieving a partial response or better. Nonparametric methods were used to compare baseline demographic and treatment characteristics of SLiM versus CRAB patients. **Results:** Overall, 617 MM patients were included in the study (49 [8%] with SLiM MM and 567 [92%] with CRAB MM). Among patients with CRAB MM, the most common presentation was osteolytic lesions (n=340, 60%), anemia (n=269, 47%), renal failure (n=118, 21%), then hypercalcemia (n=63, 11%), as defined by the IMWG (Rajkumar et al. Lancet Oncol. 2014). Among SLiM MM patients, the most common treatment indications were BM PC >60% (n=21, 42.9%), FLC ratio ≥100 (n=13, 26.5%), followed by focal lesions on MRI (n=13, 26.5%). SLiM versus CRAB MM patients had similar ages at diagnosis (median age 67.3 versus 67.5 years, respectively, p=0.889) and similar proportions of patients with ISS stage 3 disease at diagnosis (33% versus 26.5%, respectively, p=0.076). Treatment of SLiM versus CRAB patients was similar; immunomodulatory drugs or proteosome inhibitors were used in first line treatment in 90% versus 92% of patients (p=0.578), and 49% versus 44% of patients received an upfront transplant (p=0.553). SLiM versus CRAB MM patients had a similar PFS (median PFS 36.9 versus 31.8 months, respectively, p=0.365) and ORR (89% in both groups, p=0.964). However, there was a trend towards longer OS among patients presenting with SLiM versus CRAB MM (median PFS 99.5 versus 66.7 months, respectively, p=0.070). **Conclusions:** Despite similar baseline demographics and treatments, we found a trend towards improved survival among patients treated for SLiM MM. Further work is needed to identify whether survival benefits are due to persistence of less resistant clones leading to longer PFS at relapse. However, these real-world data support the current practice of early intervention in patients with SLiM MM.

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Since 2013 the registry is prospective. Four periods were defined: 1 (P1) from 2000 to 2007, in which there was only melphalan-prednisone as treatment; Period 2 (P2) from 2008 to 2013, in which thalidomide began to be used for some young patients, in addition to autologous stem cell transplantation (ASCT) in some cases; Period 3 (P3) from 2014 to 2018, in which the protocol to be used was cyclophosphamide-thalidomide-dexamethasone (CTD) and ASCT; Period 4 (P4) from 2019 to 2022, in which triplets based on bortezomib, ASCT and post-transplant maintenance with lenalidomide were used. The indications for ASCT in all periods were restrictive: Only for patients ≤60 years in very good partial response (VGPR) or better. Treatment in the different periods, early mortality (defined as death within the first 6 months of diagnosis), and OS of each group were analyzed. **Results:** There were 37 patients at P1, 56 at P2, 61 at P3, and 59 at P4. At P1, 65% of patients were treated with a melphalan-prednisone regimen, 8% VAD, and 8% with a thalidomide-based regimen. No ASCT was performed, and early mortality rate was 24%. At P2, 71% were treated with a thalidomide-based regimen (13% CTD, 87% Thaldex), 20% based on melphalan, and 2% based on bortezomib. 21% had ASCT performed and 9% received maintenance (Thalidomide-based). Early mortality was 16%. At P3, 90% received a thalidomide-based regimen (82% CTD) and 10% based on bortezomib. 33% underwent ASCT, 20% received maintenance (100% thalidomide-based) and early mortality was 16%. At P4, 97% were treated with bortezomib-based triplets. 36% were transplanted. Maintenance was administered to 75% of patients, 93% based on lenalidomide. Early mortality was 7%. With a median follow-up of 77.5 months, the median OS for the entire group was 55.1 months. The median OS of P4, P3, P2 and P1 was Not reached, 96, 35 and 25 months, respectively (p< 0.0001). **Conclusions:** OS has increased in each treatment period. Induction regimens have gone from being melphalan-based, then thalidomide-based, to finally being mostly bortezomib-based. Transplant and maintenance rates have increased over time. Early mortality has decreased, especially in the last period. The median OS of P3 is 8 years, better than expected, as the induction and maintenance regimen was mainly thalidomide-based. P4 showed a trend of an even better OS. Longer follow up is needed. In conclusion, public policies in the Chilean public system have managed to increase OS in our patients.

P-158

Experience at Son Espases University Hospital with daratumumab, bortezomib, lenalidomide and dexamethasone (D-VRd) as first line treatment in multiple myeloma

Lola Piquer Monsonis[1], Maria Galí Sampalo[1], Albert Perez Montaña[1], Jose Maria Sánchez Raga[1], Antonia Sampol Mayol[1]

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Introduction: Multiple myeloma (MM) is characterized by uncontrolled plasma cell proliferation, anaemia, renal failure, hypercalcemia, osteolytic bone lesions, and immunodeficiency. First line treatment in patients who are candidates for autologous stem cell transplantation (ASCT) is based on triplets, basically the combination of bortezomib, lenalidomide and dexamethasone (VRd) during 4-6 cycles. The latest studies add a 4th drug to current triplets, a monoclonal antibody against CD38 which seems to improve treatment responses without increasing toxicity. The main aim of our research is to show our experience on a third level hospital with a quadruple induction regimen (D-VRd) as first line treatment in MM. **Methods:** A retrospective descriptive study was carried out analyzing 11 patients diagnosed with MM and treated in first line with D-VRd from February 2022 until April 2023 at Hospital Universitari Son Espases. We analyzed clinical-biological parameters, prognostic staging systems, treatment, and clinical outcomes. **Results:** We analyzed 11 patients, 6 of whom were male (55%). Median age was 57 years old (range 41-69). Six patients had performance status ECOG 0 and 5 patients ECOG 1 at diagnosis. Based on the International Staging System (ISS): 7 patients (64%) were stage I, 2 (18%) stage II and 2 (18%) stage III. On the other hand, when analyzing R-ISS: 4 patients (36%) were stage I, 2 (18%) stage II, 2 patients (18%) stage III and lastly 3 (27%) were not classified due to lack of FISH results. Regarding stratification risk based on FISH (R-ISS criteria): 2 patients were high risk; 6 were standard-risk and 3 unknown due to lack of FISH. Average filtration rate at the beginning of treatment was 84 ml/min/1,73 m^2 (range 21-104). All patients were planned to receive 6 cycles of 28 days (bortezomib 1.3 mg/m^2 on days 1,4,8,11; lenalidomide 25 mg for 21 days; dexamethasone 40 mg on days 1-4, 9-12). Five out of eleven had finished treatment; the remaining 6 patients are either on the process of collecting stem cells or on the completion of their induction therapy. Overall response rate (ORR) was 100%. Two patients (18%) achieved complete response (CR), 5 (45%) very good partial response (VGPR) and 4 (37%) partial response (PR). Seven patients achieved its first response after the first cycle. With a median follow up of 7 months, progression free survival rate was 100%. Regarding side effects, 2 patients (18%) suffered serious adverse events (SAE): one patient had a pulmonary thromboembolism, so treatment was resumed without lenalidomide and the other patient suffered two serious pulmonary infections. Other common adverse effects were asthenia, polyneuropathy and neutropenia. **Conclusions:** In general, D-VRd treatment was well tolerated, with excellent results attending to the 100% ORR with 55% of VGPR or better in our cohort. Respiratory infections were the main serious adverse event in our experience. Results from the phase 3 trial may clarify the usefulness of this combination in a near future.

P-159

Lenalidomide maintenance in R2-ISS stratified multiple myeloma patients - real world evidence

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Since 2013 the registry is prospective. Four periods were defined: 1 (P1) from 2000 to 2007, in which there was only melphalan-prednisone as treatment; Period 2 (P2) from 2008 to 2013, in which thalidomide began to be used for some young patients, in addition to autologous stem cell transplantation (ASCT) in some cases; Period 3 (P3) from 2014 to 2018, in which the protocol to be used was cyclophosphamide-thalidomide-dexamethasone (CTD) and ASCT; Period 4 (P4) from 2019 to 2022, in which triplets based on bortezomib, ASCT and post-transplant maintenance with lenalidomide were used. The indications for ASCT in all periods were restrictive: Only for patients ≤60 years in very good partial response (VGPR) or better. Treatment in the different periods, early mortality (defined as death within the first 6 months of diagnosis), and OS of each group were analyzed. **Results:** There were 37 patients at P1, 56 at P2, 61 at P3, and 59 at P4. At P1, 65% of patients were treated with a melphalan-prednisone regimen, 8% VAD, and 8% with a thalidomide-based regimen. No ASCT was performed, and early mortality rate was 24%. At P2, 71% were treated with a thalidomide-based regimen (13% CTD, 87% Thaldex), 20% based on melphalan, and 2% based on bortezomib. 21% had ASCT performed and 9% received maintenance (Thalidomide-based). Early mortality was 16%. At P3, 90% received a thalidomide-based regimen (82% CTD) and 10% based on bortezomib. 33% underwent ASCT, 20% received maintenance (100% thalidomide-based) and early mortality was 16%. At P4, 97% were treated with bortezomib-based triplets. 36% were transplanted. Maintenance was administered to 75% of patients, 93% based on lenalidomide. Early mortality was 7%. With a median follow-up of 77.5 months, the median OS for the entire group was 55.1 months. The median OS of P4, P3, P2 and P1 was Not reached, 96, 35 and 25 months, respectively (p< 0.0001). **Conclusions:** OS has increased in each treatment period. Induction regimens have gone from being melphalan-based, then thalidomide-based, to finally being mostly bortezomib-based. Transplant and maintenance rates have increased over time. Early mortality has decreased, especially in the last period. The median OS of P3 is 8 years, better than expected, as the induction and maintenance regimen was mainly thalidomide-based. P4 showed a trend of an even better OS. Longer follow up is needed. In conclusion, public policies in the Chilean public system have managed to increase OS in our patients.

P-158

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Lukas Stejskal[16], Petr Kessler[17], Vladimir Maisnar[1], Roman Hájek[6]

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Introduction: Lenalidomide (Len) maintenance remains the cornerstone of multiple myeloma (MM) treatment in patients after upfront autologous stem cell transplantation. Yet the data about the benefit of Len monotherapy in high-risk patients remains questioned. Here we aimed on describing the benefit of Len maintenance in subgroups of patients defined by the novel R2-ISS risk stratification system. **Methods:** This was a retrospective analysis from the Czech Myeloma Group Registry of Monoclonal gammopathies (RMG). Patients with MM (followed from May 2007 until March 2023) who underwent induction therapy of at least triplet containing steroid and at least one IMID and/or PI and autologous stem cell transplantation with available baseline cytogenetic results, LDH and ISS stage were included in the analysis. Patients were stratified according to R2-ISS (D´Agostino, JCO JCO2102614.2022) and separated into two groups: no maintenance and Len maintenance. Treatment intervals (PFS, OS, TTP, TNT, DOR) were calculated and survival analysis was performed. **Results:** Overall, 927 patients were identified and suitable for final analysis. Out of these, 180 patients (19.4%) received Len maintenance whereas the others did not (no available maintenance at that time). The median age in the Len group was 62.5 years (43.8-69.6) versus 60.3 years (43.9-69.6) in the no maintenance group (p=0.014). 175/927 (18.9%) were R2-ISS-I (37/175, 21.1% in Len group), 252/927 (27.2%) were R2-ISS-II (45/252, 17.9% in Len group), 378/927 (40.1%) were R2-ISS-III (74/378, 19.6% in Len group) and 122/927 (13.2%) patients were R2-ISS-IV (24/122, 19.7% in Len group). All R2-ISS groups showed progression-free survival (PFS) benefits from MM diagnosis when Len maintenance was used. R2-ISS-I low-risk group 71.0 months (m) (95% CI 71.0-NA) versus 39.7 m (95% CI 35.0-47.2, p=0.027). R2-ISS-II intermediate-low group 54.0 months (95% CI 39.7-NA) versus 32.7 months (95% CI 30.1-36.7, p=0.001). R2-ISS-III intermediate-high group 45.7 m (95% CI 41.2-NA) versus 28.9 m (95% CI 26.4-33.3, p=0.001). R2-ISS-IV high group 34.5 m (95% CI 22.9-NA) versus 23.2 m (95% CI 20.1-29.8, p=0.168). Overall survival was not significantly different in either group. **Conclusions:** The benefit of Len maintenance was seen across all R2-ISS groups of patients confirming the importance of this therapy in all patients regardless of their risk stratification. The lowest benefit was seen in the R2-ISS-IV group (likely due to the small number of patients receiving Len maintenance in this group). In our cohort, Len maintenance significantly improved PFS across stages I-III did not completely overcome the negative impact of stage IV.

P-160

Real world data on demographics, management and outcome of ultra high risk myeloma: experience from a tertiary care centre

Saswata Saha[1], Bhausaheb Bagal[2], Hasmukh Jain[2], Lingaraj Nayak[2], Alok Shetty[2], Nishant Jindal[2], Sumeet Mirgh[2], Anant Gokarn[2], Sachin Punatar[2], Prashant Tembhare[3], Dhanlaxmi Shetty[4], Vasundhara Patil[5], Manju Sengar[2], Navin Khattry[6]

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Introduction: Multiple Myeloma (MM) is a heterogeneous disease with a genetic profile playing a major role in prognosis and treatment outcome. The high risk genetic abnormalities defined by mSMART 3.0 are t(4;14), t(14;16), t(14;20), del 17p, p53 mutation and gain 1q. Ultra High-Risk Myeloma includes double-hit MM (coexistence of two high-risk abnormalities) and triple-hit MM (coexistence of three high-risk abnormalities). Ultra High-Risk subset is associated with poor prognosis and real-world data on management are limited. **Methods:** The hospital OPD registry of newly diagnosed Multiple Myeloma patients registered between January 2016 and December 2019 was searched to find 48 patients with ultra-high-risk Myeloma. We retrospectively analyzed the demographics, management, and outcome of ultra-high-risk patients. SPSS descriptive statistics were performed for demographic characteristics. Kaplan-Meier plots were used for survival analysis. Univariate analysis was done to see the impact of baseline characteristics on progression-free survival (PFS) and overall survival (OS). **Results:** The median age of the population was 54.5 years (range 28 years – 72 years). Thirty-one patients (64.6%) were Male. ECOG PS was 0-2 in 35 patients (72.9%). Thirty-two patients (66.7%) had ISS III and R-ISS III disease. 23 (47.9%) received Proteosome Inhibitor (PI)-based triplet (VCD/VMP) and 22 (45.8%) received PI+Immunomodulatory agents (IMiD) based triplet (VRD/VTD/VPD) as initial therapy.

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The median PFS was 20 months (95% CI: 0 – 42.63), the median second progression free survival (PFS2) was 1 month (95% CI not calculable) and the median OS was 25 months (95% CI: 9.48 – 40.52). On univariate analysis, PFS and OS were not associated with baseline co-morbidities, ECOG PS, ISS, R-ISS, or the presence of plasma cells in peripheral blood. The presence or absence of del 17p or p53 mutation also did not affect survival outcomes. Similarly, the presence of double-hit versus triple-hit did not affect the PFS or OS of the patients and autologous hematopoietic stem cell transplant (auto-HSCT) was not associated with significantly improved PFS and OS in our analysis. Only 5 patients underwent auto-HSCT post-induction chemotherapy. Patients who received maintenance had a significantly better median PFS (44 months vs 8 months) and median OS (68 months vs 9 months). The magnitude of benefit from different maintenance strategies cannot be ascertained due to the small number. **Conclusions:** Our analysis gives us a real-world experience of the ultra-high-risk subgroup and adverse outcomes similar to other studies reported in this group of patients. Our study did show improved outcomes with maintenance in this subgroup of patients. Large-scale prospective data is required to understand the outcomes and best management strategies for this adverse risk group of Multiple Myeloma patients.

P-161

Impact of induction treatment on the survival of patients with multiple myeloma candidates for autologous stem cell transplantation: experience of a center

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Introduction: Actually, despite the incorporation of new treatments in multiple myeloma, autologous hematopoietic stem cell transplantation (ASCT) continues to be the frontline treatment for those patients who are candidates to intensive treatment. **Methods:** A retrospective analysis was performed in multiple myeloma patients who received ASCT from 1995 to 2020. The objective of our study was to analyze the evolution of progression-free survival (PFS) and overall survival (OS) in patients with multiple myeloma undergoing ASCT at our center. We have analyzed the results based on the type of induction received according to current clinical practice: chemotherapy (CT), Bortezomib-Dexamethasone (VD) or triplet therapy with Bortezomib, Thalidomide and Dexamethasone (VTD). We analyzed the impact of maintenance treatment with Lenalidomide in patients who have received VTD therapy. Inductions treatments were performed in different periods of time: QT (1995-2011), VD (2011-2014) and VTD (2015-2020). **Results:** Eighty patients have been included, 52 (65%) of them were male. The median age at diagnosis was 58 (34-70) years and at ASCT was 59 (39-71) years. The induction treatment received in 33 (41%) patients was CT based on VBMCP/VBAD regimen, 13 (16%) patients with VD and 34 (43%) patients with VTD. Twenty-three (29%) patients with VTD schedule received maintenance therapy with lenalidomide. Median PFS was 20.2 (95%CI, 14.6-25.8) months in patients who received CT and 16.8 (95%CI, 11.1-22.3) months for VD. Median PFS has not been reached in patients who received VTD (figure 1). PFS analysis showed statistically significant differences between VTD and QT ($p< 0.001$) and VD ($p< 0.001$). No significant differences was observed between QT and VD groups ($p=0.2$). Patients who received maintenance show a higher PFS than those who did not, despite difference is not statistically significant ($p=0.19$). Median overall survival (OS) was similar in patients who received CT and VD: 72.7 (95% CI, 64.3-81.2) months and 90.6 (46.6-134.4) months, respectively. Median OS was not reached in patients who received VTD. The OS analysis showed statistically significant difference between VTD and QT ($p< 0.001$) and VD ($p=0.002$). No differences were observed in overall survival ($p=0.8$) in patients who received maintenance with lenalidomide (figure 2). **Conclusions:** Survival analysis (PFS and OS) of patients in our center who received ASCT shows that the addition of Bortezomib combined with Dexamethasone did not provide a benefit compared to polychemotherapy. On the other hand, the incorporation of the triplet therapy with Bortezomib, Thalidomide and Dexamethasone (VTD) has improved the survival (PFS and OS) than CT and VD regimens. According to the impact of maintenance post-transplantation with lenalidomide, a trend to benefit was observed in PFS, although no differences were observed in OS. This lack of benefit may be due to the short follow-up of the series, so it should be analyzed later with a longer follow-up.

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may have anti-tumor activity in solid tumors. In this pilot study (NCT05130827), plinabulin was incorporated with the intent to shorten the duration of neutropenia after AHCT, thereby limiting the toxicities at count nadir. **Methods:** On Day 0, 40mg of intravenous plinabulin was given 1-3 hours after stem cell infusion with pegfilgrastim on Day +1. Plinabulin pharmacokinetic profiling (end of infusion, 30min, 4hr, 24hr, and 48hr), toxicities of the combination, engraftment, disease response, progression free and overall survival, and patient reported outcome (PRO) assessment of symptom burden were secondary endpoints. Eleven concurrent standard-of-care (SOC) patients had similar assessments for comparison. **Results:** Between January 2022 and February 2023, 15 patients (median age 64 (range 54-74), 67% female, 73% melphalan 200mg/m^2) received plinabulin. Median CD34+ cells/kg infused was 4.12 x 10^6 (range 2.18 – 7.85). Half the patients had hypertension (HTN) immediately after the plinabulin infusion, which is a known toxicity and resolved within a few hours. Median plinabulin serum AUC was 1249.5mg*h/L (range 192.6 -5092.5). Median WBC on Day 0, 1, and 2 was 7.67 (3.6 – 11.5), 5.2 (3.2 – 13.6), and 17.1 (5.1-59.1), respectively. Median time to ANC >0.5 x 10^9 cell/L was 11 days (range 8-16) with median days from AHCT to ANC < 0.5 of 5 days (range 5-6). Median number of days of ANC < 0.1 and < 0.5 were 2 (range 1-5) and 5 days (range 3-9), respectively. Median time to fever was 8 days from AHCT (n = 8, range 7-12), and all except one were attributed to engraftment syndrome. Median length of stay was 18 days (range 15-21). Median pRBC and platelet transfusions were 0 (range 0-3) and 2 (range 0-11), respectively. For the SOC patients, engraftment timing was similar, but 2 had HTN, 3/7 with fever had non-engraftment neutropenic fevers (NENF), and median pRBC and platelet transfusions were 1 (range 0-8) and 4 (range 1-14), respectively. **Conclusions:** The addition of plinabulin to pegfilgrastim did not add major toxicities after AHCT. Patients had elevated WBC on Day +2, low rates of NENF, and potentially less need for transfusion support. Plinabulin PK, quality of life data, and PROs will be presented. Adjusting the schedule of plinabulin to Day 3 may allow stem cells to reach the bone marrow niche prior exposure to plinabulin and thereby use the novel mechanism of action to shorten the duration of neutropenia.

P-163

Treatment patterns and outcomes in newly diagnosed multiple myeloma

Jash Yogesh Shah[1], Aditya Ranjithkumar Nair[1], Dhyey Rajkumar Mishra[1], Bhausaheb Bagal[2], Hasmukh Jain[2], Lingaraj Nayak[2], Prashant Tembhare[3], Saswata Saha[4], Anant Gokarn[2], Sachin Punatar[2], Dhanlaxmi Shetty[5], Sumeet Mirgh[2], Alok Shetty[2], Nishant Jindal[2], Vasundhara Patil[6], Manju Sengar[2], Navin Khattry[7]

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Introduction: Though significant progress has been made in therapy and outcomes of multiple myeloma, real-world outcomes remain inferior compared to clinical trial settings. Access to treatment with novel agents including autologous stem cell transplant (ASCT) and immunotherapies is limited in developing countries, which may further compromise the outcomes. This study looks at consecutive patients with newly diagnosed multiple myeloma (NDMM) patients registered over a period of 12 months to estimate overall survival and factors influencing them. **Methods:** This is a retrospective analysis of 243 consecutive NDMM patients from January 2017 to December 2017. Data was collected from Electronic medical record for treatment received, outcomes and factors affecting outcomes were evaluated using Kaplan Meier log rank test in univariate and Cox regression model for multivariate analysis. **Results:** The median age of study population was 56 years (range, 27 to 79). FISH analysis was available in 93.8% of patients and revealed hyperdiploidy in 39.5%. High-risk cytogenetics (del 17p, t (4:14), t(14;16), and t (14;20) abnormalities were found in 34.9% of the patients. R-ISS was available for 95.47% of the patients with R-ISS I, II, and III in 19 (7.8%), 128 (52.7%), and 45 (18.5%) patients respectively. First-line treatment was VCd in 174 (75.7%) patients, VRd in 26(10.7%) patients, while18 (7.40%) patients received doublet. Only 20 (8.2%) patients could underwent ASCT and 56 (22.6%) received maintenance therapy. The median overall survival was 4.3 years. On univariate analysis, female gender, R-ISS stage, raised LDH, ECOG performance status 1 or less, ASCT and use of maintenance therapy were significantly associated with better OS. On multivariate analysis female gender, ECOG performance status 1 or less and use of maintenance therapy were independent predictor of better OS. **Conclusions:** Outcomes of multiple myeloma patients in our series are inferior as compared to reported outcomes in literature. Most of patient in this time period did not receive RVd induction, ASCT and or maintenance therapy and appropriate use of these modalities may improve outcomes.

P-164

Reduction in disease symptoms/impacts after daratumumab, lenalidomide, bortezomib, and dexamethasone treatment for transplant-eligible patients with newly diagnosed multiple myeloma (GRIFFIN study)

Rebecca Silbermann[1], Jacob Laubach[2], Jonathan Kaufman[3], Douglas Sborov[4], Brandi Reeves[5], Cesar Rodriguez[6], Ajai Chari[7], Luciano Costa[8], Larry Anderson[9], Nitya Nathwani[10], Nina Shah[11], Naresh Bumma[12], Caitlin Costello[13], Andrzej Jakubowiak[14], Robert Orlowski[15], Ken Shain[16], Katharine Gries[17], Huiling Pei[18], Annelore Cortoos[19], Sharmila Patel[19], Kathryn Matt[20], Thomas Lin[19], Saad Usmani[21], Peter Voorhees[22], Paul Richardson[2]

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P-164

Reduction in disease symptoms/impacts after daratumumab, lenalidomide, bortezomib, and dexamethasone treatment for transplant-eligible patients with newly diagnosed multiple myeloma (GRIFFIN study)

Rebecca Silbermann[1], Jacob Laubach[2], Jonathan Kaufman[3], Douglas Sborov[4], Brandi Reeves[5], Cesar Rodriguez[6], Ajai Chari[7], Luciano Costa[8], Larry Anderson[9], Nitya Nathwani[10], Nina Shah[11], Naresh Bumma[12], Caitlin Costello[13], Andrzej Jakubowiak[14], Robert Orlowski[15], Ken Shain[16], Katharine Gries[17], Huiling Pei[18], Annelore Cortoos[19], Sharmila Patel[19], Kathryn Matt[20], Thomas Lin[19], Saad Usmani[21], Peter Voorhees[22], Paul Richardson[2]

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may have anti-tumor activity in solid tumors. In this pilot study (NCT05130827), plinabulin was incorporated with the intent to shorten the duration of neutropenia after AHCT, thereby limiting the toxicities at count nadir. **Methods:** On Day 0, 40mg of intravenous plinabulin was given 1-3 hours after stem cell infusion with pegfilgrastim on Day +1. Plinabulin pharmacokinetic profiling (end of infusion, 30min, 4hr, 24hr, and 48hr), toxicities of the combination, engraftment, disease response, progression free and overall survival, and patient reported outcome (PRO) assessment of symptom burden were secondary endpoints. Eleven concurrent standard-of-care (SOC) patients had similar assessments for comparison. **Results:** Between January 2022 and February 2023, 15 patients (median age 64 (range 54-74), 67% female, 73% melphalan 200mg/m^2) received plinabulin. Median CD34+ cells/kg infused was 4.12 x 10^6 (range 2.18 – 7.85). Half the patients had hypertension (HTN) immediately after the plinabulin infusion, which is a known toxicity and resolved within a few hours. Median plinabulin serum AUC was 1249.5mg*h/L (range 192.6 -5092.5). Median WBC on Day 0, 1, and 2 was 7.67 (3.6 – 11.5), 5.2 (3.2 – 13.6), and 17.1 (5.1-59.1), respectively. Median time to ANC >0.5 x 10^9 cell/L was 11 days (range 8-16) with median days from AHCT to ANC < 0.5 of 5 days (range 5-6). Median number of days of ANC < 0.1 and < 0.5 were 2 (range 1-5) and 5 days (range 3-9), respectively. Median time to fever was 8 days from AHCT (n = 8, range 7-12), and all except one were attributed to engraftment syndrome. Median length of stay was 18 days (range 15-21). Median pRBC and platelet transfusions were 0 (range 0-3) and 2 (range 0-11), respectively. For the SOC patients, engraftment timing was similar, but 2 had HTN, 3/7 with fever had non-engraftment neutropenic fevers (NENF), and median pRBC and platelet transfusions were 1 (range 0-8) and 4 (range 1-14), respectively. **Conclusions:** The addition of plinabulin to pegfilgrastim did not add major toxicities after AHCT. Patients had elevated WBC on Day +2, low rates of NENF, and potentially less need for transfusion support. Plinabulin PK, quality of life data, and PROs will be presented. Adjusting the schedule of plinabulin to Day 3 may allow stem cells to reach the bone marrow niche prior exposure to plinabulin and thereby use the novel mechanism of action to shorten the duration of neutropenia.

P-163

Treatment patterns and outcomes in newly diagnosed multiple myeloma

Jash Yogesh Shah[1], Aditya Ranjithkumar Nair[1], Dhyey Rajkumar Mishra[1], Bhausaheb Bagal[2], Hasmukh Jain[2], Lingaraj Nayak[2], Prashant Tembhare[3], Saswata Saha[4], Anant Gokarn[2], Sachin Punatar[2], Dhanlaxmi Shetty[5], Sumeet Mirgh[2], Alok Shetty[2], Nishant Jindal[2], Vasundhara Patil[6], Manju Sengar[2], Navin Khattry[7]

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P-164

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Introduction: In the final analysis of the phase 2 randomized GRIFFIN study after all patients (pts) completed 1 year of follow-up post maintenance therapy, died or withdrew (median follow-up, 49.6 months), daratumumab (dara), lenalidomide (R), bortezomib and dexamethasone (D-RVd) led to a clinically meaningful progression-free survival benefit vs RVd (hazard ratio, 0.45; 95% CI, 0.21–0.95; P=0.032). Patient-reported outcome (PRO) data also showed that D-RVd pts who continued on maintenance treatment experienced greater improvements in health-related quality of life vs RVd alone. Here, we present item-level responses from the PRO instruments to understand the degree of change after treatment (tx) on singular concepts. **Methods:** Transplant-eligible (TE) pts with newly diagnosed multiple myeloma (NDMM) were randomized 1:1 to receive 4 D-RVd/RVd induction cycles, autologous stem cell transplant (ASCT), 2 D-RVd/RVd consolidation cycles, and up to 2 years' maintenance therapy with R ± dara. PRO data were collected using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30), EORTC QLQ Multiple Myeloma Module 20-item (EORTC QLQ-MY20), and EuroQol 5-level (EQ-5D-5L) tools. Questionnaires were completed at baseline, on day 1 of cycles (C) 2, 3, 5; on day 21 of C4; post ASCT consolidation (C6 D21); and after months 6, 12, 18, and 24 of maintenance. Frequency distribution, by tx group and by visit, were summarized for PRO items reporting on MM disease symptoms and functional impacts. **Results:** A total of 207 pts were randomized (D-RVd, n=104; RVd, n=103). For both D-RVd/DR and RVd/R, pts reported a reduction in disease symptoms and impacts; when questioned on the presence of these symptoms/impacts, a greater proportion answered "not at all/a little" during maintenance vs "quite a bit/very much" at baseline. For rigorous activities and disease-specific symptoms including hip pain, trouble taking a long walk, and need to rest, a higher proportion of pts in the D-RVd/DR vs the RVd/R arm reported no symptom/impact during maintenance. For example, for trouble taking a long walk, a similar proportion of pts reported "not at all" at baseline for D-RVd/DR versus RVd/R (31.8% vs 29.8%, respectively), but a greater proportion of D-RVd/DR pts reported "not at all" at maintenance month 6 (45.3% vs 37.2%), 12 (44.6% vs 37.1%), 18 (37.2% vs 33.3%), and 24 (50.0% vs 43.5%). There were no differences in pts responding "not at all" between D-RVd/DR and RVd/R for pain in back, arm/shoulder, or chest; being tired; pain interfering with activities; and limitations of usual activities. **Conclusions:** The addition of dara to RVd/R in TE pts with NDMM led to meaningful reductions in disease symptoms/impact, with a higher proportion of D-RVd/DR pts reporting no symptom/impact after tx on items related to pain in hip, trouble taking a long walk, and needing to rest, compared to RVd/R.

P-165

Incidence, risk factors and impact of supraventricular tachycardia (SVT) with high dose therapy melphalan among myeloma patients undergoing autologous stem cell transplant (HDT/ASCT)

Kathryn Simon[1], Nisha Joseph[1], Anant Mandawat[1], Craig Hofmeister[1], Mala Shanmugam[1], Jonathan Kaufman[1], Michael Graiser[1], Sarah Wyman[1], Oyinda Adisa[1], Manali Rupji[1], Tom Matich[1], Vikas Gupta[1], Madhav Dhodapkar[1], Amelia Langston[1], Sagar Lonial[1], Ajay Nooka[1]

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Introduction: High dose therapy melphalan followed by autologous stem cell transplant (HDT/ASCT) confers an overall survival (OS) advantage and is the mainstay of frontline therapy among transplant-eligible myeloma patients. Melphalan is an arrhythmogenic chemotherapy but the incidence of developing peri-transplant supraventricular tachycardia (SVT) and its impact on OS has not been well described. We performed a single institutional analysis of 2970 patients undergoing HDT/ASCT from 2000-2021 to evaluate the incidence, risk factors and the long-term impact of SVT during the peri-transplant period. **Methods:** Variables of interest were extracted from Clinical Data Warehouse (CDW), a Structured Query Language (SQL) database as approved by Emory Institutional Review Board (IRB). A tiered algorithmic approach was developed to automate the extraction of data elements from the CDW utilizing SQL scripts which were validated by data from manual extraction and existing data from myeloma database and the transplant database. Broad tiered criteria included EKG obtained peri-transplant, anti-arrhythmic drug, ICU transfer, and cardiology consultation. **Results:** Of the 2970 patients, 614 (20.7%) underwent transplant between 2000-2010 and 445 (15%) were above the age of 70. Median age of transplant was 61.6 years, 48% had ≥ very good partial response (≥VGPR) pre-transplant, 59.6% had hypertension (HTN), 28.7% had coronary artery disease (CAD), 12.2% had prior β-blocker usage and 10.7% had prior arrhythmia. 948 (31.9%) had an EKG during the peri transplant period. 203 (6.8%) developed SVT and 155 (5.2%) required transfer to ICU. The median age of patients that developed SVT was higher (62.88 vs 60.8 years, p< 0.01) and length of stay (LOS) was increased by a day for patients that had SVT peri-transplant (16 vs 15 days, p< 0.001). Risk factors for developing SVT include HTN: 66.5% vs 56.4%, p< 0.001,

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P-165

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CAD: 35.3% vs 25.6%, p< 0.001, β-blockers: 15.5% vs 10.6%, p< 0.001, arrhythmias: 15.9% vs 8.2%, p< 0.001, age ≥70: 18.4% vs 13.4%, p< 0.001. 30-day readmit rate was 8.5% (SVT vs no SVT: 11.9% vs 6.9%, p< 0.001), 30 day mortality was 0.8% (SVT vs no SVT: 2.4% vs 0.1%, p< 0.001), 100 day mortality was 2% (SVT vs no SVT: 4.4% vs 0.8%, p< 0.001). The OS was 9 years (SVT vs no SVT: 9.3 vs 6.6 years, p< 0.001). This difference extended to patients transplanted between 2011-2021 where the OS was 10.5 years (SVT vs no SVT: 10.82 vs 6.53, p< 0.001). H/o β-blocker use was the only independent risk factor for shortened OS (HR 1.25 95% CI (1.029-1.52), p=0.025). **Conclusions:** While the data aligns with known findings of melphalan as an arrhythmogenic agent, the current data identifies prior h/o β-blocker use as an independent risk factor for shortened OS. SVT peri-transplant resulted in longer hospital LOS, significantly increased 30-day mortality and 100-day mortality and had an impact on OS. The current data supports preventive strategies aimed at decreasing the incidence of SVT peri-transplant.

P-166

Daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) vs daratumumab, carfilzomib, lenalidomide and dexamethasone (DKRd) as induction therapy in newly diagnosed multiple myeloma

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Introduction: DVRd and DKRd are promising induction regimens for newly diagnosed multiple myeloma (NDMM), resulting in deep responses and high minimal residual disease (MRD) negativity rates. Our prior work demonstrated PFS benefit in high-risk (HR) NDMM receiving KRd versus VRd. Herein, we examined early outcomes associated with DVRd and DKRd induction for transplant eligible patients (pts) with NDMM. **Methods:** We conducted a chart review study with NDMM pts treated with DVRd (N=82) and compared outcomes with pts treated with DKRd (N=79), of which 68 were on study (NCT03290950) at our center (10/5/2017 to 12/29/22). Data cutoff for analysis was 1/31/23. Pts with </=1 cycle of other therapy (tx) were included (N=10). Pts with ongoing tx with < 4 cycles of quadruplet tx were excluded. Bone marrow biopsies (BMBx) were typically performed for MRD evaluation (flow cytometry; 10-5 sensitivity) before stem cell collection or at the end of cycle (C) 8. **Results:** Median age was 66 (IQR 59-70) for DVRd- and 59 (50-65) for DKRd-treated pts (P< 0.001). DVRd group had 68% White and 16% Black, while DKRd had 78% White and 8% Black. The majority of pts in both groups were RISS Stage 2 (DVRd RISS 1/2/3: 21%/75%/5%; D-KRd: 38%/57%/5%). With HR cytogenetics defined as 1q+, t(4;14), t(14;16), t(14;20), del(17p), 26/71 (37%) in DVRd and 38/77 (49%) in DKRd had cytogenetic results that met HR criteria (P=0.12). Median number of cycles was 6 (4-6) for DVRd and 8 (7-8) for DKRd (P< 0.001). At data cutoff, 31 (39%) DVRd- and 25 (32%) DKRd-treated pts received upfront ASCT. Best ORR was 96% and 100% for DVRd and DKRd (P=0.2), respectively. Within C8 of tx, 61 (74%) DVRd- and 72 (91%) DKRd-treated pts achieved >/=VGPR (P=0.005). There were 2 pts with stable disease and 1 progressive disease as best response on DVRd. 62 DVRd and 72 DKRd pts had a BMBx /=CR on DVRd and DKRd, respectively. Among pts with BMBx </=C6, 13/60 (22%) and 36/69 (52%) were MRD negative for DVRd and DKRd, respectively. Multivariable analysis (age, gender, race, stage, cytogenetic risk, number of cycles) demonstrated that age was associated with improved CR rate (OR 1.07, 95%CI 1.02-1.13, P=0.004). There was a trend toward improved CR rate within C8 with DKRd compared to DVRd (OR 2.7, 95%CI 0.99-8.33; P=0.053). **Conclusions:** In this single center chart review, DVRd was compared to DKRd. Importantly, DKRd pts were primarily from a clinical trial, perhaps affecting demographics of the groups (DVRd group had older pts and more Black pts; DKRd group had more HR pts and received more cycles due to trial design). Best ORR was similar for both groups. Although CR rate was greater with DKRd, on multivariable analysis there was a trend toward better CR rate with DKRd vs DVRd without reaching statistical significance. Data with follow-up outcomes, including HR subgroups, will be presented at the meeting.

P-167

Serum BCMA levels evaluated by Elecsys sBCMA assay at diagnosis have prognostic value in patients with multiple myeloma

Evangelos Terpos[1], Ioannis Ntanasis-Stathopoulos[1], Panagiotis Malandrakis[1], Aliya Sarmanova[2], Despina Fotiou[1], Katharina Buck[2], Magdalini Migkou[1], Galina Babitzki[2], Evangelos Eleutherakis-Papaiakovou[1], Maria Roussou[1], Maria Gavriatopoulou[1], Meletios Dimopoulos[1], Efstathios Kastritis[1]

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Introduction: Serum B-cell maturation antigen (sBCMA) levels have emerged as potential biomarkers for disease monitoring with prognostic value in patients with multiple myeloma (MM). **Methods:** We evaluated sBCMA distribution with Elecsys® sBCMA assay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) and its potential prognostic role in patients with MM and smoldering MM (sMM) by a single institution. Patients with sBCMA values outside of measuring range (1.2-900 ng/mL) were excluded. **Results:** 166 patients diagnosed from 2018 to 2020 were included (median follow up: 38 months). The median age was 67 years (range 50-93

CAD: 35.3% vs 25.6%, p< 0.001, β-blockers: 15.5% vs 10.6%, p< 0.001, arrhythmias: 15.9% vs 8.2%, p< 0.001, age ≥70: 18.4% vs 13.4%, p< 0.001. 30-day readmit rate was 8.5% (SVT vs no SVT: 11.9% vs 6.9%, p< 0.001), 30 day mortality was 0.8% (SVT vs no SVT: 2.4% vs 0.1%, p< 0.001), 100 day mortality was 2% (SVT vs no SVT: 4.4% vs 0.8%, p< 0.001). The OS was 9 years (SVT vs no SVT: 9.3 vs 6.6 years, p< 0.001). This difference extended to patients transplanted between 2011-2021 where the OS was 10.5 years (SVT vs no SVT: 10.82 vs 6.53, p< 0.001). H/o β-blocker use was the only independent risk factor for shortened OS (HR 1.25 95% CI (1.029-1.52), p=0.025). **Conclusions:** While the data aligns with known findings of melphalan as an arrhythmogenic agent, the current data identifies prior h/o β-blocker use as an independent risk factor for shortened OS. SVT peri-transplant resulted in longer hospital LOS, significantly increased 30-day mortality and 100-day mortality and had an impact on OS. The current data supports preventive strategies aimed at decreasing the incidence of SVT peri-transplant.

P-166

Daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) vs daratumumab, carfilzomib, lenalidomide and dexamethasone (DKRd) as induction therapy in newly diagnosed multiple myeloma

Carlyn Rose Tan[1], Kylee Maclachlan[2], David Nemirovsky[3], Andriy Derkach[1], Malin Hultcrantz[2], Hani Hassoun[2], Sham Mailankody[2], Urvi Shah[2], Dhwani Patel[1], Tala Shekarkhand[1], Colin Rueda[1], Oscar Lahoud[1], Gunjan Shah[1], Michael Scordo[1], David Chung[4], Heather Landau[4], Sergio Giralt[1], Saad Usmani[1], Alexander Lesokhin[1], Neha Korde[2]

[1]Memorial Sloan Kettering Cancer Center, New York City NY, USA; [2]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City NY, USA; [3]Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center; [4]Bone Marrow Transplant and Cellular Therapy, Memorial Sloan Kettering Cancer Center, New York City NY, USA

Introduction: DVRd and DKRd are promising induction regimens for newly diagnosed multiple myeloma (NDMM), resulting in deep responses and high minimal residual disease (MRD) negativity rates. Our prior work demonstrated PFS benefit in high-risk (HR) NDMM receiving KRd versus VRd. Herein, we examined early outcomes associated with DVRd and DKRd induction for transplant eligible patients (pts) with NDMM. **Methods:** We conducted a chart review study with NDMM pts treated with DVRd (N=82) and compared outcomes with pts treated with DKRd (N=79), of which 68 were on study (NCT03290950) at our center (10/5/2017 to 12/29/22). Data cutoff for analysis was 1/31/23. Pts with </=1 cycle of other therapy (tx) were included (N=10). Pts with ongoing tx with < 4 cycles of quadruplet tx were excluded. Bone marrow biopsies (BMBx) were typically performed for MRD evaluation (flow cytometry; 10-5 sensitivity) before stem cell collection or at the end of cycle (C) 8. **Results:** Median age was 66 (IQR 59-70) for DVRd- and 59 (50-65) for DKRd-treated pts (P< 0.001). DVRd group had 68% White and 16% Black, while DKRd had 78% White and 8% Black. The majority of pts in both groups were RISS Stage 2 (DVRd RISS 1/2/3: 21%/75%/5%; D-KRd: 38%/57%/5%). With HR cytogenetics defined as 1q+, t(4;14), t(14;16), t(14;20), del(17p), 26/71 (37%) in DVRd and 38/77 (49%) in DKRd had cytogenetic results that met HR criteria (P=0.12). Median number of cycles was 6 (4-6) for DVRd and 8 (7-8) for DKRd (P< 0.001). At data cutoff, 31 (39%) DVRd- and 25 (32%) DKRd-treated pts received upfront ASCT. Best ORR was 96% and 100% for DVRd and DKRd (P=0.2), respectively. Within C8 of tx, 61 (74%) DVRd- and 72 (91%) DKRd-treated pts achieved >/=VGPR (P=0.005). There were 2 pts with stable disease and 1 progressive disease as best response on DVRd. 62 DVRd and 72 DKRd pts had a BMBx /=CR on DVRd and DKRd, respectively. Among pts with BMBx </=C6, 13/60 (22%) and 36/69 (52%) were MRD negative for DVRd and DKRd, respectively. Multivariable analysis (age, gender, race, stage, cytogenetic risk, number of cycles) demonstrated that age was associated with improved CR rate (OR 1.07, 95%CI 1.02-1.13, P=0.004). There was a trend toward improved CR rate within C8 with DKRd compared to DVRd (OR 2.7, 95%CI 0.99-8.33; P=0.053). **Conclusions:** In this single center chart review, DVRd was compared to DKRd. Importantly, DKRd pts were primarily from a clinical trial, perhaps affecting demographics of the groups (DVRd group had older pts and more Black pts; DKRd group had more HR pts and received more cycles due to trial design). Best ORR was similar for both groups. Although CR rate was greater with DKRd, on multivariable analysis there was a trend toward better CR rate with DKRd vs DVRd without reaching statistical significance. Data with follow-up outcomes, including HR subgroups, will be presented at the meeting.

P-167

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P-167

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years), 101 (61%) were males, 122 had symptomatic MM and 44 had SMM. The baseline mean sBCMA value was 162 ng/mL (SD 169) for patients with MM and 19.4 ng/mL (SD 16.5) for SMM. In a subset of patients with MM, there were available data at the time of first (n=68) and second (n=20) disease progression. At first disease progression, the mean sBCMA value was 102 ng/mL (SD 148), whereas at second disease progression the mean sBCMA value was 169 ng/mL (SD 275). There was a general trend towards decreasing sBCMA values from baseline to first disease progression (mean difference -82.9ng/mL, 95%CI: -118 to -47.8ng/mL, p< 0.0001). In general, the results were consistent among the risk stratification subgroups based on ISS staging. The sample size was rather small for the second disease progression timepoint (the estimated mean difference of 56.1% which corresponds to a 43.9% decrease from baseline, p = 0.028). The baseline mean sBCMA value was lower in patients without documented disease progression (103 ng/mL, SD 107) compared with patients who had one (200 ng/mL, SD 194) or two (198 ng/mL, SD 185) disease progressions during the follow-up period. In addition, there was no meaningful association between sBCMA baseline values and best response during first line treatment. Furthermore, patients with symptomatic MM were categorized as low (n=61) or high expressors (n=61) based on sBCMA expression at baseline; low expressors had baseline sBCMA values below 113 ng/mL (median) and high expressors had baseline sBCMA values ≥ 113 ng/mL. The median progression-free survival (PFS) was 24.7 months (95%CI: 20.1 to 32.4) for high expressors and 53.7 months (95%CI: 26.9 to not reached) for low expressors (HR 1.67, log-rank p=0.031). In the subgroup analysis according to ISS, a significant association became evident only for patients with ISS 3 (HR 2.24, 95%CI: 1.12 to 4.48, p=0.023, high versus low expressors). Interestingly, high expressors had a median OS of 58.4 months (95%CI: 46 to not reached) compared with low expressors (median OS not reached, HR 2.05, log-rank p = 0.039). **Conclusions:** MM patients with high baseline sBCMA levels seem to have a dismal prognosis compared to those with low sBCMA levels. Sequential evaluation of sBCMA in prospective studies will determine the value of incorporating sBCMA measurement in the clinical practice.

P-168

Solo G-CSF versus chemotherapy-based stem cell mobilization in Hungarian transplantation-eligible patients

Laszlo Varoczy[1], Nora Obajed Al-Ali[1], Laszlo Imre Pinczes[1], Arpad Illes[1]

[1]University of Debrecen

Introduction: Autologous peripheral stem cell transplantation (APSCT) is still a crucial part of the therapy in eligible multiple myeloma (MM) patients. The gold standard of stem cell mobilization is administering high-dose cyclophosphamide followed by granulocyte colony stimulating factor (G-CSF), however the usage of G-CSF alone can also be an effective option **Methods:** Our aim was to compare the efficacy and safety of solo G-CSF versus chemotherapy-based stem cell mobilization in our Hungarian patient population. **Results:** We reviewed 210 patients' data who underwent stem cell mobilization between 2018 and 2022. Solo G-CSF was administered in 104 cases while 106 patients received chemotherapy (cyclophosphamide or VTD-PACE regimen) which was followed by the cytokine stimulation. In the solo G-CSF group, there was a significantly higher need for plerixafor administration (45% vs 13%, p< 0.001), unsuccessful stem cell mobilization was more frequent (11% vs 3%, p=0.024) and the mean amount of collected stem cells was significantly lower (6.9 vs. 9.8 x 10^6/bwkg, p< 0.001) than in the chemotherapy group. On the other hand, infections were less frequent (4% vs 27%, p< 0.001) and the number of days spent in hospital was significantly lower (6 vs 14 days, p< 0.001). The number of therapy lines before stem cell collection had no effect on any of the outcomes. Plerixafor was more frequenty administered in those who received lenalidomide or daratumumab as part of the induction therapy than in those who were treated by other regimens (41% vs 23%, p=0.007 and 78% vs 2 %, p< 0.001, respectively). The amount of collected stem cells was negatively influenced by previous lenalidomide therapy (p< 0.001) and there was a marked, but not significant difference in the ratio of unsuccessful mobilization attempts (11.3% vs 4.3%, p=0.056). Interestingly, R-ISS stages and treatment responses had no impact on the efficacy of the mobilization procedure. **Conclusions:** The administration of solo G-CSF is a safe method of stem cell mobilization, however the higher rate of plerixafor administration and unsuccessful attempts may question its cost-effectivity.

P-169

Clinical features and outcome patterns of newly diagnosed multiple myeloma patients who are candidate for transplant: a single center experience in Paraguay

Alana Von Glasenapp[1], Elvira Enciso[1], Aline Paats[1], Lidiane Andino Neves[1]

[1]Hospital Central del Instituto de Prevision Social

Introduction: The advances in the management of multiple myeloma (MM) have yielded improved outcomes. Both the use of novel therapies and consolidation with autologous stem-cell transplantation have demonstrated superior overall response and progression-free survival rates. However, these are not readily available in most Latin American countries. Here, we aim to characterize the clinico-epidemiological features, treatment and outcome patterns of newly diagnosed MM patients in a referral center in Paraguay. **Methods:** We conducted a retrospective observational cohort study. Data were collected from clinical records, classified according to the International Staging System (ISS) and stage of the disease. Clinical and epidemiological characteristics were analyzed as well as access to first-line transplantation in newly diagnosed MM patients diagnosed from 2018 to 2022. **Results:** We included 127 patients aged 65 years and younger. Most patients were male (52%), with IgG immunoglobulin subtype (69%), and the most frequently with Kappa light chain (59%). According to the ISS classification, 40% of the patients were ISS2 at diagnosis, 34% ISS1 and 26% ISS3. Stage at diagnosis were: IIA in 32% of patients, IIB 24%, IIIA 20%, IIIB 13% IA 10% and IB 1%. Initial clinical presentations included

years), 101 (61%) were males, 122 had symptomatic MM and 44 had SMM. The baseline mean sBCMA value was 162 ng/mL (SD 169) for patients with MM and 19.4 ng/mL (SD 16.5) for SMM. In a subset of patients with MM, there were available data at the time of first (n=68) and second (n=20) disease progression. At first disease progression, the mean sBCMA value was 102 ng/mL (SD 148), whereas at second disease progression the mean sBCMA value was 169 ng/mL (SD 275). There was a general trend towards decreasing sBCMA values from baseline to first disease progression (mean difference -82.9ng/mL, 95%CI: -118 to -47.8ng/mL, p< 0.0001). In general, the results were consistent among the risk stratification subgroups based on ISS staging. The sample size was rather small for the second disease progression timepoint (the estimated mean difference of 56.1% which corresponds to a 43.9% decrease from baseline, p = 0.028). The baseline mean sBCMA value was lower in patients without documented disease progression (103 ng/mL, SD 107) compared with patients who had one (200 ng/mL, SD 194) or two (198 ng/mL, SD 185) disease progressions during the follow-up period. In addition, there was no meaningful association between sBCMA baseline values and best response during first line treatment. Furthermore, patients with symptomatic MM were categorized as low (n=61) or high expressors (n=61) based on sBCMA expression at baseline; low expressors had baseline sBCMA values below 113 ng/mL (median) and high expressors had baseline sBCMA values ≥ 113 ng/mL. The median progression-free survival (PFS) was 24.7 months (95%CI: 20.1 to 32.4) for high expressors and 53.7 months (95%CI: 26.9 to not reached) for low expressors (HR 1.67, log-rank p=0.031). In the subgroup analysis according to ISS, a significant association became evident only for patients with ISS 3 (HR 2.24, 95%CI: 1.12 to 4.48, p=0.023, high versus low expressors). Interestingly, high expressors had a median OS of 58.4 months (95%CI: 46 to not reached) compared with low expressors (median OS not reached, HR 2.05, log-rank p = 0.039). **Conclusions:** MM patients with high baseline sBCMA levels seem to have a dismal prognosis compared to those with low sBCMA levels. Sequential evaluation of sBCMA in prospective studies will determine the value of incorporating sBCMA measurement in the clinical practice.

P-168

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P-168

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Laszlo Varoczy[1], Nora Obajed Al-Ali[1], Laszlo Imre Pinczes[1], Arpad Illes[1]

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Introduction: Autologous peripheral stem cell transplantation (APSCT) is still a crucial part of the therapy in eligible multiple myeloma (MM) patients. The gold standard of stem cell mobilization is administering high-dose cyclophosphamide followed by granulocyte colony stimulating factor (G-CSF), however the usage of G-CSF alone can also be an effective option **Methods:** Our aim was to compare the efficacy and safety of solo G-CSF versus chemotherapy-based stem cell mobilization in our Hungarian patient population. **Results:** We reviewed 210 patients' data who underwent stem cell mobilization between 2018 and 2022. Solo G-CSF was administered in 104 cases while 106 patients received chemotherapy (cyclophosphamide or VTD-PACE regimen) which was followed by the cytokine stimulation. In the solo G-CSF group, there was a significantly higher need for plerixafor administration (45% vs 13%, p< 0.001), unsuccessful stem cell mobilization was more frequent (11% vs 3%, p=0.024) and the mean amount of collected stem cells was significantly lower (6.9 vs. 9.8 x 10^6/bwkg, p< 0.001) than in the chemotherapy group. On the other hand, infections were less frequent (4% vs 27%, p< 0.001) and the number of days spent in hospital was significantly lower (6 vs 14 days, p< 0.001). The number of therapy lines before stem cell collection had no effect on any of the outcomes. Plerixafor was more frequenty administered in those who received lenalidomide or daratumumab as part of the induction therapy than in those who were treated by other regimens (41% vs 23%, p=0.007 and 78% vs 2 %, p< 0.001, respectively). The amount of collected stem cells was negatively influenced by previous lenalidomide therapy (p< 0.001) and there was a marked, but not significant difference in the ratio of unsuccessful mobilization attempts (11.3% vs 4.3%, p=0.056). Interestingly, R-ISS stages and treatment responses had no impact on the efficacy of the mobilization procedure. **Conclusions:** The administration of solo G-CSF is a safe method of stem cell mobilization, however the higher rate of plerixafor administration and unsuccessful attempts may question its cost-effectivity.

P-169

Clinical features and outcome patterns of newly diagnosed multiple myeloma patients who are candidate for transplant: a single center experience in Paraguay

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Introduction: The advances in the management of multiple myeloma (MM) have yielded improved outcomes. Both the use of novel therapies and consolidation with autologous stem-cell transplantation have demonstrated superior overall response and progression-free survival rates. However, these are not readily available in most Latin American countries. Here, we aim to characterize the clinico-epidemiological features, treatment and outcome patterns of newly diagnosed MM patients in a referral center in Paraguay. **Methods:** We conducted a retrospective observational cohort study. Data were collected from clinical records, classified according to the International Staging System (ISS) and stage of the disease. Clinical and epidemiological characteristics were analyzed as well as access to first-line transplantation in newly diagnosed MM patients diagnosed from 2018 to 2022. **Results:** We included 127 patients aged 65 years and younger. Most patients were male (52%), with IgG immunoglobulin subtype (69%), and the most frequently with Kappa light chain (59%). According to the ISS classification, 40% of the patients were ISS2 at diagnosis, 34% ISS1 and 26% ISS3. Stage at diagnosis were: IIA in 32% of patients, IIB 24%, IIIA 20%, IIIB 13% IA 10% and IB 1%. Initial clinical presentations included

anemia in 75% of the patients, 53% had renal failure, and 26% had bone lesions. The first line scheme in patients without renal failure was VTD (Bortezomib, Thalidomide, Dexamethasone), and patients with renal failure received CyBorD (Cyclophosphamide, Bortezomib, Dexamethasone). About 58% of the patients were able to access a transplant in the first line of treatment. The patients who did not have access to transplantation were due to progression during first line or death due to infectious causes. **Conclusions:** To our knowledge, this is the first study that characterizes Paraguayan patients with newly diagnosed MM, which also allows us to assess the number of patients accessing a standard treatment that achieves adequate responses to be able to undergo Autologous Bone Marrow Transplantation (BMT).

P-170

Stem cell mobilization and autologous stem cell transplantation after induction with bendamustine, prednisone and bortezomib (BPV) in 135 untreated myeloma patients with variable renal function

Song-Yau Wang[1], Susann Fricke[1], Tanja Holzhey[1], Vladan Vucinic[1], Georg-Nikolaus Franke[1], Uwe Platzbecker[1], Maximilian Merz[1], Wolfram Pönisch[1]

[1]University of Leipzig

Introduction: Autologous stem cell transplantation (ASCT) is the standard first line treatment for younger patients (pts) (< 70 years) with multiple myeloma (MM). Approximately 20-50 % of all pts already display an impaired kidney function at diagnosis. However, most of MM pts with severe renal dysfunction are excluded from ASCT studies. Bortezomib and bendamustine have both been identified as quickly acting and well-tolerated drugs for pts with MM-induced renal failure. In this retrospective study we analyzed the efficacy of a BPV induction therapy prior ASCT in newly diagnosed MM pts depending on the severity of renal impairment. Furthermore, additional information is needed on stem cell toxicity of BPV-induction using chemomobilization. **Methods:** Between October 2008 and November 2019, 135 pts with newly diagnosed MM were treated with BPV-induction consisting of bendamustine 60mg/m^2 on days 1 and 2, bortezomib 1.3mg/m^2 on days 1, 4, 8 and 11 and prednisone 100mg on days 1, 2, 4, 8 and 11. PBSC collection was performed 2-3 weeks after BPV induction. **Results:** The majority of pts (n=117; 87%) responded after median 2 (range 1-6) BPV-cycles with 9 sCR, 3 CR, 12 nCR, 39 VGPR and 54 PR. For stem cell mobilization, 111 pts received cyclophosphamide 4g/m^2 and 24 pts with severe renal failure or pre-existing heart disease 1-2g/m^2. Stem cell counts of CD34+≥20x10^6/L in the peripheral blood were achieved in 131 (97%) pts after a median of 12 (range 9-17) days. Further four pts (3%) with poor stem cell mobilization on day 15 received additional plerixafor. In 96 of 135 pts (71%) a single apheresis was sufficient to reach the target of 8x10^6 CD34+/kg. Transplant related mortality was 0.7%. Engraftment was successful in 134 of 135 pts. After first ASCT ORR increased to 99% with 33 sCR, 10 CR, 32 nCR, 41 VGPR and 17 PR. With a median observation time of 51 months, median PFS was 47 months and 60 months OS was 67%. Pts were divided into four groups depending on the severity of renal impairment: group A 13 pts with eGFR < 15mL/min, group B 15 pts with eGFR 15-29mL/min, group C 19 pts with eGFR 30-59mL/min and group D 88 pts with eGFR ≥60mL/min. At the time of diagnosis, 8 out of 13 pts in group A were dialysis dependent. We observed no significant difference in the median PFS between pts with normal/mild, moderate, severe renal dysfunction and renal failure/dialysis (50 vs 47 vs 34 vs 24 months, p=0.053) and in the 60 months OS (69 vs 72 vs 58 vs 70%, p=0.23). Following the ASCT, the renal response rate improved from 61% after BPV induction to 74% with 18 CRrenal (47%), 3 PRrenal (8%) and 7 MRrenal (18%). Four of the eight dialysis-dependent pts became dialysis-independent. **Conclusions:** BPV is a highly effective and well-tolerated induction-treatment protocol prior to ASCT in patients with MM-induced renal failure. Pretreatment with two cycles of BPV has no negative influence on stem cell mobilization and hematopoietic recovery after ASCT.

P-171

The changing landscape of peri-transplant adverse events with HDT/ASCT and the impact on long term outcomes for myeloma patients

Sarah Wyman[1], Nisha Joseph[1], Oyinda Adisa[2], Tom Matich[3], Madhusmita Behera[4], Michael Graiser[1], Kathryn Simon[1], Manali Rupji[1], Jonathan Kaufman[1], Craig Hofmeister[1], Vikas Gupta[1], Madhav Dhodapkar[1], Amelia Langston[1], Sagar Lonial[1], Ajay Nooka[4]

[1]Winship Cancer Institute at Emory University, Atlanta, GA, USA; [2]Data and Technology Shared Resource, Winship Cancer Institute of Emory University; [3]IT Data Solutions, Office of Information Technology; [4]Emory University School of Medicine

Introduction: High dose therapy followed by autologous stem cell transplant (HDT/ASCT) remains standard of care for newly diagnosed transplant-eligible patients with myeloma. Given the morbidity and mortality associated with HDT/ASCT, the decision to proceed with HDT/ASCT necessitates a careful discussion and shared decision making of risks vs benefits. With the changing landscape of improved supportive care, we reviewed the rates of both immediate and long-term impact of peri-transplant complications. **Methods:** Variables of interest were extracted from the Clinical Data Warehouse (CDW), a Structured Query Language (SQL) database. A tiered algorithmic approach was developed to automate the extraction of data elements from the CDW utilizing SQL scripts, which were manually validated. Neutropenic fever rates (ASCO definition), microbiology, radiology, and culture data were all used for our automated extraction. We used two time periods (decade 1: 2000-2010, decade 2: 2011-2021) to evaluate the changes by era. All values were reported as decade 1 vs decade 2, respectively. **Results:** For the 2,970 patients that underwent HDT/ASCT from 2000-2021, 614 (20.7%) received HDT/ASCT in decade 1. Median age at transplant was 58.1 (range, 27.1-77.4) vs 62.3 years (range, 16.8-79.9), p< 0.001. Patients ≥ 70 were transplanted more in decade 2 (5.9% vs 17.4%, p< 0.001). The time from diagnosis to HDT/ASCT was shorter [10.6 (2-157) vs 6.7 months (1-231), p< 0.0001]

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P-170

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P-171

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P-170

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P-171

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and higher rates of ≥VGPR pre-transplant were achieved in decade 2 (12.5% vs 57.3%, p< 0.001). 71.6% of patients received melphalan 200 mg/m^2. C.diff occurred in 5.5% and respiratory infections in 3.3%, not different by decade. Increased incidence of SVT (4.6% vs 7.4%, p< 0.006), bacteremia (5 vs 8.9%, p< 0.001), neutropenic fevers (64.7 vs 82.4, p< 0.001), ICU transfers (2.6 vs 5.9%, p< 0.001) occurred in decade 2. Despite transplanting older patients, the rate of 30-day readmits (10.4 vs 8%; p=0.037), 30-day mortality (1.5% vs 0.7%, p=0.05) and 100-day mortality (3.6% vs 1.6%, p=0.002) decreased in decade 2. The OS improved in decade 2 (7.2 vs 10.5 years, p< 0.001). Developing bacteremia, c. diff, and respiratory infections peri-transplant as well as transplant age ≥70 did not have any impact on OS, however developing SVT (9.25 vs 6.6 years, p< 0.001) and ICU transfer peri-transplant (9.2 vs 6.3 years, p< 0.001) are associated with shorter OS. **Conclusions:** More elderly patients underwent HDT/ASCT in decade 2 and have gained the survival advantage the decade had to offer both from the benefit of modern induction therapies as seen by increased ≥VGPR rates pre-transplant as well as HDT/ASCT itself. Transplanting elderly patients did not have any impact on long term survival. Developing SVT and ICU transfer are associated with less optimal outcomes. The 30-day, 100-day mortality, re-admit rates have all improved in the last decade, allowing room for a meaningful discussion with patients favoring HDT/ASCT.

P-172

Autologous stem cell transplantation for multiple myeloma – a single center experience from India

Sanjeev Yadav[1], Faheema Hasan[1], Dinesh Chandra[1], Manish Kumar Singh[1], Khaiqur Rahman[1], Ruchi Gupta[1], Rajesh Kashyap[1], Soniya Nityanand[1]

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Introduction: Autologous stem cell transplantation (ASCT) remains the standard of care for patients with newly diagnosed multiple myeloma (MM) despite the approval of novel agents. Numerous trials have demonstrated a progression-free survival (PFS) advantage with ASCT. To study the demographics, clinical profile, and outcomes of patients with MM undergoing ASCT at a tertiary care center in northern India. **Methods:** This is a medical records review of 29 patients with MM who underwent ASCT between 2007 and 2021. The demographics, clinical profile, induction regimen, details of ASCT, and outcomes were retrieved. Descriptive analysis, Progression Free Survival (PFS), and Overall Survival (OS) were determined. Data are expressed as median and interquartile range (IQR). **Results:** The median age of the cohort was 56 years (50-61) and 21 (72%) were males. The follow-up duration from diagnosis was 60 months (18-74). The most common immunoglobulin isotype was IgG kappa (28%) followed by IgG lambda (24%) and IgA kappa (21%). R-ISS staging was available for 26 patients and 21 of 26 (72%) had stage III disease. High-risk cytogenetics were identified in 19 patients (66%). Nine patients (47%) had t(4;14) and four (21%) had deletion 17p. Triplet induction consisting of Bortezomib, dexamethasone, and IMiD was the most common induction regimen (18, 62%). Two patients received quadruplet induction consisting of daratumumab, bortezomib, lenalidomide, and dexamethasone. The median time from diagnosis to transplant was 12 months (8-22). Most patients (24, 79%) were transplanted in first complete remission (CR1). The most common conditioning regimen was high dose melphalan, dosed at 200mg/m^2. Nine patients (31%) received a reduced dose of melphalan (140mg/m^2) in view of reduced GFR, poor ECOG performance status, secondary amyloidosis, and other co-morbidities. The median stem cell dose was 5.44 x10^6/kg (4.98-6.01 x 10^6/kg). The median time to engraftment was 9 days (8-10). Mucositis was the most common complication post ASCT (26, 90%), and grade 3/4 mucositis complicated seven transplants (24%). Three patients (10.3%) died during the post-ASCT neutropenic period secondary to sepsis. Eleven patients (42%) relapsed, and the median duration of remission (PFS) post-ASCT was 34 months (30.5-40.5) (Figure 1). Of those who relapsed, five (45.5%) died of disease progression, one died (9%) of myocardial infarction and five patients (45.5%) were alive at the time of the last follow-up. The OS was 89.7% with the median survival time post-ASCT being 39 months (7-60). **Conclusions:** ASCT remains the standard of care for patients with multiple myeloma, especially in lower-middle income countries where access to second-line therapies is limited.

P-173

Development and validation of an individualized and weighted myeloma prognostic score system (MPSS) in patients with newly diagnosed multiple myeloma

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Introduction: Multiple myeloma (MM) is a malignancy of terminally differentiated antibody-secreting plasma cells in the bone marrow with highly variable survival outcomes. Precise risk stratification not only plays a vital role in predicting patient prognoses, but critically can be used to develop risk-adapted treatment regimens. However, current risk stratification models do not adequately account for the heterogeneity of patients with new-diagnosed multiple myeloma (NDMM). **Methods:** In this retrospective, multicohort study, we collected clinical data from 1792 NDMM patients and formulated a weighted Myeloma Prognostic Score System (MPSS) risk model to predict overall survival (OS). Construction of the MPSS model was carried out based on the National Longitudinal Cohort of Hematological

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P-172

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Introduction: Autologous stem cell transplantation (ASCT) remains the standard of care for patients with newly diagnosed multiple myeloma (MM) despite the approval of novel agents. Numerous trials have demonstrated a progression-free survival (PFS) advantage with ASCT. To study the demographics, clinical profile, and outcomes of patients with MM undergoing ASCT at a tertiary care center in northern India. **Methods:** This is a medical records review of 29 patients with MM who underwent ASCT between 2007 and 2021. The demographics, clinical profile, induction regimen, details of ASCT, and outcomes were retrieved. Descriptive analysis, Progression Free Survival (PFS), and Overall Survival (OS) were determined. Data are expressed as median and interquartile range (IQR). **Results:** The median age of the cohort was 56 years (50-61) and 21 (72%) were males. The follow-up duration from diagnosis was 60 months (18-74). The most common immunoglobulin isotype was IgG kappa (28%) followed by IgG lambda (24%) and IgA kappa (21%). R-ISS staging was available for 26 patients and 21 of 26 (72%) had stage III disease. High-risk cytogenetics were identified in 19 patients (66%). Nine patients (47%) had t(4;14) and four (21%) had deletion 17p. Triplet induction consisting of Bortezomib, dexamethasone, and IMiD was the most common induction regimen (18, 62%). Two patients received quadruplet induction consisting of daratumumab, bortezomib, lenalidomide, and dexamethasone. The median time from diagnosis to transplant was 12 months (8-22). Most patients (24, 79%) were transplanted in first complete remission (CR1). The most common conditioning regimen was high dose melphalan, dosed at 200mg/m^2. Nine patients (31%) received a reduced dose of melphalan (140mg/m^2) in view of reduced GFR, poor ECOG performance status, secondary amyloidosis, and other co-morbidities. The median stem cell dose was 5.44 x10^6/kg (4.98-6.01 x 10^6/kg). The median time to engraftment was 9 days (8-10). Mucositis was the most common complication post ASCT (26, 90%), and grade 3/4 mucositis complicated seven transplants (24%). Three patients (10.3%) died during the post-ASCT neutropenic period secondary to sepsis. Eleven patients (42%) relapsed, and the median duration of remission (PFS) post-ASCT was 34 months (30.5-40.5) (Figure 1). Of those who relapsed, five (45.5%) died of disease progression, one died (9%) of myocardial infarction and five patients (45.5%) were alive at the time of the last follow-up. The OS was 89.7% with the median survival time post-ASCT being 39 months (7-60). **Conclusions:** ASCT remains the standard of care for patients with multiple myeloma, especially in lower-middle income countries where access to second-line therapies is limited.

P-173

Development and validation of an individualized and weighted myeloma prognostic score system (MPSS) in patients with newly diagnosed multiple myeloma

Wenqiang Yan[1], Xuehan Mao[1], Mery David[2], Yan Xu[1], Dehui Zou[1], John Shaughnessy[2], Kenneth Anderson[3], Fenghuang Zhan[4], Lugui Qiu[1], Gang An[1]

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Introduction: Multiple myeloma (MM) is a malignancy of terminally differentiated antibody-secreting plasma cells in the bone marrow with highly variable survival outcomes. Precise risk stratification not only plays a vital role in predicting patient prognoses, but critically can be used to develop risk-adapted treatment regimens. However, current risk stratification models do not adequately account for the heterogeneity of patients with new-diagnosed multiple myeloma (NDMM). **Methods:** In this retrospective, multicohort study, we collected clinical data from 1792 NDMM patients and formulated a weighted Myeloma Prognostic Score System (MPSS) risk model to predict overall survival (OS). Construction of the MPSS model was carried out based on the National Longitudinal Cohort of Hematological

and higher rates of ≥VGPR pre-transplant were achieved in decade 2 (12.5% vs 57.3%, p< 0.001). 71.6% of patients received melphalan 200 mg/m^2. C.diff occurred in 5.5% and respiratory infections in 3.3%, not different by decade. Increased incidence of SVT (4.6% vs 7.4%, p< 0.006), bacteremia (5 vs 8.9%, p< 0.001), neutropenic fevers (64.7 vs 82.4, p< 0.001), ICU transfers (2.6 vs 5.9%, p< 0.001) occurred in decade 2. Despite transplanting older patients, the rate of 30-day readmits (10.4 vs 8%; p=0.037), 30-day mortality (1.5% vs 0.7%, p=0.05) and 100-day mortality (3.6% vs 1.6%, p=0.002) decreased in decade 2. The OS improved in decade 2 (7.2 vs 10.5 years, p< 0.001). Developing bacteremia, c. diff, and respiratory infections peri-transplant as well as transplant age ≥70 did not have any impact on OS, however developing SVT (9.25 vs 6.6 years, p< 0.001) and ICU transfer peri-transplant (9.2 vs 6.3 years, p< 0.001) are associated with shorter OS. **Conclusions:** More elderly patients underwent HDT/ASCT in decade 2 and have gained the survival advantage the decade had to offer both from the benefit of modern induction therapies as seen by increased ≥VGPR rates pre-transplant as well as HDT/ASCT itself. Transplanting elderly patients did not have any impact on long term survival. Developing SVT and ICU transfer are associated with less optimal outcomes. The 30-day, 100-day mortality, re-admit rates have all improved in the last decade, allowing room for a meaningful discussion with patients favoring HDT/ASCT.

P-172

Autologous stem cell transplantation for multiple myeloma – a single center experience from India

Sanjeev Yadav[1], Faheema Hasan[1], Dinesh Chandra[1], Manish Kumar Singh[1], Khaiqur Rahman[1], Ruchi Gupta[1], Rajesh Kashyap[1], Soniya Nityanand[1]

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P-173

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Diseases in China (NCT04645199) cohort, external validation cohort was created using TT2, TT3a, and TT3b cohorts from a series of randomized prospective studies from the University of Arkansas for Medical Sciences (UAMS). **Results:** Each risk factor was defined as its weighted value respectively according to their hazard ratio for OS (thrombocytopenia 2, elevated LDH 1, ISS III 2, one high-risk cytogenetic aberration [HRA] 1, and ≥2 HRA 2 points). In the training cohort, patients were furtherly stratified into four risk groups: MPSS I (22.5%, 0 points), II (17.6%, 1 points), III (38.6%, 2-3 points), and IV (21.3%, 4-7 points). MPSS risk stratification showed optimal discrimination, as well as calibration, of four risk groups with median OS of 91.0, 69.8, 45.0, and 28.0 months, for patients in MPSS I to IV groups (P< 0.001), respectively. Importantly, the MPSS model retained its prognostic value in the internal validation cohort and an independent external validation cohort, and exhibited significant risk distribution compared with conventional prognostic models (R-ISS, R2-ISS, and MASS). **Conclusions:** In conclusion, we formulated and validated the MPSS risk model to predict the prognosis of patients with MM using readily available standard clinical and genetic test data. The established MPSS profile shows a better performance in risk discrimination than the current R-ISS, R2-ISS, and MASS. A score-based risk stratification is derived, and identifies patients with high and ultra-high risk of death after diagnosis and may therefore aid the development of more personalized treatment strategies, especially for patients for whom current therapies are likely to fail.

P-174

Early relapse within 18 months (ER18) is a powerful dynamic predictor for prognosis and could revise static risk distribution in patients with new-diagnosed multiple myeloma

Wenqiang Yan[1], Jingyu Xu[1], Huishou Fan[2], Lugui Qiu[1], Gang An[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [2]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union Medical College

Introduction: Due to the wide application of novel agents, the survival outcomes of patients with newly-diagnosed multiple myeloma (NDMM) have significantly improved in recent years. However, almost NDMM patients eventually relapse owing to the acquisition of drug resistance and sustained residual disease. However, the definitions of ER in MM vary from study to study. **Methods:** The study was based on the National Longitudinal Cohort of Hematological Diseases in China (NCT04645199). A total of 629 patients diagnosed with NDMM between January 2013 and December 2019 were included in this study. We evaluated different ER definitions and investigated the underlying relationship between ER with static risk distribution. **Results:** We first summarized all studies about ER published to date and found that relapse within 18 months from the initial treatment or within 12 months from SCT was mostly used to define early PD in many studies. Our findings indicate that ER18 could effectively balance the bias of ER definitions for patients with or without ASCT, as well as fulfill all requirements for a dynamic risk predictor. The ER18 population (114/587; 19.4%) presented with more aggressive biologic features compared to a reference cohort (P< 0.001), with a significant short median overall survival (OS) of 28.9 months. We also described the specific transitions from static risk profile to dynamic risk distribution in our cohort and then constructed a mixed-risk pattern to identify four novel populations with distinct survival outcomes (P< 0.001). A total of 367 (67.0%) patients presented with at least one high-risk feature: those with ISS III stage, elevated LDH, and HRCAs were classified as baseline high-risk (BHR) group; 86 (23.4%) patients experienced ER18 and further defined as mixed high-risk (MHR) population, and the remaining patients were classified as static high-risk (SHR). Within patients without BHR features, the dynamic risk event (ER18) occurred in 21(11.6%) patients, defined as functional high-risk (FHR). As expected, the MHR population had the worst outcomes with a median OS of 25.9 months (P< 0.001). Of note, FHR patients had similar survival compared to SHR patients (OS: not reached vs. 71.4 months; P=0.235; Figure 3B), supporting the importance of dynamic risk factor (ER18) as a prognostic factor and further suggesting that lack of durable response could exert an adverse impact on prognosis similar to baseline high-risk variables. Moreover, we confirmed that ER18 refined the predictive accuracy of the Revised International Staging System stage (R-ISS). **Conclusions:** ER18 maintains its significance as a predictor of prognosis in the multivariate analysis. The underlying correlation between clinical features at diagnosis and dynamic predictor (ER18) was demonstrated. Our results further indicated that ER18 was a refining factor for the R-ISS staging system and that the refined model could actualize a more valuable risk distribution.

P-175

Improving Anti-BCMA CAR-T functionality with novel immunomodulatory agent Iberdomide (CC220) in Multiple Myeloma

Adolfo Aleman[1], Ariel Kogan-Zajdman[1], Bhaskar Upadhyaya[1], Oliver Van Oekelen[1], Lucia Chen[1], Violetta Leshchenko[1], Sundar Jagannath[2], Samir Parekh[1]

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Introduction: Anti-B Cell maturation antigen (BCMA) targeting Chimeric Antigen Receptor T Cells (CAR-T) is a highly effective cellular therapy for Multiple Myeloma (MM). Despite CAR-T being a promising treatment, relapse is common and there is a subset of patients that do not respond at all. Our prior studies (Oekelen et al, Blood 2021) have shown that Iberdomide can activate T and NK cells while reducing exhaustion markers (TIGIT) in MM patients. Based on this, we hypothesize that Iberdomide, could improve anti-BCMA CAR-T cell therapy in anti-MM cytotoxicity. **Methods:** In this in vitro study, we evaluated the impact of Iberdomide on the persistence, proliferation, and activation of Anti-BCMA

Diseases in China (NCT04645199) cohort, external validation cohort was created using TT2, TT3a, and TT3b cohorts from a series of randomized prospective studies from the University of Arkansas for Medical Sciences (UAMS). **Results:** Each risk factor was defined as its weighted value respectively according to their hazard ratio for OS (thrombocytopenia 2, elevated LDH 1, ISS III 2, one high-risk cytogenetic aberration [HRA] 1, and ≥2 HRA 2 points). In the training cohort, patients were furtherly stratified into four risk groups: MPSS I (22.5%, 0 points), II (17.6%, 1 points), III (38.6%, 2-3 points), and IV (21.3%, 4-7 points). MPSS risk stratification showed optimal discrimination, as well as calibration, of four risk groups with median OS of 91.0, 69.8, 45.0, and 28.0 months, for patients in MPSS I to IV groups (P< 0.001), respectively. Importantly, the MPSS model retained its prognostic value in the internal validation cohort and an independent external validation cohort, and exhibited significant risk distribution compared with conventional prognostic models (R-ISS, R2-ISS, and MASS). **Conclusions:** In conclusion, we formulated and validated the MPSS risk model to predict the prognosis of patients with MM using readily available standard clinical and genetic test data. The established MPSS profile shows a better performance in risk discrimination than the current R-ISS, R2-ISS, and MASS. A score-based risk stratification is derived, and identifies patients with high and ultra-high risk of death after diagnosis and may therefore aid the development of more personalized treatment strategies, especially for patients for whom current therapies are likely to fail.

P-174

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CAR-T cells. Using custom spectral flow cytometry panels, we captured dynamics of the CAR-T cell phenotypic composition and proliferation in response to Iberdomide treatment. Additionally, we analyzed the functional effect of Iberdomide on CAR-T cells by quantifying antigen specific cytokine production and cytotoxic activity. **Results:** Our results demonstrate that treatment with Iberdomide significantly decreases the presence of transcription factors Ikaros and Aiolos in CAR-T cells by 24 hours ($p< 0.01$). Incubation with Iberdomide promoted persistence and proliferation in IL-2 starved cells in vitro. After 96 hours, CAR-T cells treated with Iberdomide expressed significantly more Ki67 expression ($p< 0.01$) and were significantly more viable compared to control (median viability 80% compared to 30%, $p< 0.001$). The presence of Iberdomide resulted in increased activation of CAR-T cells with an increase of hallmark activation markers such as HLADR, and CD69 ($p< 0.05$) and decrease in the expression of TIGIT ($p=0.041$). Iberdomide increased antigen specific cytokine production against BCMA expressing MM cells by 6 hours, specifically increasing the antigen specific production of IL-2, IL-17a, and TNFa by CAR-T cells ($p< 0.01$). Iberdomide enhanced antigen specific toxicity by CAR-T cells by 46% compared to control by 48 hours ($p< 0.001$). These findings suggest that Iberdomide can keep CAR-T cells in an activated state counteracting exhaustion and promote the survival and function of CAR-T cells, addressing two major mechanisms underlying CAR-T failure and resistance. **Conclusions:** Our study provides evidence that combination treatment with Iberdomide can enhance the persistence and proliferation of anti-BCMA CAR-T cells in vitro. Moreover, Iberdomide induced activation of CAR-T cells leads to improved antigen specific cytokine production and cytotoxic activity. These findings highlight the potential of Iberdomide as an adjunctive therapy to overcome CAR-T cell resistance ultimately improving the therapeutic efficacy of anti-BCMA CAR-T therapy in patients with MM. We are planning further studies to validate these promising results in vivo to ultimately translate into clinical application.

P-176

ETV4-dependent transcriptional plasticity maintains MYC expression and results in IMiD resistance in multiple myeloma

Benjamin Barwick[1], Paola Neri[2], Ines Tagoug[2], Ranjan Maity[2], Caleb Stein[3], Noemie Leblay[2], Sungwoo Ahn[2], Holly Lee[2], Remi Tilmont[2], Jonathan Keats[4,5], Sagar Lonial[1], Leif Bergsagel[3], Lawrence Boise[1], Nizar Bahlis[2]

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P-177

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CAR-T cells. Using custom spectral flow cytometry panels, we captured dynamics of the CAR-T cell phenotypic composition and proliferation in response to Iberdomide treatment. Additionally, we analyzed the functional effect of Iberdomide on CAR-T cells by quantifying antigen specific cytokine production and cytotoxic activity. **Results:** Our results demonstrate that treatment with Iberdomide significantly decreases the presence of transcription factors Ikaros and Aiolos in CAR-T cells by 24 hours ($p< 0.01$). Incubation with Iberdomide promoted persistence and proliferation in IL-2 starved cells in vitro. After 96 hours, CAR-T cells treated with Iberdomide expressed significantly more Ki67 expression ($p< 0.01$) and were significantly more viable compared to control (median viability 80% compared to 30%, $p< 0.001$). The presence of Iberdomide resulted in increased activation of CAR-T cells with an increase of hallmark activation markers such as HLADR, and CD69 ($p< 0.05$) and decrease in the expression of TIGIT ($p=0.041$). Iberdomide increased antigen specific cytokine production against BCMA expressing MM cells by 6 hours, specifically increasing the antigen specific production of IL-2, IL-17a, and TNFa by CAR-T cells ($p< 0.01$). Iberdomide enhanced antigen specific toxicity by CAR-T cells by 46% compared to control by 48 hours ($p< 0.001$). These findings suggest that Iberdomide can keep CAR-T cells in an activated state counteracting exhaustion and promote the survival and function of CAR-T cells, addressing two major mechanisms underlying CAR-T failure and resistance. **Conclusions:** Our study provides evidence that combination treatment with Iberdomide can enhance the persistence and proliferation of anti-BCMA CAR-T cells in vitro. Moreover, Iberdomide induced activation of CAR-T cells leads to improved antigen specific cytokine production and cytotoxic activity. These findings highlight the potential of Iberdomide as an adjunctive therapy to overcome CAR-T cell resistance ultimately improving the therapeutic efficacy of anti-BCMA CAR-T therapy in patients with MM. We are planning further studies to validate these promising results in vivo to ultimately translate into clinical application.

P-176

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P-178

Evolution of the multiple myeloma treatment landscape in Portugal: a 5-year longitudinal analysis of treatment patterns in nationwide clinical practice

Rui Bergatim[1,2,3,4], Catarina Geraldes[5], Cristina João[6], Paulo Lúcio[6], Manuel Neves[7], Fernanda Trigo[8], Miguel Pereira Ventura[9], Diogo Ramos[10]

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Introduction: The treatment pattern evolution for Multiple Myeloma (MM) in Portugal remains unclear, particularly how therapeutic innovation impacted clinical practice. This study aimed to describe and characterize MM treatment landscape over a 5-year period in Portugal. **Methods:** A retrospective longitudinal multicenter study was conducted through secondary data from electronic health records of 11 Portuguese National Health Service hospitals between Sep/2017-Aug/2022. MM patient population was identified based on drug consumption data of MM-specific therapies (e.g., proteasome inhibitors, immunomodulators, anti-CD38 mAbs). Patient drug consumption profile was analyzed, and MM treatment regimens identified through clustering of concomitant antineoplastic drugs. Treatment patterns were characterized based on patient dynamics (naïve, ongoing, switch, drop-out), stem cell transplant (SCT) eligibility (eligible (SCT-E) vs non-eligible (SCT-NE)), and treatment lines (1L to 4L+). Outcomes included population characterization (patient number, age, sex (M:F) ratio), regimen patient share per treatment line and dynamic subgroups. Time-to-event analysis was carried between two consecutive 5-year time series (Sep/2012-Aug/2017 and Sep/2017-Aug/22) to estimate variation in treatment duration (TD) and time to next treatment (TTNT). **Results:** The treated MM population increased by 53% during the 5-year period (2017: N=825; 2022: N=1266). Age and sex distribution remained stable, with a median age of 70 years and 1,2:1 sex ratio in 2022. Naïve patients increased by 22%, averaging a 5% yearly growth, with no major shift in SCT eligibility split (1:1 ratio in 2022). Treatment line analysis showed a positive trend in patients achieving 3L+, with an increase of 12% to 21% from

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2017 to 2022. Treatment drop-out decreased in 2L to 3L and 3L to 4L+, with a drop-out rate of 17% and 19% per switch subgroup, respectively, in 2022. Main 1L regimens in SCT-E (VCd and VTd) and SCT-NE subgroups (VMP and VCd) remained stable, with daratumumab-based regimens increase in 2022 in all subgroups. Patient share in maintenance therapy increased from 5% to 16% in the overall treated population, dominated by lenalidomide in 2022. The 2L and 3L treatment pattern changed considerably, with daratumumab-based regimens dominating patient share in 2022 (2L-43%; 3L-35%). In 4L+ a heterogenous treatment pattern emerged, with no standard of care identified, being carfilzomib- and daratumumab-based regimens the most relevant in 2022. Overall median TD increased in SCT-E subgroup from 5 to 19 months between time series, driven by maintenance therapy, and remained stable for SCT-NE patients (10 months). Regarding TTNT, median time increased between 3L to 4L+ in SCT-E patients from 5.5 to 9 months. **Conclusions:** MM treatment landscape changed during a 5-year period, characterized by an increase in treated patients, patients achieving advanced treatment lines, and improved access to therapeutic innovation in earlier treatment stages of the disease.

P-179

Altered lipid metabolism in IMiD/CELMoD resistant multiple myeloma confers novel and targetable vulnerabilities

Sarah Bird[1,2], Yitao Xu[3], Fernando Sialana[1], Marco Licciardello[1], Harvey Che[1], Saleh Tamin[4], Habib Bouguenina[1], Yura Grabovska[1], Enze Liu[5], Salomon Morales[1], Yakinthi Chrisochoidou[1], Yigen Li[1], Shannon Martin[1], Amy Wilson[1], Erin Flynt[4], Brian Walker[5], Jyoti Choudhary[1], Paul Clarke[1], Hector Keun[3], Charlotte Pawlyn[1]

[1]The Institute of Cancer Research; [2]Royal Marsden Hospital; [3]Imperial College London; [4]Bristol Myers Squibb; [5]Melvin and Bren Simon Comprehensive Cancer Center, Division of Hematology and Oncology, School of Medicine, Indiana University

Introduction: IMiDs/CELMoDs are a cornerstone of myeloma treatment; however a major barrier to improving patient outcomes is the inevitable development of drug resistance. Understanding resistance mechanisms is critical to enable the advancement of targeted treatment strategies. **Methods:** Acquired IMiD/CELMoD resistant MM1s and H929 myeloma cell lines were characterised by whole exome sequencing, RNA-seq and proteomics. A genome-wide loss-of-function CRISPR screen was carried out in Iberdomide (Iber)-resistant MM1s; gene effect scores were calculated with the Chronos model and compared to parental MM1s using data from the DepMap portal. Membrane Bound Transcription Factor Peptidase Site 1 (MBTPS1) inhibitor PF-429242 was used to inhibit activation of the Sterol Regulatory-Element Binding Protein (SREBP) pathway. Stable isotope labelling experiments using 13C6-glucose assessed lipid synthesis. Using unpaired patient RNA-seq data, lipid gene transcript levels were compared between 736 newly diagnosed patients and 270 patients relapsing on lenalidomide. **Results:** Quantitative proteomic analysis identified common changes in lipid synthesis pathways, including the SREBP pathway, across the resistant cell lines. Stearoyl-CoA Desaturase (SCD), a key effector of the SREBP pathway, was one of only 5 proteins with significantly altered expression in all 6 resistant lines compared to control (log2FCs ranging from -0.37 to -1.50 (adj $p < 0.05$)). A genome-wide CRISPR screen using Iber-resistant MM1s cells identified potential new dependencies (gene effect score -0.5 in parental cells) in 47 genes including SCD and MBTPS1. MBTPS1 is critical for activation of the SREBP pathway and demonstrated one of the largest changes in gene effect (-1.4 vs –0.3). PF-429242 showed significantly greater reduction in cell proliferation in the IMiD/CELMoD resistant H929 cells compared to controls. 13C6-glucose labelling experiments showed that in Iber-resistant MM1s and H929 (compared to controls) the proportion of newly synthesised palmitic and stearic acid was reduced. The oleic acid/stearic acid and palmitoleic acid/palmitic acid ratios were also decreased, suggesting the flux of fatty acid desaturation catalysed by SCD was reduced. The fraction of glucose-derived lipogenic acetyl-CoA was also reduced in the resistant lines, indicating that resistance decreased glucose contribution to fatty acid synthesis with potential use of alternative carbon sources. There was a trend for increased synthesis of saturated fatty acids with PF-429242 treatment in Iber-resistant H929, but not its control. In patient RNA-seq data several fatty acid synthesis genes were significantly differentially expressed, including SCD and MBTPS1, suggesting the changes seen in cell lines may be replicated in patient data. **Conclusions:** The development of IMiD/CELMoD resistance is associated with alterations in lipid metabolism, suggesting a role in resistance biology that may confer novel and targetable vulnerabilities.

P-180

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2017 to 2022. Treatment drop-out decreased in 2L to 3L and 3L to 4L+, with a drop-out rate of 17% and 19% per switch subgroup, respectively, in 2022. Main 1L regimens in SCT-E (VCd and VTd) and SCT-NE subgroups (VMP and VCd) remained stable, with daratumumab-based regimens increase in 2022 in all subgroups. Patient share in maintenance therapy increased from 5% to 16% in the overall treated population, dominated by lenalidomide in 2022. The 2L and 3L treatment pattern changed considerably, with daratumumab-based regimens dominating patient share in 2022 (2L-43%; 3L-35%). In 4L+ a heterogenous treatment pattern emerged, with no standard of care identified, being carfilzomib- and daratumumab-based regimens the most relevant in 2022. Overall median TD increased in SCT-E subgroup from 5 to 19 months between time series, driven by maintenance therapy, and remained stable for SCT-NE patients (10 months). Regarding TTNT, median time increased between 3L to 4L+ in SCT-E patients from 5.5 to 9 months. **Conclusions:** MM treatment landscape changed during a 5-year period, characterized by an increase in treated patients, patients achieving advanced treatment lines, and improved access to therapeutic innovation in earlier treatment stages of the disease.

P-179

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the mechanisms driving the high-risk disease progression associated with 1q21+ have not been identified. This study aims to identify new druggable targets in the 1q21 region. **Methods:** We purified PCs from BM samples of 18 newly diagnosed MM patients. In addition, a cohort of 11 smoldering (SMM) was included in the study. Fluorescent in situ hybridization analysis was performed in purified CD138+ PCs in all patients to access copy number alterations in the 1q21 region. The expression profile of all 29 samples was generated using GeneChip ClariomD Arrays (Affymetrix Inc., Santa Clara, CA, USA). The smar package was used to identify differentially expressed genes between 1q21+ and control samples. **Results:** Among the most significant upregulated genes in our analysis, we identified the expression of PYGOPUS 2 (PYGO2), a downstream component of the Wnt signaling pathway, to be significantly upregulated in CD138+ MM cells with 1q21+ as compared to those without 1q21+ ($p= 0.0008$). Additionally, we found a significant positive correlation between gene expression and the 1q21 copy number ($p= < 0.0001$, $r= 0.6738$), correlated with 1q21 copy number but not with disease stage (SMM vs. MM). Moreover, we assessed PYGO2 mRNA and protein expression levels in a panel of MM human cell lines (HMCLs) carrying 1q21+. HMCL OCI-MY5 was used as a negative control. Our results showed that PYGO2 was higher in HMCLs with 1q21+. Furthermore, we evaluated the mRNA and protein expression levels of PYGO2 in HMCLs resistant to carfilzomib, showing that the expression of PYGO2 was consistently upregulated. Next, to investigate the functional role of PYGO2 in patients with 1q21, we generated a knockdown of PYGO2 in HMCL JJN3 using short hairpin RNA (shRNA). We found that PYGO2 transcripts were significantly downregulated in shPYGO2 when compared to scramble control. Notably, cells lacking PYGO2 have an increased rate of cell death when compared with the scramble cell line. **Conclusions:** In conclusion, our results show that the expression of PYGO2 is significantly upregulated in MM patients carrying 1q21+, and that PYGO2 inhibition by shRNA leads to an increase in cell death in HMCLs with 1q21+. Overall, our data indicate that targeting PYGO2 could represent a novel strategy to treat MM patients with 1q21+.

P-181

Towards an IMiD sensitive C57BL/KaLwRij murine model of multiple myeloma

Emma AJ. Cheney[1], Dylan Harnas[1], Jacqueline Noll[1], Kate Vandyke[1,2], Andrew Zannettino[1], Duncan Hewett[1]

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P-182

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the mechanisms driving the high-risk disease progression associated with 1q21+ have not been identified. This study aims to identify new druggable targets in the 1q21 region. **Methods:** We purified PCs from BM samples of 18 newly diagnosed MM patients. In addition, a cohort of 11 smoldering (SMM) was included in the study. Fluorescent in situ hybridization analysis was performed in purified CD138+ PCs in all patients to access copy number alterations in the 1q21 region. The expression profile of all 29 samples was generated using GeneChip ClariomD Arrays (Affymetrix Inc., Santa Clara, CA, USA). The smar package was used to identify differentially expressed genes between 1q21+ and control samples. **Results:** Among the most significant upregulated genes in our analysis, we identified the expression of PYGOPUS 2 (PYGO2), a downstream component of the Wnt signaling pathway, to be significantly upregulated in CD138+ MM cells with 1q21+ as compared to those without 1q21+ ($p= 0.0008$). Additionally, we found a significant positive correlation between gene expression and the 1q21 copy number ($p= < 0.0001$, $r= 0.6738$), correlated with 1q21 copy number but not with disease stage (SMM vs. MM). Moreover, we assessed PYGO2 mRNA and protein expression levels in a panel of MM human cell lines (HMCLs) carrying 1q21+. HMCL OCI-MY5 was used as a negative control. Our results showed that PYGO2 was higher in HMCLs with 1q21+. Furthermore, we evaluated the mRNA and protein expression levels of PYGO2 in HMCLs resistant to carfilzomib, showing that the expression of PYGO2 was consistently upregulated. Next, to investigate the functional role of PYGO2 in patients with 1q21, we generated a knockdown of PYGO2 in HMCL JJN3 using short hairpin RNA (shRNA). We found that PYGO2 transcripts were significantly downregulated in shPYGO2 when compared to scramble control. Notably, cells lacking PYGO2 have an increased rate of cell death when compared with the scramble cell line. **Conclusions:** In conclusion, our results show that the expression of PYGO2 is significantly upregulated in MM patients carrying 1q21+, and that PYGO2 inhibition by shRNA leads to an increase in cell death in HMCLs with 1q21+. Overall, our data indicate that targeting PYGO2 could represent a novel strategy to treat MM patients with 1q21+.

P-181

Towards an IMiD sensitive C57BL/KaLwRij murine model of multiple myeloma

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Introduction: Immunomodulatory imide drugs (IMiDs), such as lenalidomide, are vital agents in the therapeutic arsenal against multiple myeloma (MM). IMiDs directly promote MM cell death via cell cycle arrest and stimulate anti-tumour immune responses in the bone marrow (BM) niche. Lack of amino acid conservation between human and mouse orthologues of Cereblon (Crbn), the IMiD binding protein, render mice resistant to IMiDs. Given this, preclinical evaluation of IMiDs' pleiotropic mechanisms of action is hindered by a lack of immunocompetent MM mouse models displaying drug sensitivity. Notably, substitution of an isoleucine in murine Crbn with the analogous human valine residue (CrbnI391V) confers IMiD sensitivity to mouse cells. Here we investigate lenalidomide sensitivity in two immunocompetent MM mouse models where either the recipient mice or engrafted tumour cells harbour a humanised CrbnI391V gene. **Methods:** C57BL/6-CrbnI391V or C57BL/KaLwRij mice were intravenously inoculated with Vk*MYC or 5TGM1-CrbnI391V cells, respectively. MM tumour burden was monitored weekly by serum paraprotein quantification or bioluminescence (BLI) imaging. After tumour establishment, mice received daily intraperitoneal injections of 10mg/kg lenalidomide or 4% DMSO. C57BL/6-CrbnI391V mice (n=8-9/group) were treated for 28-days beginning at week 7 and C57BL/KaLwRij mice (n=8/group) received 14-days of treatment from week 2. Endpoint BM and splenic GFP+ tumour burden was assessed by flow cytometry. **Results:** We aimed to separately model: (1) lenalidomide-mediated BM microenvironment anti-myeloma immune responses in C57BL/6-CrbnI391V mice transplanted with Vk*MYC cells, and (2) lenalidomide-induced direct cytotoxicity in C57BL/KaLwRij mice transplanted with 5TGM1-CrbnI391V cells. Lenalidomide produced modest, non-significant reductions in whole body, BM and splenic Vk*MYC tumour burden in C57BL/6-CrbnI391V mice (t-tests, $p>0.05$). In contrast, lenalidomide's antiproliferative effects significantly delayed 5TGM1-CrbnI391V tumour growth in C57BL/KaLwRij mice. Compared to DMSO treatment, lenalidomide treated mice showed a 46.4% decrease in whole body BLI signal (two-way ANOVA, $p< 0.05$), as well as 50.4% and 58.2% reductions in paraprotein intensity (t-test, $p< 0.001$) and BM tumour burden (t-test, $p< 0.05$), respectively. **Conclusions:** Inadequate anti-myeloma efficacy of lenalidomide in the Vk*MYC model, where only the host C57BL/6-CrbnI391V mice displayed IMiD sensitivity, highlights the need for a fully IMiD-susceptible murine system. As such, a 5TGM1-CrbnI391V transplant C57BL/KaLwRij-CrbnI391V mouse model is under development. So far, we have demonstrated that CrbnI391V expression sensitises the 5TGM1 cell line to lenalidomide's direct, antiproliferative effects in vivo. C57BL/6-CrbnI391V mice have been backcrossed onto the C57BL/KaLwRij strain for 6 generations and future studies will investigate the synergy of lenalidomide-mediated tumoricidal and immunomodulatory anti-myeloma actions utilising this novel mouse model.

P-182

Natural killer cells are active against myeloma cells with loss of tumor suppressor genes

Olga Dashevsky[1,2,3,4], Sara Gandolfi[3,5,6,7], Olli Dufva[6,7], Ricardo de Matos Simoes[1,2,3,4,8], Jani Huuhtanen[6,7], Benjamin Barwick[9], Ryosuke Shirasaki[3,5,10], Michal Sheffer[3,5], Aedin Culhane[11,12], Jonathan Licht[13], Christine-Ivy Liacos[14], Evangelos Terpos[15], Efstathios Kastritis[15], Meletios Dimopoulos[15], Francisca Vazquez[3], Lawrence Boise[9], Matti Kankainen[6,7,16], Satu Mustjoki[6,7], Constantine Mitsiades[1,2,3,8]

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Introduction: In multiple myeloma (MM) and other neoplasias, it its challenging to target therapeutically tumor cells with loss of function (LOF) for tumor suppressor genes (TSGs), because pharmacological mechanisms to restore the function(s) of such genes are not considered to be readily feasible, in contrast to e.g., inhibition of oncogenic drivers. We reasoned, however, that, LOF for TSGs in MM cells leads to de-repressed cell growth, it may not necessarily protect tumor cells from immune attack. We thus explored the hypothesis that CRISPR-based loss of function of TSGs in MM cell lines may still be associated with substantial response to immune effector cells such as NK cells, which have the advantage to kill tumor cells across HLA barriers. **Methods:** We examined our genome-scale or focused CRISPR screens for LOF (CRISPR-based gene editing) or gain of function (GOF, CRISPR activation) in MM lines (KMS11, LP1 and MM1S) exposed to allogeneic donor-derived NK cells (vs. control cultures without NK cells) and specificallt evaluated the performance of genes known to represent recurrent TSGs based on genomic data of MM patient samples or cell lines; as well as candidate TSGs, based on results from genome-scale CRISPR gene editing screens (e.g., CERES or CHRONOS scores >0.4 in multiple DepMap releases and TPM>1 [RNA-seq]) in the same cell lines as the NK cell resistance screens. These analyses sought to identify any TSGs whose LOF may potentially alter the response of MM cells to NK cells. **Results:** Overall, 34 genes were identified as top recurrent TSGs in MM patient samples (e.g., based on prior genomic studies) or based on in vitro CRISPR knockout screens. These genes were evaluated for their metrics of sgRNA enrichment or depletion in genome-scale CRISPR gene editing or activation screens in the context of exposure to NK cells. These genes included known and recurrent TSGs (e.g., PTEN, FAM46C, TP53, RB1) as well as other, previously underappreciated candidate TSGs (e.g., HIF1A, ASXL1, ATRX). Perturbation of none of these genes was identified to meet criteria for association with significant resistance to allogeneic donor-derived NK cells (log2FC>1.0, at least 3-4 sgRNAs with enrichment upon CRISPR KO or depletion with CRISPR activation, p-value < 0.05, depletion [or enrichment] rank < 100) in any of the 3 MM cell lines examined in LOF or GOF CRISPR screens for NK cell resistance. In fact, for a limited set of cases (e.g., PTEN in KMS11 cells), KO of a TSG was associated with sensitization to NK cell treatment. These in-house results with MM cells exposed to NK cells are concordant with results for these TSGs in CRISPR screens of non-MM cells treated with cytotoxic T-cells (e.g., 4T1 or RENCA cells; GSE149933). **Conclusions:** MM cells deficient for diverse TSGs are equally responsive to NK cells as their TSG-proficient counterparts. NK cell-based therapies may thus be a promising approach to target TSG-deficient MM cells for which specific pharmacological therapies are not currently available.

P-183

Bottlebrush prodrugs as triplex combination therapies for multiple myeloma

Alexandre Detappe[1], Hung Nguyen[2], Irene Ghobrial[3], Peter Ghoroghchian[4], Jeremiah Johnson[2]

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Introduction: Current anticancer agents continue to face substantial challenges, including inherently narrow therapeutic indexes (TIs) as well as suboptimal therapeutic combinations stemming from mixtures of active pharmaceutical ingredients (APIs) with dissimilar properties. While nanomedicine-based platforms for drug delivery can potentially address these challenges, key questions remain such as i/ will synergies of free drug combinations translate to nanoparticles, or should synergies be screen in the context of nanoparticles?, and ii/ are multi-drug-laden nanoparticles better than mixtures of single-drug-laden nanoparticles? **Methods:** To evaluate the efficacy of Btz monotherapy, a Btz-BPD was designed to enable a 25-fold increase in API dosing compared to Btz alone, while maintaining tolerable toxicity in mice. The Btz-BPD was tested in vivo using subcutaneous and orthotopic MM models, assessing tumor progression and survival outcomes. Furthermore, BPDs carrying Btz, Pom, and Dex were synthesized for combination therapies. In vitro studies were conducted to analyze the synergistic, additive, or antagonistic patterns of the BPD combination nanomedicines compared to their free drug counterparts. Mathematical modeling was employed to provide insights into the underlying mechanisms and explain the observed results. **Results:** The Btz-BPD monotherapy demonstrated a significant reduction in tumor progression and improved survival in both subcutaneous and orthotopic MM models. Furthermore, BPDs carrying combinations of Btz, Pom, and Dex exhibited distinct in vitro patterns of synergy, additivity, or antagonism, differing from their free drug counterparts. Importantly, statistical mixtures of the three drugs in BPDs outperformed free drug combinations, single-drug BPD mixtures, and antagonistic 3-drug BPDs. Quantitative analysis using a mathematical model confirmed that statistical 3-drug BPDs were more likely to deliver a synergistic drug ratio to cells compared to mixtures of single-drug BPDs. **Conclusions:** Our results address critical gaps in the field of nanomedicine and provides new design principles for combination nanomedicines. The BPD platform offers promising strategies for improving existing mono- and combination therapies for MM. By demonstrating the superiority of statistical 3-drug BPDs over other formulations, our findings open doors for more effective and rational approaches to combination therapy in

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P-183

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MM. These results have broader implications for enhancing current cancer treatments and advancing the field of nanomedicine.

P-184

Lenalidomide: rash or no rash, that is the question

Akshitha Devaraj[1], David Sparksman[2], Cesar Gomez[2]

[1]Norfolk and Norwich University Hospitals; [2]Norfolk and Norwich University Hospital Foundation Trust

Introduction: Lenalidomide is an immunomodulatory (IMID) drug used as a backbone in many myeloma therapy regimens. Its mechanism of action is complex exerting a pleiotropic anti-myeloma effect in vitro including immune-modulation, anti-angiogenic, anti-inflammatory and anti-proliferative effects. However, the relative in vivo contribution of each is poorly understood. The toxicity profile of Lenalidomide is well known. It includes skin rash, pruritus, and photosensitivity. The mechanism by which lenalidomide may cause skin toxicity is not fully understood. However, studies suggest that lenalidomide can cause an immune-mediated reaction in the skin, particularly through T cell dysregulation. Lenalidomide is known to increase the production of Th1 cells, which are involved in the immune response. It is hypothesised that the increase in Th1 cells leads to an overactive immune response resulting in inflammation and tissue damage. Recently we have observed a high incidence of skin toxicity in patients receiving lenalidomide. This may have an impact on treatment, compliance and potentially result in cessation of treatment. **Methods:** We reviewed the notes and collected data from the medical records of all patients who received lenalidomide over a 3-year period at Norfolk and Norwich University Hospital. We identified the incidence of skin reactions with lenalidomide, the dose of lenalidomide the at the time of the skin reaction, concomitant use of anti-myeloma medication (such as ixazomib) and other medications which could result in drug interactions or polypharmacy. **Results:** Of the 279 patients receiving lenalidomide, 54 patients (19%) developed a rash during their treatment. The median time for the rash to appear after initiation of treatment was 14 days (range 3 days and 365 days). 15 patients (5%) participated in the quadruple therapy trial; out of which, 4 patients developed a skin rash. Furthermore, 3 patients (1%) participated in the triple therapy trial – interestingly, all 3 patients developed a rash. Of the 54 patients who developed a rash, lenalidomide was stopped in 20 patients; the discontinuation of treatment resulted in complete resolution of the rash. Lenalidomide was reintroduced to 7 patients (13%) and was subsequently stopped in 4 patients. The dose was reduced to 15mg from 25mg in 3 patients – these patients were continued on 15mg with no further incidences of a rash. However, when lenalidomide was reintroduced at a lower dose (15mg and 10mg) for 2 patients, they developed rash and treatment was discontinued. **Conclusions:** In conclusion, 19% of patients who received lenalidomide treatment developed a rash. A study by Nardone et al found that the overall incidence of all-grade and high-grade rash was 27.2%.[4] There was 100% resolution of symptoms when lenalidomide was stopped. With the increase in lenalidomide in multiple myeloma treatment, it is imperative that clinicians monitor their patients for skin reactions.

P-185

Discovery of novel proteasome activators that enhance antigen presentation and trigger anti-myeloma T-cell immunity

James Driscoll[1], Priyanka Rana[2], James Ignatz-Hoover[2], Ehsan Malek[1]

[1]Case Western Reserve University; [2]University Hospitals

Introduction: Transformative advances in immunotherapy have revolutionized cancer treatment and induce durable clinical responses. However, only a small fraction of patients respond to immunotherapy and cancer cells escape immunosurveillance through molecular mechanisms that remain elusive. Proteasomes play a central role in immune surveillance mechanisms by generating peptides from intracellular proteins which are presented as antigens on the cell surface for recognition by CD8+ cytotoxic T lymphocytes (CTLs). Cancer cells employ strategies to downregulate antigen presentation and impair CTL-mediated tumor recognition and lysis. Recently, we discovered that HDAC6-specific inhibitors increased proteasome activity as well as the presentation of MHC class I antigens on tumor cells. However, current HDAC6 inhibitors have pharmacologic liabilities that limit efficacy, e.g., low potency and solubility, poor PK properties and potential genotoxicity. **Methods:** We performed a high-throughput, cell-based screen of 9,600 HDAC-specific compounds to identify novel molecular entities that increased proteasome activity in MM cells. Proteasomes degrade ovalbumin to generate the neoantigenic peptide "SIINFEKL", which is presented on the cell surface in complex with the MHC class I H-2Kb molecule and quantitated by flow cytometry. We identified and then tested a curated set of hits for the ability to increase antigen presentation on tumor cells. Finally, hits were evaluated for the ability to induce tumor lysis using T-cells engineered to express a T-cell receptor (TCR) that recognized SIINFEKL. **Results:** We identified hits that increased proteasomal activity by >50%. Importantly, two novel molecules identified in the screen increased proteasome activity more potently and more rapidly than the HDAC6-specific inhibitors with comparatively low cytotoxicity. Treatment of tumor cells with the novel compounds also increased levels of the MHC-class I-SIINFEKL complex more potently and rapidly than the HDAC6 inhibitors. MM cells were then co-cultured with CTLs genetically-engineered to express a SIINFEKL-restricted TCR. Pre-treatment of lymphoma or MM cells with novel compounds and HDAC6 inhibitors significantly increased tumor lysis by CTLs that expressed the SIINFEKL-restricted TCR. CTL-mediated tumor lysis was dramatically more potent compared to known HDAC6-specific inhibitors. **Conclusions:** Taken together, our results support the development of novel proteasome activators as a paradigm-shifting approach to enhance tumor antigenicity and boost CTL-mediated anti-tumor immunity. Proteasome activators represent a paradigm-shifting approach as cancer immunotherapeutics to overcome immune escape mechanisms and boost antitumor immunity. Moreover, our data provide compelling evidence to support the development of drugs that powerfully enhance proteasome proteolytic function as a therapeutic strategy to treat cancers and other disease-causing proteinopathies.

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Akshitha Devaraj[1], David Sparksman[2], Cesar Gomez[2]

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Introduction: Lenalidomide is an immunomodulatory (IMID) drug used as a backbone in many myeloma therapy regimens. Its mechanism of action is complex exerting a pleiotropic anti-myeloma effect in vitro including immune-modulation, anti-angiogenic, anti-inflammatory and anti-proliferative effects. However, the relative in vivo contribution of each is poorly understood. The toxicity profile of Lenalidomide is well known. It includes skin rash, pruritus, and photosensitivity. The mechanism by which lenalidomide may cause skin toxicity is not fully understood. However, studies suggest that lenalidomide can cause an immune-mediated reaction in the skin, particularly through T cell dysregulation. Lenalidomide is known to increase the production of Th1 cells, which are involved in the immune response. It is hypothesised that the increase in Th1 cells leads to an overactive immune response resulting in inflammation and tissue damage. Recently we have observed a high incidence of skin toxicity in patients receiving lenalidomide. This may have an impact on treatment, compliance and potentially result in cessation of treatment. **Methods:** We reviewed the notes and collected data from the medical records of all patients who received lenalidomide over a 3-year period at Norfolk and Norwich University Hospital. We identified the incidence of skin reactions with lenalidomide, the dose of lenalidomide the at the time of the skin reaction, concomitant use of anti-myeloma medication (such as ixazomib) and other medications which could result in drug interactions or polypharmacy. **Results:** Of the 279 patients receiving lenalidomide, 54 patients (19%) developed a rash during their treatment. The median time for the rash to appear after initiation of treatment was 14 days (range 3 days and 365 days). 15 patients (5%) participated in the quadruple therapy trial; out of which, 4 patients developed a skin rash. Furthermore, 3 patients (1%) participated in the triple therapy trial – interestingly, all 3 patients developed a rash. Of the 54 patients who developed a rash, lenalidomide was stopped in 20 patients; the discontinuation of treatment resulted in complete resolution of the rash. Lenalidomide was reintroduced to 7 patients (13%) and was subsequently stopped in 4 patients. The dose was reduced to 15mg from 25mg in 3 patients – these patients were continued on 15mg with no further incidences of a rash. However, when lenalidomide was reintroduced at a lower dose (15mg and 10mg) for 2 patients, they developed rash and treatment was discontinued. **Conclusions:** In conclusion, 19% of patients who received lenalidomide treatment developed a rash. A study by Nardone et al found that the overall incidence of all-grade and high-grade rash was 27.2%.[4] There was 100% resolution of symptoms when lenalidomide was stopped. With the increase in lenalidomide in multiple myeloma treatment, it is imperative that clinicians monitor their patients for skin reactions.

P-185

Discovery of novel proteasome activators that enhance antigen presentation and trigger anti-myeloma T-cell immunity

James Driscoll[1], Priyanka Rana[2], James Ignatz-Hoover[2], Ehsan Malek[1]

[1]Case Western Reserve University; [2]University Hospitals

Introduction: Transformative advances in immunotherapy have revolutionized cancer treatment and induce durable clinical responses. However, only a small fraction of patients respond to immunotherapy and cancer cells escape immunosurveillance through molecular mechanisms that remain elusive. Proteasomes play a central role in immune surveillance mechanisms by generating peptides from intracellular proteins which are presented as antigens on the cell surface for recognition by CD8+ cytotoxic T lymphocytes (CTLs). Cancer cells employ strategies to downregulate antigen presentation and impair CTL-mediated tumor recognition and lysis. Recently, we discovered that HDAC6-specific inhibitors increased proteasome activity as well as the presentation of MHC class I antigens on tumor cells. However, current HDAC6 inhibitors have pharmacologic liabilities that limit efficacy, e.g., low potency and solubility, poor PK properties and potential genotoxicity. **Methods:** We performed a high-throughput, cell-based screen of 9,600 HDAC-specific compounds to identify novel molecular entities that increased proteasome activity in MM cells. Proteasomes degrade ovalbumin to generate the neoantigenic peptide "SIINFEKL", which is presented on the cell surface in complex with the MHC class I H-2Kb molecule and quantitated by flow cytometry. We identified and then tested a curated set of hits for the ability to increase antigen presentation on tumor cells. Finally, hits were evaluated for the ability to induce tumor lysis using T-cells engineered to express a T-cell receptor (TCR) that recognized SIINFEKL. **Results:** We identified hits that increased proteasomal activity by >50%. Importantly, two novel molecules identified in the screen increased proteasome activity more potently and more rapidly than the HDAC6-specific inhibitors with comparatively low cytotoxicity. Treatment of tumor cells with the novel compounds also increased levels of the MHC-class I-SIINFEKL complex more potently and rapidly than the HDAC6 inhibitors. MM cells were then co-cultured with CTLs genetically-engineered to express a SIINFEKL-restricted TCR. Pre-treatment of lymphoma or MM cells with novel compounds and HDAC6 inhibitors significantly increased tumor lysis by CTLs that expressed the SIINFEKL-restricted TCR. CTL-mediated tumor lysis was dramatically more potent compared to known HDAC6-specific inhibitors. **Conclusions:** Taken together, our results support the development of novel proteasome activators as a paradigm-shifting approach to enhance tumor antigenicity and boost CTL-mediated anti-tumor immunity. Proteasome activators represent a paradigm-shifting approach as cancer immunotherapeutics to overcome immune escape mechanisms and boost antitumor immunity. Moreover, our data provide compelling evidence to support the development of drugs that powerfully enhance proteasome proteolytic function as a therapeutic strategy to treat cancers and other disease-causing proteinopathies.

P-186

Proteasome regulatory ATPase PSMC2 promotes drug resistance by mitigating ER stress and portends reduced overall survival in multiple myeloma

James Driscoll[1], James Ignatz-Hoover[2], Priyanka Rana[2], Ehsan Malek[1]

[1]Case Western Reserve University; [2]University Hospitals

Introduction: Multiple myeloma (MM) remains an incurable malignancy characterized by plasma cells that synthesize and secrete massive amounts of immunoglobulin (Ig, paraprotein). Hence, MM cells are exquisitely sensitive to agents that disrupt proteostasis. The proteasome is a highly sophisticated proteolytic complex designed to carry out selective hydrolysis of client proteins. Proteasome consist of two subcomplexes: a 20S catalytic core particle (CP) capped at one or both ends by 19S regulatory particle(s) (RP) that exhibit ATPase activity. Inhibition of the 20S proteasome catalytic subunit PSMB5 is the backbone of modern MM chemotherapy and has dramatically improved patient overall survival (OS). However, drug resistance inevitably emerges through molecular mechanisms that remain elusive. We postulated that the expression of clinically relevant proteasome subunits from MM cells correlated with reduced progression-free survival (PFS) and OS. **Methods:** We correlated the expression of proteasome genes with clinical outcomes using the APEX trial dataset, which compared the effect of bortezomib vs. steroid, and the MMRF COMMPASS trial. Identified genes were then overexpressed or knocked out in MM cell lines. Biological and biochemical assays were then performed to determine the effect on proteasome structure and localization, drug sensitivity and ER stress. **Results:** Results indicated that greater expression of the proteasome 19S RP ATPases PSMC2 and PSMC6 correlated with reduced OS, even outperforming the PI target PSMB5. MM cell lines that overexpressed PSMC2 and PSMC6 were then engineered. Non-denaturing gel electrophoresis demonstrated that PSMC2 is readily incorporated into 26S proteasomes. These cells exhibit higher levels of proteasome chymotrypsin-like activity activity (1.6-fold increase in ARH77 and 3-fold increase in U266 cells compared to controls; $p < 0.01$). PSMC2 overexpression induced resistant to PI challenge (bortezomib LD50 30 nM vs. 15nM in U266 cells and LD50 18 nM vs. 10 nM in ARH77 cells). PIs increase ER stress and PSMC2 overexpressing cells are better able to mitigate PI mediated ER stress with PSMC2 overexpressing cells exhibiting less induction of ER stress sensors phospho-IRE1α, ATF4, and phospho-PERK compared to PSMC2 KD cells. Mechanistically, PSMC subunits may function in as a key player in the localization of proteasomes to the ER, recognition and degradation of misfolded ER proteins, and ER-associated protein degradation. **Conclusions:** Taken together, our results demonstrate that PSMC2 and PSMC6 expression correlates with reduced OS in MM patients. Knockout of PSMC subunits decreased proteasome activity and increased dependence on autophagy, while PSMC upregulation increased proteasome activity and decreased PI sensitivity. Our work highlights the complex interplay of proteasome subunits in MM biology and suggests a prognostic and therapeutic role for 19S RP subunits in the anti-myeloma armamentarium.

P-187

Therapeutically targeting 19S proteasome-associated subunit PSMD1/Rpn2 in multiple myeloma

Ting Du[1], Xueping Wan[1], Arghya Ray[1], Sindhu Pillai[1], Ruben Carrasco[1], Nikhil Munshi[2], Dharminder Chauhan[1], Kenneth Anderson[3]

[1]Dana-Farber Cancer Institute; [2]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/ Harvard Medical School; [3]LeBow Institute for Myeloma Therapeutics and Jerome Lipper Center for Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

Introduction: Therapeutic targeting of 20S proteasomal catalytic activities has proven successful treatment for multiple myeloma (MM) patients; however, most patients eventually develop resistance to proteasome inhibitors (PIs). The 26S proteosome is composed of 1) 20S core particle (CP) which harbor protein-degradative proteolytic activities, and 2) 19S regulatory particle (RP) whose function is to recognize, and deubiquitinate ubiquitinated proteins substrates and allow for their entry into the 20S CP for degradation. PIs block the catalytic activities of 20S proteasome resulting in accumulation of ubiquitinated proteins thereby triggering intracellular toxicity. Aberrations in PIs binding to their active sites in 20S CP may cause PI-resistance. We hypothesized whether proteasome-driven protein degradation may be as effectively inhibited at the level of 19S RP as for 20S CP and this may prevent development of PI-resistance. Here, we utilized our preclinical in vitro and in vivo models to show that targeting a 19S RP component PSMD1/Rpn2 triggers anti-MM activity and overcomes PI-resistance. **Methods:** Cell viability was determined by CellTiter-Glo Luminescent assays (Promega Corporation). Apoptosis was measured using Annexin/PI staining (Biolegend). MM cells were transiently transfected with Rpn2 siRNA using the Nucleofector Kit V. Dox-inducible Rpn2-KD MM cell line was generated using shRNA. In vivo studies were performed using a human MM xenograft model. Statistical significance was assessed with Student's t test. **Results:** 1) Immunoblot analysis showed higher Rpn2 expression in MM vs normal peripheral blood mononuclear cells. 2) Immunohistochemistry studies showed higher Rpn2 expression in BM biopsies from MM patients than from healthy individuals. 3) DepMap analysis showed that Rpn2 was essential for MM cell lines. 4) Knocking down (KD) Rpn2 using transiently transfected siRNA decreased the viability of various MM cell lines, including those that are PI-resistant (ANBL6.BR) or carry p53 alterations (JJN3, ARP1) ($p < 0.01$). 5) Transfection with Rpn2-WT rescued cells from the growth-inhibitory activity of Rpn2-siRNA. 6) Dox-inducible CRISPR/Cas9 stable Rpn2-KD and -KO MM cells reduced cell growth. 7) Mechanistically, Rpn2 blockade both inhibited proteasome-mediated protein degradation, evident by increased ubiquitinated proteins levels, and triggered cell death/apoptosis associated with the activation of caspases, and endoplasmic reticulum stress response signaling. 8) Proteomic analysis showed decreased cell-cycle- and DNA replication-related pathway proteins in Rpn2 KD vs Rpn2 -WT cells. Finally, 9) Using Dox-inducible Rpn2-KD AMO1 MM cells in a xenograft mouse model, we found that Rpn2 depletion reduced tumor growth and

P-186

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P-187

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prolonged mouse survival ($p < 0.005$). **Conclusions:** Our preclinical data demonstrate the therapeutic potential of targeting Rpn2 and provide the preclinical basis for developing Rpn2 inhibitors to overcome PI resistance in MM.

P-188

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Laure Dutrieux[1], Guillemin Antoine[1], Lin Yea-Lih[1], Malik Lutzmann[1], Guilhem Requirand[2], Nicolas Robert[2], Laure[3], Guillaume Cartron[4], Charles Herbaux[5], Raphaël Rodriguez[6], Michel Cogné[7], Philippe Pasero[1], Jérome Moreaux[2]

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Introduction: The evolution of Multiple Myeloma (MM), a plasma cell (PC) disorder, is driven by the accumulation of genomic abnormalities that lead to cell cycle dysregulation, and is therefore associated with replication stress. PCs are antibody-secreting cells associated with a high transcriptional stress. Transcription/Replication Conflicts (TRCs) arising from collisions between the replication and transcription machineries can promote tumor progression but can also represent an Achille's heel to cancer cells. Here, we investigated the therapeutic interest of increasing TRCs to target specifically malignant PCs using a G-quadruplex-stabilizing small molecule. **Methods:** The prognostic value of 13 genes involved in TRC management was evaluated in three independent cohorts of MM patients and used to build the TRC score. The G-quadruplex (G4) stabilizer Pyridostatin (PDS) was used as a strategy to increase TRCs. The response of 18 Human Myeloma Cell Lines (HMCLs) to PDS was evaluated with proliferation assay. DNA damage response was investigated using western-blot and immunofluorescence detection of γH2AX and 53BP1. The cytotoxic effect of PDS on primary cells from MM patients was determined using the co-culture of MM cells with bone-marrow microenvironment cells and flow cytometry. **Results:** A signature of genes involved in TRCs management was found overexpressed in malignant PCs compared to normal PCs, suggesting that they adapted to an elevated replication stress through the upregulation of a TRC-resolving machinery. Combining those genes into a TRC score identified high risk MM patients that could benefit from a TRCs-increasing therapy. Treatment with PDS was associated with significant toxicity in 13 HMCLs with an IC50 ≤ 4 μM whereas 5 cell lines demonstrated higher resistance to PDS. It was associated with cell cycle arrest in G2/M, DNA damage and apoptosis. Importantly, primary myeloma cells were more sensitive to PDS treatment than the normal cells of the bone marrow micro-environment. PDS was able to improve the efficacy of current MM treatments. Firstly, PDS synergized with Melphalan leading to increased DNA damage, cell cycle arrest and apoptosis. Secondly, HMCLs and primary MM cells with a high TRC score were more sensitive to Panobinostat, and increasing R-loop formation with Panobinostat and stabilizing these R-loops with PDS had a synergistic effect in HMCLs as well as on primary MM cells. Thirdly, PDS-treated HMCLs were associated with cGAS-STING pathway activation, and a high TRC score was associated with early relapse in a cohort of MM patients treated with the monoclonal antibody Daratumumab, suggesting that these patients could benefit from a TRCs-increasing strategy. **Conclusions:** TRCs represent an actionable Achille's heel for malignant PCs that could be targeted by new therapies such as G4 stabilizers, to improve the efficacy of current MM treatments and the outcome of myeloma patients.

P-189

Indirubin derivative acts as dual inhibitor targeting proteasome and autophagy for treating multiple myeloma

Teng Fang[1], Hao Sun[1], Xiyue Sun[2], Xiaoyu Zhang[2], Lixin Gong[1], Zhen Yu[1], Lanting Liu[1], Lugui Qiu[1], Mu Hao[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China.; [2]Chinese Academy of Medical Sciences and Peking Union Medical College, National Clinical Research Center for Blood Diseases, State Key Laboratory of Experimental Hematology

Introduction: Multiple myeloma (MM) remains incurable despite the availability of various therapies due to high rates of relapse and recurrence. Previous studies have highlighted the effectiveness of indirubin-3-monoxime (I3MO) as a proteasome inhibitor against MM cell proteasome activity. Histone deacetylase 6 (HDAC6) inhibitors have also shown promise in inhibiting the aggresome-autophagy pathway. Here, a novel I3MO derivative 8b was synthesized by coupling an HDAC6 inhibitor with the I3MO structure. **Methods:** We investigated the anti-MM effects of 8b both in vivo and in vitro. Western blots, immunofluorescence, and proteasome activity assay were utilized to investigate the effects of 8b on MM cell proteasome activity, aggresome and autophagosome formation. Dual-luciferase reporter gene assay was performed to identify downstream targets of 8b treatment. We further explored the function of TRIM28, the target of 8b, through shRNA knock-down (KD) and over-expression (OE) experiments. ChIP-seq and IP-MS were examined to clarify the potential target of TRIM28. **Results:** The novel derivative 8b efficiently inhibited myeloma cell proliferation and induced apoptosis in a dose- and time-dependent manner. Treatment with 8b caused cell cycle arrest in the S phase. In vivo studies confirmed the anti-MM effects of 8b treatment. Furthermore, 8b decreased proteasome activity and inhibited the formation of aggresomes and autophagosomes. Combining 8b with bortezomib (BTZ) enhanced apoptosis in MM cells both in vitro

prolonged mouse survival ($p < 0.005$). **Conclusions:** Our preclinical data demonstrate the therapeutic potential of targeting Rpn2 and provide the preclinical basis for developing Rpn2 inhibitors to overcome PI resistance in MM.

P-188

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P-189

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P-188

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Introduction: The evolution of Multiple Myeloma (MM), a plasma cell (PC) disorder, is driven by the accumulation of genomic abnormalities that lead to cell cycle dysregulation, and is therefore associated with replication stress. PCs are antibody-secreting cells associated with a high transcriptional stress. Transcription/Replication Conflicts (TRCs) arising from collisions between the replication and transcription machineries can promote tumor progression but can also represent an Achille's heel to cancer cells. Here, we investigated the therapeutic interest of increasing TRCs to target specifically malignant PCs using a G-quadruplex-stabilizing small molecule. **Methods:** The prognostic value of 13 genes involved in TRC management was evaluated in three independent cohorts of MM patients and used to build the TRC score. The G-quadruplex (G4) stabilizer Pyridostatin (PDS) was used as a strategy to increase TRCs. The response of 18 Human Myeloma Cell Lines (HMCLs) to PDS was evaluated with proliferation assay. DNA damage response was investigated using western-blot and immunofluorescence detection of γH2AX and 53BP1. The cytotoxic effect of PDS on primary cells from MM patients was determined using the co-culture of MM cells with bone-marrow microenvironment cells and flow cytometry. **Results:** A signature of genes involved in TRCs management was found overexpressed in malignant PCs compared to normal PCs, suggesting that they adapted to an elevated replication stress through the upregulation of a TRC-resolving machinery. Combining those genes into a TRC score identified high risk MM patients that could benefit from a TRCs-increasing therapy. Treatment with PDS was associated with significant toxicity in 13 HMCLs with an IC50 ≤ 4 μM whereas 5 cell lines demonstrated higher resistance to PDS. It was associated with cell cycle arrest in G2/M, DNA damage and apoptosis. Importantly, primary myeloma cells were more sensitive to PDS treatment than the normal cells of the bone marrow micro-environment. PDS was able to improve the efficacy of current MM treatments. Firstly, PDS synergized with Melphalan leading to increased DNA damage, cell cycle arrest and apoptosis. Secondly, HMCLs and primary MM cells with a high TRC score were more sensitive to Panobinostat, and increasing R-loop formation with Panobinostat and stabilizing these R-loops with PDS had a synergistic effect in HMCLs as well as on primary MM cells. Thirdly, PDS-treated HMCLs were associated with cGAS-STING pathway activation, and a high TRC score was associated with early relapse in a cohort of MM patients treated with the monoclonal antibody Daratumumab, suggesting that these patients could benefit from a TRCs-increasing strategy. **Conclusions:** TRCs represent an actionable Achille's heel for malignant PCs that could be targeted by new therapies such as G4 stabilizers, to improve the efficacy of current MM treatments and the outcome of myeloma patients.

P-189

Indirubin derivative acts as dual inhibitor targeting proteasome and autophagy for treating multiple myeloma

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Introduction: Multiple myeloma (MM) remains incurable despite the availability of various therapies due to high rates of relapse and recurrence. Previous studies have highlighted the effectiveness of indirubin-3-monoxime (I3MO) as a proteasome inhibitor against MM cell proteasome activity. Histone deacetylase 6 (HDAC6) inhibitors have also shown promise in inhibiting the aggresome-autophagy pathway. Here, a novel I3MO derivative 8b was synthesized by coupling an HDAC6 inhibitor with the I3MO structure. **Methods:** We investigated the anti-MM effects of 8b both in vivo and in vitro. Western blots, immunofluorescence, and proteasome activity assay were utilized to investigate the effects of 8b on MM cell proteasome activity, aggresome and autophagosome formation. Dual-luciferase reporter gene assay was performed to identify downstream targets of 8b treatment. We further explored the function of TRIM28, the target of 8b, through shRNA knock-down (KD) and over-expression (OE) experiments. ChIP-seq and IP-MS were examined to clarify the potential target of TRIM28. **Results:** The novel derivative 8b efficiently inhibited myeloma cell proliferation and induced apoptosis in a dose- and time-dependent manner. Treatment with 8b caused cell cycle arrest in the S phase. In vivo studies confirmed the anti-MM effects of 8b treatment. Furthermore, 8b decreased proteasome activity and inhibited the formation of aggresomes and autophagosomes. Combining 8b with bortezomib (BTZ) enhanced apoptosis in MM cells both in vitro

and in vivo. Mechanistically, the dual-luciferase reporter gene assay revealed that 8b treatment significantly down-regulated TRIM28 promoter activity, resulting in transcriptional repression of TRIM28. Bioinformatics analysis showed a positive correlation between the levels of TRIM28 and multiple proteasome subunit genes, including PSMB1 and PSMB2, in MM. ChIP-qPCR assay confirmed that TRIM28 directly bound to the promoter region of PSMB1 and PSMB2. Knock-down of TRIM28 led to decreased PSMB1 and PSMB2 expression and reduced proteasome activity, increasing MM cell sensitivity to proteasome inhibitors (PIs). Knockdown of TRIM28 also suppressed autophagosome formation, promoting sensitivity to PIs treatment in multiple MM cell lines. IP-MS and Co-IP demonstrated that TRIM28 interacts with 14-3-3ζ and mediates its ubiquitination and degradation. 14-3-3ζ is a well-known negative regulator of autophagy, and its degradation induced by TRIM28 activates autophagy in MM cells. **Conclusions:** Our study identified a novel indirubin derivative targeting proteasome and autophagy for treating myeloma. This represents a promising therapeutic approach that could assistant overcoming the PIs resistance in myeloma. Additionally, our study for the first time clarified the role of TRIM28 in MM pathogenesis, which should be considered as a potential therapeutic target for MM.

P-190

Potent pre-clinical activity of EP300/CBP bromodomain inhibitor CCS1477 in multiple myeloma

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P-191

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Mariateresa Fulciniti[1], Jessica Fong Ng[1], Joy Weiler[1], Shuhui Deng[1], Chandraditya Chakraborty[1], Mehmet Samur[1], Annamaria Gulla[2], Kenneth Anderson[3], Nikhil Munshi[4]

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therapeutic interventions impacting outcome. **Methods:** To answer this question and delineate the mechanisms that contribute to the development of an acquired drug-tolerant/resistant phenotype, we exposed venetoclax-sensitive myeloma cells to high dose treatment and generated monoclonal drug-tolerant expanded persister (DTEP) clones with a three- to ten-fold increase in IC50 compared to the parental cells. These cells were subjected to an integrated analysis including WGS, RNA-seq and proteomics, as well as drug screening. **Results:** Parental and resistant cells showed no marked differences in mutational frequencies, including the absence of genomic alterations in the BCL-2 gene such as the Gly101Val BCL-2 mutation. Instead, these clones exhibited reduced mitochondrial priming and had increased protein expression of anti-apoptotic regulators, including MCL-1, BCL-XL, and BCL-W, resulting in the sequestration of the pro-apoptotic ligand BIM. Since these data suggested a functional substitution between anti-apoptotic BCL-2 family members, we next evaluated if MCL1 or BCL-XL represent a co-dependency in resistant cells that can be therapeutically targeted to overcome resistance. Simultaneous inhibition of MCL1 (via S63845) or BCL-XL (via A155463) and BCL2 (via venetoclax) increased BIM release and enhanced cell death in the resistant clones compared to single agents, with combination index (CI) values < 0.3 in all doses tested. We next evaluated if the altered mitochondrial priming observed in the resistant cells was also responsible for a broader resistance to anti-cancer agents. Indeed, we found that most targeted agents, regardless of the mechanism of action, demonstrated a reduced ability to induce cell death in venetoclax-resistant cells compared with parental cells, suggesting a broad resistance to anti-cancer agents due to general selection for reduced apoptotic signaling. **Conclusions:** In conclusion, we report that resistance to Venetoclax in in vitro models of MM evolves from the outgrowth of persister clones with a shift in mitochondrial dependency that confers broad resistance to all anti-tumor agents, including standard-of-care myeloma drugs.

P-192

Increased serum CRBN levels are associated with improved survival in MM patients

Annita Ioanna Gkioka[1], Alexandros Gkiokas[1], Mavra Papadatou-Gigante[1], Alexandros Alexandropoulos[1], Aspasia Koudouna[1], Vasilliki Bartzi[1], Marie-Christine Kyrtsonis[1]

[1]National and Kapodistrian University of Athens

Introduction: ImiDs resistance has been linked to Cereblon (CRBN), a crucial protein in Immunomodulatory Drugs' (ImiDs') activity. Our most recent research has demonstrated the possible predictive value of serum CRBN in MM patients. 1 Thus, the purpose of the presented study was to revise our findings from earlier research on the predictive significance of serum CRBN levels in MM patients treated with RD (lenalidomide-dexamethasone) and to study any correlations with disease activity thereafter. **Methods:** We studied 92 MM patients from RD initiation until last follow up or death; Medical records were reviewed after patients' informed consent was obtained, while clinical and laboratory characteristics were collected. The median age of patients was 70 years (56% men, 44% women). Ig type was IgG in 64%, IgA in 22%, light-chain in 11% and IgD or biclonal in 3%. Thirty percent of patients were staged ISS 1, 20% ISS 2 and 51% ISS 3. RD was administered in 1st line in 8% of patients, second in 37%, third in 26%, forth in 16% and in 5th to 9th line in 13%. CRBN serum measurements at the time of RD treatment (69 patients), best response (59 patients) and at relapse/refractoriness to Rd (54 patients) were analyzed. CRBN was measured by commercially available ELISA kit (cloud clone), according to the manufacturer's instructions. Subsequent treatment lines after lenalidomide as well as patients' best responses to them, were recorded. Median serum CRBN level at each time point (RD initiation, at best response and Relapse) was used as a cut-off point in survival analysis. Statistical analysis was performed using the SPSS v28.0. software. **Results:** Median levels of CRBN were 247 pg/ml (range, 0-9760) at RD initiation, at best response to RD 142.5 pg/ml (range, 0 -9944) and at Relapse 298 pg/ml (range, 0-9840). A statistically significant decrease on CRBN serum levels was observed at best response compared to RD initiation. (p=0.001). Seven-year survival was improved in patients with CRBN levels below median at the time of RD initiation (p=0,013), during best response (p=0,032) but not in relapse/refractory patients to Rd (p=0,357) and time to next treatment (p=0.121). Regarding the disease characteristics, CRBN serum levels correlated with increased bone marrow infiltration (≥60%). (p=0.05). Furthermore, high CRBN serum levels at RD initiation correlated with patients experiencing an early relapse(≤ 12 months). Although intriguing, these patients responded to RD (≥PR) rather well. (p=0.03). **Conclusions:** Our analysis on CRBN serum levels, revealed an extended 7-year survival of our patients with serum CRBN levels below median both at RD initiation and at best response. Early resistance to RD was correlated with CRBN serum levels in our patients and further study would be beneficial.

P-193

Novel antigens LMA and KMA are expressed on malignant bone marrow plasma cells from patients at all stages of multiple myeloma and in other plasma cell dyscrasias

David Gottlieb[1], Mary Sartor[1], Rosanne Dunn[2]

[1]Centre for Cancer Research, Westmead Institute for Medical Research, Sydney, NSW, Australia; [2]HaemaLogiX Pty Ltd, Woolloomooloo, NSW, Australia

Introduction: As confirmed by flow cytometry and immunohistochemistry, lambda myeloma antigen (LMA) and kappa myeloma antigen (KMA) are found on the surface of malignant plasma cells (PCs) in multiple myeloma (MM) and other plasma cell dyscrasia (PCD) patient bone marrow (BM) samples, on human myeloma cell lines, on occasional mononuclear cells in healthy tonsillar tissue and secondary mucosal lymphoid tissue; they are not present on normal B cells in BM. KappaMab (formerly MDX-1097) clinical trials have confirmed that normal leukocytes are not depleted by the antibody with no on-target

therapeutic interventions impacting outcome. **Methods:** To answer this question and delineate the mechanisms that contribute to the development of an acquired drug-tolerant/resistant phenotype, we exposed venetoclax-sensitive myeloma cells to high dose treatment and generated monoclonal drug-tolerant expanded persister (DTEP) clones with a three- to ten-fold increase in IC50 compared to the parental cells. These cells were subjected to an integrated analysis including WGS, RNA-seq and proteomics, as well as drug screening. **Results:** Parental and resistant cells showed no marked differences in mutational frequencies, including the absence of genomic alterations in the BCL-2 gene such as the Gly101Val BCL-2 mutation. Instead, these clones exhibited reduced mitochondrial priming and had increased protein expression of anti-apoptotic regulators, including MCL-1, BCL-XL, and BCL-W, resulting in the sequestration of the pro-apoptotic ligand BIM. Since these data suggested a functional substitution between anti-apoptotic BCL-2 family members, we next evaluated if MCL1 or BCL-XL represent a co-dependency in resistant cells that can be therapeutically targeted to overcome resistance. Simultaneous inhibition of MCL1 (via S63845) or BCL-XL (via A155463) and BCL2 (via venetoclax) increased BIM release and enhanced cell death in the resistant clones compared to single agents, with combination index (CI) values < 0.3 in all doses tested. We next evaluated if the altered mitochondrial priming observed in the resistant cells was also responsible for a broader resistance to anti-cancer agents. Indeed, we found that most targeted agents, regardless of the mechanism of action, demonstrated a reduced ability to induce cell death in venetoclax-resistant cells compared with parental cells, suggesting a broad resistance to anti-cancer agents due to general selection for reduced apoptotic signaling. **Conclusions:** In conclusion, we report that resistance to Venetoclax in in vitro models of MM evolves from the outgrowth of persister clones with a shift in mitochondrial dependency that confers broad resistance to all anti-tumor agents, including standard-of-care myeloma drugs.

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Introduction: As confirmed by flow cytometry and immunohistochemistry, lambda myeloma antigen (LMA) and kappa myeloma antigen (KMA) are found on the surface of malignant plasma cells (PCs) in multiple myeloma (MM) and other plasma cell dyscrasia (PCD) patient bone marrow (BM) samples, on human myeloma cell lines, on occasional mononuclear cells in healthy tonsillar tissue and secondary mucosal lymphoid tissue; they are not present on normal B cells in BM. KappaMab (formerly MDX-1097) clinical trials have confirmed that normal leukocytes are not depleted by the antibody with no on-target

therapeutic interventions impacting outcome. **Methods:** To answer this question and delineate the mechanisms that contribute to the development of an acquired drug-tolerant/resistant phenotype, we exposed venetoclax-sensitive myeloma cells to high dose treatment and generated monoclonal drug-tolerant expanded persister (DTEP) clones with a three- to ten-fold increase in IC50 compared to the parental cells. These cells were subjected to an integrated analysis including WGS, RNA-seq and proteomics, as well as drug screening. **Results:** Parental and resistant cells showed no marked differences in mutational frequencies, including the absence of genomic alterations in the BCL-2 gene such as the Gly101Val BCL-2 mutation. Instead, these clones exhibited reduced mitochondrial priming and had increased protein expression of anti-apoptotic regulators, including MCL-1, BCL-XL, and BCL-W, resulting in the sequestration of the pro-apoptotic ligand BIM. Since these data suggested a functional substitution between anti-apoptotic BCL-2 family members, we next evaluated if MCL1 or BCL-XL represent a co-dependency in resistant cells that can be therapeutically targeted to overcome resistance. Simultaneous inhibition of MCL1 (via S63845) or BCL-XL (via A155463) and BCL2 (via venetoclax) increased BIM release and enhanced cell death in the resistant clones compared to single agents, with combination index (CI) values < 0.3 in all doses tested. We next evaluated if the altered mitochondrial priming observed in the resistant cells was also responsible for a broader resistance to anti-cancer agents. Indeed, we found that most targeted agents, regardless of the mechanism of action, demonstrated a reduced ability to induce cell death in venetoclax-resistant cells compared with parental cells, suggesting a broad resistance to anti-cancer agents due to general selection for reduced apoptotic signaling. **Conclusions:** In conclusion, we report that resistance to Venetoclax in in vitro models of MM evolves from the outgrowth of persister clones with a shift in mitochondrial dependency that confers broad resistance to all anti-tumor agents, including standard-of-care myeloma drugs.

P-192

Increased serum CRBN levels are associated with improved survival in MM patients

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Introduction: ImiDs resistance has been linked to Cereblon (CRBN), a crucial protein in Immunomodulatory Drugs' (ImiDs') activity. Our most recent research has demonstrated the possible predictive value of serum CRBN in MM patients. 1 Thus, the purpose of the presented study was to revise our findings from earlier research on the predictive significance of serum CRBN levels in MM patients treated with RD (lenalidomide-dexamethasone) and to study any correlations with disease activity thereafter. **Methods:** We studied 92 MM patients from RD initiation until last follow up or death; Medical records were reviewed after patients' informed consent was obtained, while clinical and laboratory characteristics were collected. The median age of patients was 70 years (56% men, 44% women). Ig type was IgG in 64%, IgA in 22%, light-chain in 11% and IgD or biclonal in 3%. Thirty percent of patients were staged ISS 1, 20% ISS 2 and 51% ISS 3. RD was administered in 1st line in 8% of patients, second in 37%, third in 26%, forth in 16% and in 5th to 9th line in 13%. CRBN serum measurements at the time of RD treatment (69 patients), best response (59 patients) and at relapse/refractoriness to Rd (54 patients) were analyzed. CRBN was measured by commercially available ELISA kit (cloud clone), according to the manufacturer's instructions. Subsequent treatment lines after lenalidomide as well as patients' best responses to them, were recorded. Median serum CRBN level at each time point (RD initiation, at best response and Relapse) was used as a cut-off point in survival analysis. Statistical analysis was performed using the SPSS v28.0. software. **Results:** Median levels of CRBN were 247 pg/ml (range, 0-9760) at RD initiation, at best response to RD 142.5 pg/ml (range, 0 -9944) and at Relapse 298 pg/ml (range, 0-9840). A statistically significant decrease on CRBN serum levels was observed at best response compared to RD initiation. (p=0.001). Seven-year survival was improved in patients with CRBN levels below median at the time of RD initiation (p=0,013), during best response (p=0,032) but not in relapse/refractory patients to Rd (p=0,357) and time to next treatment (p=0.121). Regarding the disease characteristics, CRBN serum levels correlated with increased bone marrow infiltration (≥60%). (p=0.05). Furthermore, high CRBN serum levels at RD initiation correlated with patients experiencing an early relapse(≤ 12 months). Although intriguing, these patients responded to RD (≥PR) rather well. (p=0.03). **Conclusions:** Our analysis on CRBN serum levels, revealed an extended 7-year survival of our patients with serum CRBN levels below median both at RD initiation and at best response. Early resistance to RD was correlated with CRBN serum levels in our patients and further study would be beneficial.

P-193

Novel antigens LMA and KMA are expressed on malignant bone marrow plasma cells from patients at all stages of multiple myeloma and in other plasma cell dyscrasias

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off-tumour effects1-3, and preclinical KMA.CAR T cell data has confirmed the antibody specificity4. KappaMab (targeting KMA) and LambdaMab (targeting LMA) bind to unique conformational epitopes in the constant regions of these sphingomyelin-associated light chains. This updated analysis confirms increased antigen (Ag) density of LMA and KMA on PCs versus decreased or stable Ag density of BCMA in disease progression from MGUS to relapsed, refractory MM (RRMM). Also, KMA is consistently found on BM PCs from plasmacytoma patients and LMA is consistently found on BM PCs from AL-amyloidosis (AL) patients. **Methods:** Patient BM samples (κ=66 and λ=41) were analysed using multiparametric FCM immunophenotyping with APC labelled LambdaMab (10B3) and KappaMab Fab'2 fragments, CD38, CD138, CD269 (BCMA), CD319 (SLAM F7), CD56 and CD45 monoclonal antibodies. PCs were identified as previously described5 by initial gating using CD38 and CD138. LMA and KMA expression was compared with the other cell markers. Ag density was calculated using QuantiBrite beads in PE. **Results:** In MGUS and SMM samples, 79% (11 of 14) of λ-type expressed LMA and 63% (10 of 16) of κ-type expressed KMA. KMA was expressed in 75% (12 of 16) of λRRMM samples and LMA was expressed in 50% (2 of 4) of λRRMM samples. Co-expression of KMA and BCMA occurred in 62% (18 of 29) of newly diagnosed (ND)MM and 63% (10 of 16) of RRMM samples. Co-expression of LMA and BCMA occurred in 59% (10 of 17) of NDMM and 50% (2 of 4) of RRMM samples. Both KMA and LMA Ag densities were higher than BCMA in the RRMM population. In the plasmacytoma BM PCs (n=5) KMA was expressed in 100% and KMA and BCMA were co-expressed in 100%. In the LMA+ AL samples (n=6), LMA was expressed in 100% and LMA and BCMA were co-expressed in 50%. **Conclusions:** KMA or LMA are expressed on PCs at all stages of MM, and all plasmacytomas and AL patient samples. The increased Ag densities of both KMA and LMA compared to BCMA on RRMM BM PCs indicates antigen persistence on a treatment resistant clone. The combination of increased and persistent antigen density and the specificity of these therapeutic antibodies could provide a significant benefit in the treatment of myeloma and PCDs. **References:** 1. Spencer. BCJ. 2019;9:58. 2. Dunn. Haematologica. 2013; 98(s1):776. 3. Kalff. Blood. 2019;134(s1):3144. 4. Li, J. Cancer Res. 2023; 83 (7Supp): 4074; Sartor M. Blood. 2021;138(Supp 1):1595.

P-194

Non-coding RNA LINC01410 interacts with the minichromosome maintenance (MCM) complex and is a dependency in multiple myeloma

Doriana Gramegna[1,5], Na Liu[1], Domenico Maisano[1], Jessica Fong Ng[1], Anais Schavgoulidze[1], Vanessa Favasuli[1], Claire Gao[1], Anil Aktas-Samur[1], Carl Novina[1], Annamaria Gulla[2], Kenneth Anderson[3], Leon Wert-Lamas[1], Mehmet Samur[1], Eugenio Morelli[1], Mariateresa Fulciniti[1], Nikhil Munshi[4]

[1]Dana-Farber Cancer Institute; [2]Candiolo Cancer Institute; [3]LeBow Institute for Myeloma Therapeutics and Jerome Lipper Center for Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; [4]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/Harvard Medical School; [5]Hematology and Cell Therapy Unit, IRCCS-Istituto Tumori 'Giovanni Paolo II', Bari, Italy

Introduction: Our initial characterization of the non-coding transcriptome identified long non-coding RNAs (lncRNAs) as key players in multiple myeloma (MM) pathobiology, with 14 lncRNA transcript signature being a strong predictor of progression-free survival. **Methods:** We performed a large CRISPR interference screen to evaluate lncRNA dependency in MM and identified LINC01410 as a top dependency in 3 MM cell lines (H929, KMS12BM, KMS11). **Results:** We further observed that LINC01410 was significantly overexpressed in MM patient cells compared to normal PC [P=0.047], with a slightly higher expression in the cytogenetic high-risk t(4;14) subgroup [t(4,14) vs other MM subgroups, [P=0.076], and higher expression was correlated with inferior overall survival in newly diagnosed MM patients [P=0.014]. We verified functional impact of LINC01410 using siRNA-mediated silencing in a larger panel of MM cell lines (n=9) covering all the genetic subtypes. We also used gapmer antisense oligonucleotides (ASO) in a subset of MM cells. Both methods found time-dependent inhibition of MM cell viability [P < 0.0001] after LINC01410 knockdown. In cell culture, LINC01410 knockdown caused a decline in the population of S-phase cells and induced apoptotic cell death, as shown by flow cytometer analysis after BrdU and Annexin-PI staining respectively. LINC01410 knockdown negatively impacted key MM cell survival pathways including cell cycle control, unfolded protein response (UPR) and oxidative stress response. Moreover, cell cycle-dependent cyclins, which are important in MM (i.e., CCND1, CCND2, CCND3), were downregulated at the RNA and protein level. To determine LINC01410's interaction partners, we used an RNA-protein pull down (RPPD) assay and found that, among others, three minichromosome maintenance proteins (MCM4, MCM5, MCM7) interacted with LINC01410, and this was confirmed by RNA immunoprecipitation using an anti-MCM5 antibody. These proteins are part of the MCM complex, which is a helicase important for DNA replication and mRNA transcription. Importantly, a Co-Immunoprecipitation of MCM5 subunit followed by Mass spectrometry analysis after LINC01410 knockdown showed the loss of interaction of MCM proteins with RNA polymerase 1 (POLR1), which transcribes ribosomal rRNA. MCM proteins have long been associated with the activity of RNA polymerase II. However, our results suggest a novel role of the MCM complex in the transcription of rRNA, mediated by LINC01410. **Conclusions:** In conclusion, we propose a model where, in MM, LINC01410 binds to the MCM complex to assist DNA replication and cell cycle progression, with a potential role also in the transcription of rRNA. These results suggest important role for LINC01410 in MM pathobiology and using small molecule inhibitors and/or Gapmers a potential therapeutic target.

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P-194

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Introduction: Our initial characterization of the non-coding transcriptome identified long non-coding RNAs (lncRNAs) as key players in multiple myeloma (MM) pathobiology, with 14 lncRNA transcript signature being a strong predictor of progression-free survival. **Methods:** We performed a large CRISPR interference screen to evaluate lncRNA dependency in MM and identified LINC01410 as a top dependency in 3 MM cell lines (H929, KMS12BM, KMS11). **Results:** We further observed that LINC01410 was significantly overexpressed in MM patient cells compared to normal PC [P=0.047], with a slightly higher expression in the cytogenetic high-risk t(4;14) subgroup [t(4,14) vs other MM subgroups, [P=0.076], and higher expression was correlated with inferior overall survival in newly diagnosed MM patients [P=0.014]. We verified functional impact of LINC01410 using siRNA-mediated silencing in a larger panel of MM cell lines (n=9) covering all the genetic subtypes. We also used gapmer antisense oligonucleotides (ASO) in a subset of MM cells. Both methods found time-dependent inhibition of MM cell viability [P < 0.0001] after LINC01410 knockdown. In cell culture, LINC01410 knockdown caused a decline in the population of S-phase cells and induced apoptotic cell death, as shown by flow cytometer analysis after BrdU and Annexin-PI staining respectively. LINC01410 knockdown negatively impacted key MM cell survival pathways including cell cycle control, unfolded protein response (UPR) and oxidative stress response. Moreover, cell cycle-dependent cyclins, which are important in MM (i.e., CCND1, CCND2, CCND3), were downregulated at the RNA and protein level. To determine LINC01410's interaction partners, we used an RNA-protein pull down (RPPD) assay and found that, among others, three minichromosome maintenance proteins (MCM4, MCM5, MCM7) interacted with LINC01410, and this was confirmed by RNA immunoprecipitation using an anti-MCM5 antibody. These proteins are part of the MCM complex, which is a helicase important for DNA replication and mRNA transcription. Importantly, a Co-Immunoprecipitation of MCM5 subunit followed by Mass spectrometry analysis after LINC01410 knockdown showed the loss of interaction of MCM proteins with RNA polymerase 1 (POLR1), which transcribes ribosomal rRNA. MCM proteins have long been associated with the activity of RNA polymerase II. However, our results suggest a novel role of the MCM complex in the transcription of rRNA, mediated by LINC01410. **Conclusions:** In conclusion, we propose a model where, in MM, LINC01410 binds to the MCM complex to assist DNA replication and cell cycle progression, with a potential role also in the transcription of rRNA. These results suggest important role for LINC01410 in MM pathobiology and using small molecule inhibitors and/or Gapmers a potential therapeutic target.

P-195

Loss of GABARAP mediates resistance to immunogenic chemotherapy by altering protein trafficking of calreticulin on the cell surface

Annamaria Gulla[1], Eugenio Morelli[2], Megan Johnstone[2], Marcello Turi[1], Mehmet Samur[2], Cirino Botta[3], Selma Cifric[2], Pietro Folino[2], Delaney Vinaixa[4], Francesca Barello[1], Cole Clericuzio[4], Vanessa Favasuli[2], Srikanth Talluri[2], Giada Bianchi[5], Mariateresa Fulciniti[2], Kenneth Wen[2], Keiji Kurata[2], Jiye Liu[2], Johany Panailillo[2], Alberto Bragoni[1], Paul Richardson[2], Dharminder Chauhan[2], Teru Hideshima[2], Nikhil Munshi[6], Kenneth Anderson[7]

[1]Candiolo Cancer Institute FPO-IRCCS; [2]Dana-Farber Cancer Institute; [3]University of Palermo; [4]Northeastern University; [5]Brigham and Women/s Hospital/Harvard Medical School/Dana Farber Cancer Institute; [6]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/Harvard Medical School; [7]LeBow Institute for Myeloma Therapeutics and Jerome Lipper Center for Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

Introduction: The induction of immunogenic cell death (ICD) is a critical mechanism by which the proteasome inhibitor bortezomib stimulates an anti-multiple myeloma (MM) immune response. During ICD, the dying cancer cell releases danger signals, such as calreticulin (CRT), which attract dendritic cells (DCs) to phagocytose the dying cell and present its antigens to T cells. Cancer cells employ several strategies to prevent this, including interfering with the exposure of CRT on the cell surface. Such resistance mechanisms may underlie the relapse and poor clinical outcome observed in MM patients. **Methods:** To find resistance mechanisms, we overlapped the CRT interactome after ICD induction with transcriptomic data from the IFM/DFCI dataset (n=360) and found that GABARAP both interacted with CRT and was associated with worse clinical outcomes at low expression levels (p=0.0017). We observed a strong correlation between GABARAP protein levels and the intensity of CRT exposure after BTZ treatment in 10 MM cell lines (R2: 0.62). Consequently, GABARAP KO in 4 ICD-sensitive cell lines impaired the exposure of CRT, thus diminishing ICD, as assessed by MM cell phagocytosis by DCs and T cell activation both in vitro and in vivo in an immunocompetent model. ICD was restored by add-back experiments using recombinant CRT or GABARAP overexpression. **Results:** To confirm this mechanism is active in patients, we analyzed single-cell RNA-seq from 80 MM patients and found a positive correlation between the expression of GABARAP and the ICD signature. Interestingly, low intratumor expression of GABARAP was associated with a lower T cell infiltration both at the single-cell level and by IHC analysis of bone marrow patient samples (n=10). Importantly, this mechanism generalizes to all MM cells but is especially relevant for those carrying a high-risk deletion of the 17p chromosome, where the gene is located. Mechanistically, proteomic analysis, confocal and transmission electron microscopy showed that GABARAP loss significantly altered the morphology of the Golgi apparatus, causing alterations in the vesicular transport systems and autophagy. This effectively stopped CRT transport to the surface, thus hindering ICD. By combining BTZ with autophagy inducers, we could restore vesicular transport of CRT to the cell surface and the subsequent MM-cell phagocytosis by DCs. Importantly, we also found this mechanism to be relevant in other cancer types, such as lung cancer cells. **Conclusions:** We propose a model by which dying cancer cells become resistant to ICD when the autophagy regulator GABARAP is low. The autophagy defects then disrupt the Golgi apparatus's structure, which then cannot export CRT to the cell surface. Without CRT, the dying cell cannot trigger an immune response. Therefore, coupling an ICD inducer, like bortezomib, with an autophagy inducer, like rapamycin, may improve patient outcomes in a variety of cancers and, specifically, in MM, where del(17p) is common and leads to worse outcomes.

P-196

Impact of preferential codonic loss of arginine in multiple myeloma

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Introduction: Several nonsynonymous somatic mutations are known to occur in the genome of Multiple Myeloma (MM) that may lead to loss or gain of gene functions in the growing tumor. The somatic codonic changes translate to corresponding alternate amino acid substitutions, some of which may facilitate the oncogenic circuitry and thus impact disease progression or clinical outcomes. **Methods:** Codonic changes were identified in whole exomes of malignant plasma cells (PCs) obtained from 109 PCPD patients including 71 MM patients. Whole exome sequencing data (generated using Nextera Exome library prep kit) were analyzed with Illumina Dragen pipeline. Circulating arginine levels in blood plasma were measured with Abcam's L-Arginine assay kit. **Results:** A preferential net loss of arginine specific codons (CGG (73%) > CGC (66%) > CGA (47%) > CGT (35%) >AGG (32%) > AGA (22%)) was observed in MM exome. The circulating arginine levels measured in blood plasma of such patients were also significantly reduced (p=0.03). Arginine (R) is not only a key player in cell metabolism but also marks the conserved cleavage sites (such as RXXR↓R) of proprotein convertase enzyme Furin. Mutations involving arginine over furin cleavage sites were mapped and highlighted the functional involvement of different furin sensitive proteins across PCPD. For example, furin sensitive RNF43 and TG were mutated at their furin cleavage sites in MGUS, while TNC, ADAM22 IGSF10 were mutated in SMM and others like MMP15, SLC9A3 were found to be mutated in MM. Kaplan Meier curve analyses showed a significant correlation between no loss of arginine with inferior PFS (p=0.012). Plausibly, if there is no loss of arginine, its continued abundance would tend to favor tumor progression and thus inferior outcomes. Further, mutations in arginine at furin cleavage sites in neoplastic plasma cells were found to be significantly associated with shorter PFS in MM (p=0.011) and could have prognostic value. **Conclusions:** The main novel finding of this study is that there is a selective net loss of arginine codon usage in MM that may have

P-195

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P-196

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an impact on PFS. A targeted deprivation of Arginine in the tumor microenvironment is a potential therapeutic modality under trials in certain cancers and could be deeply investigated in MM. Arginine substitutions affect furin cleavage of important proteins involved in myelomatogenesis and contribute to PFS. Identification of furin sensitive substrates in early precursor stages of MGUS/SMM may help unveil potential targets for early therapy/ early prognosis and warrant further studies in this direction.

P-197

Tissue factor as a new target for CAR-NK cell immunotherapy of multiple myeloma

Ming Liu[1], Tiffany Hughes[1], Rulong Shen[1], Junan Li[1], Bei Liu[1], Don Benson[1], Zhiwei Hu[1]

[1]The Ohio State University

Introduction: Multiple myeloma (MM) is a bone marrow-resident hematological malignancy of plasma cells and the second most diagnosed blood cancer. Despite the development of myeloma-targeted immunotherapies, MM has remained largely incurable. It is well documented that a suppressive bone marrow tumor microenvironment (TME), including dysfunctional natural killer (NK) cells, can cause the failure of current immunotherapies such as immune checkpoint blockade therapy (ICBT). The objective of this research is to target tissue factor as a new MM target and test corresponding chimeric antigen receptor-modified NK (CAR-NK) cell therapy as a monotherapy and in combination therapy to overcome the suppressive TME to enhance ICBT efficacy in MM. **Methods:** To validate TF as a new target in MM, we examined its expression on human MM lines (U266.B1, MM.1S, OPM2 and IM9) using flow cytometry. To target TF for CAR-NK cell immunotherapy, we developed TF-targeted human CAR constructs, which are composed of human fVII light chain followed sequentially by a hinge region of human IgG1, CD28 transmembrane and cytoplasmic domains and then by the cytoplasmic domains of 4-1BB and CD3ζ (TF-CAR dimer). To test the in vivo efficacy of TF CAR-NK cells as a monotherapy, we generated subcutaneous xenograft mouse models of human MM (U266.B1) and treated the animals with TF CAR-NK cells and control NK cells. To test the efficacy of TF CAR-NK cells in a novel combination therapy with ICBT (anti-PD-1 antibody, Ab), we first generated human MM xenografts in immunodeficient NSG mice (to mimic the suppressive TME) and then treated the animals with TF CAR-NK cells and anti-PD-1 Ab, TF CAR-NK cells plus IgG isotype control and control NK cells plus IgG isotype control. Whole body weights were recorded and blood chemistry from terminal blood samples were assayed as part of safety studies. **Results:** We showed and verified tissue factor expression in all four examined human MM cell lines, of which U266.B1 has a relatively higher expression level. After verifying TF expression in MM lines, we showed that TF CAR-NK cells alone are effective and safe for the treatment of human MM in preclinical mouse models. Furthermore, we showed that TF CAR-NK cells are more effective in combination therapy with ICBT (anti-PD-1 Ab) than TF CAR-NK cell alone in preclinical mouse models. There was no significant difference in whole body weights and blood chemistry panels between treated and control animals, suggesting that TF CAR-NK cells are safe. **Conclusions:** This study established the proof of concept of targeting TF as a new target in CAR-NK immunotherapy for effective and safe treatment of MM as a monotherapy and in a novel combination therapy with ICBT and may warrant further preclinical study and potentially future investigation in MM patients.

P-198

Impact of blocking the CD47 axis on phagocytosis of myeloma cells treated with CD38 antibodies and proteasome inhibitors

Katja Klausz[1], Carina Lynn Gehlert[1], Steffen Krohn[2], Dorothee Winterberg[1], Marta Lustig[1], Ammelie Svea Boje[1], Lenka Besse[3], Andrej Besse[3], Christoph Driessen[3], Matthias Peipp[1], Martin Gramatzki[3]

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an impact on PFS. A targeted deprivation of Arginine in the tumor microenvironment is a potential therapeutic modality under trials in certain cancers and could be deeply investigated in MM. Arginine substitutions affect furin cleavage of important proteins involved in myelomatogenesis and contribute to PFS. Identification of furin sensitive substrates in early precursor stages of MGUS/SMM may help unveil potential targets for early therapy/ early prognosis and warrant further studies in this direction.

P-197

Tissue factor as a new target for CAR-NK cell immunotherapy of multiple myeloma

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P-199

Novel antibodies identified by phage display induce direct myeloma cell death

Steffen Krohn[1], Carina Lynn Gehlert[2], Dorothee Winterberg[2], Ammelie Svea Boje[2], Monika Brüggemann[2], Katja Weisel[3], Martin Gramatzki[4], Matthias Peipp[2], Katja Klausz[2]

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P-200

MAP4K2 inhibition reinforces sensitivity to iberdomide in RAS-mutated MM through a CRBN-independent mechanism

Shirong Li[1], Jing Fu[1], Guifen Liu[1], Huihui Ma[1], Markus Mapara[2], Christophe Marcireau[3], Suzanne Lentzsch[1]

[1]Columbia University Irving Medical Center, New York, NY, USA; [2]Columbia Center for Translational Immunology; [3]Sanofi

Introduction: MAP4K2 is predominantly and highly expressed in the germinal center of B cells. We have shown that MAP4K2 knockdown in K- or N-RAS mutated MM cells inhibits cell growth associated with the downregulation of IKZF1/3, BCL-6, and c-MYC (Blood, 2021; 137:1754). Since IKZF1 regulates IRF4 and c-MYC transcription in MM, we hypothesized that IKZF1 degradation is one of the major mechanisms mediating MAP4K2-knockdown-induced MM cell death. **Methods:** IKZF1 Q146H mutant, which abrogates E3 ligase cereblon (CRBN)-mediated IKZF1 degradation, was constructed by mutagenesis PCR. MM.1SRASmut cells were lentivirally transduced to overexpress IKZF1WT or IKZF1Q146H and treated by MAP4K2 inhibitor (TL4-12), lenalidomide, or iberdomide. IKZF1 degradation was detected by WB and MM growth inhibition by proliferation assay. To investigate the combined effects of Iberdomide with MAP4K2 silencing on MM tumor growth, we generated subcutaneous MM xenografts in NOD/SCID mice using the inducible MAP4K2 shRNA MM.1SRASmut cells. MAP4K2 silencing was induced by doxycycline diet after the tumor was established. **Results:** As expected, lenalidomide failed to induce IKZF1-degradation in IKZF1Q146H MM.1SRASmut cells, confirming that IMiDs-induced IKZF1 degradation is mediated by CRBN. In contrast, IKZF1Q146H did not protect MM.1SRASmut from MAP4K2 inhibitor TL4-12-induced IKZF1 downregulation. Proliferation assays confirmed that IKZF1Q146H MM.1S cells were resistant to LEN-induced cell growth inhibition but not to TL4-12, demonstrating that MAP4K2 inhibition causes IKZF1 degradation and cell growth inhibition through a mechanism different from that of lenalidomide. We further evaluated the effects of MAP4K2 silencing in IKZF1Q146H MM.1SRASmut cells. MAP4K2 knockdown resulted in significant inhibition of cell proliferation and increase of apoptotic cells in both IKZF1WT and IKZF1Q146H MM.1S. IKZF1WT or IKZF1Q146H were also overexpressed in IMiDs resistant (RPMI-8266RASmut) MM

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P-199

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P-200

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Introduction: MAP4K2 is predominantly and highly expressed in the germinal center of B cells. We have shown that MAP4K2 knockdown in K- or N-RAS mutated MM cells inhibits cell growth associated with the downregulation of IKZF1/3, BCL-6, and c-MYC (Blood, 2021; 137:1754). Since IKZF1 regulates IRF4 and c-MYC transcription in MM, we hypothesized that IKZF1 degradation is one of the major mechanisms mediating MAP4K2-knockdown-induced MM cell death. **Methods:** IKZF1 Q146H mutant, which abrogates E3 ligase cereblon (CRBN)-mediated IKZF1 degradation, was constructed by mutagenesis PCR. MM.1SRASmut cells were lentivirally transduced to overexpress IKZF1WT or IKZF1Q146H and treated by MAP4K2 inhibitor (TL4-12), lenalidomide, or iberdomide. IKZF1 degradation was detected by WB and MM growth inhibition by proliferation assay. To investigate the combined effects of Iberdomide with MAP4K2 silencing on MM tumor growth, we generated subcutaneous MM xenografts in NOD/SCID mice using the inducible MAP4K2 shRNA MM.1SRASmut cells. MAP4K2 silencing was induced by doxycycline diet after the tumor was established. **Results:** As expected, lenalidomide failed to induce IKZF1-degradation in IKZF1Q146H MM.1SRASmut cells, confirming that IMiDs-induced IKZF1 degradation is mediated by CRBN. In contrast, IKZF1Q146H did not protect MM.1SRASmut from MAP4K2 inhibitor TL4-12-induced IKZF1 downregulation. Proliferation assays confirmed that IKZF1Q146H MM.1S cells were resistant to LEN-induced cell growth inhibition but not to TL4-12, demonstrating that MAP4K2 inhibition causes IKZF1 degradation and cell growth inhibition through a mechanism different from that of lenalidomide. We further evaluated the effects of MAP4K2 silencing in IKZF1Q146H MM.1SRASmut cells. MAP4K2 knockdown resulted in significant inhibition of cell proliferation and increase of apoptotic cells in both IKZF1WT and IKZF1Q146H MM.1S. IKZF1WT or IKZF1Q146H were also overexpressed in IMiDs resistant (RPMI-8266RASmut) MM

cell line. MAP4K2 knockdown showed similar effects on IKZF1 degradation, cell proliferation, and apoptosis in IKZF1Q146H compared to IKZF1WT RPMI8266RASmut MM cells, confirming that MAP4K2 inhibition induces anti-MM effects by degrading IKZF1 via a CRBN independent mechanism and subsequently overcomes IMiDs resistance. Combination of iberdomide and MAP4K2-silencing led to synergistic in vitro anti-MM effects in RASMut MM cells. In our MM.1S xenograft mice model, combination of iberdomide with MAP4K2-silencing using a doxycycline-inducible shRNA approach further enhanced tumor inhibition and significantly prolonged mice survival compared to the single treatment. **Conclusions:** Combination of MAP4K2 inhibition with Iberdomide results in synergetic anti-cancer effects in lenalidomide-resistant MM. Our findings demonstrate that MAP4K2 is a novel therapeutic target to bypass IMiDs resistance in RAS-mutated MM. Therefore, this approach will provide a strategy to manage relapsed or refractory patients with multi-drug resistance and RAS-mutated MM.

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Induction of pyroptosis for the treatment of multiple myeloma

Xinliang Mao[1], Yuanming He[1], Shuoyi Jiang[1], Zhenqian Huang[1]

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Introduction: Pyroptosis is a novel type of cell death and induction of pyroptosis by small molecule chemicals has been proven to be a promising strategy for the treatment of hematologic malignancies, including acute myeloid leukemia (Johnson DC et al., Nat Med, 2018). However, little is known about myeloma cell pyroptosis. We recently found that proteasome inhibitors, the most important class of the mainstay anti-myeloma agents, trigger pyroptosis in a BAX and GSDME-dependent manner (Liang J et al., Acta Pharmacol Sin, 2023). Gasdermins are the executor of pyroptosis but the detailed regulatory mechanism is not well known. Novel agents to induce MM cell pyroptosis remained discovered. **Methods:** We applied phase contrast microscopy and ELISA to evaluate myeloma cell pyroptosis; RNA dequencing was performed to find out associated genes involved in clioquinol (CLQ)-induced MM cell pyroptosis. Western blotting was performed to examine GSDME activation and associated protein changes. Immunoprecipitation/immunoblotting was performed to examine the interaction between BAX, GSDME and IFIT1/T3. MM-cell line-derived myeloma xenografts were established by injection s.c MM cel lines into nude mice. **Results:** In the present study, we found that Clioquinol (CLQ), an anti-parasitic drug that has been proven to leukemia and myeloma cell apoptosis and autophagy, could also induce myeloma cell pyroptosis, featured with appearance of balloon-like morphology, leakage of lactate dehydrogenase (LDH) and cytochrome C, in both MM cell lines and primary cells. Moreover, CLQ induces MM cell pyroptosis through Caspase-3-mediated cleavage of GSDME. To find out the underlying mechanism, we performed an RNA sequencing on CLQ-induced pyroptotic cells. The results showed that interferon-inducible genes including IFIT1 and IFIT3 were strikingly upregulated by CLQ. IFIT1/T3 was downregulated in both primary and MM cell lines and they could be induced by CLQ. However, neither IFIT1 nor IFIT3 could induce MM cell pyroptosis. In contrast, both IFIT1 and IFIT3 could significantly enhance GSDME activation induced by CLQ. We further found that IFIT1/T3 bound to GSDME and increased the mitochondrial distribution of N-GSDME. Furthermore, we found that BAX bound to N-GSDME that could be markedly increased by IFIT1/T3 and IFIT1/T3 facilitated the translocalization of N-GSDME to mitochondria in the presence of BAX. Lastly, we found that CLQ displayed synergistic effects in myeloma cell pyroptosis with venetoclax, a specific inhibitor of Bcl-2 and an activator of BAX. The combination of CLQ and venetoclax displayed potent anti-MM activity in vivo in association with the induction of IFIT1/T3 and MM cell pyroptosis. **Conclusions:** This study therefore not only illustrates IFIT1/T3 is a important factor to enhance CLQ-induced myeloma cell pyroptosis. We also show the potential application of CLQ/VEN in myeloma therapy.

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SLAMF1-derived peptide P7N4-Pen as anti-myeloma treatment

Ingvild Mestvedt[1], Therese Standal[2], Maria Yurchenko[1], Terje Espevik[1], Kristine Misund[3], Hanne Hella[3], Tobias Slørdahl[4]

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cell line. MAP4K2 knockdown showed similar effects on IKZF1 degradation, cell proliferation, and apoptosis in IKZF1Q146H compared to IKZF1WT RPMI8266RASmut MM cells, confirming that MAP4K2 inhibition induces anti-MM effects by degrading IKZF1 via a CRBN independent mechanism and subsequently overcomes IMiDs resistance. Combination of iberdomide and MAP4K2-silencing led to synergistic in vitro anti-MM effects in RASMut MM cells. In our MM.1S xenograft mice model, combination of iberdomide with MAP4K2-silencing using a doxycycline-inducible shRNA approach further enhanced tumor inhibition and significantly prolonged mice survival compared to the single treatment. **Conclusions:** Combination of MAP4K2 inhibition with Iberdomide results in synergetic anti-cancer effects in lenalidomide-resistant MM. Our findings demonstrate that MAP4K2 is a novel therapeutic target to bypass IMiDs resistance in RAS-mutated MM. Therefore, this approach will provide a strategy to manage relapsed or refractory patients with multi-drug resistance and RAS-mutated MM.

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derived peptides; variants in a human MM cell line revealed several peptides with striking anti-cancer potential. One of these peptides, P7N4, linked to Penetratin for intracellular delivery (P7N4-Pen), was shown to efficiently inhibit the viability and proliferation of both IL-6 dependent (INA-6, ANBL-6, OH-2, IH-1, KJON) and IL-6 independent (U266, JJN3, AMO-1) human MM cell lines. Additionally, P7N4-Pen induced cell death of primary CD138+ tumor cells from patients with MM (obtained with patient consent and REC approval). At the same time, P7N4-Pen showed no toxicity towards human PBMCs from healthy donors. Further, P7N4-Pen strongly inhibited the viability of human MM cells resistant to proteasome inhibitors and showed resilient potential together with the alkylating drug melphalan. The latter allows for a marked dose-reduction of melphalan, which could have strong benefits for patients' well-being. At the protein level P7N4-Pen induces cleavage of caspase-3 and PARP, H2AX phosphorylation and reduced levels of pro-survival proteins such as c-Myc, β-catenin and IRF4. **Conclusions:** Altogether, with the ability to induce cell death and inhibit several central MM survival factors, P7N4-Pen is a promising novel drug-candidate for treatment of MM, which could be tested in the future as monotherapy or in combination with other drugs.

P-203

Rationale and design of three ongoing phase 1/2 trials of modakafusp alfa, an innate immunity enhancer, in patients with multiple myeloma: The innovate clinical development program

Hira Mian[1], Cyrille Touzeau[2], Sarah Holstein[3], Edwin Kingsley[4], Dan Vogl[5], Richard Zuniga[6], Kihyun Kim[7], Kaveri Suryanarayan[8], Shining Wang[8], Laura Thesillat-Versmee[8], Yuyin Liu[8], Tian Chen[8], Yefei Zhang[8], Xavier Parot[8], Hans Lee[9]

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Introduction: There is an unmet need for novel, targeted therapies for patients (pts) with multiple myeloma (MM), particularly those with prior exposure and/or refractoriness to multiple drugs. The first-in-class innate immunity enhancer, modakafusp alfa (moda), delivers attenuated interferon (IFN) specifically to immune and MM cells. IFN signaling activates innate and adaptive immune cells and induces direct anti-proliferative and apoptotic effects in MM cells. Moda is composed of two IFN-α2b molecules fused to an IgG4 monoclonal antibody (mAb), which binds to a unique epitope on CD38; the IgG4 backbone has limited effector function. In preclinical xenograft studies, moda demonstrated prolonged inhibition of tumor growth when combined with standard-of-care (SOC) agents, such as immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 mAbs. As moda and daratumumab (dara) do not bind to the same epitope, they may have complementary mechanisms of action; furthermore, moda has been shown to increase CD38 expression on immune and MM cells. **Methods:** In the phase 2 iinnovate-1 extension study (NCT03215030), pts are randomized to receive moda 120 mg or 240 mg every four weeks to define the single-agent dose with the optimal benefit/risk profile in pts with ≥3 prior lines of therapy (LoT) who are at least triple-class refractory (to an IMiD, a PI, and an anti-CD38 mAb). The primary endpoint is overall response rate (ORR). In the phase 1b, 3-group iinnovate-2 study (NCT05556616), the safety and tolerability of moda are investigated in combination with SOC agents in pts with newly diagnosed MM (group 1) or relapsed/refractory MM (groups 2 and 3; group 3 will follow on from group 2). In all 3 groups, moda is escalated/de-escalated as part of doublet or triplet therapy depending on the safety observed. In group 1, moda is combined with lenalidomide (len) as post-transplant maintenance therapy. In group 2, moda is given as part of a doublet with a PI or IMiD. In group 3, moda will be given as part of a triplet and the starting dose will be guided by data from group 2. The primary endpoint for all 3 groups is safety. In the phase 1/2a iinnovate-3 study (NCT05590377), the safety, tolerability, and preliminary efficacy of moda combined with dara are evaluated. Pts with ≥3 prior LoTs including an IMiD, a PI, and an anti-CD38 mAb (or triple-class refractory regardless of LoT) are being enrolled in the phase 1 dose escalation. For the phase 2a dose optimization, two dose levels from phase 1 will be further evaluated in pts who have received 1–3 prior LoTs and are len-refractory and sensitive (non-refractory) or naïve to anti-CD38 therapy. The primary endpoint is safety for phase 1, and ORR for phase 2a. **Conclusions:** The ongoing iinnovate-1-2-3 studies are assessing the optimal dose of moda as a single agent and as part of doublet and triplet combinations with SOC agents for different MM pt populations, including those with high unmet medical needs.

P-204

Targeting TENT5C-associated regulation of antibody synthesis against multiple myeloma

Enrico Milan[1], Massimo Resnati[2], Sara Pennacchio[2], Lisa Viviani[2], Tommaso Perini[3], Simone Cenci[3]

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Introduction: TENT5C locus on chromosome 1p12 is mutated or deleted in up to 20% of myeloma (MM) patients, indicating a plasma cell (PC)-specific tumor suppressor activity. TENT5C is a non-canonical poly(A)polymerase that selectively polyadenylates and stabilizes mRNA encoding immunoglobulins (Igs) and endoplasmic reticulum (ER)-targeted proteins, thus promoting the proteomic reshaping occurring during B to PC differentiation and sustaining humoral immune responses. We have recently demonstrated that MM cells have an advantage in losing TENT5C to restrict Ig production saving energy for proliferation. In line, its re-expression in mutated MM lines boosts the secretory activity beyond sustainability,

derived peptides; variants in a human MM cell line revealed several peptides with striking anti-cancer potential. One of these peptides, P7N4, linked to Penetratin for intracellular delivery (P7N4-Pen), was shown to efficiently inhibit the viability and proliferation of both IL-6 dependent (INA-6, ANBL-6, OH-2, IH-1, KJON) and IL-6 independent (U266, JJN3, AMO-1) human MM cell lines. Additionally, P7N4-Pen induced cell death of primary CD138+ tumor cells from patients with MM (obtained with patient consent and REC approval). At the same time, P7N4-Pen showed no toxicity towards human PBMCs from healthy donors. Further, P7N4-Pen strongly inhibited the viability of human MM cells resistant to proteasome inhibitors and showed resilient potential together with the alkylating drug melphalan. The latter allows for a marked dose-reduction of melphalan, which could have strong benefits for patients' well-being. At the protein level P7N4-Pen induces cleavage of caspase-3 and PARP, H2AX phosphorylation and reduced levels of pro-survival proteins such as c-Myc, β-catenin and IRF4. **Conclusions:** Altogether, with the ability to induce cell death and inhibit several central MM survival factors, P7N4-Pen is a promising novel drug-candidate for treatment of MM, which could be tested in the future as monotherapy or in combination with other drugs.

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Introduction: There is an unmet need for novel, targeted therapies for patients (pts) with multiple myeloma (MM), particularly those with prior exposure and/or refractoriness to multiple drugs. The first-in-class innate immunity enhancer, modakafusp alfa (moda), delivers attenuated interferon (IFN) specifically to immune and MM cells. IFN signaling activates innate and adaptive immune cells and induces direct anti-proliferative and apoptotic effects in MM cells. Moda is composed of two IFN-α2b molecules fused to an IgG4 monoclonal antibody (mAb), which binds to a unique epitope on CD38; the IgG4 backbone has limited effector function. In preclinical xenograft studies, moda demonstrated prolonged inhibition of tumor growth when combined with standard-of-care (SOC) agents, such as immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 mAbs. As moda and daratumumab (dara) do not bind to the same epitope, they may have complementary mechanisms of action; furthermore, moda has been shown to increase CD38 expression on immune and MM cells. **Methods:** In the phase 2 iinnovate-1 extension study (NCT03215030), pts are randomized to receive moda 120 mg or 240 mg every four weeks to define the single-agent dose with the optimal benefit/risk profile in pts with ≥3 prior lines of therapy (LoT) who are at least triple-class refractory (to an IMiD, a PI, and an anti-CD38 mAb). The primary endpoint is overall response rate (ORR). In the phase 1b, 3-group iinnovate-2 study (NCT05556616), the safety and tolerability of moda are investigated in combination with SOC agents in pts with newly diagnosed MM (group 1) or relapsed/refractory MM (groups 2 and 3; group 3 will follow on from group 2). In all 3 groups, moda is escalated/de-escalated as part of doublet or triplet therapy depending on the safety observed. In group 1, moda is combined with lenalidomide (len) as post-transplant maintenance therapy. In group 2, moda is given as part of a doublet with a PI or IMiD. In group 3, moda will be given as part of a triplet and the starting dose will be guided by data from group 2. The primary endpoint for all 3 groups is safety. In the phase 1/2a iinnovate-3 study (NCT05590377), the safety, tolerability, and preliminary efficacy of moda combined with dara are evaluated. Pts with ≥3 prior LoTs including an IMiD, a PI, and an anti-CD38 mAb (or triple-class refractory regardless of LoT) are being enrolled in the phase 1 dose escalation. For the phase 2a dose optimization, two dose levels from phase 1 will be further evaluated in pts who have received 1–3 prior LoTs and are len-refractory and sensitive (non-refractory) or naïve to anti-CD38 therapy. The primary endpoint is safety for phase 1, and ORR for phase 2a. **Conclusions:** The ongoing iinnovate-1-2-3 studies are assessing the optimal dose of moda as a single agent and as part of doublet and triplet combinations with SOC agents for different MM pt populations, including those with high unmet medical needs.

P-204

Targeting TENT5C-associated regulation of antibody synthesis against multiple myeloma

Enrico Milan[1], Massimo Resnati[2], Sara Pennacchio[2], Lisa Viviani[2], Tommaso Perini[3], Simone Cenci[3]

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Introduction: TENT5C locus on chromosome 1p12 is mutated or deleted in up to 20% of myeloma (MM) patients, indicating a plasma cell (PC)-specific tumor suppressor activity. TENT5C is a non-canonical poly(A)polymerase that selectively polyadenylates and stabilizes mRNA encoding immunoglobulins (Igs) and endoplasmic reticulum (ER)-targeted proteins, thus promoting the proteomic reshaping occurring during B to PC differentiation and sustaining humoral immune responses. We have recently demonstrated that MM cells have an advantage in losing TENT5C to restrict Ig production saving energy for proliferation. In line, its re-expression in mutated MM lines boosts the secretory activity beyond sustainability,

derived peptides; variants in a human MM cell line revealed several peptides with striking anti-cancer potential. One of these peptides, P7N4, linked to Penetratin for intracellular delivery (P7N4-Pen), was shown to efficiently inhibit the viability and proliferation of both IL-6 dependent (INA-6, ANBL-6, OH-2, IH-1, KJON) and IL-6 independent (U266, JJN3, AMO-1) human MM cell lines. Additionally, P7N4-Pen induced cell death of primary CD138+ tumor cells from patients with MM (obtained with patient consent and REC approval). At the same time, P7N4-Pen showed no toxicity towards human PBMCs from healthy donors. Further, P7N4-Pen strongly inhibited the viability of human MM cells resistant to proteasome inhibitors and showed resilient potential together with the alkylating drug melphalan. The latter allows for a marked dose-reduction of melphalan, which could have strong benefits for patients' well-being. At the protein level P7N4-Pen induces cleavage of caspase-3 and PARP, H2AX phosphorylation and reduced levels of pro-survival proteins such as c-Myc, β-catenin and IRF4. **Conclusions:** Altogether, with the ability to induce cell death and inhibit several central MM survival factors, P7N4-Pen is a promising novel drug-candidate for treatment of MM, which could be tested in the future as monotherapy or in combination with other drugs.

P-203

Rationale and design of three ongoing phase 1/2 trials of modakafusp alfa, an innate immunity enhancer, in patients with multiple myeloma: The innovate clinical development program

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inducing intracellular ATP shortage, ROS accumulation and reduced cell growth in vitro. Our goal is to challenge the effects of TENT5C manipulation in in vivo models of MM, and to dissect the precise molecular circuits coordinating intensive Ig synthesis in PCs to unveil new MM vulnerabilities. **Methods:** To dissect the molecular mechanisms involved in TENT5C oncosuppressive role in MM, we combined cutting-edge molecular biology, protein biochemistry and unbiased proteomics, and adopted in vivo models. **Results:** To assess the impact of TENT5C manipulation in vivo, we silenced or overexpressed the protein in AMLC-2 cells that bear a hemizygous loss in chromosome 1p. Following intravenous and subcutaneous injections of TENT5C-manipulated cells into Rag2–/– IL2rg–/– mice, we found remarkably reduced tumor growth and longer survival in recipients of TENT5C-overexpressing cells, despite higher initial circulating LC levels. This in vivo association of higher proliferation with drastically decreased secretory activity clearly reveals that the presence of TENT5C mutations uncouples monoclonal component levels from disease burden. In parallel, we disclosed that TENT5C promotes the presence of calreticulin and CD38 in the cell surface, with translational implications for immunotherapies. Finally, to clarify how TENT5C manages to orchestrate a global cellular reshaping towards secretion, we focused on the few TENT5C-modulated proteins not belonging to the secretory apparatus. Upon TENT5C overexpression, we found a specific induction of nucleolar methyltransferases of rRNAs and tRNAs, whose functions are to promote ribosome assembly and to improve the translation of rare codons. This suggests that TENT5C mRNA stabilizing activity is coordinated with mechanisms that optimize protein translation in order to harmonize intensive antibody synthesis with cellular homeostasis, thus revealing a potential novel Achille's heel of MM. **Conclusions:** Altogether, our data disclose an unexpected molecular network, centered on TENT5C, regulating the trade-off between Ig synthesis and cell growth that may be exploited to design new therapeutic strategies aiming at altering PC protein homeostasis, eliminating the pathogenic clone, and improving the efficacy of current therapeutic options.

P-205

Heme promotes venetoclax resistance in multiple myeloma

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P-206

3D in vitro modelling of relapsed/refractory multiple myeloma to unveil mechanisms of acquired resistance to therapy

Matilde Oriani[1], Nour Alassi[1], Chiara Spadazzi[1], Matteo Paganelli[1], Michele Zanoni[1], Alessandro De Vita[1], Giacomo Feliciani[1], Alice Rossi[1], Giovanni Martinelli[1], Claudio Cerchione[1], Giorgia Simonetti[1], Matteo Marchesini[1]

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Introduction: Relapsed/refractory (R/R) multiple myeloma (MM) patients have limited therapeutic options and poor outcome. A major limitation for the development of targeted therapies in this setting is the poor predictive value of preclinical models. In fact,

inducing intracellular ATP shortage, ROS accumulation and reduced cell growth in vitro. Our goal is to challenge the effects of TENT5C manipulation in in vivo models of MM, and to dissect the precise molecular circuits coordinating intensive Ig synthesis in PCs to unveil new MM vulnerabilities. **Methods:** To dissect the molecular mechanisms involved in TENT5C oncosuppressive role in MM, we combined cutting-edge molecular biology, protein biochemistry and unbiased proteomics, and adopted in vivo models. **Results:** To assess the impact of TENT5C manipulation in vivo, we silenced or overexpressed the protein in AMLC-2 cells that bear a hemizygous loss in chromosome 1p. Following intravenous and subcutaneous injections of TENT5C-manipulated cells into Rag2–/– IL2rg–/– mice, we found remarkably reduced tumor growth and longer survival in recipients of TENT5C-overexpressing cells, despite higher initial circulating LC levels. This in vivo association of higher proliferation with drastically decreased secretory activity clearly reveals that the presence of TENT5C mutations uncouples monoclonal component levels from disease burden. In parallel, we disclosed that TENT5C promotes the presence of calreticulin and CD38 in the cell surface, with translational implications for immunotherapies. Finally, to clarify how TENT5C manages to orchestrate a global cellular reshaping towards secretion, we focused on the few TENT5C-modulated proteins not belonging to the secretory apparatus. Upon TENT5C overexpression, we found a specific induction of nucleolar methyltransferases of rRNAs and tRNAs, whose functions are to promote ribosome assembly and to improve the translation of rare codons. This suggests that TENT5C mRNA stabilizing activity is coordinated with mechanisms that optimize protein translation in order to harmonize intensive antibody synthesis with cellular homeostasis, thus revealing a potential novel Achille's heel of MM. **Conclusions:** Altogether, our data disclose an unexpected molecular network, centered on TENT5C, regulating the trade-off between Ig synthesis and cell growth that may be exploited to design new therapeutic strategies aiming at altering PC protein homeostasis, eliminating the pathogenic clone, and improving the efficacy of current therapeutic options.

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standard two-dimensional (2D) cultures do not recapitulate the complexity of the tumour microenvironment (TME) that has a crucial role in cancer progression and therapy response. This limitation most likely explains the massive failure of the approval rate of novel treatments from international medical agencies. Here we developed in vitro three-dimensional (3D) scaffolds with biomimetic tissue like properties and leveraged this platform for drug testing and for the identification of TME-mediated mechanisms of drug resistance in R/R MM. **Methods:** Bone marrow-like 3D scaffolds (BM3Ds) were obtained through a crosslinking and a freeze-drying process by combining collagen type I and hydroxyapatite (30:70 wt% ratio). Human Stromal (HS5), Human Umbilical Vein Endothelial Cells (HUVEC) and MM cell lines H929 or JJN3 were co-cultured in BM3Ds, imaged by confocal microscopy after immunofluorescence staining or embedded in paraffin for immunohistochemistry. Cells were treated with increasing concentrations of Bortezomib (BTZ) and Lenalidomide (LEN) to calculate the half maximal inhibitory concentration (IC50) by cell viability assays. **Results:** BM3Ds displayed a highly reproducible micro-architecture resembling clinical BM specimens and a tunable structure enabling applications in 96/wells format. HUVEC and HS5 widely colonized the inner space of the scaffold with a multilayer cell organization. Conversely, MM cell lines grouped between the collagen fibers supported by the layers of stroma and endothelium when in co-cultures. By comparing 2D and 3D conditions we observed no differences in the growth rate of MMs, while HUVEC and HS5 showed a decreased proliferation at 72 hours from seeding when cultured in BM3Ds ($P < 0.001$). In BM3Ds, H929 cells showed decreased IC50 to both LEN and BTZ (0.60 μM and 0.0009 μM) compared to 2D culture (1.58 μM and 0.0019 μM). JJN3 did not respond to LEN and showed a doubled IC50 when treated with BTZ in BM3Ds (0.002 μM) with respect to 2D culture (0.001 μM). Then we optimized a 5 days protocol for a standardized process of drug discovery/testing. Specifically, HUVEC and HS5 are seeded in BM3Ds (3×10^5/each) at day 0 followed by JJN3 or H929 (5×10^5) at day 3. Treatments are carried out at day 4 prior to the drug sensitivity evaluation at day 5. **Conclusions:** BM3Ds is an alternative biomimetic 3D approach to model R/R MM for preclinical drug screening and drug discovery application. Ongoing single cell RNASeq experiments of stromal, endothelium and MM cells co-cultured in 2D or in BM3Ds after BTZ and LEN treatment will inform on molecular pathways driving mechanisms of drug resistance. This platform is expected to increase the consistency of preclinical data and to foster the clinical translation of new discoveries.

P-207

Targeting iron homeostasis in combination with IMiDs as a therapeutic strategy in multiple myeloma

Sara Ovejero[1], Julie Devin[1], Tatiana Cañeque[2], Laura Henry[1], Laura Alibert[1], Guilhem Requirand[3], Nicolas Robert[3], Alizée Steer[4], Amélie Machura[4], Christophe Hirtz[5], Angélique Bruyer[4], Laure Vincent[6], Guillaume Cartron[7], Charles Herbaux[8], Raphaël Rodriguez[2], Caroline Bret[9], Jérome Moreaux[3]

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Introduction: In most cases, multiple myeloma (MM) remains an incurable disease despite the survival improvement provided by current treatments. The persisting clinical challenge resides in its high ability to resist drugs as shown by the frequent relapses observed regardless of the treatment. Abnormal iron homeostasis is implicated in tumorigenesis and the progression of several cancers. Ironomycin is a small synthetic derivative of salinomycin that induces DNA damage and non-apoptotic cell death by sequestering iron in lysosomes. Preclinical studies in Acute Myeloid Leukemia and Diffuse Large B-Cell Lymphoma have revealed the therapeutic interest of ironomycin in treating hematological malignancies. Here, we evaluate the therapeutic interest of targeting iron homeostasis with ironomycin to target MM cells. **Methods:** The prognostic value of genes related to iron metabolism in cancer was evaluated in 4 independent MM cohorts and used to build the Iron Score (IS). Cytotoxic effect of ironomycin on primary cells from MM patients was evaluated by flow cytometry. The response of 9 HMCLs (Human Myeloma Cell Lines) to ironomycin was evaluated by Cell-Titer Glo (CTG). Three cell lines with different sensitivities were selected for further characterization. Metabolic and transcriptional changes induced by ironomycin in 3 HMCLs were evaluated by Seahorse assay, metabolomics analysis, and RNA-seq. The synergistic effects of the combination of ironomycin and immunomodulatory drugs (IMiDs), lenalidomide and pomalidomide, were determined by synergy matrixes using R package "SynergyFinder". **Results:** High iron score value predicts a poor outcome of MM patients in 4 independent cohorts. Ironomycin exerts cytotoxicity on HMCLs at nanomolar concentrations. Primary plasma cells from patients are more sensitive to ironomycin than other cell types from the microenvironment. Ironomycin reduces MM cells proliferation and viability, causes DNA damage and triggers caspase-dependent apoptosis. It also affects the expression of several oncogenes and causes epigenetic dysregulation. Ironomycin induces a metabolic shift from energetic to quiescent or glycolytic metabolism, together with an activation of the interferon response. Ironomycin synergizes with lenalidomide and pomalidomide to kill MM cells. Drug combination downregulates several oncogenes, increases DNA damage and interferon signaling, leading to apoptosis. **Conclusions:** Ironomycin causes significant cytotoxicity on MM cells mediated by DNA damage, interferon signaling activation and triggering of apoptosis. Targeting iron homeostasis with ironomycin is a new potential anti-myeloma strategy alone and in combination with IMiDs lenalidomide and pomalidomide.

standard two-dimensional (2D) cultures do not recapitulate the complexity of the tumour microenvironment (TME) that has a crucial role in cancer progression and therapy response. This limitation most likely explains the massive failure of the approval rate of novel treatments from international medical agencies. Here we developed in vitro three-dimensional (3D) scaffolds with biomimetic tissue like properties and leveraged this platform for drug testing and for the identification of TME-mediated mechanisms of drug resistance in R/R MM. **Methods:** Bone marrow-like 3D scaffolds (BM3Ds) were obtained through a crosslinking and a freeze-drying process by combining collagen type I and hydroxyapatite (30:70 wt% ratio). Human Stromal (HS5), Human Umbilical Vein Endothelial Cells (HUVEC) and MM cell lines H929 or JJN3 were co-cultured in BM3Ds, imaged by confocal microscopy after immunofluorescence staining or embedded in paraffin for immunohistochemistry. Cells were treated with increasing concentrations of Bortezomib (BTZ) and Lenalidomide (LEN) to calculate the half maximal inhibitory concentration (IC50) by cell viability assays. **Results:** BM3Ds displayed a highly reproducible micro-architecture resembling clinical BM specimens and a tunable structure enabling applications in 96/wells format. HUVEC and HS5 widely colonized the inner space of the scaffold with a multilayer cell organization. Conversely, MM cell lines grouped between the collagen fibers supported by the layers of stroma and endothelium when in co-cultures. By comparing 2D and 3D conditions we observed no differences in the growth rate of MMs, while HUVEC and HS5 showed a decreased proliferation at 72 hours from seeding when cultured in BM3Ds ($P < 0.001$). In BM3Ds, H929 cells showed decreased IC50 to both LEN and BTZ (0.60 μM and 0.0009 μM) compared to 2D culture (1.58 μM and 0.0019 μM). JJN3 did not respond to LEN and showed a doubled IC50 when treated with BTZ in BM3Ds (0.002 μM) with respect to 2D culture (0.001 μM). Then we optimized a 5 days protocol for a standardized process of drug discovery/testing. Specifically, HUVEC and HS5 are seeded in BM3Ds (3×10^5/each) at day 0 followed by JJN3 or H929 (5×10^5) at day 3. Treatments are carried out at day 4 prior to the drug sensitivity evaluation at day 5. **Conclusions:** BM3Ds is an alternative biomimetic 3D approach to model R/R MM for preclinical drug screening and drug discovery application. Ongoing single cell RNASeq experiments of stromal, endothelium and MM cells co-cultured in 2D or in BM3Ds after BTZ and LEN treatment will inform on molecular pathways driving mechanisms of drug resistance. This platform is expected to increase the consistency of preclinical data and to foster the clinical translation of new discoveries.

P-207

Targeting iron homeostasis in combination with IMiDs as a therapeutic strategy in multiple myeloma

Sara Ovejero[1], Julie Devin[1], Tatiana Cañeque[2], Laura Henry[1], Laura Alibert[1], Guilhem Requirand[3], Nicolas Robert[3], Alizée Steer[4], Amélie Machura[4], Christophe Hirtz[5], Angélique Bruyer[4], Laure Vincent[6], Guillaume Cartron[7], Charles Herbaux[8], Raphaël Rodriguez[2], Caroline Bret[9], Jérome Moreaux[3]

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P-208

Infectious risks in newly diagnosed multiple myeloma (NDMM) patients receiving (or treated with) daratumumab based regimens: a multicentric Italian experience

Angela Rago[1], Francesca Fioritoni[2], Massimo Offidani[3], Ombretta Annibali[4], Roberta Poggiali[5], Tommaso Za[6], Luca Franceschini[7], Laura de Padua[8], Alfonso Piciocchi[9], Alessia Fiorini[10], Tommaso Caravita di Toritto[1]

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Introduction: Patients with multiple myeloma are at higher risk for infections due to disease pathogenesis and administered therapies. Infection is a significant cause of morbidity and the leading cause of death in patients (pts) with newly diagnosed multiple myeloma (NDMM). The risk of infection may be associated with neutropenia, hypogammaglobulinemia, and NK cell depletion. Daratumumab is approved for NDMM or relapsed/refractory multiple myeloma (RRMM). The use of daratumumab (dara) has improved patient outcomes but has changed the frequency and epidemiology of infections. The overall risk of infection with daratumumab treatment is around 38%, being upper respiratory tract infections the most common.The purpose of this study was to evaluate the number, the type and risk of infection events (IE) associated with the use of dara in patients with NDMM in the induction phase of transplant eligible and transplant ineligible NDMM patients. **Methods:** We retrospectively evaluated 308 pts with NDMM treatment in 8 Italian Hematology Centers who underwent induction therapy based on dara-bortezomib, thalidomide and dexamethasone (D-VTD), dara-lenalidomide and dexamethasone (D-Rd) and dara-bortezomib and dexamethasone (D-VMP) between 2020 and 2023.. **Results:** Overall, 105/308 (34%) developed an infection of any grade, 30/105 in D-VTD, 61/105in D-Rd and 14/105 in D-VMP arm. There was no difference on antiviral and antimicrobial prophylaxis in the 3 treatment groups. The median time to infection events was similar between the 3 groups D-VMP 161 days (104-243), D-Rd 156 days (97-370) and D-VTD 82 days (44-184) (p=0.064). Type of IE were upper respiratory tract infection in 81/105 pts (77%), SARS-COV2 infection 12/105 pts (11%), herpes simplex and varicella zoster virus (VZV) in 2/105 pts (1.9%), abdominal infection 3/105 pts (2.8%) and infection of urinary tract 2/105 pts (1.9%) of any grade. No differences were present in the grade and in the duration of IE. In all groups a statistically significant reduction was seen in the IgA level at the time of the IE (p=0.006), while no differences were present for IgG and IgM level in 3 treatment group. Moreover, a significant difference in neutropenia (p=0.002) and lymphocytophenia pre and post IE (p=0.006) resulted in all three groups. In our experience, no significant differences were found between the three treatment groups in terms of incidence, type and degree of infections, while significant differences were found between baseline IgA levels, neutropenia and lymphopenia at the time of the IE. **Conclusions:** A larger patient cohort and further studies are warranted to confirm these data and to identify patients at higher risk for infection, understanding the potential benefit of infectious prophylaxis in the clinical management in this setting of NDMM.

P-209

Multiple myeloma-derived circulating extracellular vesicles affect normal human stromal cell behaviour and promote tumor progression: a multi-omic approach

Antonia Reale[1], Rong Xu[1], Irena Carmichael[1], Tiffany Khong[1], Nicholas Bingham[1], Haoyun Fang[2], David Greening[2], Maoshan Chen[1], Andrew Spencer[1]

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Introduction: We showed that human stromal cells (HS5) treated with extracellular vesicles (EV) derived from plasma of myeloma (MM) patients (MM-EV) promoted adhesion of human MM cell lines (HMCL), with preliminary proteomic profiling of MM- vs healthy donors HD-EV revealing enrichment of factors implicated in cell migration and adhesion. Aims: demonstrate that MM-EV induce the formation of a tumor microenvironment (TME) favouring MM progression; identify the protein content of MM-EV promoting this; discover signaling drivers of EV-mediated functional remodelling of HS5 towards a pre-metastatic phenotype. **Methods:** EV were enriched from 1mL plasma using a commercial kit. We performed: proteomic profiling of EV [x10 HD, x8 MM, x4 asymptomatic MM, x10 premalignant stage MGUS]; phosphoproteomic profiling and gene expression analysis (RNA sequencing) of HS5 cells pre-treated with MM- vs HD/MGUS-EV; in vitro (co-cultures) and in vivo (NSG MM-bearing mice) studies. **Results:** HS5 cells treated with MM-EV induced HMCL proliferation (p =.0026) and drug resistance (p =.0013) to anti-MM drugs when compared to untreated HS5-cells. Preconditioning mice with MM-EV significantly enhanced tumour growth vs control mice. Importantly, a higher number of disseminated HMCL was observed in liver, kidneys, heart in the preconditioned mice, indicating an augmented (extramedullary) metastatic potential. 412 proteins were quantified by proteomic profiling of EV with 8/13 corresponding to universal cancer EV markers. Gene ontology analysis of identified proteins (G:Profiler; p <.05) revealed enrichment for cellular component terms, eg "extracellular vesicles/exosomes", and for biological processes, eg "cell communication", "endocytosis". Comparative analysis between our dataset and publicly available datasets revealed EV-markers with potential discriminatory specificity for MM. Comparative analysis revealed 40 proteins differentially regulated between HD- and MM-EV (p <.05; log2 fold change ≥2). A specific protein signature was found in ≥30% of MM-EV vs ≤30% HD-EV. These proteins were not found in human whole plasma (Lehallier et al, Nat Med 2019) or solid tumors-EV (Hoshino et al, Cell 2020; Vinik et al, Science Advances 2020). 120 phosphosites were differentially expressed between HS5 pre-treated with MM-EV vs HD-EV (>1.5-fold change, p<.05). Among the differentially expressed proteins were kinases, phosphatases, translation and transcription regulators. 624 gene terms were differentially expressed between HS5 pre-treated

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Introduction: Patients with multiple myeloma are at higher risk for infections due to disease pathogenesis and administered therapies. Infection is a significant cause of morbidity and the leading cause of death in patients (pts) with newly diagnosed multiple myeloma (NDMM). The risk of infection may be associated with neutropenia, hypogammaglobulinemia, and NK cell depletion. Daratumumab is approved for NDMM or relapsed/refractory multiple myeloma (RRMM). The use of daratumumab (dara) has improved patient outcomes but has changed the frequency and epidemiology of infections. The overall risk of infection with daratumumab treatment is around 38%, being upper respiratory tract infections the most common.The purpose of this study was to evaluate the number, the type and risk of infection events (IE) associated with the use of dara in patients with NDMM in the induction phase of transplant eligible and transplant ineligible NDMM patients. **Methods:** We retrospectively evaluated 308 pts with NDMM treatment in 8 Italian Hematology Centers who underwent induction therapy based on dara-bortezomib, thalidomide and dexamethasone (D-VTD), dara-lenalidomide and dexamethasone (D-Rd) and dara-bortezomib and dexamethasone (D-VMP) between 2020 and 2023.. **Results:** Overall, 105/308 (34%) developed an infection of any grade, 30/105 in D-VTD, 61/105in D-Rd and 14/105 in D-VMP arm. There was no difference on antiviral and antimicrobial prophylaxis in the 3 treatment groups. The median time to infection events was similar between the 3 groups D-VMP 161 days (104-243), D-Rd 156 days (97-370) and D-VTD 82 days (44-184) (p=0.064). Type of IE were upper respiratory tract infection in 81/105 pts (77%), SARS-COV2 infection 12/105 pts (11%), herpes simplex and varicella zoster virus (VZV) in 2/105 pts (1.9%), abdominal infection 3/105 pts (2.8%) and infection of urinary tract 2/105 pts (1.9%) of any grade. No differences were present in the grade and in the duration of IE. In all groups a statistically significant reduction was seen in the IgA level at the time of the IE (p=0.006), while no differences were present for IgG and IgM level in 3 treatment group. Moreover, a significant difference in neutropenia (p=0.002) and lymphocytophenia pre and post IE (p=0.006) resulted in all three groups. In our experience, no significant differences were found between the three treatment groups in terms of incidence, type and degree of infections, while significant differences were found between baseline IgA levels, neutropenia and lymphopenia at the time of the IE. **Conclusions:** A larger patient cohort and further studies are warranted to confirm these data and to identify patients at higher risk for infection, understanding the potential benefit of infectious prophylaxis in the clinical management in this setting of NDMM.

P-209

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with MM- vs HD-EV (GSEA, FDR < 0.05), including epidermal growth factor (EGF), tumor necrosis factor alpha (TNFA), epithelial to mesenchymal transition (EMT) signaling. **Conclusions:** In this first of its kind studies in MM we show that MM-EV may play a key role in disease progression by re-programming the TME. Ongoing studies will indicate: the value of MM-EV as biomarkers; whether targeting interactions between MM-EV and the (pre)metastatic niche could enforce current therapeutic strategies.

P-210

Novel pro-survival role for tryptophan 2,3 dioxygenase 2 in multiple myeloma

Julia Reinke[1], Kanita Chaudhry[2], Louise Carlson[1], Daniela Petrusca[1], Peng Peng[2], Kelvin Lee[3]

[1]Indiana University School of Medicine; [2]Roswell Park Comprehensive Cancer Center; [3]Melvin and Bren Simon Comprehensive Cancer Center, Division of Hematology and Oncology, School of Medicine, Indiana University

Introduction: Multiple Myeloma (MM) cells are critically dependent on the bone marrow microenvironment (BMME) for their survival. Our lab has previously shown that the CD28 receptor on MM cells interacting with its ligands CD80 and CD86 on dendritic cells (DC) in the BMME transduces an essential pro-MM survival/chemotherapy-resistance signal. "Backsignaling" through CD80/CD86 also leads to the upregulation/activation of Indoleamine 2,3-dioxygenase 1 (IDO1) in the DC. IDO1 catabolyzes tryptophan (TRP) to kynurenine (KYN) - leading to the depletion of TRP/accumulation of KYN in the BMME. TRP depletion suppressed T cell activation, and KYN activation of its receptor Aryl Hydrocarbon Receptor (AHR) transduces a significant pro-survival signal in vitro and in vivo to MM cells, in part by upregulating MM CD28 expression in a self-reinforcing feedback loop. MM cells express both CD28 and CD86; our lab has previously found that MM cells generate KYN in the absence of DC co-culture, indicating that MM cells are at least partially able to create this feedback loop on their own. This may assist MM in escaping its dependance on the BMME. Determining how MM cells independently facilitate the conversion of TRP>KYN could lead to greater understanding of survival pathways and new treatment targets. **Methods:** Patient RNA expression data was taken from the CoMMpass database. MM cell lines U266, 8226, MM1S and KMS11 were measured for expression of TRP>KYN metabolizing enzymes through western blot and qPCR. MM cell lines were treated with the tryptophan 2,3 dioxygenase 2 (TDO2) inhibitor or with TDO2 knockdown (KD) shRNA, and also with CD28 blocking peptides. Cell viability was measured by flow cytometry and KYN production by the Ehrlich KYN detection assay. **Results:** We found that MM cells don't express IDO1, but do express the TRP>KYN metabolizing enzyme TDO2. The biological role for TDO2 in MM is completely uncharacterized, but its significance is suggested by our finding that in patients, TDO2 expression increased with disease progression and that patients with the highest quartile of TDO2 expression have significantly shorter progression free and overall survival. Inhibition of TDO2 pharmacologically or by shRNA KD lead to significantly reduced cell viability. Treatment with CD28-blocking peptides lead to reduced production of KYN, indicating a previously unrecognized regulation of TDO2 by CD28. **Conclusions:** We have made the novel observations that MM cells express TDO2, which would allow them to generate TRP-depleted immunosuppression as well as pro-MM survival KYN-AhR signaling without an extrinsic BM ME partner. TDO2 expression correlates with disease progression and shorter PFS and OS in MM patients, and direct TDO2 inhibition in vitro kills MM cells. TDO2 expression in MM cells appears to be regulated at least in part by MM CD28, mirroring CD28's role in IDO1 induction in the BM ME. Altogether these findings suggest that TDO2 is a novel therapeutic target in MM.

P-211

Antiviral treatment improves outcome for individuals with multiple myeloma and other monoclonal gammopathies associated with Hepatitis B or C viruses

Alba Rodríguez-García[1], Nicolas Mennesson[2], Gema Hernández-Ibarburu[3], María Luz Morales[1], Laurent Garderet[4], Lorine Boucherau[2], Sophie Allain-Maillet[2], Eric Piver[5], Irene Marbán[3], David Rubio[3], Edith Bigot-Corbel[2], Joaquín Martínez-López[6], María Linares[1], Sylvie Hermouet[2]

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Introduction: Subsets of patients with multiple myeloma (MM) and monoclonal gammopathies of undetermined significance (MGUS) present with a monoclonal immunoglobulin that specifically recognizes hepatitis C virus (HCV), which suggests that the plasmacytic clone may be HCV-driven in these patients. Supporting this hypothesis, antiviral treatment can lead to the disappearance of antigen stimulation and improved control of clonal plasma cells in HV-associated MGUS and MM patients. **Methods:** We investigated the role of hepatitis B virus (HBV) in the pathogenesis of MGUS and MM in 45 HBV-infected patients diagnosed with monoclonal gammopathy. Firstly, we analysed the specificity of recognition of the monoclonal immunoglobulin of these patients using the multiplex infectious antigen (MIAA) and dot blot assays. Secondly, we analysed the efficacy of antiviral treatment (AVT) in large cohorts of MM patients infected with HBV (n=1367) or HCV (n=1220) prior to the diagnosis of MM, in a federated database (Trinetx). **Results:** For 18/45 (40%) HBV-infected patients, the target of the monoclonal immunoglobulin was identified: the most frequent target was HBV (n=11), followed by other infectious pathogens (n=6) and a self-antigen, glucosylsphingosine (n=1). Two patients whose monoclonal immunoglobulin targeted HBV, implying that their gammopathy

with MM- vs HD-EV (GSEA, FDR < 0.05), including epidermal growth factor (EGF), tumor necrosis factor alpha (TNFA), epithelial to mesenchymal transition (EMT) signaling. **Conclusions:** In this first of its kind studies in MM we show that MM-EV may play a key role in disease progression by re-programming the TME. Ongoing studies will indicate: the value of MM-EV as biomarkers; whether targeting interactions between MM-EV and the (pre)metastatic niche could enforce current therapeutic strategies.

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Introduction: Subsets of patients with multiple myeloma (MM) and monoclonal gammopathies of undetermined significance (MGUS) present with a monoclonal immunoglobulin that specifically recognizes hepatitis C virus (HCV), which suggests that the plasmacytic clone may be HCV-driven in these patients. Supporting this hypothesis, antiviral treatment can lead to the disappearance of antigen stimulation and improved control of clonal plasma cells in HV-associated MGUS and MM patients. **Methods:** We investigated the role of hepatitis B virus (HBV) in the pathogenesis of MGUS and MM in 45 HBV-infected patients diagnosed with monoclonal gammopathy. Firstly, we analysed the specificity of recognition of the monoclonal immunoglobulin of these patients using the multiplex infectious antigen (MIAA) and dot blot assays. Secondly, we analysed the efficacy of antiviral treatment (AVT) in large cohorts of MM patients infected with HBV (n=1367) or HCV (n=1220) prior to the diagnosis of MM, in a federated database (Trinetx). **Results:** For 18/45 (40%) HBV-infected patients, the target of the monoclonal immunoglobulin was identified: the most frequent target was HBV (n=11), followed by other infectious pathogens (n=6) and a self-antigen, glucosylsphingosine (n=1). Two patients whose monoclonal immunoglobulin targeted HBV, implying that their gammopathy

with MM- vs HD-EV (GSEA, FDR < 0.05), including epidermal growth factor (EGF), tumor necrosis factor alpha (TNFA), epithelial to mesenchymal transition (EMT) signaling. **Conclusions:** In this first of its kind studies in MM we show that MM-EV may play a key role in disease progression by re-programming the TME. Ongoing studies will indicate: the value of MM-EV as biomarkers; whether targeting interactions between MM-EV and the (pre)metastatic niche could enforce current therapeutic strategies.

P-210

Novel pro-survival role for tryptophan 2,3 dioxygenase 2 in multiple myeloma

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Introduction: Multiple Myeloma (MM) cells are critically dependent on the bone marrow microenvironment (BMME) for their survival. Our lab has previously shown that the CD28 receptor on MM cells interacting with its ligands CD80 and CD86 on dendritic cells (DC) in the BMME transduces an essential pro-MM survival/chemotherapy-resistance signal. "Backsignaling" through CD80/CD86 also leads to the upregulation/activation of Indoleamine 2,3-dioxygenase 1 (IDO1) in the DC. IDO1 catabolyzes tryptophan (TRP) to kynurenine (KYN) - leading to the depletion of TRP/accumulation of KYN in the BMME. TRP depletion suppressed T cell activation, and KYN activation of its receptor Aryl Hydrocarbon Receptor (AHR) transduces a significant pro-survival signal in vitro and in vivo to MM cells, in part by upregulating MM CD28 expression in a self-reinforcing feedback loop. MM cells express both CD28 and CD86; our lab has previously found that MM cells generate KYN in the absence of DC co-culture, indicating that MM cells are at least partially able to create this feedback loop on their own. This may assist MM in escaping its dependance on the BMME. Determining how MM cells independently facilitate the conversion of TRP>KYN could lead to greater understanding of survival pathways and new treatment targets. **Methods:** Patient RNA expression data was taken from the CoMMpass database. MM cell lines U266, 8226, MM1S and KMS11 were measured for expression of TRP>KYN metabolizing enzymes through western blot and qPCR. MM cell lines were treated with the tryptophan 2,3 dioxygenase 2 (TDO2) inhibitor or with TDO2 knockdown (KD) shRNA, and also with CD28 blocking peptides. Cell viability was measured by flow cytometry and KYN production by the Ehrlich KYN detection assay. **Results:** We found that MM cells don't express IDO1, but do express the TRP>KYN metabolizing enzyme TDO2. The biological role for TDO2 in MM is completely uncharacterized, but its significance is suggested by our finding that in patients, TDO2 expression increased with disease progression and that patients with the highest quartile of TDO2 expression have significantly shorter progression free and overall survival. Inhibition of TDO2 pharmacologically or by shRNA KD lead to significantly reduced cell viability. Treatment with CD28-blocking peptides lead to reduced production of KYN, indicating a previously unrecognized regulation of TDO2 by CD28. **Conclusions:** We have made the novel observations that MM cells express TDO2, which would allow them to generate TRP-depleted immunosuppression as well as pro-MM survival KYN-AhR signaling without an extrinsic BM ME partner. TDO2 expression correlates with disease progression and shorter PFS and OS in MM patients, and direct TDO2 inhibition in vitro kills MM cells. TDO2 expression in MM cells appears to be regulated at least in part by MM CD28, mirroring CD28's role in IDO1 induction in the BM ME. Altogether these findings suggest that TDO2 is a novel therapeutic target in MM.

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P-212

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Introduction: Recent studies have focused on understanding the role of the gut microbiota and its production of active metabolites in hematological malignancies, including multiple myeloma (MM). Urolithin A (UA) is a natural compound produced by gut microbiota from ellagic acid that has a positive influence on the regulation of biological functions and several physiological processes. Thus its effect has been reported as beneficial in numerous diseases, including cancer. In this work, we have characterized the human microbiota and its microbial metabolites, including UA, in different stages of MM from pre-malignant stages. We also have studied the possible therapeutic potential of this metabolite in MM. **Methods:** We collected 46 stool and serum samples from patients with monoclonal gammopathy of undetermined significance (n=11), smoldering myeloma (SMM) (n=9) and newly diagnosed multiple myeloma (NDMM) (n=9), at relapse/refractory (RRMM) and at complete remission (CRMM) (n=5). Furthermore, healthy patients (n=8) whose median age and gender ratio was similar to that of the patients, were included as controls. Taxonomic characterization in stool samples was performed by 16S rRNA using Illumina® MiSeq ™. LC-MS determined UA levels in serum samples. In vitro studies were performed on JJN3-GFP and U266-GFP MM cell lines as dose-response studies, western blot, immunohistochemistry, qPCR and flow cytometry. A MM xenograft model after 4 weeks of treatment with UA was used to validate the efficacy in mice. **Results:** We evaluated whether the levels of UA were changed by the monoclonal gammopathy progression and its response to treatment. When we classified patients according to whether or not they had detectable urolithins levels, we found that the majority group with undetectable levels was active MM (NDMM and RRMM) (56%), while only 15% of patients with urolithin detectable levels had active disease (p=0.043). When we analyzed the levels of the microbiota related to the production of urolithins, we found some microorganisms productors of UA we associated to achieving complete remission and a higher survival. The study of the treatment with UA showed an anti-proliferative effect in monotherapy and in combination with bortezomib in MM cell lines. UA treatment significantly improved survival in an in vivo model of MM, compared to the control group (p=0.0048). **Conclusions:** The presence of gut microbiota related to the production of UA and its levels were associated improving of response and survival in patients with MM. UA had an anti – tumor effect in an in vitro and in vivo a MM model. Our results suggests that this microbiota metabolite could have an anti-myeloma effect, although more studies are needed to validate its therapeutic potential.

P-213

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signaling in vitro and in vivo. BMF-219 exhibited a strong anti-proliferative effect on various menin-dependent cell lines including acute myeloid leukemia (AML), diffuse large B-cell lymphoma (DLBCL) representing Double/Triple Hit Lymphoma (DHL/THL) & Double Expressor Lymphoma (DEL), multiple myeloma (MM) with diverse mutational backgrounds. BMF-219 also exhibits high potency ex vivo in patient samples from MLL-rearranged and NPM1-mutant AML, THL and MYC-amplified DLBCL, bone marrow mononuclear cells from treatment-naive and R/R MM, and CLL patient specimens with various cytogenetic backgrounds. **Methods:** COVALENT-101 is a prospective, open-label, multi-cohort, non-randomized, Phase I study evaluating the safety, tolerability, and clinical activity of escalating doses of BMF-219 in patients with relapsed or refractory (R/R) acute leukemia (AL), DLBCL, MM and CLL who have received standard therapy. The primary objective of the study is to determine independently for each cohort, the optimal biological dose/recommended Phase 2 dose of BMF-219 monotherapy. Key secondary objectives include further evaluation of safety and tolerability, characterization of the pharmacodynamics and pharmacokinetics of BMF-219, and assessment of antitumor activity based on best overall response rate, duration of response, progression-free survival, and time to progression. Food-effect studies will be performed at certain dose levels. Utilizing an accelerated titration design, doses of BMF-219 will be escalated in single-subject cohorts independently for each indication until 1 subject experiences either a ≥ Grade 2 related adverse event or dose limiting toxicity. At that point, the cohort will switch to a classical "3 + 3" design. Treatment continues in 28-day cycles until progression or intolerability. Expansion cohorts for each indication will be enrolled to obtain further safety and efficacy data. Patients with R/R AL, DLBCL who received at least 2 prior therapies, MM who received at least 3 prior therapies, CLL who received at least 2 prior therapies and have either failed or are ineligible for any standard therapies are eligible. Patients must have ECOG PS ≤ 2, and adequate organ function. Key exclusion criteria include known CNS disease involvement and clinically significant cardiovascular disease. **Results:** As of May 2023 the study is enrolling at 16 sites in the United States, Spain and the Netherlands. Other European sites in Greece, Italy and France are in startup. **Conclusions:** Enrollment commenced in January 2022 in the United States and in May 2023 in Europe.

P-214

A phase 2 trial of leflunomide, pomalidomide, and dexamethasone for relapsed/refractory multiple myeloma

Michael Rosenzweig[1], James Sanchez[1], Arnab Chowdhury[1], Nitya Nathwani[1], Murali Janakiram[1], Myo Htut[1], Firoozeh Sahebi[1], Tricia Walker[1], Flavia Pichiorri[1], Joycelynne Palmer[1], Amrita Krishnan[1], Jonathan Keats[1,2], Steven Rosen[1]

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P-215

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signaling in vitro and in vivo. BMF-219 exhibited a strong anti-proliferative effect on various menin-dependent cell lines including acute myeloid leukemia (AML), diffuse large B-cell lymphoma (DLBCL) representing Double/Triple Hit Lymphoma (DHL/THL) & Double Expressor Lymphoma (DEL), multiple myeloma (MM) with diverse mutational backgrounds. BMF-219 also exhibits high potency ex vivo in patient samples from MLL-rearranged and NPM1-mutant AML, THL and MYC-amplified DLBCL, bone marrow mononuclear cells from treatment-naive and R/R MM, and CLL patient specimens with various cytogenetic backgrounds. **Methods:** COVALENT-101 is a prospective, open-label, multi-cohort, non-randomized, Phase I study evaluating the safety, tolerability, and clinical activity of escalating doses of BMF-219 in patients with relapsed or refractory (R/R) acute leukemia (AL), DLBCL, MM and CLL who have received standard therapy. The primary objective of the study is to determine independently for each cohort, the optimal biological dose/recommended Phase 2 dose of BMF-219 monotherapy. Key secondary objectives include further evaluation of safety and tolerability, characterization of the pharmacodynamics and pharmacokinetics of BMF-219, and assessment of antitumor activity based on best overall response rate, duration of response, progression-free survival, and time to progression. Food-effect studies will be performed at certain dose levels. Utilizing an accelerated titration design, doses of BMF-219 will be escalated in single-subject cohorts independently for each indication until 1 subject experiences either a ≥ Grade 2 related adverse event or dose limiting toxicity. At that point, the cohort will switch to a classical "3 + 3" design. Treatment continues in 28-day cycles until progression or intolerability. Expansion cohorts for each indication will be enrolled to obtain further safety and efficacy data. Patients with R/R AL, DLBCL who received at least 2 prior therapies, MM who received at least 3 prior therapies, CLL who received at least 2 prior therapies and have either failed or are ineligible for any standard therapies are eligible. Patients must have ECOG PS ≤ 2, and adequate organ function. Key exclusion criteria include known CNS disease involvement and clinically significant cardiovascular disease. **Results:** As of May 2023 the study is enrolling at 16 sites in the United States, Spain and the Netherlands. Other European sites in Greece, Italy and France are in startup. **Conclusions:** Enrollment commenced in January 2022 in the United States and in May 2023 in Europe.

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P-215

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[1]Dana-Farber Cancer Institute; [2]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/ Harvard Medical School

Introduction: Multiple myeloma (MM) is associated with significant DNA damage and genomic instability, enabling them to acquire new characteristics for growth and disease progression. We previously identified apurinic/apyrimidinic nuclease 1 (APEX1) as part of a gene signature that correlated with genomic instability in MM cells. APEX1 is best known for its critical role in the base-excision repair pathway. However, APEX1 is also known to participate in transcriptional regulation. In multiple myeloma cells, APEX1 binds to P73 at the RAD51 promotor to regulate the expression of RAD51, a key factor in homologous DNA repair (HR). **Methods:** To find APEX1-interaction sites throughout the myeloma genome, we did Chromatin Immuno-precipitation (IP) with APEX1 antibody followed by sequencing (ChIP-seq). To find APEX1 and RAD51 proteomes in myeloma cells, we performed IP using APEX1, RAD51 or IgG followed by mass spectrometry. **Results:** Using ChIP-seq, we found that ~60% of the APEX1 interaction sites are in the expressed regions of the genome i.e., in promoters, exons, introns or UTRs. APEX1 was predominantly bound to genes involved in immune function, growth, and cancer-related pathways. Interestingly, treatment with camptothecin (CPT), a chemical that induces double-strand DNA breaks, redirected APEX1 to genes involved in the cell cycle, DNA repair, mTOR signaling and cancer-related pathways. Some of the genes where APEX1 peaks appeared were TP53 (involved in DNA repair and apoptosis), GADD 45B (involved in DNA repair, cell cycle and the ability of the cell to cope with genotoxic stress), LMNA (involved in the maintenance of chromatin structure, telomeres, DNA repair and gene expression), IKBKB (involved in immune response, growth control) and MAP2K1 (involved in growth, adhesion, survival and differentiation). Since coordination among cell cycle, DNA repair and apoptosis pathways is required for regulating growth and genome stability, our data suggest a possible role of APEX1 in the coordination of these vital processes. We previously demonstrated that elevated APEX1 impacts genome stability through dysregulation of base excision repair as well as HR. To further study the mechanisms and protein networks involved in APEX-related dysregulation of HR and genomic instability, we investigated proteins interacting with APEX1 and RAD51. Thirteen proteins were common in APEX1 and RAD51 proteomes. For example, PARP1, which contributes to both single and double stranded DNA break repair (through recruitment of BRCA1), is part of both APEX1 and RAD51 proteomes. This further confirms the functional link between APEX1 (base excision repair) and RAD51 (HR) related pathways. **Conclusions:** Our data suggest that APEX1, in addition to its canonical DNA repair function, is also involved in the regulation of the cell cycle, apoptosis and multiple DNA repair pathways and may assist in coordination of these vital processes. Thus, inhibitors of APEX1 have the potential to target genomic instability and growth of MM cells.

P-216

The PBK-FOXM1 axis disrupts the DREAM transcriptional repressor complex, contributing to the growth and genomic instability of myeloma

Lai Shi[1], Srikanth Talluri[1], Subodh Kumar[1], Jiangning Zhao[1], Laksmi Potluri[2], Chengcheng Liao[1], Leutz Buon[1], Chandraditya Chakraborty[1], Masood Shammas[1], Nikhil Munshi[3]
[1]Dana-Farber Cancer Institute; [2]Wayne State University/DMC Sinai Grace Hospital; [3]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/Harvard Medical School

Introduction: The dysregulation of cell cycle checkpoints and DNA repair pathways is a common feature of cancer cells and contributes to their continued growth and genomic evolution. Previously, we identified a six-gene kinase signature that correlated with genomic instability in nine human cancers including multiple myeloma (MM). PBK, a top kinase in the signature, was investigated further. The DREAM complex represses cell cycle genes during quiescence through scaffolding MuvB proteins with E2F4-p130. Upon cell cycle entry, MuvB dissociates from E2F4 and recruits FOXM1 for up-regulating mitotic gene expression. **Methods:** RNA sequencing was done following PBK inhibition to investigate the genes/pathways regulated by PBK. Co-immunoprecipitation followed by western blotting and/or mass-spectrometry was done to find interacting partners of PBK, LIN54 and FOXM1. To investigate FOXM1 regulated genes following PBK inhibition, we performed Chromatin Immunoprecipitation (ChIP), followed by qPCR. Subcutaneous xenograft study using MM cells was done to evaluate the in vivo efficacy of the PBK inhibitor. **Results:** RNA seq. analysis showed that E2F and FOXM1 were among the top six pathways down-regulated by the PBK inhibitor and that there was a notable overlap between the affected genes and target genes of the DREAM complex. Using Co-IP and ChIP experiments, we found that PBK interacts with and phosphorylates FOXM1, thus upregulating FOXM1 target genes such as RAD51, EXO1 and CDC25a. To get further insight into PBK-mediated regulation of the DREAM complex, we immunoprecipitated LIN54 (a major component of MuvB) in PBK-overexpression and PBK-knockdown MM cells. We found that PBK-overexpression increases the phosphorylated FOXM1-LIN54 interaction and disrupts the repressive DREAM complex, as evident from reduced LIN54-E2F4 interaction. On the contrary, PBK-knockdown or PBK inhibitor promoted the DREAM repressive complex (LIN54-E2F4 interaction) and reduced the phosphorylated FOXM1-LIN54 interaction. These data demonstrate that elevated PBK disrupts the repressive DREAM complex by dissociating MUVB from E2F4 and recruiting it to FOXM1, thus promoting mitosis and contributing to genomic instability. Consistently, the comparative gene expression profiling of paired myeloma cell samples collected at diagnosis and again after chemotherapy (melphalan) relapse (GSE19554), showed significant upregulation of PBK at relapse. In MM cells, treatment with PBK inhibitor inhibited spontaneous and chemotherapy-induced genomic instability ($P < 0.05$), as assessed by micronucleus assay. Moreover, in a subcutaneous mouse model of MM, treatment with PBK inhibitor also impaired tumor growth and significantly

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increased the efficacy of a chemotherapeutic agent (P = 0.0011). **Conclusions:** Inhibitors of PBK have the potential to inhibit growth and increase the cytotoxicity of chemotherapeutic agents while minimizing spontaneous as well as chemotherapy-induced genomic instability in MM.

P-217

ULK3-mediated autophagy is a tractable therapeutic target for the treatment of multiple myeloma

Marilena Tauro[1], Tao Li[1], Mark Meads[1], Praneeth Sudalagunta[1], Raghunandan Alugubelli[1], Nicholas Lawrence[1], Ernst Schinbrunn[1], Ryan Bishop[1], Harshani Lawrence[1], Ken Shain[1], Conor Lynch[1]

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Introduction: Multiple myeloma (MM) remains incurable despite advances in therapy. Our group is the first to demonstrate that ULK3-mediated autophagy in MM is a key program that sustains cell survival upon treatment. MM is characterized by high basal levels of autophagy and, currently, specific ULK3 inhibitors are lacking. Here we have generated novel multiple kinase inhibitors that can block ULK3 activity and demonstrate their efficacy in vitro, in vivo and in ex vivo human specimens. **Methods:** We performed RNASeq analysis of CD138+ MM patient cells collected at the Moffitt Cancer Center (n=815) and demonstrated ULK3 is highly expressed across the disease spectrum. We also show it is crucial for MM progression using CRISPR and in vivo preclinical models (5TGM1Luc, U266Luc). We characterized novel small molecule inhibitors SG3014/MA9060 that target multiple kinases including ULK3 with nanomolar potency and demonstrate their impact on MM cell viability. We also use a novel ex vivo platform developed at Moffitt to demonstrate the efficacy of these reagents and their effect on ULK3 mediated autophagy. **Results:** ULK3 protein levels correlate with MM patients' progression stages. In fact, refractory patients have increased autophagy activity and significantly higher expression of ULK3. Genetic ablation of ULK3 by CRISPR guides in U266/ 8226/ MM1.S cell lines results in rapid cessation of the downstream autophagy mediators (ULK1, ATG13, pATG13). Importantly, using a vesicle labelling tool (CytoID), we demonstrated shutdown of autophagy in ULK3 knockout cells. We also show that MA9060/SG3014 decrease ULK3 levels and autophagy as measured by immunoblot and CytoID. Using an in vivo model of MM progression in the skeleton (U266) we observed that MA9060 reduced tumor burden, protected against myeloma induced bone disease and significantly extended overall survival (CTRL untreated n=65 days vs MA9060 n=110 days). Importantly, we noted no overt toxicity and protected effect against myeloma-induced bone disease. Ex vivo, we demonstrated the efficacy of MA9060 for the treatment of CD138+ MM derived from newly diagnosed and refractory patients both as a single agent and in combination with standard of care therapies such as the proteasome inhibitor, carfilzomib. **Conclusions:** ULK3 is a key regulator of autophagy in multiple myeloma and its genetic or pharmacological inhibition significantly limits MM viability making it an attractive therapeutic target for the treatment of the disease.

P-218

TLR-activation may promote drug resistance and disease progression in multiple myeloma

Synne Stokke Tryggestad[1], Kristin Roseth Aass[1], Ingrid Aass Roseth[1], Therese Standal[1]

[1]Norwegian University of Science and Technology

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P-219

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P-217

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Marilena Tauro[1], Tao Li[1], Mark Meads[1], Praneeth Sudalagunta[1], Raghunandan Alugubelli[1], Nicholas Lawrence[1], Ernst Schinbrunn[1], Ryan Bishop[1], Harshani Lawrence[1], Ken Shain[1], Conor Lynch[1]

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TLR-activation may promote drug resistance and disease progression in multiple myeloma

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Introduction: Multiple myeloma (MM) is the second most common hematological malignancy in the world and remains largely incurable. We previously demonstrated that MM cells are dependent on intact proteostasis mechanisms and are specifically sensitive to perturbations of this balance. For instance, proteasome inhibitors (PI) such as bortezomib, carfilzomib and ixazomib are part of the treatment of MM across all stages of disease. However, acquired resistance is inevitable for most patients, leading to shorter remissions and eventual patient demise. New therapeutic strategies to overcome resistance are therefore urgently needed. We recently showed that the aspartic protease DDI2 is necessary for MM cell survival due to its critical role in activating the proteasome stress response (PSR) master-regulator NRF1, leading to de novo proteasome subunit transcription. We hypothesized that targeting DDI2 is a novel therapeutic strategy in MM. Specific DDI2 inhibitors are not available and mammalian reporter cell lines of PSR activation do not exist, limiting our capabilities to successfully screen for new compounds. We herein set out to develop MM reporter cell lines to conduct high-throughput repurposing screening of FDA-approved small molecules. **Methods:** We generated a reporter construct comprising 8 repeats of antioxidant response elements (ARE) upstream of a minimal promoter followed by destabilized GFP. To monitor for successful transfection, copy number integration and global changes in transcription, the same construct will lead to expression of mCherry under an EF1α promotor. We transduced MM cell lines with varying baseline sensitivities to PI with this construct. We also used AMO1-VR, but DDI2 WT and DDI2 KO, as a model of acquired bortezomib resistance with intact or impaired PSR. To induce PSR, we pulse treated cells with a sublethal dose of carfilzomib as previously described (Chen et al, Blood Adv 2022) and monitored changes in the ratio of GFP/mCherry intensity over time via flow cytometry and immunofluorescence. **Results:** We found that the reporter cell lines showed a peak of GFP/mCherry intensity 8-12 hours after pulse treatment with carfilzomib, consistent with our prior data showing peak of proteasome subunit transcription after PI treatment around 10 hours. Importantly, the GFP/mCherry ratio returned to baseline after approximately 24 hours from treatment, in the absence of significant cell apoptosis. DDI2 KO AMO1-VR showed significantly blunted peak of GFP/mCherry intensity, consistent with reduced capability of de novo proteasome subunit transcription. **Conclusions:** Our data showed that we have successfully developed the first mammalian reporter cell line of PSR with preliminary data showing adequate delta and kinetics to assist in pharmacological screening of molecules blocking the PSR and inducing apoptosis in MM. This powerful tool will inform screening and subsequent validation of newly found/synthesized DDI2 inhibitors, currently under development.

P-220

Discovery of tumor-reactive T cell receptors by functional single cell interaction analyses in patients with newly diagnosed multiple myeloma

Tim Wagner[1], Niklas Kehl[1], Simon Steiger[2,3], Michael Kilian[4,5], Tamara Boschert[6], Katharina Lindner[6], Bruno Schönfelder[6], Karsten Rippe[3], Carsten-Müller Tidow[1], Hartmut Goldschmidt[1], Marc Raab[1], Michael Platten[6], Stefan Eichmüller[6], Mirco Friedrich[7]

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Introduction: Innovative immunotherapy approaches such as adoptive transfer of chimeric antigen receptor (CAR) T cells or tumor infiltrating lymphocytes (TILs) have shown great success in the treatment of solid tumors and hematological malignancies. Although treatment of multiple myeloma with CAR T cells can induce deep responses, relapses frequently occur due to antigen escape and limited CAR T cell persistence. TCR-engineered T cells may show prolonged persistence in vivo and could mediate sustained antitumor effects. A further benefit of TCR transgenic T cells is the ability to target intracellular antigens that are inaccessible to CAR T cells, expanding the range of potential targets for immunotherapy. **Methods:** In our project, we propose to identify T cell receptors (TCRs) specifically targeting autologous myeloma cells. Tumor-reactive T cells were identified using the Berkeley Lights Lightning platform, allowing simultaneous functional analysis of up to 1500 individual T cell/target cell interactions on a chip. Reactive T cells were identified upon detection of secreted cytokines (IFNγ, TNFα, IL¬ 2) and measurement of 4-1BB (CD137) surface expression. **Results:** Tumor-reactive T cells showing various cytokine secretion patterns and 4-1BB expression profiles were detected in each myeloma patient (7 to 26 cells of approx. 1500 cells tested per patient). Individual tumor-reactive T cells have been isolated and their TCRs were sequenced. TCR sequences of tumor-reactive T cells were mapped to single-cell RNA sequencing data of individual multiple myeloma patients to reveal gene expression signatures of myeloma-reactive T cells. TCR genes of reactive T cells were cloned and overexpressed in autologous T cells for functional validation and analysis of tumor derived neoepitope specificity. **Conclusions:** In summary, we present a pipeline allowing identification of myeloma-recognizing T cells and recovery of bona fide tumor-reactive TCRs eligible for patient-individualized T cell therapy.

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P-221

PIM2 kinase regulates TIGIT expression and energy metabolism in NK cells from multiple myeloma patients

Hao Wang[1], Zhaoyun Liu[1], Rong Fu[1]
[1]Tianjin Medical University General Hospital

Introduction: PIM2 kinase is highly expressed in myeloma cells and reportedly inhibits their apoptosis,participates in the pathogenesis of myeloma bone disease, negatively regulates T cell-mediated immune response, and maintains B cell proliferation before survival restriction. However, only a few studies have examined the effects of PIM2 kinase on NK cell function in patients with multiple myeloma (MM).The functional suppression of NK cells through surface immune checkpoints is a key mechanism of immune escape in MM. One of the immune checkpoints, TIGIT, is highly expressed on NK cells in patients with MM and binds to PVR/CD155 to inhibit NK cell function. Previous studies have shown that of the presence of NK cells and the expression of IFN-γ, CD107a, TNF, and other molecules are reduced in the tumor microenvironment. Therefore, immunotherapy targeting NK cells has become a new idea of tumor immunotherapy.Although PIM2 kinase is known to regulate T and B cells, its role in natural killer (NK) cells remains unclear.To investigate the effect and mechanism of Pim-2 kinase inhibitor on NK cell therapy. **Methods:** PIM2 kinase expression was analyzed in NK cells from MM patients and healthy donors using single-cell RNA sequencing (RNA-seq). Immune checkpoint expression, cell apoptosis, and NK cell function were evaluated using flow cytometry. The TIGIT promoter was predicted using NCBI, UCSC, JASPAR, and GEPIA databases. NK-92 cells with ETS-1 knockdown were established using shRNA. PIM2 kinase inhibition by 160 natural flavonoids was analyzed using kinase functional assays (ADP-Glo), mass spectrometry, and RNA-seq. The oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured using assay kits. the expression of TIGIT on NK cells, cell apoptosis, and NK cell function were detected using flow cytometry in U266 cells and NK-cells co-culture system or U266 cells, bone marrow mesenchymal stem cell (BMSC) and NK-cells co-culture. **Results:** PIM2 kinase was highly expressed in NK cells from patients with MM and PIM2 kinase inhibition increased NK cell function and downregulated TIGIT expression. ETS-1, which binds directly to the TIGIT promoter, was upregulated by PIM2 kinase, thereby increasing TIGIT transcription in NK cells. The natural flavonoids kaempferol and quercetin dihydrate inhibited PIM2 kinase with higher efficiency, at low doses in MM cells and altered TIGIT expression and energy metabolism in NK-92 cells. PIM2 kinase inhibitors activated NK cell killing and decreased TIGIT expression in vitro, while promoting MM cell apoptosis. **Conclusions:** PIM2 kinase regulates NK cell anti-myeloma activity by modulating TIGIT expression and energy metabolism.

P-222

Development of pERp1-ADC as a novel therapeutic for multiple myeloma

Jianhong Lin[1], Kylin Emhoff[1], Mohsin Maqbool[1], Eric Irons[1], Tyler Alban[1], Danai Dima[2], Meng-Han Chang[1], Esther Dai[1], Hanna Hong[3], Rie Maeda[3], Joelle Jeon[1], Louis Williams[2], Jennifer Yu[1], Timothy Chan[1], Justin Lathia[1], Faiz Anwer[2], Jason Valent[2], Jae Jung[1], Jianjun Zhao[1]
[1]Cleveland Clinic Lerner Research Institute; [2]Cleveland Clinic Taussig Cancer Institute; [3]Cleveland Clinic Lerner College of Medicine

Introduction: Monoclonal antibody (mAb) drugs are already in clinical use to treat multiple myeloma (MM) but all MM patients eventually develop drug resistance. Therefore, novel targeted therapy is urgently needed to overcome the drug resistance. The plasma cell-induced ER resident protein 1 (pERP1) is one of the co-chaperone proteins specifically required for the differentiation and function of antibody-secreting cells in a T cell independent immune response. High pERP1 expression has been specifically linked to B cell malignancy such as chronic lymphocytic leukemia, follicular lymphoma, and diffuse large B-cell lymphoma correlates with poorer prognosis and shorter survival times in patients. The expression pattern of pERP1 in MM patients is unclear. **Methods:** We performed 10X scRNA seq analysis to simultaneously identify distinct immune cell populations and MM cells using bone marrow samples from patients. Through scRNA seq analysis, we identified the most highly upregulated and downregulated genes in each immune cell cluster. To test whether pERP1 might be a novel immunotarget for MM treatment, we have developed an pERP1 antibody drug conjugate (ADC). We further tested pERP1 ADC in our newly developed preclinical third generation AIDCreERT2+/-, EYFP LSL/-, P53L/L, BrafV600ELSL/-, cMYCLSL/- (AEY-PVM) MM mouse model. **Results:** By means of single cell RNA seq analysis, we identified the most upregulated gene signatures in patients to include those of CD138, CD38, BCMA, and pERP1. When we look for other chaperone proteins including GRP78 and GRP94, we found them to be broadly expressed in bone marrow cells while not finding specific expression in the MM cell population, which underscoring the importance of pERP1 in the development of MM and its potential as a therapeutic target. Our studies further demonstrate high expression of pERP1 on the surface of MM cell lines and on CD138+ plasma cells in MM patients as compared with those from healthy donors. Then, we developed a pERP1 ADC against human pERP1 antigen, verified by using Biacore S200 Surface Plasmon Resonance (SPR) assay. We determined the IC50 of the pERP1 ADC drug against the human cell line RPM18226 to be 1.034 nM. We then tested the pERP1ADC drug in our third generation AEY-PVM mice after they developed MM disease as determined by M spike detection on an SPE gel. We used only 1.25mg/kg of the pERP1 ADC drug, which is lower than the dose of the currently clinically used ADC drugs belantamab mafodotin (2.5-3.4 mg/kg), to treat the AEY-PVM MM mice. Furthermore the survival data from 5 MZB1-ADC treated AEY-PMV mice and 5 control mice confirmed that pERP1 mAb can significantly prolong the survival of AEY-PMV MM mice. **Conclusions:** In conclusion,

P-221

PIM2 kinase regulates TIGIT expression and energy metabolism in NK cells from multiple myeloma patients

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Introduction: PIM2 kinase is highly expressed in myeloma cells and reportedly inhibits their apoptosis,participates in the pathogenesis of myeloma bone disease, negatively regulates T cell-mediated immune response, and maintains B cell proliferation before survival restriction. However, only a few studies have examined the effects of PIM2 kinase on NK cell function in patients with multiple myeloma (MM).The functional suppression of NK cells through surface immune checkpoints is a key mechanism of immune escape in MM. One of the immune checkpoints, TIGIT, is highly expressed on NK cells in patients with MM and binds to PVR/CD155 to inhibit NK cell function. Previous studies have shown that of the presence of NK cells and the expression of IFN-γ, CD107a, TNF, and other molecules are reduced in the tumor microenvironment. Therefore, immunotherapy targeting NK cells has become a new idea of tumor immunotherapy.Although PIM2 kinase is known to regulate T and B cells, its role in natural killer (NK) cells remains unclear.To investigate the effect and mechanism of Pim-2 kinase inhibitor on NK cell therapy. **Methods:** PIM2 kinase expression was analyzed in NK cells from MM patients and healthy donors using single-cell RNA sequencing (RNA-seq). Immune checkpoint expression, cell apoptosis, and NK cell function were evaluated using flow cytometry. The TIGIT promoter was predicted using NCBI, UCSC, JASPAR, and GEPIA databases. NK-92 cells with ETS-1 knockdown were established using shRNA. PIM2 kinase inhibition by 160 natural flavonoids was analyzed using kinase functional assays (ADP-Glo), mass spectrometry, and RNA-seq. The oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured using assay kits. the expression of TIGIT on NK cells, cell apoptosis, and NK cell function were detected using flow cytometry in U266 cells and NK-cells co-culture system or U266 cells, bone marrow mesenchymal stem cell (BMSC) and NK-cells co-culture. **Results:** PIM2 kinase was highly expressed in NK cells from patients with MM and PIM2 kinase inhibition increased NK cell function and downregulated TIGIT expression. ETS-1, which binds directly to the TIGIT promoter, was upregulated by PIM2 kinase, thereby increasing TIGIT transcription in NK cells. The natural flavonoids kaempferol and quercetin dihydrate inhibited PIM2 kinase with higher efficiency, at low doses in MM cells and altered TIGIT expression and energy metabolism in NK-92 cells. PIM2 kinase inhibitors activated NK cell killing and decreased TIGIT expression in vitro, while promoting MM cell apoptosis. **Conclusions:** PIM2 kinase regulates NK cell anti-myeloma activity by modulating TIGIT expression and energy metabolism.

P-222

Development of pERp1-ADC as a novel therapeutic for multiple myeloma

Jianhong Lin[1], Kylin Emhoff[1], Mohsin Maqbool[1], Eric Irons[1], Tyler Alban[1], Danai Dima[2], Meng-Han Chang[1], Esther Dai[1], Hanna Hong[3], Rie Maeda[3], Joelle Jeon[1], Louis Williams[2], Jennifer Yu[1], Timothy Chan[1], Justin Lathia[1], Faiz Anwer[2], Jason Valent[2], Jae Jung[1], Jianjun Zhao[1]
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P-223

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Daniel Lechner-Radner[1,2], Richard Greil[3], Maria-Theresa Krauth[4], Ursula Maria Vogl[5,6], Bernd Hartmann[7], Heinz Gisslinger[8], Sigrid Machherndl-Spandl[1], Irene Strassl[1], Hildegard Greinix[8], Siegfried Sormann[8], Johannes Andel[9], Ernst Rechberger[10], Beatrice Schwarzer[11], Catharina Arnold-Schrauf[11], Hermine Agis[4]

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P-224

Single-center experience of selinexor-based combination therapies for relapsed multiple myeloma

Noreen Ahmed[1], Shucen Wan[1], Noa Biran[1], Pooja Phull[1], Andrew Ip[1], Kimberley Doucette[2], David Vesole[1], David Siegel[3], Harsh Parmar[1]

[1]Hackensack University Medical Center; [2]Georgetown University Hospital; [3]Institute for Multiple Myeloma Hackensack Meridian Health Center for Discovery & Innovation, Hackensack, NJ, USA

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we have found pERP1 to be highly expressed on the surface of MM cell lines in culture and of MM cells from patients in comparison with plasma cells from healthy donors, underscoring the potential of pERP1 as a novel immunotherapy target by using mAb or ADC.

P-223

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P-224

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MM. **Methods:** All pts with MM who were treated with selinexor-based combinations were included in the institutional review board approved study. Demographic characteristics, molecular studies, treatment and response information were recorded and included in the study. Survival analysis was performed using the Kaplan-Meir method including PFS and overall survival (OS). The IMWG response criteria were utilized for response assessment. **Results:** We identified 101 pts who were treated consecutively between May 2019 and March 2023 with selinexor-based combinations. 58.4% (n=59) were male, median age was 68.9 years, median time from diagnosis to treatment initiation was 5.9 yrs. Pts had received a median of 4 prior lines of therapies (range 2-13). 85.1% (n=86) were triple class refractory, 97% (n=98) were anti-CD38 refractory. 91.1% (n=92) had received at least 1 autologous stem cell transplant. 67% of the FISH evaluable pts had high risk genetic profiles, defined as those with t(4;14), t(14;16), 17p(-), 1q(+) or t(14;20), 21.7% pts were ISS-3, at diagnosis. Baseline characteristics are summarized in Table 1. Combination agents included pomalidomide (31.6%, n=32), carfilzomib (31.6%, n=32), bortezomib (12.8%, n=13), daratumumab (15.8%, n=16), ixazomib (0.9%, n=1) and dexamethasone (6.9%, n=7). Median starting dose of selinexor was 80 mg (range 40mg to 100mg). Dose reduction for toxicity was necessary in 19 pts (18.8%). The most common reasons for dose reduction were fatigue and thrombocytopenia. Overall response rate (ORR) (partial remission or better) for the entire cohort was 32.7%. The median PFS was 3.0 mos (Graph 1), the median OS was 14.1 mos (Graph 2) and median duration of response (DOR) was 7.8 mos. Median time to best response was 30 days. Efficacy data are summarized in Table 1 **Conclusions:** In our single-center experience, selinexor-based combinations were overall well tolerated, with few pts needing dose modifications. Similar to the real-world outcomes reported by Kastritis et al., a low response rate was observed in our larger cohort of pts with the use of selinexor in several combinations. However, clinical benefit with a moderate duration of response was observed.

P-225

Uninvolved hypogammaglobulinemia was not a predictor of the infection risk in anti-CD38 chemotherapy

Firas Al-Kaisi[1], Sofia Kazmi[1], Michael Acquah[1]

[1]The Royal Derby Hospital

Introduction: Infections are major causes of morbidity with myeloma treatment. Anti-CD38 antibodies are important additions to myeloma chemotherapy. Through their effect on normal plasma cells, they can reduce the levels of uninvolved immunoglobulins (Ig). We sought to investigate if there was any relationship between the changes in the uninvolved Ig levels during anti-CD38 therapy and the risk of developing infections. We also compared the levels of Ig across different anti-CD38 therapies at different time points. **Methods:** This is a retrospective single-centre analysis of myeloma patients treated with anti-CD38 therapy (single agent or in combination). The levels of the uninvolved Ig and lymphocytes were recorded at baseline and at three-monthly intervals in addition to the number of infections requiring inpatient treatment for up to 18 chemotherapy cycles. Patients who had less than 3 months of treatment and those in the induction phase were excluded. **Results:** Between March 2018 and March 2023, 108 patients were treated with Isatuximab-Pomalidomide-Dexamethasone (IPD), Daratumumab-Bortezomib-Dexamethasone (DVd) and Daratumumab monotherapy (n=28, 49 and 32 respectively). The median age at the start of treatment was 73 (range 41 to 90). The median number of treatment cycles was 11 (range 3 to 45). Thirty-two patients (29%) had at least one infective episode requiring hospitalisation during the course of treatment. Of those, 25% had Daratumumab monotherapy and the rest were equally divided between the IPD and the DVd groups (37.5% each). The median uninvolved Ig levels were subnormal at all the time points assessed within the three regimens. There was no significant change in the uninvolved IgG and IgM levels in the infected group at all time points. The non-infected group showed a significant drop in the uninvolved IgM and IgG levels at the 3 and 6-month time points after which the levels were not significantly different from the baseline. There was a significant drop in the uninvolved IgA levels which persisted at all the time points in both the infected and the non-infected groups. The lymphocyte count changes were not significant in both groups at all time points. The analysis of the uninvolved Ig changes subgrouped by the treatment regimen showed a significant and maintained drop in the IgA levels with Daratumumab monotherapy and DVd and a significant drop in the IgM levels at the early time points with DVd. Comparing the levels of the Ig isotypes across regimens revealed no significant changes attributable to the underlying chemotherapy treatment. **Conclusions:** Uninvolved hypogammaglobulinemia was universal with various anti-CD38 regimens but did not predict infection risk. Uninvolved Ig reduction was most pronounced with IgA but did not correlate with the development of infections. We conclude that the uninvolved hypogammaglobulinemia is a poor predictor of the infection risk with anti-CD38 therapy.

P-226

Safety and clinical activity of belantamab mafodotin combined with carfilzomib, lenalidomide, and dexamethasone after at least one prior line of therapy, interim results from phase 1 clinical trial

Shebli Atrash[1], James Symanowski[1], Barry Paul[1], Cindy Varga[1], Xhevahire Begic[1], Sarah Norek[1], Manisha Bhutani[2], Peter Voorhees[3]

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MM. **Methods:** All pts with MM who were treated with selinexor-based combinations were included in the institutional review board approved study. Demographic characteristics, molecular studies, treatment and response information were recorded and included in the study. Survival analysis was performed using the Kaplan-Meir method including PFS and overall survival (OS). The IMWG response criteria were utilized for response assessment. **Results:** We identified 101 pts who were treated consecutively between May 2019 and March 2023 with selinexor-based combinations. 58.4% (n=59) were male, median age was 68.9 years, median time from diagnosis to treatment initiation was 5.9 yrs. Pts had received a median of 4 prior lines of therapies (range 2-13). 85.1% (n=86) were triple class refractory, 97% (n=98) were anti-CD38 refractory. 91.1% (n=92) had received at least 1 autologous stem cell transplant. 67% of the FISH evaluable pts had high risk genetic profiles, defined as those with t(4;14), t(14;16), 17p(-), 1q(+) or t(14;20), 21.7% pts were ISS-3, at diagnosis. Baseline characteristics are summarized in Table 1. Combination agents included pomalidomide (31.6%, n=32), carfilzomib (31.6%, n=32), bortezomib (12.8%, n=13), daratumumab (15.8%, n=16), ixazomib (0.9%, n=1) and dexamethasone (6.9%, n=7). Median starting dose of selinexor was 80 mg (range 40mg to 100mg). Dose reduction for toxicity was necessary in 19 pts (18.8%). The most common reasons for dose reduction were fatigue and thrombocytopenia. Overall response rate (ORR) (partial remission or better) for the entire cohort was 32.7%. The median PFS was 3.0 mos (Graph 1), the median OS was 14.1 mos (Graph 2) and median duration of response (DOR) was 7.8 mos. Median time to best response was 30 days. Efficacy data are summarized in Table 1 **Conclusions:** In our single-center experience, selinexor-based combinations were overall well tolerated, with few pts needing dose modifications. Similar to the real-world outcomes reported by Kastritis et al., a low response rate was observed in our larger cohort of pts with the use of selinexor in several combinations. However, clinical benefit with a moderate duration of response was observed.

P-225

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P-226

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P-226

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Preliminary clinical data support the use of BM with a proteasome inhibitor and IMiD-based therapy. To capitalize on the efficacy of BM and decrease keratopathy, we conducted a phase 1/2 clinical trial evaluating lower doses of BM administered q8 weeks in combination with the KRd backbone for pts with early relapse of MM. **Methods:** Pts with RRMM after 1-3 prior lines of therapy (LOT) were enrolled in a phase 1 trial with a 3+3 dose escalation followed by an expansion cohort to better inform the recommended phase II dose (RP2D). The primary objective for the phase 1 portion of the trial was to establish the maximum tolerated dose (MTD) of BM when given with KRd as determined by dose-limiting toxicities (DLTs) in cycle 1. Secondary objectives included ORR, depth of response, DOR, progression-free survival, overall survival, and safety. Two doses of BM were tested: 1.4 mg/kg and 1.9 mg/kg given IV over 30 – 60 minutes every 8 weeks with KRd (K 20/56 mg/m^2 days 1,8,15; R 25 mg po days1-21; and d 20/40 mg po weekly) in 28-day cycles for up to 18 cycles followed by R maintenance. **Results:** With a data cutoff of March 6, 2023, 11 pts were enrolled, 6 pts at 1.4 mg/kg and 5 pts at 1.9 mg/kg. 63.6% of pts were male, 45.5% black, and 18% had high-risk cytogenetics and 64% including 1q gain. 91% were refractory to a maintenance dose of R, all were bortezomib exposed, and 27% were daratumumab refractory. The median LOT was 1 (range 1-3). All 11 enrolled pts were DLT evaluable. At the 1.4 mg/kg dose level, one DLT of grade 4 thrombocytopenia was reported out of 6 pts. No DLTs were reported among the pts enrolled at the 1.9 mg/kg dose level (including a 6th pt treated after data cutoff). The most common adverse events were non-specified eye disorders (81.1%), blurred vision (63.6%), hypokalemia (63.6%), diarrhea (63.6%), fatigue (63.6%), constipation (45.5%), and pain (45.5%). Four pts experienced G3 keratopathy, and the median time to recovery was 25 days (range 8-29 days). All pts achieved at least a PR, the VGPR(+) rate was 73%, and the CR(+) rate was 45%. With a median follow-up of 9.2 months, only one pt has progressed with extramedullary liver disease. The remainders are alive without disease progression. **Conclusions:** The dose escalation portion of the phase 1 trial has established a BM dose of 1.9 mg/kg given q8 weeks in combination with KRd as the MTD. Keratopathy was common but of slower onset and associated with less severe, high-grade subjective symptoms relative to what is seen with 2.5 mg/kg dosing given q3 weeks. Enrollment into the expansion cohort to better inform the RP2D is ongoing, and updated data will be presented at the meeting.

P-227

Safety and clinical activity of ruxolitinib combined with carfilzomib and dexamethasone for patients with carfilzomib-refractory multiple myeloma: results from a phase 1 clinical trial

Shebli Atrash[1], James Symanowski[1], Sarah Norek[1], Xhevahire Begic[1], Manisha Bhutani[2], Barry Paul[1], Cindy Varga[1], Andrew Kin[3], Jeffrey[3], Peter Voorhees[4], Saad Usmani[5]

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Introduction: Ruxolitinib (Rux) is a selective Janus kinase 1/2 inhibitor approved for the treatment of patients with polycythemia vera, myelofibrosis, and refractory Graft-versus-host disease. Preclinical studies showed Rux could block the expression of MUC1 and inhibit the STAT pathway leading to modulation of IL-6-mediated myeloma cell refractoriness and reverse checkpoint inhibition by downregulating PD-L1 and PD-L2 expression on both myeloma and stromal cells (Chen et al. 2019). We conducted a phase 1 trial to determine the safety and preliminary efficacy of Rux in combination with carfilzomib for patients with carfilzomib-refractory, relapsed/refractory multiple myeloma. **Methods:** A 3+3 dose escalation design was used for dose escalation. Patients received oral Rux twice daily continuously at three doses across three cohorts (5mg, 10 mg, and 15 mg) in addition to carfilzomib 20/56 mg/m^2 on days 1,2,8,9,15,16; and dexamethasone 40 mg po days 1,8,15; in 28-day cycles. The primary objective was to identify the maximum tolerated dose as defined by the emergence of dose limiting toxicities during cycle 1 of therapy. Secondary objectives included response rate, depth of response, progression-free survival, overall survival and safety. Patients were enrolled from Jan/2019 to Dec/2022. The study accrual was placed on hold during 2020-2021 due to the COVID19 pandemic related institutional resource constraints. **Results:** As of the data cutoff date of March 6, 2023, a total of 12 patients were enrolled. The median follow up time was 42.2 months. The median age for the enrolled population was 66 years, female 25%, high-risk cytogenetics 42%, all subjects were IMiD refractory, CD38 refractory 83%. The median lines of prior therapies were 5. Eight patients were dose-limiting toxicity evaluable and dose escalation occurred from the 5mg cohort (0 DLTs out of 3 subjects) and from the 10mg cohort (0 DLTs out of 3 subject). In the 15mg cohort, one DLT occurred out of 2 subjects. The most common adverse events were anemia (83%), decreased platelet count (50%), dyspnea (50%), and increased creatinine (41.7%). TEAEs by maximum severity grade occurring in at least 25% of subjects are shown in Table 1. The best response observed in this trial was a VGPR in one subject. The overall response rate was 25%. The median progression-free survival time was 3.2 months, and the overall survival time was 15.8 months. The study was terminated early due to withdrawal of sponsor funding for not meeting accrual goals during the COVID19 pandemic. **Conclusions:** Ruxolitinib may have an acceptable safety profile in combination with carfilzomib at a dose of 10 mg po bid. Despite early encouraging data with 15 mg, the trial could not conclude the safety of this dose. In this proof-of-principle trial, ruxolitinib may have the potential to overcome refractoriness to carfilzomib. However, more studies are needed.

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P-227

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P-228

Use of cilta-cel CAR T cells following previous use of a BCMA-directed CAR T-cell product in heavily treated patients with relapsed/refractory multiple myeloma: a single institution case series

Narsis Attar[1], Diana Cirstea[2], Andrew Branagan[2], Andrew Yee[2], Matthew Frigault[2], Noopur Raje[2]

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Introduction: BCMA-directed CAR T-cell (CAR T) therapy has demonstrated remarkable efficacy in patients with relapsed/refractory multiple myeloma (rrMM). Pivotal trials such as the KarMMa and CARTITUDE studies using ide-cel and cilta-cel, respectively, have shown ORR of 73% and 98%, leading to FDA approval of these products. Notably, ide-cel conferred a median OS of 19.4 months with a median DOR of 10.7 months. Similarly, cilta-cel conferred 27-month PFS and OS rates of 55% and 70.4%, respectively. Although these and real-world outcomes are promising, relapse after BCMA CAR T therapy remains a challenge. **Methods:** This is a case series of 5 patients with rrMM from a single institution treated with BCMA-directed CAR T therapy between 2019-2022, followed by a second BCMA-directed CAR T therapy using cilta-cel at the time of relapse. Here we report the response and toxicity profile following the second CAR T therapy. **Results:** Patients had a median age of 64 (40-76). 2 out of 5 patients had high risk disease based on cytogenetics. Prior to the second CAR T therapy, patients had received a median of 7 (5-8) lines of treatment including the first CAR T therapy. For the first CAR T therapy, 3 patients received an investigational BCMA-directed CAR T therapy at the recommended doses of the product and 2 patients received ide-cel. At the time of subsequent relapse all patients eventually received a second CAR T therapy with cilta-cel. ORR to first CAR T-cell therapy was 80%; 4 patients achieved ≥ VGPR (n=2 VGPR; n= 2 sCR), and 1 patient had PD, with a median DOR of 16 months (7-22 months) for responders. The time between two CAR T therapies ranged from 8-38 months, with all patients receiving at least 1 and up to 2 lines of treatment including bridging therapy before cilta-cel. At the time of this report, with a follow up ranging from 3.1-11 months after the second CAR T therapy, 4 out of 5 patients had achieved a response (n=3 CR; n=1 PR). One patient had refractory disease and required subsequent treatment. Notably, this was the same patient who had progressed on the previous CAR T cell therapy. Grade 2 CRS after cilta-cel was seen in 1 out of 5 patients. Hematologic toxicities were seen in all patients with grade 3-4 neutropenia in 5, grade 3 anemia in 3 and grade 4 thrombocytopenia in 2 patients. Prolonged grade 3-4 thrombocytopenia was seen in 1 responder requiring transfusions and thrombopoietin analogs. Three out of 4 responders had hypogammaglobulinemia with levels recovering in 2 patients within 8-12 weeks. One patient had prolonged hypogammaglobulinemia requiring IVIG beyond this time point. **Conclusions:** This case series demonstrates the early efficacy and safety of a second BCMA-directed CAR T therapy, specifically in patients previously responsive to similar BCMA-directed therapy. This highlights the need to better understand the clinical utility of this approach and to delineate the heterogenous disease course and mechanism of resistance post BCMA CAR T therapy.

P-229

Exposure-response analysis of venetoclax in combination with carfilzomib and dexamethasone in t(11;14)-positive relapsed/refractory multiple myeloma patients

Mohamed Badawi[1], Benjamin Engelhardt[1], Edyta Dobkowska[2], Rong Deng[3], Jonathan Kaufman[4], Rajeev Menon[1], Ahmed Hamed Salem[1]

[1]AbbVie Inc.; [2]Pharmacyclics Switzerland GmbH, an AbbVie Company, Schaffhausen, Switzerland; [3]Genentech Inc.; [4]Winship Cancer Institute of Emory University, Atlanta, GA, USA

Introduction: Venetoclax is a first in class, selective BCL2 inhibitor that has gained approval for the treatment of CLL and AML and is currently being evaluated in other hematological indications including multiple myeloma (MM). This analysis aimed to characterize the exposure-response relationship of venetoclax (Ven) when administered in combination with carfilzomib and dexamethasone (Kd) in the biomarker selected, t(11;14)-positive relapsed/refractory MM patients. **Methods:** 55 subjects enrolled in Study NCI: NCT02899052 (37 receiving VenKd and 18 in the control arm receiving Kd) were included in the analysis. A population pharmacokinetic model was developed, and individual post hoc empirical Bayes parameter estimates were used to derive individual subject venetoclax exposures (average area under the concentration time curve to the time of event [AUCavg] and steady state AUC [AUCss]). Quartile plots and logistic regression models were used to evaluate the exposure-efficacy and exposure-safety relationships of venetoclax. Efficacy endpoints assessed included clinical response of overall response rate (ORR), very good partial response or better (≥VGPR) rate and complete response or better (≥CR) rate. Safety endpoints evaluated included Grade ≥3 neutropenia, Grade ≥3 infections, Grade ≥3 treatment emergent adverse events and any grade serious treatment-emergent adverse events. **Results:** Quartile plots demonstrated that compared to the control arm (Kd), adding venetoclax resulted in higher OR, ≥VGPR and ≥CR rates. Within the VenKd treatment arms, a flat exposure-response relationship for Ven was observed for all efficacy endpoints (ORR, ≥VGPR and ≥CR rates) suggesting that efficacy is maximized, and higher venetoclax exposures may not be associated with improved efficacy compared to lower exposures at the studied dose range of 400-800 mg. Both 400 mg and 800 mg venetoclax were generally tolerated, however exposure-safety analysis demonstrated that higher venetoclax exposures (associated with 800 mg venetoclax) trended with higher rates of Grade ≥3 neutropenia. Higher venetoclax exposures were not associated with higher rates of Grade ≥3 infections, Grade ≥3 treatment-emergent adverse events, or serious treatment-emergent adverse events (any grade). Study is ongoing and enrolling subjects; more mature data may be presented at the congress. **Conclusions:** Exposure-response analyses confirm the benefit of adding venetoclax at 400-800 mg doses to carfilzomib and dexamethasone and support

P-228

Use of cilta-cel CAR T cells following previous use of a BCMA-directed CAR T-cell product in heavily treated patients with relapsed/refractory multiple myeloma: a single institution case series

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Introduction: BCMA-directed CAR T-cell (CAR T) therapy has demonstrated remarkable efficacy in patients with relapsed/refractory multiple myeloma (rrMM). Pivotal trials such as the KarMMa and CARTITUDE studies using ide-cel and cilta-cel, respectively, have shown ORR of 73% and 98%, leading to FDA approval of these products. Notably, ide-cel conferred a median OS of 19.4 months with a median DOR of 10.7 months. Similarly, cilta-cel conferred 27-month PFS and OS rates of 55% and 70.4%, respectively. Although these and real-world outcomes are promising, relapse after BCMA CAR T therapy remains a challenge. **Methods:** This is a case series of 5 patients with rrMM from a single institution treated with BCMA-directed CAR T therapy between 2019-2022, followed by a second BCMA-directed CAR T therapy using cilta-cel at the time of relapse. Here we report the response and toxicity profile following the second CAR T therapy. **Results:** Patients had a median age of 64 (40-76). 2 out of 5 patients had high risk disease based on cytogenetics. Prior to the second CAR T therapy, patients had received a median of 7 (5-8) lines of treatment including the first CAR T therapy. For the first CAR T therapy, 3 patients received an investigational BCMA-directed CAR T therapy at the recommended doses of the product and 2 patients received ide-cel. At the time of subsequent relapse all patients eventually received a second CAR T therapy with cilta-cel. ORR to first CAR T-cell therapy was 80%; 4 patients achieved ≥ VGPR (n=2 VGPR; n= 2 sCR), and 1 patient had PD, with a median DOR of 16 months (7-22 months) for responders. The time between two CAR T therapies ranged from 8-38 months, with all patients receiving at least 1 and up to 2 lines of treatment including bridging therapy before cilta-cel. At the time of this report, with a follow up ranging from 3.1-11 months after the second CAR T therapy, 4 out of 5 patients had achieved a response (n=3 CR; n=1 PR). One patient had refractory disease and required subsequent treatment. Notably, this was the same patient who had progressed on the previous CAR T cell therapy. Grade 2 CRS after cilta-cel was seen in 1 out of 5 patients. Hematologic toxicities were seen in all patients with grade 3-4 neutropenia in 5, grade 3 anemia in 3 and grade 4 thrombocytopenia in 2 patients. Prolonged grade 3-4 thrombocytopenia was seen in 1 responder requiring transfusions and thrombopoietin analogs. Three out of 4 responders had hypogammaglobulinemia with levels recovering in 2 patients within 8-12 weeks. One patient had prolonged hypogammaglobulinemia requiring IVIG beyond this time point. **Conclusions:** This case series demonstrates the early efficacy and safety of a second BCMA-directed CAR T therapy, specifically in patients previously responsive to similar BCMA-directed therapy. This highlights the need to better understand the clinical utility of this approach and to delineate the heterogenous disease course and mechanism of resistance post BCMA CAR T therapy.

P-229

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P-231

ABBV-383, a BCMA-CD3 bispecific antibody, in relapsed/refractory multiple myeloma: a multicenter, phase 1b dose optimization study with step-up dosing

Muhamed Baljevic[1], Hila Magen[2], Emma Searle[3], Ziyi Jin[4], Elise Strange[4], Anders Svensson[4], Shaji Kumar[5]

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dose of ABBV-383) to both onset and to resolution; no events were life-threatening or fatal. Neutropenia (37%) and anemia (29%) were the most common hematological AEs. Step-up dosing strategies, where a lower initial dose is given prior to the full dose, have been effectively utilized for other T-cell targeting therapeutics in myeloma as well as other diseases to lower the risk of severe CRS. The intent with this Phase 1b trial, which is currently enrolling, is to evaluate step-up dosing of ABBV-383 in Cycle 1 as a mitigation strategy for CRS. **Methods:** The primary objective is to assess frequency and severity of CRS in patients with RRMM treated with ABBV-383 monotherapy with step-up dosing. Primary and secondary endpoints are Grade ≥2 CRS during Cycle 1 and any CRS during the study, respectively. Secondary objectives are to assess safety and tolerability of ABBV-383 in these patients. Exploratory efficacy endpoints are clinical activity as defined by IMWG 2016 criteria, including objective response rates, time to response, duration of response, and progression-free survival. Eligible patients are aged ≥18 years with ECOG status 0–2 and RRMM with documented progression after last treatment. Patients must be BCMA-targeted therapy-naïve and have received ≥3 lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody. The study consists of 2 phases: step-up dose optimization and dose expansion. In the dose optimization phase, patients receive the step-up dose on Day 1 of treatment Cycle 1 and the target dose on Day 4 of Cycle 1. In Cycle 2 and all subsequent cycles, patients receive the target dose on Day 1. Therapy continues until disease progression, withdrawal, or discontinuation. Patients are hospitalized for 24 hours during both step-up and target dosing in Cycle 1. In the dose expansion phase, patients will receive the optimum step-up dose on Day 1 and the target dose on Day 4 of Cycle 1. Patients receive the target dose on Day 1 of subsequent cycles. This trial is currently enrolling at 34 sites in 7 countries: US, Canada, Denmark, France, Israel, Spain, and the UK.

P-232

Effectiveness of anti-B-cell maturation antigen (BCMA)-targeting therapy after selinexor treatment

Muhamed Baljevic[1], Philippe Moreau[2], Sascha Tuchman[3], Natalie Callander[4], Suzanne Lentzsch[5], Dane Van Domelen[6], Ohad Benture[6], Jorge Monge[7], Noa Biran[8]

[1]Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center; [2]University Hospital Hôtel-Dieu, Nantes, France; [3]University of North Carolina – Chapel Hill Comprehensive Cancer Center; [4]University of Wisconsin; [5]Columbia University Medical Center, New York, NY, USA; [6]Karyopharm; [7]Weill Cornell Medicine Myeloma Center; [8]Hackensack University Medical Center, Hackensack, NJ, USA

Introduction: Multiple myeloma (MM) remains incurable, with the disease typically becoming refractory to three main classes of standard therapies: immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and anti-CD38 monoclonal antibodies (αCD38 mAbs). Treatments with novel mechanisms of action, including the XPO1 inhibitor selinexor and T-cell engaging anti-B-cell maturation antigen (αBCMA)-agents (antibody drug conjugates [ADC], bi-specific antibodies [BiS]), are increasingly used for treatment of relapsed and/or refractory MM (RRMM) after standard therapies have failed. Emerging data suggests a deleterious impact on T cell function with certain MM treatments, including alkylators and PIs, leading to inferior clinical outcomes. The influence of selinexor-based treatment on T cell function, which may alter the efficacy of αBCMA agents following selinexor treatment, is unknown. **Methods:** We analyzed the effectiveness of non-cellular αBCMA (NCA) therapies in pts with MM treated in 4 clinical studies (STORM [NCT02336815]; STOMP [NCT02343042]; BOSTON [NCT03110562], XPORT-MM-028 [NCT04414475]) with selinexor + dexamethasone (Xd), with or without PIs, IMiDs, or αCD38 mAbs, followed by therapy with NCA. After end of treatment with selinexor, survival follow-up data was collected every 3 months for 1 (STORM, STOMP, XPORT-MM-028) to 5 years (BOSTON). **Results:** Across the 4 clinical studies, 724 pts received selinexor, 404 of which had therapy post-selinexor documented. Thirty-seven pts (median age: 68, range: 40-87) received NCA therapy at any time following a selinexor regimen (Xd, n=12; Xd + bortezomib, n=9; Xd + pomalidomide, n=6; Xd + daratumumab, n=3; Xd + carfilzomib, n=5; Xd + ixazomib, n=2). NCAs included the ADC belantamab mafodotin (n=28), the BiS teclistamab (n=2), SEA-BCMA (n=2), AMG 701 (n=1), elranatamab (n=1), MEDI2228 (n=1), and investigational (n=3; 2 had αBCMA bispecific antibodies and 1 had αBCMA BITE) (1 pt received 2 NCAs, belantamab and teclistamab). For the selinexor-based regimens, the median number of previous lines of therapy was 5 (range: 2-11) and 21 (56.8%) pts had triple-class refractory MM including 8 (21.6%) with penta-refractory MM. Median time from last dose of selinexor to NCA was 8 weeks (range: 2-117). Median time to treatment discontinuation with NCA was 4.4 months (95% CI: 2.1, NE). The median overall survival from initiation of NCA was 12.0 months (95% CI: 9.4, NE) with a median follow-up of 7.8 months. **Conclusions:** In this cohort of heavily-pretreated pts with MM who received a selinexor regimen prior to NCA, overall survival was in the range of 1 year, akin to historical results seen with ADCs. The 8-week median time between administration of selinexor and NCAs suggests that selinexor, with various partner agents, did not negatively impact overall survival with subsequent NCA therapy.

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P-233

Physician perspectives regarding conventional marrow testing and MRD assessments to guide decision-making in myeloma

Rahul Banerjee[1], Faiza Zafar[2], Nate Way[3], Kushal Modi[3], Sean Carey[3], Emily Mulvihill[3], Allicia Girvan[4], Seema Tulsian[4], Sophia Li[2]

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P-232

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P-233

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P-232

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P-233

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Introduction: Background: Decision-making in multiple myeloma (MM) is complex as there are numerous treatment options available across multiple lines of therapy. A recent survey suggested many MM physicians are interested in MRD-guided decision making (Derman et al., 2022). We thus conducted an online survey to investigate physicians' attitudes toward MRD assessments and conventional marrow testing (e.g., FISH or karyotyping) and how these tests modify treatment selection. **Methods:** Methods: Board-certified hematologists and/or oncologists (N=75) who had ≥10 patients with MM, spent ≥50% of time in clinical practice in the US, and had been in clinical practice for at least two years completed an online survey. Descriptive statistics assessed practice characteristics, testing procedures, and attitudinal items. **Results:** Results: Most physicians practiced in a community setting (69%) with a substantial number of MM patients under their care (M=60.5, SD=57.1, Mdn=40.0, IQR 25-75). Most physicians routinely ordered bone marrow karyotyping or FISH (M=77.8%, SD=33.0, Mdn=100.0%, IQR 50-100%), while a significant minority routinely ordered MRD assessments (M=41.3%, SD=36.9, Mdn=30.0%, IQR 10-80%). Among cases where such tests were ordered, physicians chose or modified treatment based on the results of karyotyping/FISH half the time (M=53.3%, SD=37.5, Mdn=50.0%, IQR 23-100%) and chose or modified treatment based on the results of MRD assessments only a third of the time (M=39.4%, SD=32.5, Mdn=30.0%, IQR 10-60%). On an agreement scale anchored at 1 (prefer personalized treatment approaches) versus 5 (prefer standard treatment approaches that consistently work), physicians reported a slight preference for targeted treatments (M=2.3, SD=1.1, Mdn=2.0, IQR 2-3). On a 1-5 Likert-type agreement scale, physicians reported it is important to educate patients about how specific features of their MM may affect response rates (M=4.1, SD=0.7, Mdn=4.0, IQR 4-5) and time to progression (M=4.1, SD=0.8, Mdn=4.0, IQR 4-5). **Conclusions:** Conclusions: In our study of physicians primarily based in a community setting, most ordered conventional karyotyping or FISH testing for their patients and utilized these test results to guide treatment choices. MRD assessments were ordered in a third of cases and used to guide management in a third of cases when ordered. These findings highlight the importance of establishing clear pathways to guide decision-making in MM.

P-234

Daratumumab in relapsed/refractory multiple myeloma patients – real world evidence – experiences of the Croatian cooperative group for hematologic diseases (KROHEM)

Josip Batinić[1,2], Barbara Dreta[1], Davor Galušić[3], Milan Vujčić[3], Marin Šimunić[3], Delfa Radić Krišto[2,4], Karla Mišura Jakobac[4], Mario Piršić[5], Anica Sabljić[5], Goran Rinčić[6], Klara Brčić[6], Fran Petričević[6], Jasminka Sinčić-Petričević[7], Vlatka Periša[8], Toni Valković[9], Tajana Grenko[10], Hrvoje Holik[11], Martina Morić Perić[12], Ivan Zekanović[12], Ivan Krečak[13], Petra Berneš[14], Luka Kužat[15], Ranata Babok Flegarić[16], Elizabeta Čorović-Arneri[17], Sandra Bašić-Kinda[1]

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Introduction: Introduction of daratumumab in treatment of multiple myeloma (MM) lead to major improvements of patient's outcomes, both in the newly diagnosed and in the relapse/refractory (RR) settings. However, there are significant differences between outcomes reported in clinical trials and real-world evidence (RWE) data. The aim of this study was to analyze data for RR multiple myeloma patients treated with daratumumab and to compare it with those reported in literature (both RWE and clinical trials). **Methods:** We performed a retrospective analysis of outcomes of RRMM patients treated with daratumumab, in combination with bortezomib and dexamethasone (DVd) or lenalidomide and dexamethasone (DRd) in 12 Croatian hematology centers in the period between June 2019 and February 2023 (daratumumab available and reimbursed since June 2019). **Results:** A total of 329 patients with RR myeloma were included. Median age at the start of daratumumab treatment for the whole group was 68 years (range 42 – 93). There were 166 male and 163 female subjects. Median number of previous lines of therapies was 3 (range 2 – 8). 156 patients (47%) previously underwent autologous stem cell transplantation (ASCT) in the first line of treatment and 3 patients had allogeneic stem cell transplant. 302 patients (92%) were bortezomib exposed and 81 (25%) lenalidomide exposed. Only 11 (3%) and 21 (6%) of patients were exposed to carfilzomib and ixazomib, respectively. DVd was choice of therapy in 76 patients (23%) and DRd in 253 patients (77%). In the DVd group response rate (better or equal to partial response; PR) was 66%, while in the DRd group response rate was 76.8%. In the DVd group median follow up was 13 months and median progression free survival (PFS) was 18 months. In the DRd group median follow up was 15.2 months and median PFS was 24 months. Overall survival at 2 years was 63% in DRd group and 59% in DVd group. In the DRd group anemia, neutropenia and thrombocytopenia were reported in 51%, 40% and 56% patients, respectively. In the DVd group anemia, neutropenia and thrombocytopenia were reported in 50%, 42% and 16% patients, respectively. Infective complications were reported in 46% of patients in both groups. During follow up a total of 112 patients died (43 in the DVd and 83 in the DRd group. **Conclusions:** This RWE analysis validates efficacy of daratumumab in RR MM patients with acceptable and manageable toxicities. Similar outcomes were also reported in RR MM group of patients by other RWE analyses. There are significant discrepancies between RWE data and data reported in clinical trials; median PFS being much shorter in RWE analyses. These discrepancies are possibly due to different study populations.

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P-234

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Introduction: Introduction of daratumumab in treatment of multiple myeloma (MM) lead to major improvements of patient's outcomes, both in the newly diagnosed and in the relapse/refractory (RR) settings. However, there are significant differences between outcomes reported in clinical trials and real-world evidence (RWE) data. The aim of this study was to analyze data for RR multiple myeloma patients treated with daratumumab and to compare it with those reported in literature (both RWE and clinical trials). **Methods:** We performed a retrospective analysis of outcomes of RRMM patients treated with daratumumab, in combination with bortezomib and dexamethasone (DVd) or lenalidomide and dexamethasone (DRd) in 12 Croatian hematology centers in the period between June 2019 and February 2023 (daratumumab available and reimbursed since June 2019). **Results:** A total of 329 patients with RR myeloma were included. Median age at the start of daratumumab treatment for the whole group was 68 years (range 42 – 93). There were 166 male and 163 female subjects. Median number of previous lines of therapies was 3 (range 2 – 8). 156 patients (47%) previously underwent autologous stem cell transplantation (ASCT) in the first line of treatment and 3 patients had allogeneic stem cell transplant. 302 patients (92%) were bortezomib exposed and 81 (25%) lenalidomide exposed. Only 11 (3%) and 21 (6%) of patients were exposed to carfilzomib and ixazomib, respectively. DVd was choice of therapy in 76 patients (23%) and DRd in 253 patients (77%). In the DVd group response rate (better or equal to partial response; PR) was 66%, while in the DRd group response rate was 76.8%. In the DVd group median follow up was 13 months and median progression free survival (PFS) was 18 months. In the DRd group median follow up was 15.2 months and median PFS was 24 months. Overall survival at 2 years was 63% in DRd group and 59% in DVd group. In the DRd group anemia, neutropenia and thrombocytopenia were reported in 51%, 40% and 56% patients, respectively. In the DVd group anemia, neutropenia and thrombocytopenia were reported in 50%, 42% and 16% patients, respectively. Infective complications were reported in 46% of patients in both groups. During follow up a total of 112 patients died (43 in the DVd and 83 in the DRd group. **Conclusions:** This RWE analysis validates efficacy of daratumumab in RR MM patients with acceptable and manageable toxicities. Similar outcomes were also reported in RR MM group of patients by other RWE analyses. There are significant discrepancies between RWE data and data reported in clinical trials; median PFS being much shorter in RWE analyses. These discrepancies are possibly due to different study populations.

P-235

Clinical and sociodemographic characterization of multiple myeloma patients with symptomatic relapse and/or refractory disease under treatment in Portugal: an observational, multicenter study

Rui Bergatim[1,2,3,4], José Guilherme Freitas[5], Cristina Gonçalves[6,7], Helena Martins[8], Herlander Marques[9,10,11], Henrique Coelho[12], Patrícia Seabra[6], Adriana Roque[13,14], Márcio Márcio Ferreira[15], Pedro Pinto[16], Ana Rita Francisco[17], Joana Tato[17], Catarina Geraldes[18,19,20,21]

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Introduction: Multiple Myeloma (MM) is an incurable plasma cell neoplasm associated with high mortality and morbidity. Regardless of the remarkable advances in the last decade, more effective, well-tolerated therapies and personalized strategies are needed, especially in the setting of relapsed/refractory MM (RRMM). The CharisMMa-Portugal is the first study in Portugal aiming to describe RRMM patients'(pts) characteristics and management. **Methods:** This was an observational, cross-sectional, multicenter study on RRMM pts routinely treated at 7 public hospitals in Portugal. The study enrolled RRMM pts diagnosed in the previous 5 years presenting with RRMM in the 6 months prior to data collection. Data were collected from medical records during the clinical appointments (2020-2022). Sociodemographic, diagnosis-related information, clinical characterization of the last RR episode as well as treatment details since diagnosis were collected. Pts provided their written informed consent (ClincialTrials.gov ID - NCT04135963). **Results:** Out of the 74 pts screened, 62 were analyzed. Most pts (55%) were male, median age at diagnosis was 65 (IQR: 57-71) years. Nearly 68% were urban residents and the median home-to-hospital distance was 24.5 km (IQR:10-50). Most pts had completed at least the 9th school grade (65.5%) and were retired (62.3%). International Staging System (ISS) stages II and III (37.1% and 40.3%, respectively), and ECOG-PS 0 and ECOG-PS 1 (37.3% each) were the most common. Triplet regimens were used as the first treatment after diagnosis in 69.4% of the pts. The preferred route of administration was the combination of oral plus subcutaneous (78.9%), and 30.6% received a prior stem cell transplant. At the last RRMM episode, nearly 63% of pts had at least one comorbidity. Eleven of 24 (45.8%) pts presented cytogenetic abnormalities, of which 8 were high risk and three were not classified.. At the last RRMM episode, 75% of pts initiated second-line treatment, 23.2% third-line and 1.8% fourth-line. Triplets were the most common (67.1%), while oral plus subcutaneous (39.6%) and all-oral (32.1%) were the most frequent routes of administration. Overall, proteasome inhibitors (PIs) and immunomodulators (IMIDs) were prevalent in most treatment combinations (PIs = 26.8%, IMIDs = 37,5%, PI+IMIDs = 17,9%). At last relapse, median number of visits to the hospital were four, while 51.6% of pts required a CT scan and 32.3% an MRI. **Conclusions:** This study provides a comprehensive picture of the current real world landscape of RRMM in Portugal. The treatment patterns described reveal the complexity of treating the refractory stages of the disease with several previous treatment lines. The socio-demographic and clinical characterization of these pts as well as the healthcare resource utilization in this setting can inform stakeholders' decision making on optimizing health policies.

P-236

Cutaneous presentation of multiple myeloma in relapse after AutoPBSCT

Lejla Ibricevic Balic[1], Lejla Burazerovic[1]

[1]Clinical Center Sarajevo University

Introduction: Cutaneous manifestations of multiple myeloma are very rare with fewer than 100 cases described in the literature so far. Lesions appear in the form of nodules or plaques that can be erythematous, purple or skin-colored with a diameter of 0.5 to 3 cm. These lesions are sign of poor prognosis and refractory to standard therapy. We present the case of a 49-year-old male patient with multiple myeloma, who at the time of relapse presented with skin lesions, so far first reported case in BIH. **Methods:** The diagnosis of multiple myeloma, IgG kappa in clinical stage III – R/ISS was made in May 2020 at the Clinic of Hematology of the Clinical Center of the University of Sarajevo. Until October 2021, he was treated with chemotherapy, irradiation, and autologous transplantation followed by maintenance therapy with Revlimid. In decembar 2021. the patient was admitted with painful purple skin nodules localized in the right femoral region. Biochemical findings were consistent with anemia (Hb 96), thrombocytopenia (Plt 58),

P-235

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renal imparement (urea 11.2, creatinine 208), increased IgG, kappa light chains and Bence-Jonce proteinuria. A punch biopsy of the nodule showed infitration of entire dermis with monoclonal plasma cells. The cells were: CD38+, CD138+, CD117 focal+, CD56 +, LCA-, MPO staining of individual cells, CK-, CD34 + in blood vessels. Numerous atypical mitoses are present. A bone marrow biopsy showed up to 5% moncolonal plasma cells. He received Revlimid/Melphalan/Dexa, one cycle. Skin lesions resolved partially. Unfortunately he deceased month later, due to the progressionth of myeloma. **Results:** Cutaneous lesions of myloma tend to occur with relapses and in highly aggressive and progressive forms of multiple myeloma. In both cases the prognosis is poor with an average life expectancy of 12 months post diagnosis median survival is about 8 months, with less than 20% of patients found to be progression free at 5 years. Histopathological findings are characterised by monomorphic dermal and subcutaneous infiltrates of plasma cells. Immunohistochemically we see monoclonality of the plasma cells which have strong immunoexpression for CD138 (6). These lesions can occur anywhere in the skin but are most commonly seen in the chest and abdomen (44%) involvement of the skin of the extremities is less common. **Conclusions:** Treatment for cutaneous plasmacytoma in multiple myeloma involves chemotherapy, steroids and local radiotherapy. Surgical excision has a role in lesions resistant to radiotherapy or where lesions are very large and symptomatic.

P-237

Bendamustine (B) is associated with low response rates in heavily pretreated relapsed refractory multiple myeloma (RRMM)

Zhubin Gahvari[1], Timothy Schmidt[1], Matthew Brunner[1], Jason Bergsbaken[1], Natalie Callander[1]

[1]University of Wisconsin

Introduction: Bendamustine (B), singly or in combination, is reported to have significant activity in relapsed multiple myeloma, with several publications noting overall response rates (ORR) of 49%-60%, and PFS of 11.3 months when given in combination with bortezomib and lenalidomide (1, 2). The advent of CAR-T has also called into question the use of B, due to potential harmful effects on lymphocytes, that could ultimately influence the ability to collect adequate T cells for use, or possibly response to bispecific engagers. **Methods:** We performed a retrospective analysis of all RRMM patients who received B or a B combination between 2015 to 2022. **Results:** A total of 44 pts were treated. Median age 67 (range 41-83), Female (12/44 or 27%). Median previous lines of therapy 6 (range 3-15); 98% of pts were triple refractory (only 1 pt had not received anti CD 38 antibody therapy), and the majority (90%) had previous autologous transplant, and most were penta-refractory. Twenty-seven % of patients had high risk cytogenetics at diagnosis. Median time from diagnosis to B combination was 26 mo. (range 3-192 mo.). The median time on treatment was 3 mo. (range 1-12 mo.). ORR was 25% (11/44, with 1 VGPR, 10 PR) with a median PFS of 6.5 mo. and median OS of 18 mo. (range 3-48 mo.) calculated from time of B combo until death. One pt died of sepsis, grade 3/4 hematologic toxicity occurred in 50% of pts. Inclusion of bortezomib, pomalidomide or lenalidomide in the regimen did not appear to increase response rate. After failing B, the most effective salvage appeared to be second auto transplant or bispecific engager. Six patients subsequently received BCMA directed therapy, with 2/4 failing CAR-T treatment within 30 days of transplant. **Conclusions:** Conclusion: B either as a single agent or combination was associated with a 25% overall response rate. In heavily pretreated RRMM patients, alternative therapies should probably be considered, and B should likely be avoided in patients who are undergoing CAR-T transplantation. **References:** 1. Cerchione C, Catalano L, Nappi D, Rocco S, Palmieri S, Pareto AE, et al. Bendamustine-Bortezomib-Dexamethasone (BVD) in Heavily Pretreated Multiple Myeloma: Old/New in NOVEL Agents' Era. Blood. 2020;136(Supplement 1):2-3. 2. Kumar SK, Krishnan A, LaPlant B, Laumann K, Roy V, Zimmerman T, et al. Bendamustine, lenalidomide, and dexamethasone (BRD) is highly effective with durable responses in relapsed multiple myeloma. Am J Hematol. 2015;90(12):1106-10.

P-238

A real-world observational study of belantamab mafodotin (belamaf) as a treatment for relapsed/refractory multiple myeloma (RRMM)

Michele Cavo[1], Michel Delforge[2], Meletios Dimopoulos[3], Fernando Escalante[4], Malin Hultcrantz[5], David Kleinman[6], Hans Lee[7], Ravi Vij[8], Nirali Kotowsky[9], Leena Camadoo-O'Byrne[10], Jacopo Bitetti[11], Tim D'Estrube[12], Mark Fry[10], Carla Vossen[13]

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Introduction: Belamaf, a first-in-class B-cell maturation antigen-targeting antibody-drug conjugate approved in the EU for treatment of RRMM, has demonstrated deep and durable responses as monotherapy. This study explores real-world (RW) use, effectiveness, and safety of belamaf in Europe, including the monitoring and management of ocular events. **Methods:** This ongoing non-interventional, retrospective and prospective study includes adult patients (pts) with RRMM receiving belamaf in routine clinical care, consistent with approved labelling. The primary objective is to characterize RW pt demographics and disease characteristics. The key secondary objective is to identify pts who experience belamaf-related ocular adverse events (AEs) of special interest (AESI). Secondary outcomes include incidence of ocular AESIs,

renal imparement (urea 11.2, creatinine 208), increased IgG, kappa light chains and Bence-Jonce proteinuria. A punch biopsy of the nodule showed infitration of entire dermis with monoclonal plasma cells. The cells were: CD38+, CD138+, CD117 focal+, CD56 +, LCA-, MPO staining of individual cells, CK-, CD34 + in blood vessels. Numerous atypical mitoses are present. A bone marrow biopsy showed up to 5% moncolonal plasma cells. He received Revlimid/Melphalan/Dexa, one cycle. Skin lesions resolved partially. Unfortunately he deceased month later, due to the progressionth of myeloma. **Results:** Cutaneous lesions of myloma tend to occur with relapses and in highly aggressive and progressive forms of multiple myeloma. In both cases the prognosis is poor with an average life expectancy of 12 months post diagnosis median survival is about 8 months, with less than 20% of patients found to be progression free at 5 years. Histopathological findings are characterised by monomorphic dermal and subcutaneous infiltrates of plasma cells. Immunohistochemically we see monoclonality of the plasma cells which have strong immunoexpression for CD138 (6). These lesions can occur anywhere in the skin but are most commonly seen in the chest and abdomen (44%) involvement of the skin of the extremities is less common. **Conclusions:** Treatment for cutaneous plasmacytoma in multiple myeloma involves chemotherapy, steroids and local radiotherapy. Surgical excision has a role in lesions resistant to radiotherapy or where lesions are very large and symptomatic.

P-237

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P-238

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P-237

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Zhubin Gahvari[1], Timothy Schmidt[1], Matthew Brunner[1], Jason Bergsbaken[1], Natalie Callander[1]

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Introduction: Bendamustine (B), singly or in combination, is reported to have significant activity in relapsed multiple myeloma, with several publications noting overall response rates (ORR) of 49%-60%, and PFS of 11.3 months when given in combination with bortezomib and lenalidomide (1, 2). The advent of CAR-T has also called into question the use of B, due to potential harmful effects on lymphocytes, that could ultimately influence the ability to collect adequate T cells for use, or possibly response to bispecific engagers. **Methods:** We performed a retrospective analysis of all RRMM patients who received B or a B combination between 2015 to 2022. **Results:** A total of 44 pts were treated. Median age 67 (range 41-83), Female (12/44 or 27%). Median previous lines of therapy 6 (range 3-15); 98% of pts were triple refractory (only 1 pt had not received anti CD 38 antibody therapy), and the majority (90%) had previous autologous transplant, and most were penta-refractory. Twenty-seven % of patients had high risk cytogenetics at diagnosis. Median time from diagnosis to B combination was 26 mo. (range 3-192 mo.). The median time on treatment was 3 mo. (range 1-12 mo.). ORR was 25% (11/44, with 1 VGPR, 10 PR) with a median PFS of 6.5 mo. and median OS of 18 mo. (range 3-48 mo.) calculated from time of B combo until death. One pt died of sepsis, grade 3/4 hematologic toxicity occurred in 50% of pts. Inclusion of bortezomib, pomalidomide or lenalidomide in the regimen did not appear to increase response rate. After failing B, the most effective salvage appeared to be second auto transplant or bispecific engager. Six patients subsequently received BCMA directed therapy, with 2/4 failing CAR-T treatment within 30 days of transplant. **Conclusions:** Conclusion: B either as a single agent or combination was associated with a 25% overall response rate. In heavily pretreated RRMM patients, alternative therapies should probably be considered, and B should likely be avoided in patients who are undergoing CAR-T transplantation. **References:** 1. Cerchione C, Catalano L, Nappi D, Rocco S, Palmieri S, Pareto AE, et al. Bendamustine-Bortezomib-Dexamethasone (BVD) in Heavily Pretreated Multiple Myeloma: Old/New in NOVEL Agents' Era. Blood. 2020;136(Supplement 1):2-3. 2. Kumar SK, Krishnan A, LaPlant B, Laumann K, Roy V, Zimmerman T, et al. Bendamustine, lenalidomide, and dexamethasone (BRD) is highly effective with durable responses in relapsed multiple myeloma. Am J Hematol. 2015;90(12):1106-10.

P-238

A real-world observational study of belantamab mafodotin (belamaf) as a treatment for relapsed/refractory multiple myeloma (RRMM)

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Introduction: Belamaf, a first-in-class B-cell maturation antigen-targeting antibody-drug conjugate approved in the EU for treatment of RRMM, has demonstrated deep and durable responses as monotherapy. This study explores real-world (RW) use, effectiveness, and safety of belamaf in Europe, including the monitoring and management of ocular events. **Methods:** This ongoing non-interventional, retrospective and prospective study includes adult patients (pts) with RRMM receiving belamaf in routine clinical care, consistent with approved labelling. The primary objective is to characterize RW pt demographics and disease characteristics. The key secondary objective is to identify pts who experience belamaf-related ocular adverse events (AEs) of special interest (AESI). Secondary outcomes include incidence of ocular AESIs,

dose modifications, treatment discontinuation, and treatment response. **Results:** This first interim analysis (as of March 17, 2023) included 37 pts from Italy, Austria, Norway, Germany, Belgium, Spain, and Greece (34 received ≥1 belamaf dose). Mean age was 70.4 years (≥75 years, n=15; 44%); 68% were female. Median time since diagnosis was 86.4 months. Prior therapy data were available for 31 pts (91%): 25 (74%) had ≥4 prior lines of therapy; all 31 had prior exposure to proteasome inhibitors, anti-CD38 therapies (daratumumab 85%), and immunomodulatory therapies; and 91% were triple-class refractory. At baseline, 24 pts (71%) had ≥1 prior/ongoing comorbidity including cardiac disease (n=11; 32%), diabetes (n=10; 29%), eye disease (n=10; 29%), pulmonary disease (n=9; 27%), vascular disorders (n=9; 27%), endocrine disorders (n=7; 21%), and renal disease (n=7; 21%). Most pts (n=29, 85%) saw an ophthalmologist before initiating belamaf; 80%, 78%, and 90% visited an ophthalmologist prior to their 2nd, 3rd and 4th doses. Median treatment time was 4.8 months, and 16 pts (47%) had ≥4 months of follow-up. Overall, 22 pts (65%) reported ocular AESIs including keratopathy (n=16; 47% [Grade ≥2, n=12]), best corrected visual acuity change (n=5; 15%), corneal erosion (n=2; 6%), and dry eye (n=1; 3%). AESIs led to dose reduction in 2 pts (6%) and dose delays in 10 pts (29%). Discontinuation was due to disease progression (n=7; 21%) or AESI (n=3; 9%); 9 pts experienced disease progression or died. Median RW progression-free survival was 3.9 months. Efficacy data are subject to additional follow-up and will be presented. **Conclusions:** This study demonstrates that in Europe belamaf is used routinely in later lines of therapy, in line with the current approved indication in the EU, including in pts who are aged ≥75 years, have current or prior comorbidities, and/or are triple class refractory. Our data suggest that ocular AEs are being monitored appropriately with ophthalmologist visits and managed using dose modifications. Treatment discontinuations occurred primarily due to progressive disease. Updated RW clinical efficacy data will be forthcoming.

P-239

Dynamic risk model: a novel approach incorporating functional high risk factors for predicting survival outcomes in patients with relapsed/refractory multiple myeloma

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Introduction: Early relapse and refractoriness to novel agents have been recognized as high-risk features associated with resistance to subsequent therapy and reduced overall survival in patients with multiple myeloma (MM). Newly identified risk factors following such treatments are referred to as functional high risk or dynamic high risk. In this study, we propose a novel risk model aimed at predicting survival outcomes in patients with relapsed/refractory MM (RRMM), incorporating functional high risk factors. **Methods:** We conducted a retrospective review of medical records for RRMM patients who underwent a second line of therapy at Kyungpook National University Hospital and Chungnam National University Hospital between 2011 and 2021. Early relapse was defined as biochemical or overt relapse occurring within 18 months after the initiation of frontline therapy. We assigned weighted scores based on the range of hazard ratio (HR) derived from the Cox hazard model for each risk factor. Subsequently, we classified risk groups by summing the scores for each risk factor. **Results:** A total of 141 patients with RRMM were included in the analysis. The median age at diagnosis was 65.7 years (range: 33-80). Early relapse was observed in 77 patients (54.6%). Following relapse, all of the patients received carfilzomib (72.3%)- or ixazomib (27.7%)-based treatment. Early relapse was identified as a significant risk factor for survival prediction (HR 2.56, p= 0.002). Other variables at relapse, including hemoglobin (Hb), platelet count, LDH, albumin, beta 2 microglobulins (B2GM), and plasmacytoma, were determined to be relevant risk factors affecting survival outcomes. The scores assigned were 2 for early relapse, LDH, and plasmacytoma, 0.5 for Hb, and 1 for albumin. Platelet count and B2GM were excluded from the weighting score calculation due to their relatively insignificant HR values. The risk model for survival prediction, referred to as the Dynamic Risk Model, classified RRMM patients into three stages: stage I (total score 0-2), stage II (2.5-4), and stage III (4.5-7.5). Seventy patients were included in the survival outcome analysis using the Dynamic Risk Model, after excluding 71 patients due to missing laboratory or imaging data. Of the analyzed patients, 29 (41.4%) were classified as stage I, 25 (35.7%) as stage II, and 16 (22.9%) as stage III. The new model effectively differentiated survival outcomes among the stages in RRMM patients, with 24-month OS rates of 95.7%, 42.3%, and 16.2% in stages I, II, and III, respectively ($p < 0.001$). The 24-month progression-free survival rates were 57.3%, 35.7%, and 0.0% in stages I, II, and III, respectively ($p < 0.001$). **Conclusions:** The integration of early relapse and readily accessible variables within the Dynamic Risk Model demonstrated a remarkable ability to prognosticate survival outcomes in patients with RRMM. Significantly, this model represents the first application of functional high risk in reevaluating risk stratification within the RR setting.

P-240

Efficacy and safety of ciltacabtagene autoleucel in patients with relapsed/refractory multiple myeloma and prior noncellular anti-BCMA therapy: CARTITUDE-2 cohort C

Adam Cohen[1], Yaël Cohen[2], Attaya Suvannasankha[3], Niels van de Donk[4], Jesús San-Miguel[5], Kevin De Braganca[6], Carolyn Jackson[6], Jordan Schecter[6], Philip Vlummens[7], Helen Varsos[6], Christina Corsale[6], Pankaj Mistry[8], Qingxuan Song[6], Tito Roccia[9], Dong Geng[10], Jieqing Zhu[10], Muhammad Akram[10], María-Victoria Mateos[11]

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dose modifications, treatment discontinuation, and treatment response. **Results:** This first interim analysis (as of March 17, 2023) included 37 pts from Italy, Austria, Norway, Germany, Belgium, Spain, and Greece (34 received ≥1 belamaf dose). Mean age was 70.4 years (≥75 years, n=15; 44%); 68% were female. Median time since diagnosis was 86.4 months. Prior therapy data were available for 31 pts (91%): 25 (74%) had ≥4 prior lines of therapy; all 31 had prior exposure to proteasome inhibitors, anti-CD38 therapies (daratumumab 85%), and immunomodulatory therapies; and 91% were triple-class refractory. At baseline, 24 pts (71%) had ≥1 prior/ongoing comorbidity including cardiac disease (n=11; 32%), diabetes (n=10; 29%), eye disease (n=10; 29%), pulmonary disease (n=9; 27%), vascular disorders (n=9; 27%), endocrine disorders (n=7; 21%), and renal disease (n=7; 21%). Most pts (n=29, 85%) saw an ophthalmologist before initiating belamaf; 80%, 78%, and 90% visited an ophthalmologist prior to their 2nd, 3rd and 4th doses. Median treatment time was 4.8 months, and 16 pts (47%) had ≥4 months of follow-up. Overall, 22 pts (65%) reported ocular AESIs including keratopathy (n=16; 47% [Grade ≥2, n=12]), best corrected visual acuity change (n=5; 15%), corneal erosion (n=2; 6%), and dry eye (n=1; 3%). AESIs led to dose reduction in 2 pts (6%) and dose delays in 10 pts (29%). Discontinuation was due to disease progression (n=7; 21%) or AESI (n=3; 9%); 9 pts experienced disease progression or died. Median RW progression-free survival was 3.9 months. Efficacy data are subject to additional follow-up and will be presented. **Conclusions:** This study demonstrates that in Europe belamaf is used routinely in later lines of therapy, in line with the current approved indication in the EU, including in pts who are aged ≥75 years, have current or prior comorbidities, and/or are triple class refractory. Our data suggest that ocular AEs are being monitored appropriately with ophthalmologist visits and managed using dose modifications. Treatment discontinuations occurred primarily due to progressive disease. Updated RW clinical efficacy data will be forthcoming.

P-239

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Introduction: Early relapse and refractoriness to novel agents have been recognized as high-risk features associated with resistance to subsequent therapy and reduced overall survival in patients with multiple myeloma (MM). Newly identified risk factors following such treatments are referred to as functional high risk or dynamic high risk. In this study, we propose a novel risk model aimed at predicting survival outcomes in patients with relapsed/refractory MM (RRMM), incorporating functional high risk factors. **Methods:** We conducted a retrospective review of medical records for RRMM patients who underwent a second line of therapy at Kyungpook National University Hospital and Chungnam National University Hospital between 2011 and 2021. Early relapse was defined as biochemical or overt relapse occurring within 18 months after the initiation of frontline therapy. We assigned weighted scores based on the range of hazard ratio (HR) derived from the Cox hazard model for each risk factor. Subsequently, we classified risk groups by summing the scores for each risk factor. **Results:** A total of 141 patients with RRMM were included in the analysis. The median age at diagnosis was 65.7 years (range: 33-80). Early relapse was observed in 77 patients (54.6%). Following relapse, all of the patients received carfilzomib (72.3%)- or ixazomib (27.7%)-based treatment. Early relapse was identified as a significant risk factor for survival prediction (HR 2.56, p= 0.002). Other variables at relapse, including hemoglobin (Hb), platelet count, LDH, albumin, beta 2 microglobulins (B2GM), and plasmacytoma, were determined to be relevant risk factors affecting survival outcomes. The scores assigned were 2 for early relapse, LDH, and plasmacytoma, 0.5 for Hb, and 1 for albumin. Platelet count and B2GM were excluded from the weighting score calculation due to their relatively insignificant HR values. The risk model for survival prediction, referred to as the Dynamic Risk Model, classified RRMM patients into three stages: stage I (total score 0-2), stage II (2.5-4), and stage III (4.5-7.5). Seventy patients were included in the survival outcome analysis using the Dynamic Risk Model, after excluding 71 patients due to missing laboratory or imaging data. Of the analyzed patients, 29 (41.4%) were classified as stage I, 25 (35.7%) as stage II, and 16 (22.9%) as stage III. The new model effectively differentiated survival outcomes among the stages in RRMM patients, with 24-month OS rates of 95.7%, 42.3%, and 16.2% in stages I, II, and III, respectively ($p < 0.001$). The 24-month progression-free survival rates were 57.3%, 35.7%, and 0.0% in stages I, II, and III, respectively ($p < 0.001$). **Conclusions:** The integration of early relapse and readily accessible variables within the Dynamic Risk Model demonstrated a remarkable ability to prognosticate survival outcomes in patients with RRMM. Significantly, this model represents the first application of functional high risk in reevaluating risk stratification within the RR setting.

P-240

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P-239

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P-240

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Aviv University, Tel Aviv, Israel; [3]Indiana University Simon Cancer Center and Roudebush VAMC, Indianapolis, IN, USA; [4]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Department of Hematology, Amsterdam, Netherlands, and Cancer Center Amsterdam, Amsterdam, Netherlands; [5]Cancer Center Clinica Universidad de Navarra, Centro Investigacion Medica Aplicada, Instituto de Investigacion de Navarra, Centro Investigacion Biomedica en Red Cancer, Pamplona, Spain; [6]Janssen Research & Development, Raritan, NJ, USA; [7]Janssen Research & Development, Beerse, Belgium; [8]Janssen Research & Development, High Wycombe, UK; [9]Janssen Global Services, Raritan, NJ, USA; [10]Legend Biotech USA Inc, Somerset, NJ, USA; [11]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain

Introduction: B-cell maturation antigen (BCMA)-targeting therapies are promising treatments (tx) for patients (pts) with multiple myeloma (MM), and data are required to understand tx sequencing to optimize pt outcomes. CARTITUDE-2 (NCT04133636) is a phase 2, multicohort study evaluating the efficacy and safety of ciltacabtagene autoleucel (cilta-cel), an approved anti-BCMA chimeric antigen receptor (CAR)-T cell therapy, in several MM pt populations. CARTITUDE-2 Cohort C enrolled pts with heavily pretreated relapsed/refractory MM who were previously exposed to a noncellular anti-BCMA tx. We present efficacy and safety results for cohort C pts with a median follow-up of 18.0 months (mo). **Methods:** Cohort C pts had progressive MM after tx with a proteasome inhibitor, immunomodulatory drug, anti-CD38 antibody, and a noncellular BCMA-targeting agent. A single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg [range: $0.5–1.0\times10^6$ CAR+ viable T cells/kg]) was administered 5–7 days post lymphodepletion. The primary endpoint was minimal residual disease (MRD) negativity at 10^{-5} threshold. Secondary endpoints included response rates (per International Myeloma Working Group criteria) and safety. **Results:** As of June 1, 2022, 20 pts (13 ADC, 7 BsAb exposed; 1 pt in the ADC group had prior BsAb tx) received cilta-cel. 6 pts (30%) had anti-BCMA tx as their last line of therapy (LOT; n=4 ADC, n=2 BsAb). At baseline, median age was 62.5 years (range, 44–81); 60% were male; 15% had high-risk cytogenetics (all del17p); 25% had extramedullary disease; received a median of 8 (range, 4–13) prior LOT. Median cilta-cel dose administered was 0.61×10^6 (range, 0.21×10^6–0.83×10^6) CAR+ viable T cells/kg; 1 pt received a below-target dose range. At a median follow-up of 18.0 mo (range, 0.6–22.7), 7 of 10 evaluable pts (70%) in the full cohort were MRD negative at 10^{-5} threshold (5 of 7 [71.4%] in the ADC group, and 2 of 3 [66.7%] in the BsAb group). The overall response rate was 60%; ADC, 61.5%; BsAb, 57.1%. Median duration of response was 12.3 mo (95% CI, 7.2–NE); ADC, 13.3 mo (7.2–NE); BsAb, 8.2 mo (4.4–NE). Median progression-free survival was 9.1 mo (95% CI, 1.5–13.8); ADC, 9.5 mo (1.0–15.2); BsAb, 5.3 mo (0.6–NE). The most common adverse events (AEs) were hematologic.12 pts had cytokine release syndrome (6 in ADC, 6 in BsAb, [all grade 1/2]); resolved in all. 4 pts had immune effector cell-associated neurotoxicity syndrome (2 in ADC [grade 3/4]; 2 in BsAb [1 grade 3/4]); resolved in 3. No pt had movement or neurocognitive tx-emergent AE/parkinsonism. Total of 12 deaths occurred (7 in ADC; 5 in BsAb [1 due to tx-related C. difficile colitis]). **Conclusions:** These results in the context of published data, including CARTITUDE-1, suggest that cilta-cel in anti-BCMA naive pts offers better outcomes, although this interpretation needs to be cautioned by the small number of pts. Updated results and additional correlative analyses will be presented.

P-241

African American relapsed/refractory multiple myeloma patients have a progression free survival benefit with selinexor treatment in the STORM study

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Introduction: Multiple Myeloma (MM) is the 2nd most common hematologic malignancy in the US, though survival in patients with MM has increased over the past decade. Survival improvements in African Americans (AAs) have been smaller, which may be due to disparity in access to therapies. There are also key differences in MM biology between races. Given underrepresentation of minorities in clinical trials, we analyzed whether outcomes were similar between AAs and other races in the phase 2 STORM trial (NCT02336815) of selinexor. Selinexor, an oral, first-in-class selective inhibitor of nuclear export via exportin 1, has proven efficacy for refractory MM. This is the first race subgroup analysis of selinexor in MM clinical trials. **Methods:** Pts from STORM who received study drug (N=202) were included. Pts with heavily pretreated MM, including triple-class and penta- refractory MM refractory to the last line of therapy were given selinexor (80mg) + dexamethasone (20mg) twice weekly. We conducted a retrospective racial subgroup analysis. Cox proportional modeling was used to determine the hazard ratio (HR) for MM relapse between races controlling for covariates. **Results:** AAs represented 17% of pts (35 AAs, 148 White, 2 Asian, 11 other and 6 missing). AAs were younger compared to other races (median age 60.7 vs 65.3) with more females (74.3% vs 40.7%). Cytogenetic abnormalities and R-ISS staging were similar between races. AAs had a median progression free survival (PFS) of 6.5 mos (95% CI 4.7, NR) compared with 3.7 mos (95% CI 2.8, 4.6; p = 0.035) for other races. Overall response rate (ORR) was 25.7% (95% CI 12.5, 43.3) in AA pts vs 23.4% [17.2, 30.5] in other races), clinical benefit rate (37.1% [21.5, 55.1] vs 35.9% [28.7, 43.7]), median duration of response (5.6 mos [2.1, NR] vs 5.3 [3.6, NR]), median duration of treatment (9 wks [IQR 3-22 wks] vs 8 wks [4-16 wks]), and mean dose intensity (117.9 mg/wks [STD 35.1] vs 117.1 [34.7]) were similar between groups. Rates of Adverse Events (AEs) ≥ grade 3 (94.3% vs 95.8%), and AE-related dose reductions (45.7% vs 54.5%), discontinuations (22.9% vs 30.5%), and deaths (5.7% vs 10.8%) were also similar. The adjusted HR for MM relapse in AAs was 0.45 (95% CI 0.22, 0.92; p=0.028) after controlling for

Aviv University, Tel Aviv, Israel; [3]Indiana University Simon Cancer Center and Roudebush VAMC, Indianapolis, IN, USA; [4]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Department of Hematology, Amsterdam, Netherlands, and Cancer Center Amsterdam, Amsterdam, Netherlands; [5]Cancer Center Clinica Universidad de Navarra, Centro Investigacion Medica Aplicada, Instituto de Investigacion de Navarra, Centro Investigacion Biomedica en Red Cancer, Pamplona, Spain; [6]Janssen Research & Development, Raritan, NJ, USA; [7]Janssen Research & Development, Beerse, Belgium; [8]Janssen Research & Development, High Wycombe, UK; [9]Janssen Global Services, Raritan, NJ, USA; [10]Legend Biotech USA Inc, Somerset, NJ, USA; [11]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain

Introduction: B-cell maturation antigen (BCMA)-targeting therapies are promising treatments (tx) for patients (pts) with multiple myeloma (MM), and data are required to understand tx sequencing to optimize pt outcomes. CARTITUDE-2 (NCT04133636) is a phase 2, multicohort study evaluating the efficacy and safety of ciltacabtagene autoleucel (cilta-cel), an approved anti-BCMA chimeric antigen receptor (CAR)-T cell therapy, in several MM pt populations. CARTITUDE-2 Cohort C enrolled pts with heavily pretreated relapsed/refractory MM who were previously exposed to a noncellular anti-BCMA tx. We present efficacy and safety results for cohort C pts with a median follow-up of 18.0 months (mo). **Methods:** Cohort C pts had progressive MM after tx with a proteasome inhibitor, immunomodulatory drug, anti-CD38 antibody, and a noncellular BCMA-targeting agent. A single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg [range: $0.5–1.0\times10^6$ CAR+ viable T cells/kg]) was administered 5–7 days post lymphodepletion. The primary endpoint was minimal residual disease (MRD) negativity at 10^{-5} threshold. Secondary endpoints included response rates (per International Myeloma Working Group criteria) and safety. **Results:** As of June 1, 2022, 20 pts (13 ADC, 7 BsAb exposed; 1 pt in the ADC group had prior BsAb tx) received cilta-cel. 6 pts (30%) had anti-BCMA tx as their last line of therapy (LOT; n=4 ADC, n=2 BsAb). At baseline, median age was 62.5 years (range, 44–81); 60% were male; 15% had high-risk cytogenetics (all del17p); 25% had extramedullary disease; received a median of 8 (range, 4–13) prior LOT. Median cilta-cel dose administered was 0.61×10^6 (range, 0.21×10^6–0.83×10^6) CAR+ viable T cells/kg; 1 pt received a below-target dose range. At a median follow-up of 18.0 mo (range, 0.6–22.7), 7 of 10 evaluable pts (70%) in the full cohort were MRD negative at 10^{-5} threshold (5 of 7 [71.4%] in the ADC group, and 2 of 3 [66.7%] in the BsAb group). The overall response rate was 60%; ADC, 61.5%; BsAb, 57.1%. Median duration of response was 12.3 mo (95% CI, 7.2–NE); ADC, 13.3 mo (7.2–NE); BsAb, 8.2 mo (4.4–NE). Median progression-free survival was 9.1 mo (95% CI, 1.5–13.8); ADC, 9.5 mo (1.0–15.2); BsAb, 5.3 mo (0.6–NE). The most common adverse events (AEs) were hematologic.12 pts had cytokine release syndrome (6 in ADC, 6 in BsAb, [all grade 1/2]); resolved in all. 4 pts had immune effector cell-associated neurotoxicity syndrome (2 in ADC [grade 3/4]; 2 in BsAb [1 grade 3/4]); resolved in 3. No pt had movement or neurocognitive tx-emergent AE/parkinsonism. Total of 12 deaths occurred (7 in ADC; 5 in BsAb [1 due to tx-related C. difficile colitis]). **Conclusions:** These results in the context of published data, including CARTITUDE-1, suggest that cilta-cel in anti-BCMA naive pts offers better outcomes, although this interpretation needs to be cautioned by the small number of pts. Updated results and additional correlative analyses will be presented.

P-241

African American relapsed/refractory multiple myeloma patients have a progression free survival benefit with selinexor treatment in the STORM study

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P-242

Real-world treatment patterns and clinical outcomes amongst patients with relapsed/refractory multiple myeloma previously treated with lenalidomide and an anti-CD38 monoclonal antibody

Andrew Cowan[1], Jessica Katz[2], Carrie Ho[3], Tao Gu[2], Thomas Marshall[2], Fangyi Gu[2], Yuexin Tang[2]

[1]University of Washington, Seattle, WA, USA; [2]Bristol Myers Squibb, Princeton, NJ, USA; [3]University of Washington/Fred Hutch Cancer Center, Seattle, WA, USA

Introduction: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend the use of novel-immune based therapies in late relapse (≥3 prior therapies) and triple-class exposed (TCE)/penta-refractory patients (pts) with multiple myeloma (MM). Limited guidance is provided in pts with early relapsed (1–3 prior therapies) MM regarding anti-CD38 monoclonal antibody (mAb) exposure, with increasing use of lenalidomide (LEN) and an anti-CD38 mAb in 1L/2L (first-/second-line) treatment (Tx). Real-world evidence is needed to better understand Tx patterns and clinical outcomes post-LEN and an anti-CD38 mAb. **Methods:** This retrospective cohort study used Flatiron Health electronic medical records from January 1st, 2011 to June 30th, 2022. Pts with MM were included if they were previously treated with LEN and an anti-CD38 mAb in the same or different lines, and had initiated the next line of Tx (index regimen). Descriptive analyses were conducted to assess baseline demographics, clinical factors, Tx history, and index Tx patterns. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier plots. Subgroup analyses of the survival outcomes were conducted by selected risk groups: high-risk cytogenetics (≥1 cytogenetic factors: del 17p, t(4;14), t(14;16), t(14;20), and amplification 1q21), elderly (≥75 years old), ECOG score ≥2, and refractory to anti-CD38 mAbs. Multivariate cox proportional hazard regressions were used to assess the association between baseline pt characteristics and survival outcomes. **Results:** Of 845 pts, 96.4% started the index regimen during 2017–2022. The median age at start of index regimen (index date) was 69; 64.4% were White and 15.0% were African American. Most pts (85.7%) were treated in the community setting; 35.5% had high-risk cytogenetics; 18.3% had ECOG score ≥2. Median time from initial MM diagnosis to index date was 36.5 months. Only 6.9% initiated the index regimen at 2L Tx, while 32.1% and 61.1% initiated at 3L and 4L+ Tx, respectively. Most pts (93.4%) were TCE and 44.8% were refractory to an anti-CD38 mAb. Daratumumab (DARA)/pomalidomide (POM)/dexamethasone (DEX) (10.7%), carfilzomib (CAR)/POM/DEX (5.2%), and CAR/DEX (4.7%) were the most frequently used index regimens. The median PFS and OS were 5.3 and 23.1 months, respectively. Those with high-risk cytogenetics, ECOG score ≥2, and refractory to anti-CD38 had shorter survival than their counterparts. **Conclusions:** In pts previously treated with LEN and an anti-CD38 mAb, DARA, CAR, and POM-based regimens were most used; however, there is no clear standard of care. Poor survival outcomes in the overall population and certain subgroups highlight the need for novel, effective, and safe agents to address unmet medical needs of this rapidly growing pt population with prior exposure to LEN and an anti-CD38 mAb. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma 3.2023.

P-243

Improved outcomes in allo-HCT for multiple myeloma patients with thiotepa-busulfan-fludarabine conditioning regimen and post-transplant cyclophosphamide, sirolimus and mycophenolate mofetil

Javier de la Rubia[1], Juan Montoro[1], Jaime Sanz[1], Aitana Balaguer[1], Manuel Guerreiro[1], Ana Facal[1], Marta Villalba[1], Pedro Chorao[1], Mario Arnao[1], Alberto Louro[1], Miguel Sanz[1]

[1]Hospital La Fe

Introduction: The use of allogeneic hematopoietic stem cell transplantation (allo-HCT) in the treatment of multiple myeloma (MM) is a matter of ongoing controversy due to the transplant-related mortality (NRM) and relapse rate. Despite these limitations, efforts to improve supportive care measures, less toxic conditioning regimens, and more effective strategies to prevent graft-versus-host disease (GVHD) are being made to enhance the success of allo-HCT in MM. **Methods:** This study includes 25 patients with MM from a single institution who underwent allo-HCT with thiotepa-fludarabine-busulfan (TBF) conditioning regimen between January 2017 and December 2020. GVHD prophylaxis consisted of post-transplant cyclophosphamide (PTCy), sirolimus, and mycophenolate mofetil (MMF). Disease status at allo-HCT was defined based on the IMWG criteria. The probabilities of engraftment, acute and chronic GVHD, NRM, and relapse were estimated using the cumulative incidence method. Competing risk data were considered for different events. Kaplan-Meier estimate was used for unadjusted time-to-event analyses. GRFS analysis considered grade III-IV aGVHD, chronic extensive GVHD, relapse, graft failure, and death as events. **Results:** The median age at allo-HCT was 54 years. According to R-ISS at diagnosis, 5 (20%) pts were stage I, 11 (44%) stage II, 4 (16%) stage III, and was not available in 5 (20%). Nine (36%) pts had high-risk cytogenetic abnormalities. All patients received induction therapy with novel agents, and 24 (96%) received a triple-based one. The median number of prior lines of treatment before allo-HCT was 2 (range, 1-5). Twenty-three (92%) patients had received prior auto-HCT and 8 (32%) were refractory before allo-HCT. Disease status

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P-242

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P-243

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P-242

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P-243

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at allo-HCT was complete response/very good partial response (n=18, 72%), partial response (PR) (n=6, 24%), and less than PR (n=1, 4%). Donor type distribution was as follows: MSD (n=12, 48%), MUD (n=7, 28%), and Haplo (n=6, 24%). Peripheral blood was the stem cell source in 23 (92%) patients. All patients engrafted. Cumulative incidence of acute GVHD grade II-IV and III-IV were 20% (95%CI, 38-70%) and 8% (1-23%), respectively. The 3-year cumulative incidence of NRM was 22% (95%CI: 3-52%) and of chronic GVHD 27% (95%CI: 11-47%). The 3-year OS, EFS, and GRFS were 74% (58-95%), 69% (52-91%), and 54% (37-79%), respectively. **Conclusions:** In this real-life cohort study, allo-HCT with the TBF conditioning regimen and GCHD prophylaxis with PTCy, sirolimus, and MMF showed encouraging results. It led to reduced acute and chronic GVHD incidence, improved GRFS, and favorable survival rates. These findings suggest that this combination holds promise as an effective treatment option for MM patients considered candidates for an allo-HCT.

P-244

Teclistamab versus Belgian real-world clinical practice in triple-class exposed relapsed and refractory multiple myeloma patients using adjusted comparison

Michel Delforge[1], Sébastien Anguille[2], Julien Depaus[3], Nathalie Meuleman[4], Ann Van De Velde[2], Isabelle Vande Broek[5], Joris Diels[6], Nichola Erler-Yates[7], Sébastien Van Causenbroeck[8], Kirsten Van Nimwegen[9], Sophie Vandervennet[8], Susanne Lub[10], Marie-Christiane Madeleine Vekemans[11]

[1]University of Leuven, Leuven, Belgium; [2]Antwerp University Hospital; [3]CHU UCL Namur; [4]Institut Jules Bordet; [5]AZ Nikolaas; [6]Janssen Pharmaceutica NV, Beerse, Belgium; [7]Janssen-Cilag GmbH; [8]Janssen-Cilag NV; [9]Janssen-Cilag B.V; [10]Janssen-Cilag; [11]Department of Internal Medicine, Université Catholique de Louvain (UCLouvain), Brussels, Belgium

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P-245

Belantamab mafodotin in patients with severely impaired renal function: a phase I, 2-part study to evaluate pharmacokinetics, safety and efficacy in patients with relapsed/refractory multiple myeloma

Seema Shafi-Harji[1], Courtney Nugent[2], Geraldine Ferron-Brady[2], Sosana Delimpasi[3], Meletios Dimopoulos[4], Yunxin Chen[5], Wee Joo Chng[6], Jae Hoon Lee[7], Sikander Ailawadhi[8], Krisstina Gowin[9], Michael Arning[10], Herbert Struemper[11]

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at allo-HCT was complete response/very good partial response (n=18, 72%), partial response (PR) (n=6, 24%), and less than PR (n=1, 4%). Donor type distribution was as follows: MSD (n=12, 48%), MUD (n=7, 28%), and Haplo (n=6, 24%). Peripheral blood was the stem cell source in 23 (92%) patients. All patients engrafted. Cumulative incidence of acute GVHD grade II-IV and III-IV were 20% (95%CI, 38-70%) and 8% (1-23%), respectively. The 3-year cumulative incidence of NRM was 22% (95%CI: 3-52%) and of chronic GVHD 27% (95%CI: 11-47%). The 3-year OS, EFS, and GRFS were 74% (58-95%), 69% (52-91%), and 54% (37-79%), respectively. **Conclusions:** In this real-life cohort study, allo-HCT with the TBF conditioning regimen and GCHD prophylaxis with PTCy, sirolimus, and MMF showed encouraging results. It led to reduced acute and chronic GVHD incidence, improved GRFS, and favorable survival rates. These findings suggest that this combination holds promise as an effective treatment option for MM patients considered candidates for an allo-HCT.

P-244

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rate (GFR) ≥30 mL/min. DREAMM-12 includes renally impaired pts (GFR < 30 mL/min) to provide belamaf dose recommendations for this population. **Methods:** In Part 1 of the ongoing DREAMM-12 study (NCT04398745), 2 groups of pts with RRMM (≥2 lines of prior therapy) were studied: Control Group 1, GFR ≥60 mL/min (normal/mild renal impairment [RI]); Group 2, GFR of 15–29 mL/min (severe RI). Pts were treated with belamaf (2.5 mg/kg Q3W). Endpoints were pharmacokinetics (PK) by non-compartmental analysis (primary), safety (secondary) and efficacy (exploratory). **Results:** Median (range) GFR was 84 mL/min (67–129) in Group 1 (10 pts) and 25 mL/min (20–28) in Group 2 (9 pts). Pts in both groups had received a median of 5 prior therapies. Median age was 61 years in Group 1 and 73 in Group 2. Median dose intensity was similar between groups. The PK population comprised 16 pts (n=8 per group) matched for body weight and albumin, with ≥80% PK collection at Cycle 1. PK analysis showed pts in Group 2 had lower geometric mean ADC plasma concentrations, total antibody and cys-mcMMAF than pts in Group 1. Exposures between groups were largely overlapping: differences were not considered clinically meaningful and were confirmed in a separate population PK analysis [1]. Urine PK analysis suggested renal elimination was not the primary route of cys-mcMMAF excretion (median < 10%). Adverse event (AE) incidence, severity and duration was similar between groups (any AE: Group 1, 100%; Group 2, 89%; Grade ≥3 AEs, Group 1, 70%; Group 2, 56%). There were 3 fatal AEs (Group 1, n=1, intestinal ischaemia; Group 2, n=2, pneumonia, intracerebral haemorrhage). The most common AEs by class (eye disorders: Group 1, 80%; Group 2, 56%), and most common serious AE (infections/infestations: Group 1, 20%; Group 2, 22%) showed no clinically meaningful differences across groups. Investigator assessed overall response rates (≥partial response) were n=5 of 10 pts in Group 1 vs n=4 of 9 pts in Group 2. **Conclusions:** No clinically meaningful PK, safety or efficacy differences were seen between pts with normal/mild RI (Group 1) and severe RI (Group 2): based on these data, no belamaf dose adjustment is necessary for pts with severe RI and GFR as low as 15 mL/min. Part 2 of this study will assess belamaf 2.5 mg/kg Q3W in pts with end stage renal disease (GFR < 15 mL/min) on and not on dialysis.

P-246

Real-world attrition rates after second-line therapy or later in patients from the flatiron database with relapsed/refractory multiple myeloma refractory to lenalidomide

Binod Dhakal[1], Hermann Einsele[2], Jordan Schecter[3], William Deraedt[4], Nikoletta Lendvai[3], Ana Slaughter[5], Carolina Lonardi[6], Sandhya Nair[7], Jianming He[8], Akshay Kharat[9], Patricia Cost[8], Satish Valluri[8], Rafael Fonseca[10]

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Introduction: To explore unmet need in patients with relapsed/refractory multiple myeloma (RRMM) refractory to lenalidomide (len), we report real-world attrition rates and treatment duration for len-refractory patients from the Flatiron multiple myeloma (MM) database who have had 1 prior line of therapy (LOT). **Methods:** Data from January 2016 to April 2022 were extracted from the Flatiron Health deidentified US electronic health records database. Eligible patients had len-refractory RRMM (defined as having a change in treatment within 60 days of last len therapy without len as a component of the immediate next LOT), 1 prior LOT including a proteasome inhibitor and an immunomodulatory drug, and an ECOG performance status < 2. After meeting inclusion criteria, patients were observed over their next 4 LOTs (LOT 2–5). Attrition rate was defined as the proportion of patients without a record of subsequent MM treatment. **Results:** From ~13,000 patients in the Flatiron database, we identified 561 at LOT 2 (first postinclusion LOT) with len-refractory RRMM. All patients received LOT 2. The attrition rate between LOT 2 and 3 was 43%, including 13% of patients who died and 30% with no subsequent treatment or lost follow-up. Noncumulative attrition rates after LOT 3 and 4 were 44% and 54%, respectively, including mortality rates of 13% and 15% at each LOT and an additional 31% and 39% of patients with no subsequent treatment or lost follow-up. Cumulatively, 85% patients (n=479) were lost to attrition by LOT 5, including 25% patients (n=141) who died and 60% patients (n=338) who received no subsequent treatment or were lost to follow-up. In LOT 2, 3, 4, and 5, a respective 38%, 14%, 8%, and 4% of the 561 patients received a National Comprehensive Cancer Network (NCCN)-recommended regimen (NCCN Guidelines for MM, Version 3. 2023) for len-refractory RRMM; and 41%, 26%, 14%, and 5% received other NCCN-endorsed RRMM regimens. In each of LOTs 2–5, 0.7–2.9% of the 561 patients participated in clinical trials. Median duration of each LOT was 4.5 month in LOT 2, 5.5 month in LOT 3, 4.9 month in LOT 4, and 5.2 month in LOT 5. **Conclusions:** Our findings of high attrition rates across LOTs (43–54%) for patients with len-refractory RRMM are consistent with previous results in patients with newly diagnosed MM (eligible and ineligible for transplant). In published literature, attrition rates were 21–57% after LOT 1 and 31–46% for the next 3 LOTs. The short median durations of treatment (each LOT < 6 month) observed in this analysis highlights the ineffectiveness of existing therapies. Together, these data underscore the need for more effective treatments early, before patients are lost to attrition, instead of reserving effective regimens for later LOTs.

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P-247

Efficacy and safety of linvoseltamab 200 mg in patients with relapsed/refractory multiple myeloma (RRMM): analysis of the LINKER-MM1 study

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Introduction: Linvoseltamab is a fully human BCMA×CD3 bispecific antibody (Ab) that demonstrated encouraging efficacy and a generally manageable safety profile in patients (pts) with RRMM in a Phase (Ph) 1/2 dose-escalation/expansion study (LINKER-MM1; Lee et al. ASCO 2023). Here, we report a detailed analysis of pts who received linvoseltamab 200 mg, identified as the recommended dose. **Methods:** LINKER-MM1 (NCT03761108) enrolled adults with MM who progressed on/after ≥3 lines of therapy (LoT) including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 Ab; the Ph 2 portion also included pts who were ≥triple-class (PI/IMiD/anti-CD38 Ab) refractory. In Ph 2, pts received linvoseltamab QW in Cycles 1–3 followed by Q2W dosing; dosing frequency was reduced to Q4W for pts who achieved ≥VGPR after Cycle 6. The Ph 2 primary endpoint was objective response rate (ORR). Key secondary endpoints included duration of response and minimal residual disease (MRD) status. **Results:** As of Feb 28, 2023, 117 pts had received linvoseltamab 200 mg (Ph 1, n=12; Ph 2, n=105): Median age, 70 yrs (range 37–91); Black/African American ethnicity, 17%; extramedullary plasmacytomas, 14%; high-risk cytogenetics, 36%; bone marrow plasma cells ≥50%, 22%. Pts had received a median of 5 (range 2–14) prior LoT, and 74% were ≥triple-class refractory. ORR was 71%, with 59% of pts achieving ≥VGPR and 30% achieving ≥CR, at a median duration of follow-up of 5.6 months (range 0.2–28.2). Median time to ≥VGPR and ≥CR was 1.87 months and 5.32 months, respectively. In pts who had prior BCMA-targeted therapy exposure with belantamab mafodotin (n=10), ORR was 60%. The median duration of ≥VGPR was not reached, and the probability of maintaining at least this level of response at 6/12 months was 89%/83%. The most common TEAEs (>30%) were cytokine release syndrome (CRS; 45% [Gr 3: 1%]), cough (33% [Gr ≥3: 0]), fatigue (32% [Gr ≥3: 0]), diarrhea (32% [Gr ≥3: 2%]), and neutropenia (32% [Gr ≥3: 31%]). CRS onset usually occurred on the day of dosing (median [range] time to first CRS onset from most recent dose, 14.8 h [0–177]), and resolved within 1 day (median [range] CRS duration, 16.5 h [1–144]); a temporal analysis to understand the relationship between tocilizumab use and recurrent CRS will be presented. ICANS (investigator-assessed) was reported in 6% (Gr ≥3: 3%) of pts. Infections occurred in 60% (Gr ≥3: 37%; Gr 5: 9%) of pts, with the most commonly identified infection types being pneumonia (17%; Gr ≥3: 14%), COVID-19 (12%; Gr ≥3: 5%) and upper respiratory tract infection (12%; Gr ≥3: 3%). **Conclusions:** Linvoseltamab 200 mg is efficacious and shows a generally manageable safety profile in triple-class exposed pts. We will present additional analyses, including the timing and durability of deep (≥VGPR) responses to linvoseltamab, and MRD status, which support further investigation at the recommended dose.

P-248

Real-world outcomes of triple-class exposed multiple myeloma patients by treatment experience: the assocaition of prior lines and penta-refractoriness with progression-free and overall survival

Aster Meche[1], Felix Rondeau[2], Ariane Faucher[2], Jinma Ren[1], Alexander Schepart[1], Patrick Hlavacek[1], James Farrell[1], Didem Aydin[1], Guido Nador[1], Marco DiBonaventura[1]

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P-248

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and, separately, whether they were penta-refractory (yes [PENTA+] vs no [PENTA-]). Differences across subgroups were evaluated with respect to patient (pt) characteristics (age, sex, ISS, ECOG, cytogenetics) and treatment history. Progression-free survival (PFS) and overall survival (OS) were compared across these subgroups using Kaplan-Meier methods. **Results:** N=686 TCE MM pts were included from the COTA database (52.3% had received ≥4 LOT [range 4-14]; 8.6% were PENTA+). Pts with fewer LOT were more likely to have high-risk cytogenetics (26.0% vs 16.7%) but the pt characteristics were otherwise generally similar to pts with ≥4 LOT. There was significant variability in the index treatment regimen, but daratumumab+pomalidomide+ dexamethasone (DPd) (13.5% and 9.7%, respectively) was the most common index regimen for both subgroups. No pt characteristic varied by PENTA status, though DPd was more common among those who were PENTA- (12.0% vs 6.8%). N=787 TCE MM pts were included from the FH database (41.7% had received ≥4 LOT; 4.4% were PENTA+). Pt characteristics did not vary by LOT group; DPd was the most common regimen for both < 4 LOT (7.3%) and ≥4 LOT (9.8%). PENTA+ pts were slightly younger (64.3 vs 67.8 yrs, p<.05) but otherwise similar to PENTA- pts. DPd (9.0%) was the most common regimen among PENTA- while carfilzomib+cyclophosphamide+dexamethasone (11.4%) was the most common regimen among PENTA+ pts. Pts with ≥4 LOT reported shorter PFS than pts with < 4 LOT (medians: 6.1 vs 17.8 months [COTA]; 7.3 vs 16.6 months [FH]; log-rank ps<.05) and OS (medians: 19.4 vs 24.5 months [COTA], log-rank p=.10; 14.2 vs 33.0 months [FH], log-rank p<.05). Similarly, pts who were PENTA+ had shorter PFS than PENTA- (medians: 4.7 vs 10.2 months [COTA]; 3.7 vs 14.8 months [FH]; log-rank ps<.05) and OS (medians: 14.3 vs 21.9 months [COTA], log-rank p<.05; 11.8 vs 21.3 months [FH], log-rank p=.21). **Conclusions:** Although TCE MM pts report poor outcomes overall, significant differences in real-world outcomes are observed based on their treatment histories. Pts with more prior LOTs or who were penta-refractory had significantly shorter PFS and OS, despite similar treatment regimens in their index line.

P-249

The association between age, performance status, frailty and outcomes in real-world clinical practice among patients with triple-class exposed multiple myeloma

Aster Meche[1], Felix Rondeau[2], Sarasa Johnson[2], Jinma Ren[1], Alexander Schepart[1], Patrick Hlavacek[1], James Farrell[1], Didem Aydin[1], Guido Nador[1], Marco DiBonaventura[1]

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Introduction: Disease management in multiple myeloma (MM) among those with advanced age and poorer functioning can be particularly challenging (Grant et al 2023). The objective of the current study was to examine the extent to which patient outcomes vary by age, performance status based on the ECOG score, and frailty, based on a modified IMWG frailty index, among those who have already been exposed to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody (ie, triple-class exposed [TCE]). **Methods:** Patients ≥18 years with MM who initiated a subsequent therapy (ie, index regimen) after becoming TCE were identified through two US electronic health record databases (COTA and Flatiron Health). In each database, patients were stratified by age (< 65 vs ≥65; < 75 vs ≥75), ECOG score (< 2 vs ≥2), and frailty score (non-frail: < 2 vs frail: ≥2) based on a modified IMWG frailty index incorporating age, ECOG, and comorbidities. Differences across subgroups were evaluated with respect to patient characteristics (age, sex, ISS, cytogenetics) and treatment history. Progression-free survival (PFS) and overall survival (OS) were compared across these subgroups using Kaplan-Meier methods. **Results:** A total of N=686 TCE MM patients were included from the COTA database: 64.1% were ≥65 years (yrs), 27.6% were ≥75 yrs, 11.8% were ECOG≥2, and 25.5% were frail. Though median (m)PFS tended to be shorter for older and poorer functioning patients, PFS results were not statistically significantly different across all comparisons. However, patients ≥65 yrs had significantly shorter OS than patients < 65 yrs (mOS=17.6 vs 28.7 months, log-rank p<.05) and patients ≥75 yrs had significantly shorter OS than patients < 75 yrs (mOS=17.0 vs 24.1 months, log-rank p<.05). Similarly, ECOG≥2 and frail patients had significantly shorter (log-rank ps<.05) OS than ECOG< 2 and non-frail patients, respectively (mOS=8.1 vs 21.0 months; 12.7 vs 21.9 months). Results within the Flatiron database (N=787) were generally similar: 62.1% were ≥65 yrs, 28.8% were ≥75 yrs, 19.4% were ECOG≥2, and 40.9% were frail. PFS results were not statistically significantly different across all comparisons (log-rank p≥.05). As in the COTA database, patients ≥75 yrs had significantly shorter OS than patients < 75 yrs (mOS=17.5 vs 23.3 months, log-rank p<.05). Similarly, ECOG≥2 and frail patients had significantly shorter OS than ECOG< 2 and non-frail patients respectively (mOS=11.4 vs 25.0 months, log-rank p<.05; mOS=12.9 vs 27.4 months, log-rank p<.05). **Conclusions:** Older age, higher ECOG score, and being frail were generally not significantly predictive of shorter PFS, but they were predictive of shorter OS.

P-250

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Introduction: Triple-class exposed (TCE) multiple myeloma (MM) patients who present with extramedullary disease (EMD) or high-risk cytogenetics can experience disproportionately poor outcomes. The current study sought to examine the real-world relationship between these disease attributes, treatment patterns, and future outcomes. **Methods:** Using two US electronic health record databases (COTA and Flatiron Health), MM patients ≥18

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and, separately, whether they were penta-refractory (yes [PENTA+] vs no [PENTA-]). Differences across subgroups were evaluated with respect to patient (pt) characteristics (age, sex, ISS, ECOG, cytogenetics) and treatment history. Progression-free survival (PFS) and overall survival (OS) were compared across these subgroups using Kaplan-Meier methods. **Results:** N=686 TCE MM pts were included from the COTA database (52.3% had received ≥4 LOT [range 4-14]; 8.6% were PENTA+). Pts with fewer LOT were more likely to have high-risk cytogenetics (26.0% vs 16.7%) but the pt characteristics were otherwise generally similar to pts with ≥4 LOT. There was significant variability in the index treatment regimen, but daratumumab+pomalidomide+ dexamethasone (DPd) (13.5% and 9.7%, respectively) was the most common index regimen for both subgroups. No pt characteristic varied by PENTA status, though DPd was more common among those who were PENTA- (12.0% vs 6.8%). N=787 TCE MM pts were included from the FH database (41.7% had received ≥4 LOT; 4.4% were PENTA+). Pt characteristics did not vary by LOT group; DPd was the most common regimen for both < 4 LOT (7.3%) and ≥4 LOT (9.8%). PENTA+ pts were slightly younger (64.3 vs 67.8 yrs, p<.05) but otherwise similar to PENTA- pts. DPd (9.0%) was the most common regimen among PENTA- while carfilzomib+cyclophosphamide+dexamethasone (11.4%) was the most common regimen among PENTA+ pts. Pts with ≥4 LOT reported shorter PFS than pts with < 4 LOT (medians: 6.1 vs 17.8 months [COTA]; 7.3 vs 16.6 months [FH]; log-rank ps<.05) and OS (medians: 19.4 vs 24.5 months [COTA], log-rank p=.10; 14.2 vs 33.0 months [FH], log-rank p<.05). Similarly, pts who were PENTA+ had shorter PFS than PENTA- (medians: 4.7 vs 10.2 months [COTA]; 3.7 vs 14.8 months [FH]; log-rank ps<.05) and OS (medians: 14.3 vs 21.9 months [COTA], log-rank p<.05; 11.8 vs 21.3 months [FH], log-rank p=.21). **Conclusions:** Although TCE MM pts report poor outcomes overall, significant differences in real-world outcomes are observed based on their treatment histories. Pts with more prior LOTs or who were penta-refractory had significantly shorter PFS and OS, despite similar treatment regimens in their index line.

P-249

The association between age, performance status, frailty and outcomes in real-world clinical practice among patients with triple-class exposed multiple myeloma

Aster Meche[1], Felix Rondeau[2], Sarasa Johnson[2], Jinma Ren[1], Alexander Schepart[1], Patrick Hlavacek[1], James Farrell[1], Didem Aydin[1], Guido Nador[1], Marco DiBonaventura[1]

[1]Pfizer Inc; [2]Statlog

Introduction: Disease management in multiple myeloma (MM) among those with advanced age and poorer functioning can be particularly challenging (Grant et al 2023). The objective of the current study was to examine the extent to which patient outcomes vary by age, performance status based on the ECOG score, and frailty, based on a modified IMWG frailty index, among those who have already been exposed to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody (ie, triple-class exposed [TCE]). **Methods:** Patients ≥18 years with MM who initiated a subsequent therapy (ie, index regimen) after becoming TCE were identified through two US electronic health record databases (COTA and Flatiron Health). In each database, patients were stratified by age (< 65 vs ≥65; < 75 vs ≥75), ECOG score (< 2 vs ≥2), and frailty score (non-frail: < 2 vs frail: ≥2) based on a modified IMWG frailty index incorporating age, ECOG, and comorbidities. Differences across subgroups were evaluated with respect to patient characteristics (age, sex, ISS, cytogenetics) and treatment history. Progression-free survival (PFS) and overall survival (OS) were compared across these subgroups using Kaplan-Meier methods. **Results:** A total of N=686 TCE MM patients were included from the COTA database: 64.1% were ≥65 years (yrs), 27.6% were ≥75 yrs, 11.8% were ECOG≥2, and 25.5% were frail. Though median (m)PFS tended to be shorter for older and poorer functioning patients, PFS results were not statistically significantly different across all comparisons. However, patients ≥65 yrs had significantly shorter OS than patients < 65 yrs (mOS=17.6 vs 28.7 months, log-rank p<.05) and patients ≥75 yrs had significantly shorter OS than patients < 75 yrs (mOS=17.0 vs 24.1 months, log-rank p<.05). Similarly, ECOG≥2 and frail patients had significantly shorter (log-rank ps<.05) OS than ECOG< 2 and non-frail patients, respectively (mOS=8.1 vs 21.0 months; 12.7 vs 21.9 months). Results within the Flatiron database (N=787) were generally similar: 62.1% were ≥65 yrs, 28.8% were ≥75 yrs, 19.4% were ECOG≥2, and 40.9% were frail. PFS results were not statistically significantly different across all comparisons (log-rank p≥.05). As in the COTA database, patients ≥75 yrs had significantly shorter OS than patients < 75 yrs (mOS=17.5 vs 23.3 months, log-rank p<.05). Similarly, ECOG≥2 and frail patients had significantly shorter OS than ECOG< 2 and non-frail patients respectively (mOS=11.4 vs 25.0 months, log-rank p<.05; mOS=12.9 vs 27.4 months, log-rank p<.05). **Conclusions:** Older age, higher ECOG score, and being frail were generally not significantly predictive of shorter PFS, but they were predictive of shorter OS.

P-250

The relationship of extramedullary disease and high-risk cytogenetics on real-world outcomes among patients with triple-class exposed multiple myeloma

Aster Meche[1], Felix Rondeau[2], Francis Vekeman[2], Jinma Ren[1], Alexander Schepart[1], Patrick Hlavacek[1], James Farrell[1], Didem Aydin[1], Guido Nador[1], Marco DiBonaventura[1]

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Introduction: Triple-class exposed (TCE) multiple myeloma (MM) patients who present with extramedullary disease (EMD) or high-risk cytogenetics can experience disproportionately poor outcomes. The current study sought to examine the real-world relationship between these disease attributes, treatment patterns, and future outcomes. **Methods:** Using two US electronic health record databases (COTA and Flatiron Health), MM patients ≥18

years who initiated a subsequent therapy (ie, index regimen) after becoming TCE (ie, exposed to ≥1 PI, ≥1 IMiD, ≥1 anti-CD38) between November 2015 and June 2022 (COTA)/August 2021 (Flatiron) were included. Within the COTA database, patients were stratified by the presence versus absence of EMD (EMD+ vs. EMD-) and high-risk cytogenetics (HRC) (defined based on the presence of t(4:14), t(14:16), or del17p [ie, HRC+] or the absence of all three [HRC-] at the point of index). Because EMD was not reliably captured in the Flatiron Health database, only HRC comparisons were made in that data source. Differences across subgroups were evaluated with respect to patient characteristics (age, sex, ISS, ECOG), and treatment history. Progression-free survival (PFS) and overall survival (OS) were compared across these subgroups using the Kaplan-Meier method. **Results:** Of the N=686 TCE MM patients included from the COTA database, 12.0% were EMD+ and 21.1% were HRC+. No demographic or disease characteristic differences were observed between subgroups. There was significant variability in treatment regimens with no regimen occurring in more than 13% of either subgroup. Daratumumab+pomalidomide+dexamethasone (DPd) was the most common for all subgroups (EMD+: 9.8%; EMD-: 11.8%; HRC+:13.8%; HRC-: 10.9%). Of the N=787 TCE MM patients included from the Flatiron database, 22.4% were HRC+. HRC+ patients were slightly younger (65.2 vs. 68.3 years, p<.05) but otherwise similar with respect to demographics and disease characteristics compared with HRC-. DPd was also the most common regimen for both HRC+ (6.3%) and HRC- (9.5%). In the COTA database, EMD+ patients reported directionally shorter PFS (median: 4.7 vs 9.9 months, log-rank p=.08) and significantly shorter OS compared with EMD- (median: 11.6 vs. 24.0 months, log-rank p<.05). HRC+ patients had directionally shorter PFS (COTA: median 8.3 vs. 9.5 months, log-rank p=.17; Flatiron: median 7.0 vs. 12.1, p=.09) but significantly shorter OS (COTA: 13.7 vs. 23.9 months, log-rank p<.05; Flatiron: 11.8 vs. 25.2 months, log-rank p<.05) across both data sources. **Conclusions:** Among TCE MM patients in the real world, the presence of EMD and HRC was significantly predictive of poorer OS. Trends indicating that these factors predict poorer PFS were observed as well, though studies with larger samples sizes might be required to detect significant effects.

P-251

Variation in real-wolrd outcomes among patients with triple-class exposed mutliple myeloma across clinical subgroups: a German registry analysis

Evi Zhuleku[1], Sabrina Mueller[1], Lenka Kellerman[2], Claudia Herzberg[3], Regina Grabow-Schlesinger[3], Leonie Berger[3], Niclas Kuerschner[3], Guido Nador[4], Jinma Ren[4], Patrik Hlavacek[4], James Farrell[4], Marco DiBonaventura[4]

[1]Cytel; [2]TriNetX Oncology GmbH; [3]Pfizer Pharma GmbH; [4]Pfizer Inc

Introduction: Multiple myeloma (MM) patients who have been exposed to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody (ie, triple-class exposed [TCE]) experience poor outcomes. This analysis examined the variation of real-world TCE outcomes as a function of ECOG performance status and number of prior lines of therapy (LOTs). **Methods:** Data from the Therapy Monitor-Multiple Myeloma (TM-MM) Germany registry were used, which includes approximately 8,000 patients (pts) with MM from a representative sample of >100 treating institutions. Pts were included in the analysis if they had physician-documented MM per IMWG diagnosis criteria, were TCE, and initiated a subsequent therapy after becoming TCE (ie, index date) between May 2016 and March 2022, allowing for a minimum 6-month follow-up window until the end of data availability (September 2022). Pts with smoldering disease or active plasma cell leukemia were excluded, as were pts who had received an investigational treatment line as part of a clinical trial. Eligible pts were stratified by clinical subgroups including ECOG score (0 vs 1 vs 2 vs 3-4) and the number of prior LOTs (< 4 vs ≥4). Using Kaplan-Meier estimates, progression-free survival (PFS), defined as time from index to progression (with initiation of the next treatment line as a proxy) or death due to any cause and overall survival (OS), defined as time from index until death due to any cause, were calculated. **Results:** A total of N=1,028 TCE pts were included in the analyses (median age=72.7 years [range: 44.1 to 94.2], 57.6% male. At the index date, 10.4% were high-risk based on the presence of t(4:14), t(14:16), and/or del17p (ie, genomic features based on R-ISS; though 77.0% of pts had unknown/unassessed cytogenetic risk); 10.1%, 44.6%, and 36.2% had ECOG scores of 0, 1, and 2, with the remaining 7.4% having an ECOG of 3 or 4. Pts had received a median of 3 prior LOTs with 35.8% being quad-exposed. Median PFS (mPFS) decreased with increasing ECOG score category: ECOG 0=11.7 months (95% confidence interval: 11.3 months, 12.1 months); ECOG 1=10.2 months (9.0, 11.4); ECOG 2=9.6 months (8.0, 10.6); and ECOG 3/4=7.8 months (5.9, 9.9). Similarly, shorter mPFS (5.8 months [5.0, 7.2] vs 11.0 months [10.4, 11.6] was observed for prior LOT≥4 and < 4, respectively). mOS also decreased with increasing ECOG score category: ECOG 0=not estimable (NE) (30.0, NE); ECOG 1=21.1 months (17.8, 27.0); ECOG 2=19.4 months (17.8, 24.7); ECOG 3/4=10.7 months (9.1, 14.6). Shorter mOS (8.7 months [7.0, 12.2] vs 24.3 months [21.3, 27.5]) was also observed for pts with ≥4 prior LOTs. **Conclusions:** Although TCE MM pts in Germany experience poor outcomes overall, this was particularly true for pts with higher ECOG scores and more prior LOTs. The results highlight the necessity to use all available therapeutic options in early lines of therapy.

P-252

Impact of belantamab mafodotin vs pomalidomide/low-dose dexamethasone treatment on health-related quality of life and vision-related functioning in patients with relapsed/refractory multiple myeloma

Meletios Dimopoulos[1], Katja Weisel[2], Vania Hungria[3], Sandhya Sapra[4], Neal Sule[4], Mary Li[4], Astrid McKeown[5], Gbenga Kazeem[5], Margaret Polinkovsky[6], Juliette Meunier[7], Angely Loubert[7], Laurine Bunod[7], Sue Perera[8], Brooke Currie[9]

years who initiated a subsequent therapy (ie, index regimen) after becoming TCE (ie, exposed to ≥1 PI, ≥1 IMiD, ≥1 anti-CD38) between November 2015 and June 2022 (COTA)/August 2021 (Flatiron) were included. Within the COTA database, patients were stratified by the presence versus absence of EMD (EMD+ vs. EMD-) and high-risk cytogenetics (HRC) (defined based on the presence of t(4:14), t(14:16), or del17p [ie, HRC+] or the absence of all three [HRC-] at the point of index). Because EMD was not reliably captured in the Flatiron Health database, only HRC comparisons were made in that data source. Differences across subgroups were evaluated with respect to patient characteristics (age, sex, ISS, ECOG), and treatment history. Progression-free survival (PFS) and overall survival (OS) were compared across these subgroups using the Kaplan-Meier method. **Results:** Of the N=686 TCE MM patients included from the COTA database, 12.0% were EMD+ and 21.1% were HRC+. No demographic or disease characteristic differences were observed between subgroups. There was significant variability in treatment regimens with no regimen occurring in more than 13% of either subgroup. Daratumumab+pomalidomide+dexamethasone (DPd) was the most common for all subgroups (EMD+: 9.8%; EMD-: 11.8%; HRC+:13.8%; HRC-: 10.9%). Of the N=787 TCE MM patients included from the Flatiron database, 22.4% were HRC+. HRC+ patients were slightly younger (65.2 vs. 68.3 years, p<.05) but otherwise similar with respect to demographics and disease characteristics compared with HRC-. DPd was also the most common regimen for both HRC+ (6.3%) and HRC- (9.5%). In the COTA database, EMD+ patients reported directionally shorter PFS (median: 4.7 vs 9.9 months, log-rank p=.08) and significantly shorter OS compared with EMD- (median: 11.6 vs. 24.0 months, log-rank p<.05). HRC+ patients had directionally shorter PFS (COTA: median 8.3 vs. 9.5 months, log-rank p=.17; Flatiron: median 7.0 vs. 12.1, p=.09) but significantly shorter OS (COTA: 13.7 vs. 23.9 months, log-rank p<.05; Flatiron: 11.8 vs. 25.2 months, log-rank p<.05) across both data sources. **Conclusions:** Among TCE MM patients in the real world, the presence of EMD and HRC was significantly predictive of poorer OS. Trends indicating that these factors predict poorer PFS were observed as well, though studies with larger samples sizes might be required to detect significant effects.

P-251

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P-252

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P-251

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P-252

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[1]National and Kapodistrian University of Athens; [2]University Medical Center of Hamburg-Eppendorf, Hamburg, Germany; [3]Department of Hematology, Clinica São Germano, São Paulo, Brazil; [4]GSK, Upper Providence, USA; [5]GSK, Stevenage, England, UK; [6]GSK, Durham, USA; [7]Modus Outcomes, Lyon, France; [8]GSK, London, UK; [9]GSK, Rockville, USA

Introduction: The Phase 3, open-label, randomised, DREAMM-3 trial (NCT04162210) assessed single-agent belantamab mafodotin (belamaf), an antibody-drug conjugate targeting BCMA, vs pomalidomide + low-dose dexamethasone (Pd) in adults with relapsed/refractory multiple myeloma (RRMM) at second relapse or later. Trends in health-related quality of life (HRQL) and vision-related functioning (VRF) in DREAMM-3 are reported. **Methods:** Patients (pts) were randomised (2:1) to belamaf or Pd and completed electronic pt-reported outcome measures including EORTC QLQ-C30 (fatigue, physical and role functioning, global health), EORTC MM module (QLQ-MY20, disease pain), and the Ocular Surface Disease Index (OSDI, impact of ocular adverse events of special interest on VRF) at baseline (BL) and every 3 weeks. Proportions of pts with meaningful deterioration from BL in EORTC scores (≥10-point change) and time to first meaningful deterioration in fatigue were assessed. Meaningful deterioration in VRF (≥12.5-point change) and subsequent improvements were analysed. All were post hoc analyses. **Results:** 325 patients with RRMM were enrolled (belamaf, n=218; Pd, n=107). Compared to Pd, lower proportions of pts on belamaf experienced meaningful deterioration from BL in fatigue, functioning (physical, role), and global health; this pattern was seen across most visits through Week 31 and was most notable and consistent for role functioning and fatigue. For worsening disease pain, no difference was noted between arms. Time to first meaningful deterioration in fatigue was significantly delayed (P< 0.01) for pts receiving belamaf compared with Pd (median 148 days vs 64). Among pts with BL and ≥1 post-BL OSDI assessment (n=262), meaningful VRF deterioration was seen in both belamaf (67%) and Pd (49%) arms. Median days to first meaningful VRF deterioration was 45 for belamaf vs 44.5 in Pd. Lack of improvement after meaningful deterioration was similar across arms (belamaf 11%, Pd 12%). Among 92 pts in the belamaf arm with ≥3 OSDI assessments after first meaningful VRF deterioration, 82 (89%) pts had meaningful improvement, including 75 who returned to within 12.5 points of BL VRF score (defined recovery range). Mean global health and functioning scores remained stable for pts receiving belamaf who experienced VRF deterioration over the study. **Conclusions:** This descriptive analysis suggests positive trends in HRQL outcomes for pts treated with belamaf vs Pd, including fewer pts experiencing meaningful HRQL deterioration related to this progressive disease, and significantly delayed worsening of fatigue in pts on belamaf. In line with previous studies (DREAMM-2 and -3), improvement following VRF deterioration showed that ocular issues resolved for most pts receiving belamaf within 3 months. Importantly, stable functioning scores and global health status were seen for pts receiving belamaf who experienced deterioration in VRF, suggesting vision changes did not impact pts' overall HRQL.

P-253

Real world data of safety and efficacy profile of daratumumab in relapsed/refractory multiple myeloma patients: low grade respiratory infections and high efficacy in all treatment lines

Vasiliki Douka[1], Eleni Paphianou[1], Chrysavgi Lalayanni[1], Sotiria Dimou-Besikli[1], Michail Iskas[1], Maria Papathanasiou[1], Chrysanthi Vadikoliou[1], Grigorios Salvaras[1], Vasiliki Kanava[1], Ioanna Sakellari[1]

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Introduction: Duration of response in multiple myeloma (MM) patients has significantly ameliorated. Daratumumab is an approved treatment option in both first line and relapse-refractory (R/R) setting. The aim of our study is the efficacy and safety of daratumumab in R/R MM patients in daily practice. **Methods:** In a cohort of 29 patients, daratumumab combination regimens were administered in 15/7/4/3 in 2nd/3rd/4th and 5th treatment line. Daratumumab in combination with lenalidomide and dexamethasone (DRd) was administered in 8 patients, with pomalidomide and dexamethasone (DPd) in 6 patients, with bortezomib and dexamethasone (DVd) in 4 patients, with Carfilzomib and dexamethasone (DKd) in one patient, with dexamethasone only in 7 patients. One patient received D-VRd. The cohort consisted of male/female: 18/11 patients with median age 63 (41-77) years old, IgG/IgA/IgD/FLC/non secretory=14/3/1/8/3. ISS at diagnosis was: I/II/III=6/12/11 patients. Plasmacytoma was detected in 4 patients, 1 with extraosseous location and 7 patients had elevated serum LDH levels. Conventional karyotype and FISH were available in 24 and 14 patients respectively. Twenty patients had normal karyotype, 1 hyperdiploid, 3 complex. Regarding FISH, 5/14 patients had del17p, 2/14 del1p/add1q, 1/14 t(4;14), 2/14 t(11;14). Overall, 24/29 (83%) experienced a pulmonary infection adverse event. **Results:** Median PFS for patients in first relapse was not reached (3-49 months) and best response was CR/VGPR in 9/15 (60%) patients. All patients experienced a pulmonary infection adverse event, grade 3 requiring hospitalization in 2 patients and grade 2 in the rest. COVID-19 was detected in 7 patients. Nine patients developed neutropenia, grade 3/2/1=2/5/2 patients. Median PFS for patients beyond first relapse was 15 (1-60) months and best response was VGPR or better in 5/14 (36%). Nine out of 14 (64%) patients experienced a pulmonary infection adverse event, grade 2= 8/9 and only one grade 3. COVID-19 was detected in 4/14 (28%) patients. None of the COVID infected patients had fatal outcome or required ICU admission. Seven out of fourteen patients developed neutropenia grade 2. **Conclusions:** Daratumumab induced long and deep responses in all treatment lines. Even patients with multiple prior lines achieved durable responses. Although pulmonary infections were seen in the majority of patients, they were manageable with no fatalities.

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Introduction: The Phase 3, open-label, randomised, DREAMM-3 trial (NCT04162210) assessed single-agent belantamab mafodotin (belamaf), an antibody-drug conjugate targeting BCMA, vs pomalidomide + low-dose dexamethasone (Pd) in adults with relapsed/refractory multiple myeloma (RRMM) at second relapse or later. Trends in health-related quality of life (HRQL) and vision-related functioning (VRF) in DREAMM-3 are reported. **Methods:** Patients (pts) were randomised (2:1) to belamaf or Pd and completed electronic pt-reported outcome measures including EORTC QLQ-C30 (fatigue, physical and role functioning, global health), EORTC MM module (QLQ-MY20, disease pain), and the Ocular Surface Disease Index (OSDI, impact of ocular adverse events of special interest on VRF) at baseline (BL) and every 3 weeks. Proportions of pts with meaningful deterioration from BL in EORTC scores (≥10-point change) and time to first meaningful deterioration in fatigue were assessed. Meaningful deterioration in VRF (≥12.5-point change) and subsequent improvements were analysed. All were post hoc analyses. **Results:** 325 patients with RRMM were enrolled (belamaf, n=218; Pd, n=107). Compared to Pd, lower proportions of pts on belamaf experienced meaningful deterioration from BL in fatigue, functioning (physical, role), and global health; this pattern was seen across most visits through Week 31 and was most notable and consistent for role functioning and fatigue. For worsening disease pain, no difference was noted between arms. Time to first meaningful deterioration in fatigue was significantly delayed (P< 0.01) for pts receiving belamaf compared with Pd (median 148 days vs 64). Among pts with BL and ≥1 post-BL OSDI assessment (n=262), meaningful VRF deterioration was seen in both belamaf (67%) and Pd (49%) arms. Median days to first meaningful VRF deterioration was 45 for belamaf vs 44.5 in Pd. Lack of improvement after meaningful deterioration was similar across arms (belamaf 11%, Pd 12%). Among 92 pts in the belamaf arm with ≥3 OSDI assessments after first meaningful VRF deterioration, 82 (89%) pts had meaningful improvement, including 75 who returned to within 12.5 points of BL VRF score (defined recovery range). Mean global health and functioning scores remained stable for pts receiving belamaf who experienced VRF deterioration over the study. **Conclusions:** This descriptive analysis suggests positive trends in HRQL outcomes for pts treated with belamaf vs Pd, including fewer pts experiencing meaningful HRQL deterioration related to this progressive disease, and significantly delayed worsening of fatigue in pts on belamaf. In line with previous studies (DREAMM-2 and -3), improvement following VRF deterioration showed that ocular issues resolved for most pts receiving belamaf within 3 months. Importantly, stable functioning scores and global health status were seen for pts receiving belamaf who experienced deterioration in VRF, suggesting vision changes did not impact pts' overall HRQL.

P-253

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P-254

Cardiac and hidden toxicity of carfilzomib in presence of cardiometabolic syndrome and early-stage heart failure with reduced ejection fraction

Panagiotis Efentakis[1], Aimilia Varela[2], Sofia Lamprou[1], Eleni-Dimitra Papanagnou[1], Michail Chatzistefanou[1], Andriana Christodoulou[1], Costantinos Davos[2], Maria Gavriatopoulou[3], Ioannis Trougakos[1], Meletios Dimopoulos[1], Ioanna Andreadou[1], Evangelos Terpos[3]

[1]National and Kapodistrian University of Athens; [2]Biomedical Research Foundation (BRFAA) of the Academy of Athens; [3]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Greece

Introduction: Cancer therapy-related Cardiovascular adverse events (CAEs) in presence of comorbidities, such as Cardiometabolic Syndrome (CMS) and Early-Stage Heart Failure with reduced Ejection Fraction (HFrEF), are in the spotlight of the Cardio-oncology guidelines, with proteasome inhibitors standing among anticancer therapies with most prominent cardiotoxicity. Carfilzomib (Cfz) indicated for relapsed/refractory multiple myeloma (MM), presents with serious CAEs. MM is often accompanied with coexisting comorbidities. However, Cfz use in MM patients with CMS or HFrEF is questionable. **Methods:** ApoE-/- and C57BL6/J male mice received 14 weeks High Fat Diet (HFD) for the establishment of CMS. C57BL6/J male mice underwent permanent LAD ligation for 14 days in order to establish Early-stage HFrEF. CMS- and HFrEF-burdened mice received Cfz for 2 consecutive days or for 6 days, on alternate days intraperitoneally (i.p.), whereas Control mice received Normal Saline (0.9%) at the same dose regimen i.p. Daily Metformin and Atorvastatin administrations were performed additionally to Cfz, as possible prophylactic interventions. Mice underwent complete echocardiography analysis, while proteasome activity, biochemical and molecular analyses were conducted. **Results:** CMS did not exacerbate Cfz Left Ventricular (LV) dysfunction, while Cfz led to metabolic complications, including decrease of fasting blood glucose and impairment of the lipid profile, in both CMS models. Cfz induced autophagy and Ca2+ homeostasis dysregulation, whereas Metformin and Atorvastatin prevented Cfz-mediated LV dysfunction and molecular deficits in the CMS-burdened myocardium. Early-stage HFrEF led to a depressed LV function and an increased PP2A activity. Cfz further increased myocardial PP2A activity, inflammation and Ca2+-cycling dysregulation. Met co-administration exerted an anti-inflammatory potential in the myocardium, without improving LV function. **Conclusions:** CMS and HFrEF seem to exacerbate Cfz's CAEs by presenting metabolism-related hidden toxicity and PP2A-related cardiac inflammation, respectively. Met retains its prophylactic potential in the presence of CMS, while mitigated inflammation and Ca2+ signalling dysregulation HFrEF myocardium.

P-255

Efficacy of a second autologous stem cell transplant for multiple myeloma and correlation with response to initial transplant: a single-center experience

Hamid Ehsan[1], Myra Robinson[1], Shebli Atrash[1], Ami Ndiaye[1], Jordan Robinson[1], Manisha Bhutani[2], Cindy Varga[1], Paul Eldridge[1], Jing Ai[1], Nilanjan Ghosh[1], Peter Voorhees[3], Barry Paul[1], Kristen Cassetta[1]

[1]Levine Cancer Institute, Atrium Health; [2]Division of Plasma Cell Disorders, Department of Hematologic Oncology & Blood Disorders, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [3]Levine Cancer Institute, Atrium Health Wake Forest University School of Medicine

Introduction: High-dose melphalan (HDM) and autologous stem cell transplant (ASCT) has consistently been shown to improve depth of response and PFS in large phase 3 trials of myeloma patients. However, the role of a second (salvage) transplant (sASCT) for relapsed refractory multiple myeloma (RRMM) in the era of novel therapies is less clear. **Methods:** We retrospectively evaluated 43 RRMM patients who underwent a sASCT between Nov 2014 and June 2022 at our institution. **Results:** Median time between first and sASCT was 4.4 yrs. The median follow-up from MM diagnosis was 7.6 yrs, and from sASCT was 2.9 yrs. The majority of pts had standard risk cytogenetics (77%). The most common cytogenetic abnormalities at diagnosis were monosomy 13 (35%) followed by t(11;14), del 17p, and gain/amp of 1q21 (each 14%). The most common induction regimen was RVD (51%) followed by CyBorD (11.6%). Most patients (76.7%) received maintenance therapy after initial transplant with IMiD (72%), PI (15%) and doublet (12.4%) regimens being most common. After sASCT the majority of patients (85.4%) received maintenance with IMiD (45%), triplet (17%), PI (14%), daratumumab (8.6%), doublets (8.6%), or Selinexor (5.7%). The median total number of lines of therapies was 5 (3-15). Two patients (4.7%) succumbed to sASCT-related mortality, with 41 patients being response-evaluable. Responses were deep, with most patients achieving a CR or sCR (70%), or VGPR (18.6%) as best response after sASCT, while only three patients (7 %) achieved 4 years (n=10) also supported this association (log-rank test p4 years of PFS1 was 4.3 years. Using cox proportional hazards models, the risk of progression or death after sASCT in those with PFS1 4 years. **Conclusions:** Our data suggest a significant benefit for sASCT in RRMM patients, especially those that achieved at least a 4-year PFS from their first ASCT. Additionally, most patients achieved deep responses (CR or sCR). While our dataset is small and only represents a single-center experience, it implies that even in the era of novel therapies such as CAR-Ts and bispecific antibodies, there remains a role for sASCT in select patients.

P-254

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P-256

Initial report of a single institution experience with teclistamab for relapsed or refractory multiple myeloma including prior BCMA

Beth Faiman[1], Danai Dima[1], Marissa Duco[1], Mikhaila Rice[1], Joslyn Rudoni[1], Faiz Anwer[1], Jack Khouri[1], Sandra Mazzoni[1], Shahzad Raza[1], Christy Samaras[1], Louis Williams[1], Jason Valent[1]

[1]Cleveland Clinic Taussig Cancer Institute

Introduction: Despite the rapidly evolving treatment armamentarium, multiple myeloma (MM), remains an incurable cancer. Teclistamab (TEC) is the first CD3 x BCMA, T-cell redirecting bispecific antibody indicated for the treatment of adult patients (pts) with relapsed or refractory MM (RRMM). Unfortunately, pts who received TEC in clinical trials (CT) are not representative of the real-world population. Here, we describe our initial experience among RRMM pts who received TEC at our institution from Dec 2022 to May 2023. **Methods:** This retrospective study included 26 pts with a confirmed diagnosis of MM who received TEC outside of a CT. Descriptive analyses were performed for baseline characteristics. The 2016 IMWG criteria were used to assess disease response and/or refractoriness to prior LOT. All pts were admitted to the hospital for TEC step-up doses and mandatory 48 hours of observation post-administration. All pts were given acyclovir and sulfamethoxazole-trimethoprim prophylaxis, or an alternative. **Results:** The median age of our cohort was 64 (range 45-75) yrs; 54% were females and 73% were Caucasian. The median number of prior LOT were seven (range 4-17), including nine (38%) pts with previous anti-BCMA (idecabtagene vicleucel) and one belantamab. One hundred percent and 92% of pts had the triple and penta-refractory disease, respectively. Ten (38%) pts had prior HSCT. Twenty-two (85%) pts developed cytokine release syndrome (CRS), which in most cases was mild (95% grade 1-2, 5% grade 3, 0% grade 4-5); of these 22 pts, 18 (82%) required tocilizumab (median number of total doses was one) and eight (36%) steroids. The most common CRS presentation was fever (91%), followed by hypoxia (9%) and hypotension (4.5%). TEC led to immune effector cell-associated neurotoxicity syndrome (ICANS) in five (19%) pts during the step-up period (100% grade 1-2); of them, 4 had CRS and 3 received steroids. Only seven pts experienced infections during the step-up period, of whom two had severe infections requiring intravenous (IV) therapies (COVID-19 infection treated with remdesivir, septic arthritis treated with IV antibiotics). For efficacy analysis, one pt was excluded due to recurrent ICANS with following doses mandating TEC discontinuation. After a median follow-up of 2.5 months, the best responses achieved were: four (16%) pts achieved complete response, five (20%) very good partial response, six (24%) partial response, four (16%) had stable disease, while three (12%) progressed and three (12%) died without achieving any response. Eventually, six (24%) pts progressed and four (16%) died. **Conclusions:** TEC is a promising therapy for pts with RRMM including those with prior BCMA exposure. Cytopenias and infections were reported but not significantly different from prior studies. No new safety signals were identified. These initial findings support the safety and efficacy of TEC in BCMA naïve and exposed pts and early anti-IL6 therapy to prevent escalation of CRS. Analysis of long-term outcomes is ongoing.

P-257

Real-world treatment patterns and clinical outcomes among patients with triple-class exposed (TCE) multiple myeloma (MM)

Rafael Fonseca[1], Jennifer Harper[2], Hoa Le[2], Alex Fu[2,3], Saurabh Patel[4], Bingcao Wu[2], Xinke Zhang[2]

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Introduction: Despite the advancements in available therapeutics for MM, MM remains an incurable disease, and most patients relapse and require further treatment. Patients who are TCE to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies have particularly high unmet needs. With rapid treatment landscape changes, the aim of this study is to describe characteristics, treatment patterns, and clinical outcomes of these patients in recent years. **Methods:** Patients with MM who started subsequent line of treatment (LOT) after they were TCE from July 03, 2019 (Selinexor approval date) to December 31, 2020 were selected from the Komodo Healthcare Map—a US claims dataset and were followed until the earliest of death, last claim, or end of study period (June 30, 2021). The primary analysis included patients with a subsequent LOT after becoming TCE. Patients who were post TCE with 4+ PLs and quadruple-class exposed (QCE; TCE + exposed to B-cell maturation antigen targeted drug) were also analyzed. Index date was defined as LOT start date after each exposure definitions. Descriptive statistics were reported for patient characteristics and treatment patterns. Clinical outcomes such as time to treatment discontinuation or death (TTD), and time to next treatment or death (TTNT) were estimated using the Kaplan-Meier method. Here we reported data for TCE and TCE with 4+ prior PLs; data for QCE cohort will be presented in the future. **Results:** A total of 1,704 TCE patients were included, among whom 1,072 had 4+ PLs. For TCE and TCE with 4+ PLs cohorts, the mean (median) ages were 64.6 (64.0) and 64.9 (64.0), and 46.6% and 47.4% were females, respectively. The mean (median) number of prior LOTs before index date were 3.9 (4.0) and 4.7 (4.0), respectively. Most patients who were TCE and TCE with 4+ PLs were exposed to daratumumab (D; 99.9% and 99.8%), lenalidomide (85.6% and 86.4 %), and bortezomib (84.2 % and 83.0%) before index date. The most common post-TCE treatments were pomalidomide (P)- (36.0%), D- (35.0%), and carfilzomib (K)- (33.7%) based regimens. Similarly, the most common post-TCE with 4+ PLs treatments were P- (33.8%), K- (33.8%), and D- (30.5%) based regimens. At the regimen level, D+P±dexamethasone was the most commonly used post-index regimen (8.0% and 6.7% for TCE and TCE with 4+ PLs, respectively). The median TTD (months) were 5.8 (95% CI 5.4-6.5) for TCE and 5.1 (95% CI 4.8-5.6) for TCE with 4+ PLs, while the median TTNT (months) were 8.4 (95% CI 7.9-9.4) for TCE and 7.1 (95% CI 6.7-7.8) for TCE with 4+ PLs. **Conclusions:** These

P-256

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P-257

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Rafael Fonseca[1], Jennifer Harper[2], Hoa Le[2], Alex Fu[2,3], Saurabh Patel[4], Bingcao Wu[2], Xinke Zhang[2]

[1]Division of Hematology/Oncology, Mayo Clinic, Phoenix, AZ, USA; [2]Janssen Scientific Affairs, LLC; [3]Georgetown University Medical Center, Washington, DC, USA; [4]Janssen US Oncology Medical Affairs, Janssen Pharmaceuticals

Introduction: Despite the advancements in available therapeutics for MM, MM remains an incurable disease, and most patients relapse and require further treatment. Patients who are TCE to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies have particularly high unmet needs. With rapid treatment landscape changes, the aim of this study is to describe characteristics, treatment patterns, and clinical outcomes of these patients in recent years. **Methods:** Patients with MM who started subsequent line of treatment (LOT) after they were TCE from July 03, 2019 (Selinexor approval date) to December 31, 2020 were selected from the Komodo Healthcare Map—a US claims dataset and were followed until the earliest of death, last claim, or end of study period (June 30, 2021). The primary analysis included patients with a subsequent LOT after becoming TCE. Patients who were post TCE with 4+ PLs and quadruple-class exposed (QCE; TCE + exposed to B-cell maturation antigen targeted drug) were also analyzed. Index date was defined as LOT start date after each exposure definitions. Descriptive statistics were reported for patient characteristics and treatment patterns. Clinical outcomes such as time to treatment discontinuation or death (TTD), and time to next treatment or death (TTNT) were estimated using the Kaplan-Meier method. Here we reported data for TCE and TCE with 4+ prior PLs; data for QCE cohort will be presented in the future. **Results:** A total of 1,704 TCE patients were included, among whom 1,072 had 4+ PLs. For TCE and TCE with 4+ PLs cohorts, the mean (median) ages were 64.6 (64.0) and 64.9 (64.0), and 46.6% and 47.4% were females, respectively. The mean (median) number of prior LOTs before index date were 3.9 (4.0) and 4.7 (4.0), respectively. Most patients who were TCE and TCE with 4+ PLs were exposed to daratumumab (D; 99.9% and 99.8%), lenalidomide (85.6% and 86.4 %), and bortezomib (84.2 % and 83.0%) before index date. The most common post-TCE treatments were pomalidomide (P)- (36.0%), D- (35.0%), and carfilzomib (K)- (33.7%) based regimens. Similarly, the most common post-TCE with 4+ PLs treatments were P- (33.8%), K- (33.8%), and D- (30.5%) based regimens. At the regimen level, D+P±dexamethasone was the most commonly used post-index regimen (8.0% and 6.7% for TCE and TCE with 4+ PLs, respectively). The median TTD (months) were 5.8 (95% CI 5.4-6.5) for TCE and 5.1 (95% CI 4.8-5.6) for TCE with 4+ PLs, while the median TTNT (months) were 8.4 (95% CI 7.9-9.4) for TCE and 7.1 (95% CI 6.7-7.8) for TCE with 4+ PLs. **Conclusions:** These

findings demonstrate that in the real-world, patients have limited treatment options after TCE and are often retreated with the same therapies or therapies in the same classes. Patients who were TCE discontinued treatment and moved on to next treatment shortly after initial treatment. These outcomes were even shorter for those with 4+ PLs. The findings highlight the continued need for effective treatments for heavily treated patients with MM.

P-258

Carfilzomib in relapsed/refractory multiple myeloma patients – real world evidence: experiences of the Croatian cooperative group for hematologic diseases (KROHEM)

Davor Galušić[1], Josip Batinić[2,3], Barbara Dreta[2], Delfa Radić Krišto[3,4], Mario Piršić[5], Goran Rinčić[6], Jasminka Sinčić-Petričević[7], Toni Valković[8], Milan Vujčić[1], Marin Šimunić[1], Karla Mišura Jakobac[4], Martina Sedinić Lacko[5], Klara Brčić[6], Vlatka Periša[7], Fran Petričević[6], Dragan Grohovac[8], Hrvoje Holik[9], Martina Morić Perić[10], Ivan Zekanović[10], Ivan Krečak[11], Petra Berneš[12], Luka Kužat[13], ilenia Romić[14], Dubravka Županić Krmek[15], Sandra Bašić-Kinda[2]

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[1]UB-Therapeutics; [2]Technion

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P-258

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apoptosis in cancer cell lines, and showed anti-cancer activity in vivo.The cyclic peptide Ub4a displayed stability in human plasma for multiple days, with a half-life of 60 hours, suggesting its potential for therapeutic applications. Overall, the study highlights the promising therapeutic potential of cyclic peptides as a novel approach for cancer treatment by targeting ubiquitin protein chains. **Conclusions:** This comprehensive investigation encompassed pre-formulation characterization, assessment of apoptotic activity, cell viability inhibition, pharmacokinetic profiling, analytical method development, determination of MTD, and evaluation of in vivo efficacy. The results provide valuable insights into the therapeutic potential of the novel cyclic peptides as anti-cancer agents, demonstrating their promise for further development and potential clinical applications.

P-260

Ipilimumab after CD34-selected allogeneic stem cell transplantation (Allo HCT) for patients with relapsed/refractory multiple myeloma (RRMM)

Arnab Ghosh[1], Katherine Nagel[1], Kinga Hosszu[1], Ambika Datta[1], Christina Thompson[1], Khayla Levia[1], Alyssa Kamrowski[1], Devin McAvoy[1], David Chung[2], Heather Landau[2], Michael Scordo[1], Sergio Giralt[1], Gunjan Shah[1]

[1]Memorial Sloan Kettering Cancer Center, New York City NY, USA; [2]Bone Marrow Transplant and Cellular Therapy, Memorial Sloan Kettering Cancer Center, New York City NY, USA

Introduction: Despite recent advances in the therapeutic landscape of multiple myeloma (MM), a subgroup of patients with poorer than expected outcomes, remains at a high risk of rapid progression and death. Allogeneic hematopoietic cell transplantation (alloHCT) is considered for select patients in this subgroup with some success. Immune checkpoint blockade (ICB) has the theoretical potential to enhance the effectiveness of the alloHCT, but concerns of an unrestrained immune system causing graft versus host disease (GVHD) or allograft rejection has tempered the enthusiasm for testing these strategies to prevent or delay relapse after alloHCT. Given the lower probability of GVHD with CD34+selected alloHCT, we explored if adding ipilimumab (ipi), a CTLA-4 blocking antibody after CD34+selected alloHCT would be safe and effective in a phase I trial. **Methods:** Patients with RRMM in remission who had a 10/10 matched donor underwent conditioning with busulfan, melphalan, fludarabine, and rabbit ATG followed by an ex-vivo CD34+selected alloHCT. If in remission at day 100, patients then received ipi 3 mg/kg every 3 weeks for 4 doses followed by once every 3 months for 4 doses unless limited by DLT or disease relapse. Preventive and supportive care was as per institutional standards. The trial was approved by MSK institutional review board. **Results:** Between July 2021-July 2022, three patients enrolled prior to study closure for slow enrollment; 1 of these patients progressed prior to day 100 and was not eligible for treatment with ipi. The 2 patients who received ipi were male and aged 61 and 63. Patient 1 had 8 prior lines of treatment including 2 autologous HCT and patient 2 having 9 prior lines including 2 autologous HCTs and BCMA CAR T cells. Patient 1 received 5 doses of ipi before progressing at 309 days after alloHCT. Patient 2 received 3 doses of ipi prior to progression at 160 days after alloHCT. Neither of the two patients had GVHD or rejection of allograft. Patient 1 developed an ipi-associated rash that resolved with topical steroids and pericarditis related to a parainfluenza respiratory infection. We performed high-dimensional multicolor flow cytometry of peripheral blood and bone marrow before and after alloHCT, that showed expansion of T cells after alloHCT. At time points closer to relapse there were increased myeloid-derived suppressor cells and numbers of PD-1 expressing T cells. **Conclusions:** Our study suggests that ICB with ipi can be used after CD34+selected alloHCT without GVHD or allograft rejection in select patients. Further studies are needed to understand if the expanding T cell subsets participate in graft versus myeloma effects and into mechanisms that affect the durability of ICB therapy. Our trial underscores the significance of meticulous patient selection for ICB after alloHCT as a strategy to delay relapse of MM in platforms with low GVHD potential.

P-261

Comparison of different cutoffs of time from last drug exposure to disease progression for defining drug refractoriness in multiple myeloma

Utkarsh Goel[1], Charalampos Charalampous[1], Prashant Kapoor[1], Moritz Binder[1], Francis Buadi[1], David Dingli[1], Angela Dispenzieri[1], Amie Fonder[1], Morie Gertz[1], Wilson Gonsalves[1], Suzanne Hayman[1], Miriam Hobbs[1], Yi Hwa[1], Taxiarchis Kourelis[1], Martha Lacy[1], Nelson Leung[1], Yi Lin[1], Rahma Warsame[1], Robert Kyle[1], Vincent Rajkumar[1], Shaji Kumar[1]

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Introduction: Defining refractoriness to specific drugs/ drug classes is important for determining eligibility for clinical trials and to compare results across studies in multiple myeloma (MM). As such, MM that is nonresponsive or progresses within 60 days of last therapy is currently considered to be refractory to that therapy. We hypothesized that subgroups of MM that typically exhibit faster response/ relapse kinetics (e.g., high risk MM) might require different intervals from last exposure for defining refractoriness, as compared to the current 60 days definition. **Methods:** We retrospectively reviewed all newly diagnosed MM patients (pts) at our institute between January 2004 and December 2018 who experienced disease progression with first line lenalidomide (Len) containing regimens, and subsequently received another Len containing regimen at any time during the disease course. We collected the time duration from last Len dose to first disease progression, and assigned 30 days, 60 days, and 120 days as cut-offs for defining Len refractoriness. We then assessed progression free survival (PFS) for next line therapy and the next Len containing line of therapy using Kaplan Meier and Cox models and used Harrell's Concordance Index (C) to measure the performance of different models. **Results:** A total of 202 pts were included. Overall, 43%, 39%, and 18% pts were International Staging System Stage I, II, and III; 32% pts had high risk FISH as per mSMART. For Len refractory vs not refractory pts,

apoptosis in cancer cell lines, and showed anti-cancer activity in vivo.The cyclic peptide Ub4a displayed stability in human plasma for multiple days, with a half-life of 60 hours, suggesting its potential for therapeutic applications. Overall, the study highlights the promising therapeutic potential of cyclic peptides as a novel approach for cancer treatment by targeting ubiquitin protein chains. **Conclusions:** This comprehensive investigation encompassed pre-formulation characterization, assessment of apoptotic activity, cell viability inhibition, pharmacokinetic profiling, analytical method development, determination of MTD, and evaluation of in vivo efficacy. The results provide valuable insights into the therapeutic potential of the novel cyclic peptides as anti-cancer agents, demonstrating their promise for further development and potential clinical applications.

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P-261

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Utkarsh Goel[1], Charalampos Charalampous[1], Prashant Kapoor[1], Moritz Binder[1], Francis Buadi[1], David Dingli[1], Angela Dispenzieri[1], Amie Fonder[1], Morie Gertz[1], Wilson Gonsalves[1], Suzanne Hayman[1], Miriam Hobbs[1], Yi Hwa[1], Taxiarchis Kourelis[1], Martha Lacy[1], Nelson Leung[1], Yi Lin[1], Rahma Warsame[1], Robert Kyle[1], Vincent Rajkumar[1], Shaji Kumar[1]

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Introduction: Defining refractoriness to specific drugs/ drug classes is important for determining eligibility for clinical trials and to compare results across studies in multiple myeloma (MM). As such, MM that is nonresponsive or progresses within 60 days of last therapy is currently considered to be refractory to that therapy. We hypothesized that subgroups of MM that typically exhibit faster response/ relapse kinetics (e.g., high risk MM) might require different intervals from last exposure for defining refractoriness, as compared to the current 60 days definition. **Methods:** We retrospectively reviewed all newly diagnosed MM patients (pts) at our institute between January 2004 and December 2018 who experienced disease progression with first line lenalidomide (Len) containing regimens, and subsequently received another Len containing regimen at any time during the disease course. We collected the time duration from last Len dose to first disease progression, and assigned 30 days, 60 days, and 120 days as cut-offs for defining Len refractoriness. We then assessed progression free survival (PFS) for next line therapy and the next Len containing line of therapy using Kaplan Meier and Cox models and used Harrell's Concordance Index (C) to measure the performance of different models. **Results:** A total of 202 pts were included. Overall, 43%, 39%, and 18% pts were International Staging System Stage I, II, and III; 32% pts had high risk FISH as per mSMART. For Len refractory vs not refractory pts,

apoptosis in cancer cell lines, and showed anti-cancer activity in vivo.The cyclic peptide Ub4a displayed stability in human plasma for multiple days, with a half-life of 60 hours, suggesting its potential for therapeutic applications. Overall, the study highlights the promising therapeutic potential of cyclic peptides as a novel approach for cancer treatment by targeting ubiquitin protein chains. **Conclusions:** This comprehensive investigation encompassed pre-formulation characterization, assessment of apoptotic activity, cell viability inhibition, pharmacokinetic profiling, analytical method development, determination of MTD, and evaluation of in vivo efficacy. The results provide valuable insights into the therapeutic potential of the novel cyclic peptides as anti-cancer agents, demonstrating their promise for further development and potential clinical applications.

P-260

Ipilimumab after CD34-selected allogeneic stem cell transplantation (Allo HCT) for patients with relapsed/refractory multiple myeloma (RRMM)

Arnab Ghosh[1], Katherine Nagel[1], Kinga Hosszu[1], Ambika Datta[1], Christina Thompson[1], Khayla Levia[1], Alyssa Kamrowski[1], Devin McAvoy[1], David Chung[2], Heather Landau[2], Michael Scordo[1], Sergio Giralt[1], Gunjan Shah[1]

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Introduction: Despite recent advances in the therapeutic landscape of multiple myeloma (MM), a subgroup of patients with poorer than expected outcomes, remains at a high risk of rapid progression and death. Allogeneic hematopoietic cell transplantation (alloHCT) is considered for select patients in this subgroup with some success. Immune checkpoint blockade (ICB) has the theoretical potential to enhance the effectiveness of the alloHCT, but concerns of an unrestrained immune system causing graft versus host disease (GVHD) or allograft rejection has tempered the enthusiasm for testing these strategies to prevent or delay relapse after alloHCT. Given the lower probability of GVHD with CD34+selected alloHCT, we explored if adding ipilimumab (ipi), a CTLA-4 blocking antibody after CD34+selected alloHCT would be safe and effective in a phase I trial. **Methods:** Patients with RRMM in remission who had a 10/10 matched donor underwent conditioning with busulfan, melphalan, fludarabine, and rabbit ATG followed by an ex-vivo CD34+selected alloHCT. If in remission at day 100, patients then received ipi 3 mg/kg every 3 weeks for 4 doses followed by once every 3 months for 4 doses unless limited by DLT or disease relapse. Preventive and supportive care was as per institutional standards. The trial was approved by MSK institutional review board. **Results:** Between July 2021-July 2022, three patients enrolled prior to study closure for slow enrollment; 1 of these patients progressed prior to day 100 and was not eligible for treatment with ipi. The 2 patients who received ipi were male and aged 61 and 63. Patient 1 had 8 prior lines of treatment including 2 autologous HCT and patient 2 having 9 prior lines including 2 autologous HCTs and BCMA CAR T cells. Patient 1 received 5 doses of ipi before progressing at 309 days after alloHCT. Patient 2 received 3 doses of ipi prior to progression at 160 days after alloHCT. Neither of the two patients had GVHD or rejection of allograft. Patient 1 developed an ipi-associated rash that resolved with topical steroids and pericarditis related to a parainfluenza respiratory infection. We performed high-dimensional multicolor flow cytometry of peripheral blood and bone marrow before and after alloHCT, that showed expansion of T cells after alloHCT. At time points closer to relapse there were increased myeloid-derived suppressor cells and numbers of PD-1 expressing T cells. **Conclusions:** Our study suggests that ICB with ipi can be used after CD34+selected alloHCT without GVHD or allograft rejection in select patients. Further studies are needed to understand if the expanding T cell subsets participate in graft versus myeloma effects and into mechanisms that affect the durability of ICB therapy. Our trial underscores the significance of meticulous patient selection for ICB after alloHCT as a strategy to delay relapse of MM in platforms with low GVHD potential.

P-261

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P-262

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Introduction: Patients (pts) with multiple myeloma (MM) typically receive several different regimens, with the disease eventually becoming refractory to most of the included drugs. For late-line MM refractory to most available therapies, retreatment with a drug that the disease had earlier become refractory to might be one option. In this study we assessed the patterns of care and clinical outcomes of retreatment with previously refractory drugs in pts with MM **Methods:** We reviewed 1141 MM pts at our institute who started a new line of therapy for disease progression after January 2015. Of these, 315 pts received a drug that their disease had progressed on previously (index drug) and were included in the study. We collected the duration of initial regimen with index drug and the time gap between last dose of initial regimen and start of retreatment. We then assessed the best response with retreatment according to the IMWG criteria, and progression free survival (PFS) and overall survival (OS) using Kaplan Meier and Cox models **Results:** The median age for the cohort was 61 years; 58% pts were male. At diagnosis, 33%, 42%, and 25% pts were International Staging System (ISS) stage I, II, and III; 31% had high risk FISH as per mSMART; median number of prior lines before retreatment was 2 (range 1-12). The index drug was lenalidomide for 45% of pts, bortezomib for 30%, pomalidomide for 11%, and daratumumab for 6% pts. For all pts, the overall response rate (ORR) was 85% (28% ≥VGPR), the median PFS was 11 months (95% CI: 9-13), and the median OS was 53 months (95% CI: 46-66) with retreatment. Of the total 315, 163 (52%) pts were retreated with the index refractory drug in the immediate next line of therapy, and 152 (48%) were retreated with at least 1 intervening line between initial regimen and retreatment. After adjusting for age, ISS stage, high risk FISH, and number of prior lines; pts retreated after 1 or more index drug-free lines had a numerically better PFS (HR=0.7, 95% CI: 0.6-1.1) and OS (HR=0.7, 95% CI: 0.4-1.0) compared to pts retreated in the very next line. After adjusting for above parameters in the subgroup of pts treated after a gap (n=152), pts in quartile (Q) 4 of time gap between last dose of initial regimen and start of retreatment (>34 months) had a better retreatment PFS (HR=0.6, 95% CI: 0.3-1.1) and OS (HR=0.4, 95% CI: 0.2-0.9) as compared to pts in Q1 (< 8 months gap). HRs (95% CI) for Q2 and Q3 were 1.3 (0.7-2.5) and 1.3 (0.7-2.3) for PFS; and 0.9 (0.5-2.0) and 0.8 (0.4-1.7) for OS. **Conclusions:** Retreatment with previously refractory MM drugs might be a viable option, demonstrating an 85% ORR and a 28% ≥VGPR rate in our cohort. Pts retreated with at least 1 intervening line and longer gaps between initial regimen and retreatment had better outcomes than pts retreated in the immediate next line and with shorter index drug-free durations, respectively. These finding highlight the complexity of using refractoriness definitions in defining patient populations for clinical trials.

P-263

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Hartmut Goldschmidt[1], Ravi Vij[2], David Kuter[3], David Cella[4], Philippe Moreau[5], Brian Durie[6], Maria-Teresa Petrucci[7], Yuexin Tang[8], Sujith Dhanasiri[9], Jin Gu[9], Susan Fish[9], Karthik Ramasamy[10]

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the median PFS for next Len containing therapy was 10 months (95% CI: 6-13) vs 31 months (95% CI: 22-40) using a 30-days cutoff, and 10 months (95% CI: 6-13) vs 32 months (95% CI: 25-43) using 60-days and 120-days cutoffs (p< 0.001 for all). In the high-risk subgroup: for Len refractory vs not refractory pts, the median PFS for next Len containing therapy was 5 months (95% CI: 4-10) vs 41 months (95% CI: 19-NR) using a 30-days cutoff, and 5 months (95% CI: 4-7) vs 42 months (95% CI: 25- NR) using 60-days and 120-days cutoffs (p< 0.001 for all). Harrell's C (95% CI) for 30-days, 60-days, and 120-days cutoffs were 0.605 (0.564-0.646), 0.637 (0.598-0.676), and 0.636 (0.597-0.675) respectively. In the high-risk subgroup, Harrell's C for 30-days, 60-days, and 120-days cutoffs were 0.684 (0.613-0.755), 0.708 (0.641-0.775), and 0.708 (0.641-0.775) respectively. Similar trends were observed for all pts and high-risk MM pts for PFS with 2nd line therapy as well. **Conclusions:** We did not find an improvement in separation of survival curves or Harrell's C when using 30 days or 120 days as cutoffs for defining refractoriness, as compared to 60 days. The current 60 days cutoff from last drug exposure to disease progression functions well for defining refractoriness to MM drugs.

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P-263

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and 2020. Patients eligible for this study were previously treated with LEN and an anti-CD38 mAb in the same or different lines of therapy (LOTs) and initiated a subsequent LOT (index date=date of subsequent LOT initiation). Demographics, clinical characteristics, treatment history, and index treatment regimens were summarized descriptively. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method in the overall population and across subgroups defined by region (United States [US] vs ex-US), index LOT (2-4L vs 5L+), age (< 75 vs ≥75 years), and refractory status [refractory to both LEN and an anti-CD38 mAb vs not, triple-class refractory (TCR) vs not]. **Results:** Of 215 eligible patients, most were male (55.8%) and from the US (52.1%), and the median age was 69 years (range 45–92 years). Median time from MM diagnosis to index date was 3.8 years (range 0.3–29.3 years). Median number of prior treatment lines was 3 (range 1–12). Over half (50.7%) of all patients had undergone stem cell transplantation prior to the index date. All patients had previously received daratumumab; 95.8% of patients were also exposed to a proteasome inhibitor, the majority of whom had received bortezomib (95.1%). 80.9% of patients were refractory to LEN and an anti-CD38 mAb and more than half (69.3%) were TCR. Patients' index regimens included approximately 70 different treatment combinations, with carfilzomib ± dexamethasone (Kd; 13.0%), daratumumab/pomalidomide ± dexamethasone (DPd; 7.9%), and pomalidomide ± dexamethasone (Pd; 6.5%) being the most common. The median PFS in the cohort was 5.2 months (95% confidence interval [CI] 3.7–6.7 months) and the median OS was 16.2 months (95% CI 10.3–not reached [NR] months). Some subgroups had numerically worse survival outcomes (ex-US, later LOTs, ≥75 years, refractory to both LEN and an anti-CD38 mAb, and TCR), but only patients who were TCR had significantly shorter OS than those who were not (16.0 months, 95% CI 12.3–21.2 months vs 31.2 months, 95% CI 25.6–NR months). **Conclusions:** Data from this analysis show that after exposure to LEN and an anti-CD38 mAb, MM patients have poor survival outcomes and no clear standard of care. This analysis highlights the need for more effective treatment options for this patient population.

P-264

A phase 1b study of isatuximab and bendamustine for triple-class refractory multiple myeloma

Scott Goldsmith[1], Michael Slade[2], Mark Fiala[2], Melinda Harding[2], Zachary Crees[2], Mark Schroeder[2], Keith Stockerl-Goldstein[2], Ravi Vij[2]

[1]City Of Hope National Medical Center, Duarte, CA, USA; [2]Washington University School of Medicine in St. Louis

Introduction: Triple-class refractory MM is associated with poor outcomes. Bendamustine (Benda) has is an active cytotoxic chemotherapy regimen for MM that is well-tolerated with outpatient administration. Isatuximab (Isa) induces caspase-dependent cytotoxicity similar to rituximab. We hypothesized that Isa may synergize with Benda in patients with triple-class refractory disease. **Methods:** We conducted a single-center, phase 1b dose-escalation study to assess the safety, tolerability, and RP2D/MTD of Benda in combination with Isa in patient with triple-class refractory multiple myeloma, defined as treatment with proteasome inhibitor, an immunomodulatory drug, and daratumumab in combination or as single-agents and progression within 60 days of last dose. The study was approved by the local IRB and registered with clinicaltrials.gov (NCT04083898). Patients were enrolled according to a 3+3 dose-escalation design. Isa was administered as 10 mg/kg IV on days 1, 8, 15, and 22 of cycle 1, and days 1 and 15 thereafter. Benda dose levels included: 50, 75, and 100 mg/m^2 administered on days 1 and 2 of each cycle. Patients received methylprednisolone with each dose of Isa, and prednisone on days 2-4. After approval of standard-of-care CAR T therapy, patients were only enrolled if they had progressed after or were considered ineligible for CAR T. Adverse events were grade by CTCAE v 5.0. DLTs definitions adhered to standards for MM clinical trials. **Results:** 15 patients were treated; 3 at 50 Benda, and 6 each at dose 75 and 100. The median age was 71 (56-85) and 10 were male. 8 had high-risk cytogenetics and 9 had extramedullary disease. The median prior lines of MM treatment was 3 (range 2-9) and 60% had underwent ASCT. The median time post-daratumumab was 40 weeks (range 6-168). Cytopenias were common but rarely required intervention. There was only 1 DLT, at 50 benda (G3 thrombocytopenia with bleeding). 7 patients had infectious complications. The median number of cycles administered was 2 (range 1-13); at the time of abstract 2 patients are receiving treatment, both with bulky EMD and objective responses. There was 1 CR, 1 VGPR, 1 PR, and 9 SD. **Conclusions:** Isa + Benda is a safe combination and the MTD was not reached. RP2D is 100mg/m^2 of Benda on days 1 and 2 with conventional Isa dosing. Despite advanced disease with daratumumab-refractoriness, patients had notable disease control, including objective responses at the RP2D in patients with bulky EMD, a difficult subgroup. Unlike other cytoreductive chemotherapy for MM, this regimen allows for outpatient administration. Bendamustine may affect engineering and efficacy of cellular therapies, and is generally avoided pre-leukapheresis. However, Isa-Benda may serve as a reasonable bridging therapy that allows for disease control while reducing risk of severe cytopenias. Recent experience with Benda as a lymphodepleting agent has suggested comparable outcomes. Consequently, Isa-Benda as a novel MM lymphodepleting combination may warrant prospective study.

P-265

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and 2020. Patients eligible for this study were previously treated with LEN and an anti-CD38 mAb in the same or different lines of therapy (LOTs) and initiated a subsequent LOT (index date=date of subsequent LOT initiation). Demographics, clinical characteristics, treatment history, and index treatment regimens were summarized descriptively. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method in the overall population and across subgroups defined by region (United States [US] vs ex-US), index LOT (2-4L vs 5L+), age (< 75 vs ≥75 years), and refractory status [refractory to both LEN and an anti-CD38 mAb vs not, triple-class refractory (TCR) vs not]. **Results:** Of 215 eligible patients, most were male (55.8%) and from the US (52.1%), and the median age was 69 years (range 45–92 years). Median time from MM diagnosis to index date was 3.8 years (range 0.3–29.3 years). Median number of prior treatment lines was 3 (range 1–12). Over half (50.7%) of all patients had undergone stem cell transplantation prior to the index date. All patients had previously received daratumumab; 95.8% of patients were also exposed to a proteasome inhibitor, the majority of whom had received bortezomib (95.1%). 80.9% of patients were refractory to LEN and an anti-CD38 mAb and more than half (69.3%) were TCR. Patients' index regimens included approximately 70 different treatment combinations, with carfilzomib ± dexamethasone (Kd; 13.0%), daratumumab/pomalidomide ± dexamethasone (DPd; 7.9%), and pomalidomide ± dexamethasone (Pd; 6.5%) being the most common. The median PFS in the cohort was 5.2 months (95% confidence interval [CI] 3.7–6.7 months) and the median OS was 16.2 months (95% CI 10.3–not reached [NR] months). Some subgroups had numerically worse survival outcomes (ex-US, later LOTs, ≥75 years, refractory to both LEN and an anti-CD38 mAb, and TCR), but only patients who were TCR had significantly shorter OS than those who were not (16.0 months, 95% CI 12.3–21.2 months vs 31.2 months, 95% CI 25.6–NR months). **Conclusions:** Data from this analysis show that after exposure to LEN and an anti-CD38 mAb, MM patients have poor survival outcomes and no clear standard of care. This analysis highlights the need for more effective treatment options for this patient population.

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Introduction: MEZI is a novel oral cereblon E3 ligase modulator (CELMoD™) with enhanced antimyeloma effects compared with immunomodulatory drugs (IMiDs®). Preclinically, MEZI alone shows potent tumoricidal activity against MM cells and may hold potential as a monotherapy (e.g. where corticosteroids are not desired or indicated). Here we report results from the dose-escalation cohort of the CC-92480-MM-001 trial (NCT03374085) evaluating MEZI monotherapy in patients (pts) with RRMM. **Methods:** Eligible pts had RRMM; ≥3 prior lines of therapy, including ≥2 consecutive cycles of lenalidomide, pomalidomide, a proteasome inhibitor (PI), a glucocorticoid, and an anti-CD38 monoclonal antibody; and disease progression on or within 60 days of last myeloma therapy. MEZI was started at 0.6mg, with possible escalation to 0.8 and 1.0mg, on days 1–21 of each 28-day cycle. De-escalation to 0.4mg was allowed if 0.6mg was not tolerated. Granulocyte-colony stimulating factor was prohibited during the dose-limiting toxicity (DLT) evaluation period (cycle 1). The primary objectives were safety, pharmacokinetics/pharmacodynamics (PD), and determination of the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Efficacy was an exploratory objective. **Results:** As of March 22, 2023, 17 pts received MEZI (12 at 0.6mg, 5 at 0.4mg). Median age was 69 (50–76) years. Median number of prior therapies was 5 (3–10), including stem cell transplantation (70.6%); 14 (82.4%) pts were triple-class refractory. Median follow-up was 4.7 (0.4–12.0) months, median number of cycles received was 4 (1–12), and 4 (23.5%) pts were on treatment at data cutoff. Treatment discontinuation was mostly due to progressive disease (52.9%). Grade (Gr) 3–4 treatment-emergent adverse events (TEAEs) occurred in 15 (88.2%) pts. The most frequent hematologic Gr 3–4 TEAEs were neutropenia (76.5%), anemia (41.2%), and leukopenia (29.4%). Gr 3–4 infections were reported in 2/17 pts; rates of other non-hematologic Gr 3–4 TEAEs were low. Twelve (70.6%) and 3 (17.6%) pts had MEZI dose interruptions and reductions due to TEAEs, respectively. No pts discontinued MEZI due to TEAEs. Of the 13 evaluable pts, 1 had a DLT (persistent Gr 4 neutropenia). To date, the MTD/RP2D has not been reached. Overall response rate (ORR) at 0.6mg was 50.0% (6/12) with 1 complete response, 1 very good partial response, and 4 partial responses. Duration of response was immature. There were no responses (0/5) at 0.4mg. MEZI monotherapy was pharmacodynamically active at both 0.4 and 0.6mg doses, promoting target substrate degradation, T-cell proliferation, and reductions in peripheral B cells. **Conclusions:** In pts with heavily pretreated RRMM, MEZI monotherapy at the 0.6mg dose demonstrated a low incidence of severe non-hematologic toxicities with manageable cytopenias, and efficacy consistent with that of MEZI+DEX. Its preliminary safety, efficacy, and PD profile support further development as a corticosteroid-sparing approach in MM.

P-266

Pre-clinical characterization of SAR442257, a CD38xCD28xCD3 trispecific T-cell engager in relapsed/refractory multiple myeloma

Anna Grab[1], Peter Kim[2], Kamlesh Bisht[2], Hongfang Wang[2], Halgi Vandevelde[2], Lukas John[3,4], Debarati Shome[5], Irene Sarka[5], Niels Weinhold[3,4], Marc Raab[3]

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Introduction: Despite new treatment approaches, most patients with multiple myeloma (MM) develop relapsed/refractory disease (RRMM). CD38-targeting immunomodulators are becoming the standard of care in RRMM. Here we are investigating the first time SAR442257, an anti-CD38/CD3xCD28 trispecific antibody for RRMM. This antibody targets CD38-on MM cells and has a cross-over dual variable (CODV), anti-CD3xCD28 arm that can co-engage and co-stimulate CD3 and CD28 on T-cells, We therefore investigated i) the CD38/CD28-target expression of 100 NDMM and 40 RRMM patients, ii) the enhancement of avidity interaction between MM and T-cell, and iii) the mode of action as well as predictive biomarkers for drug efficiency in 40 RRMM patients (cohort 1: Daratumumab-relapse, 2: Bite-relapse, 3: ELO/POM-relapse). **Methods:** i) We determined the CD28/CD38 expression with FACS and ii) measured cell interaction force between T-cells and MM cells mediated by SAR442257 using a microfluidic approach. iii) The composition of RRMM bone marrow microenvironment was characterized one month after last therapy. For functional assays, CD138+ MM cells and CD3+ T-cellss were isolated from bone marrow of 40 RRMM patients. Dose dependent TC activation, cytokine release and MM cell lysis were measured with FACS. **Results:** The T cell cytotoxicity mediated by SAR442257 is influenced by the binding avidity, primarily depending on target antigen expression. Significantly more RRMM patients (86%) than NDMM patients (14%) expressed CD28, and cell avidity for multi-specific engagers ranked according to target expression (MFI CD38: 380-64000; MFI CD28: 70-1400), reaching more than 50% T-cell-to-MM cell-binding within the first 7min of interaction time. Functional assays showed RRMM patients with Daratumumab-, BiTE- or ELO/POM-treatment could independently be grouped in 2 drug-efficiency-cohorts at 1nM SAR442257: the highly responsive cohort was characterized by complete lysis of MM cells, 80% of autologous T-cell-activation, and patients with Daratumumab-relapse had additionally a factor of 20 lower TGF-B levels. SAR442257 mediated significantly higher MM cell killing compared to bi-specific functional-knockout controls for

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all relapse cohorts, which correlated with enhanced T-cell activation and degranulation (Pearson´s r=0.7). **Conclusions:** SAR442257 has increased binding capacity for RRMM due to CD38 and CD28 targets and demonstrated activity on RRMM cells as reasonable alternative for future RRMM therapy approach.

P-267

Teclistamab is safe and effective in relapse refractory multiple myeloma patients with end stage renal disease: a case series

Patrick Hagen[1]

[1]*Loyola University Chicago*

Introduction: Targeting B-cell maturation antigen (BCMA) has changed treatment approaches in relapsed refractory myeloma (RRMM). Teclistamab is a bi-specific antibody that targets CD3 expressed on T cells and BCMA expressed on myeloma cells. Recently FDA approved based on the MajesTEC-1 trial which excluded patients with a CrCl < 40 mL/min, there is a need to better understand safety and efficacy of RRMM with chronic kidney disease (CKD) seen in up to 50% of RRMM patients as well as those with end stage renal disease (ESRD). Other therapies have been shown to be safe and effective in ESRD patients but there are no reports of teclistamab in this patient population. **Methods:** This was a retrospective study evaluating patients with RRMM with ESRD treated with teclistimab since FDA approval at our institution. **Results:** We report here our experience with two RRMM patients with ESRD who received Teclistamab. The first patient was a 63 year old male with IgG-Lambda MM and R-ISS stage II disease at diagnosis. Prior to treatment, his lambda light chain was 4547.5 mg/L and an IgG 1930 mg/dL with the following high risk features: 8 prior lines of therapy including belantamab; high risk genomics (loss of TP53, amplification 1q, 13q deletion); extramedullary disease. The second patient was a 55 year old male with kappa light chain MM and R-ISS stage II disease at diagnosis. Prior to treatment, his kappa light chain was 1379.6 mg/L with the following high risk features: 8 prior lines of therapy; early progression following transplantation; high risk genomics with amplification of 1q; cirrhosis. Both patients received Teclistimab in standard step up followed by weekly dosing as per package insert immediately following hemodialysis (HD). Adverse events were similar to that reported on the MajesTEC-1 trial with only 1 grade 1 CRS event and both were promptly discharged to continue outpatient treatment without further CRS or neurotoxicity. They both achieved a prompt very good partial response with ongoing disease assessments planned. Importantly, no unexpected adverse events were noted. **Conclusions:** Severe manufacturing shortages of BCMA directed CAR-T therapy (idecel and ciltacel) are daunting with no clear solution in sight. Thus an efficacious bispecific antibody targeting BCMA is sorely needed. Cytopenias and CKD/ESRD would have made both of our patients above ineligible for the MajesTEC-1 trial. Based on the clinical trial data, pharmacodynamics, pharmacokinetics, and experience with other bispecific antibodies, we elected to dose teclistamab in these ESRD patients immediately following HD. Teclistamab can be safely given to high risk RRMM patients with ESRD without unexpected adverse events and responses on par with the MajesTEC-1 trial. Although this preliminary report is promising, further research is warranted and with several other bispecific antibodies showing promising responses in RRMM, our experience should guide further treatments in this challenging patient population.

P-268

An innovative interactive case-based online education tool significantly increases knowledge and competence of clinicians managing triple-class refractory multiple myeloma

Victoria Harvey-Jones[1], *Sanneke Koekkoek*[1], *Yelena Parada*[1], *María-Victoria Mateos*[2]

[1]*WebMD/Medscape Oncology Global;* [2]*University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain*

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all relapse cohorts, which correlated with enhanced T-cell activation and degranulation (Pearson´s r=0.7). **Conclusions:** SAR442257 has increased binding capacity for RRMM due to CD38 and CD28 targets and demonstrated activity on RRMM cells as reasonable alternative for future RRMM therapy approach.

P-267

Teclistamab is safe and effective in relapse refractory multiple myeloma patients with end stage renal disease: a case series

Patrick Hagen[1]

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online, interactive case-based models to transform access to new educational opportunities and improve knowledge and competence of hem/oncs in managing patients with triple class refractory MM. This could lead to improvements in the management of this patient population.

P-269

Effectiveness of online education in improving knowledge, competence and confidence of physicians in the management of multiple myeloma

Victoria Harvey-Jones[1], Sanneke Koekkoek[1], Jacob Cohen[1]

[1]WebMD/Medscape Oncology Global

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P-270

Effectiveness of micro CME at improving clinical knowledge and competence related to BCMA-targeted therapies for relapsed/refractory multiple myeloma

Victoria Harvey-Jones[1], Sarah Bomba[1], Sanneke Koekkoek[1]

[1]WebMD/Medscape Oncology Global

Introduction: With BCMA-targeted therapies available for multiple myeloma (MM), it is important that physicians are knowledgeable and competent in how to use these agents. This study aimed to determine whether online continuing medical education consisting of micro-chapters could improve the knowledge, competence, and confidence of hematologists/oncologists (hem/oncs) in managing patients with relapsed/refractory MM who are candidates for BCMA-targeted therapy. **Methods:** The educational initiative consisted of a collection of five online video-based micro-CME chapters, presented by three respected MM experts, allowing learners to choose the chapters for participation. The education effects were assessed using a repeated pairs pre-assessment/post-assessment study design, where individual participants served as their own control. McNemar's tests (P <.05) determined statistical significance overall in level of mastery of the content (made at least 1 more decision correctly or improved confidence in their correct decisions from pre- to post-education). At the question level, a paired-analysis confidence-based assessment (CBA) measured changes in competence and confidence in learners' pre/post responses to identify learners who are correct and confidence (mastery), correct but not confident (doubt), incorrect or confident (uninformed), and incorrect but confident (misinformed). 1 question was asked per micro chapter. Data were collected from 30/12/22 to 18/04/23. **Results:** Data from 60 hem/oncs who completed the pre/post questions were included in the analysis. Improvements in percentage of correct decisions answered confidently were seen from pre- to post (36% vs 63%, P< 0.001). Overall, 68% hem/oncs improved their knowledge, competence, and confidence. Further results showed: 1. Knowledge regarding the rationale for BCMA-directed therapies for R/R MM: 39% improved (P < 0.001); 225% increase in mastery; 36% decrease uninformed. 2. Knowledge regarding BCMA-directed bispecific antibodies: 43% improved (P < 0.01); 86% increase in mastery; 77% decrease uninformed. 3. Knowledge regarding BCMA-directed CAR T-cell therapies: 54% improved (P < 0.01); 100% increase in mastery; 86% decrease uninformed. 4. Competence related to managing treatment-related adverse events of BCMA-directed antibody conjugates: 45% improved (P=0.058); 23% increase in mastery; 50% decrease uninformed. Knowledge

online, interactive case-based models to transform access to new educational opportunities and improve knowledge and competence of hem/oncs in managing patients with triple class refractory MM. This could lead to improvements in the management of this patient population.

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Introduction: With BCMA-targeted therapies available for multiple myeloma (MM), it is important that physicians are knowledgeable and competent in how to use these agents. This study aimed to determine whether online continuing medical education consisting of micro-chapters could improve the knowledge, competence, and confidence of hematologists/oncologists (hem/oncs) in managing patients with relapsed/refractory MM who are candidates for BCMA-targeted therapy. **Methods:** The educational initiative consisted of a collection of five online video-based micro-CME chapters, presented by three respected MM experts, allowing learners to choose the chapters for participation. The education effects were assessed using a repeated pairs pre-assessment/post-assessment study design, where individual participants served as their own control. McNemar's tests (P <.05) determined statistical significance overall in level of mastery of the content (made at least 1 more decision correctly or improved confidence in their correct decisions from pre- to post-education). At the question level, a paired-analysis confidence-based assessment (CBA) measured changes in competence and confidence in learners' pre/post responses to identify learners who are correct and confidence (mastery), correct but not confident (doubt), incorrect or confident (uninformed), and incorrect but confident (misinformed). 1 question was asked per micro chapter. Data were collected from 30/12/22 to 18/04/23. **Results:** Data from 60 hem/oncs who completed the pre/post questions were included in the analysis. Improvements in percentage of correct decisions answered confidently were seen from pre- to post (36% vs 63%, P< 0.001). Overall, 68% hem/oncs improved their knowledge, competence, and confidence. Further results showed: 1. Knowledge regarding the rationale for BCMA-directed therapies for R/R MM: 39% improved (P < 0.001); 225% increase in mastery; 36% decrease uninformed. 2. Knowledge regarding BCMA-directed bispecific antibodies: 43% improved (P < 0.01); 86% increase in mastery; 77% decrease uninformed. 3. Knowledge regarding BCMA-directed CAR T-cell therapies: 54% improved (P < 0.01); 100% increase in mastery; 86% decrease uninformed. 4. Competence related to managing treatment-related adverse events of BCMA-directed antibody conjugates: 45% improved (P=0.058); 23% increase in mastery; 50% decrease uninformed. Knowledge

regarding the value of soluble BCMA as a prognostic biomarker: 61% improved (P < 0.01); 69% increase in mastery; 50% decrease uninformed **Conclusions:** This study demonstrates the success of an online CME activity with micro video chapters on improving knowledge, competence, and confidence of hem/oncs related to BCMA-targeted therapies for R/R MM. Additional gaps were identified for future educational targets.

P-271

Online CME improves clinical decision-making in the management of patients with relapsed/refractory multiple myeloma

Victoria Harvey-Jones[1], Sanneke Koekkoek[1], Yelena Parada[1]

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Introduction: Managing relapsed/refractory multiple myeloma (R/R MM) is complex for hematologists/oncologists (hem/oncs), with many treatment options available with varying adverse event profiles. We assessed whether an online, virtual patient simulation (VPS) activity could improve the performance of hem/oncs in ordering appropriate tests, treating R/R MM with available therapies, and managing ocular toxicity associated with a MM treatment. **Methods:** This CME-certified VPS consisted of 2 patient cases presented in a platform that allowed physicians to assess the patients and complete open-field entries, choosing from an extensive database of diagnostic and treatment options reflecting the scope and depth of actual practice. After each decision, learners received clinical guidance (CG) based on current evidence and faculty recommendations. Clinical decisions were compared pre- and post-CG using a 2-tailed paired t-test to determine P values (P<.05 is significant). Rationales for clinical decisions were collected in real time. Data were collected between March 2022 and September 2022 and reported here as % relative improvement, P value. **Results:** *Case 1 (n=286 hem/oncs).* 70-yr-old man with a history of MM who has received multiple lines of therapy and requires further treatment. Significant changes observed for: 1. Ordering appropriate tests to evaluate the patient (UIFE, 12%, P<.01; LDH, 10%, P<.01; serum Ig, 16%, P<.01; serum IFE, 10%, P<.01; serum FLC, 13%, P<.01; renal function, 13%, P<.01; peripheral blood smear, 15%, P<.01; LFTs, 10%, P<.01; FBC, 8%, P<.05; BM cytogenetics, 8%, P<.05; 24hr urine protein, 10%, P<.01). 2. Treating patients with R/R MM therapies (selinexor + dexamethasone, 23%, P<.001; idecabtagene vicleucel, 15%, P<.01; zoledronic acid, 45%, P<.001; order follow-up visits, 13%, P<.01). *Case 2 (n=286 hem/oncs).* 76-yr-old man with a history of MM, hypertension, and type 2 diabetes who has completed 3 cycles of belantamab mafodotin (BM) and complained of blurred vision. Significant changes observed for: Management of ocular toxicity associated with therapy for R/R MM (discontinue BM, 31%, P<.001; start preservative-free eye drops, 47%, P<.001; order the following: ophthalmology consult, 45%, P<.001; comprehensive eye exam, 9%, P<.05; compliance with eye drop use, 26%, P<.001; avoid contact lens use, 24%, P<.001; advice regarding operating machinery or driving, 28%, P<.001; patient follow-up, 21%, P<.01) **Conclusions:** These results demonstrate the success of immersive, online VPS education that engages physicians in a practical learning experience in improving their performance in choosing the optimal therapy for patients with R/R MM, as well as managing treatment-related adverse events.

P-272

Belantamab mafodotin for relapsed/refractory multiple myeloma: a real-world observational study update

Malin Hultcrantz[1], David Kleinman[2], Ravi Vij[3], Fernando Escalante[4], Michel Delforge[5], Nirali Kotowsky[6], Jacopo Bitetti[7], Natalie Boytsov[6], Leena Camadoo-O'Byrne[8], Lindsey Powers Happ[9], Mujib Rohman[10], Guillaume Germain[11], Mei Sheng Duh[12], Francois Laliberte[13], Malena Mahendran[13], Ana Urosevic[13], Hans Lee[14]

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regarding the value of soluble BCMA as a prognostic biomarker: 61% improved (P < 0.01); 69% increase in mastery; 50% decrease uninformed **Conclusions:** This study demonstrates the success of an online CME activity with micro video chapters on improving knowledge, competence, and confidence of hem/oncs related to BCMA-targeted therapies for R/R MM. Additional gaps were identified for future educational targets.

P-271

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P-272

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P-271

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P-272

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the most frequent were keratopathy (83% and 83%), blurred vision (57% and 66%), dry eye (35% and 37%), and keratitis (20% and 23%). Among pts with ≥4 months of follow-up, mean time to first ocular AE was 39 (SD: 34) days. Most ocular AEs were managed by therapy hold (69%; of which 73% restarted belamaf) and/or AE treatment (63%). The median dose hold due to ocular AEs was 43 days (physician-reported keratopathy: mild, 21 days; moderate/severe, 56 days). In all pts, 39 (21%) had a derived tumor response based on serum free light chain levels, (partial response: 74%, very good partial response: 51%). For all pts, the estimated median DoR was 9.1 months, PFS 4.5 months, and OS 7.9 months. The 6-month DoR, PFS and OS rates were 57%, 46%, and 58%, respectively. **Conclusions:** Overall, belamaf was effective in the real-world setting in heavily pre-treated pts with RRMM and limited therapy options. The AE profile was consistent with DREAMM-2. Ocular AEs were manageable and despite their occurrence, a high percentage of pts remained on treatment, suggesting belamaf may fill an unmet need for triple-class refractory pts with RRMM.

P-273

Isatuximab monotherapy or combination therapy with dexamethasone in older adult patients with relapsed/refractory multiple myeloma: a single institution experience

Masaki Iino[1], Takahiro Mikawa[1], Shinji Kido[1], Ken Fujimori[1]

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Introduction: Isatuximab monotherapy (20 mg/kg div, Isa20) or combination therapy with dexamethasone (Isa20+D) has proven effective and safe in patients with relapsed/refractory multiple myeloma (RRMM). Because of the low incidence of severe adverse events, these treatments have been used for disease control in older adult patients who are intolerant to prior treatment and/or to maintain the efficacy of prior treatment in our hospital. In this study, we retrospectively evaluated the efficacy and safety of Isa20 and Isa20+D in older adult patients. **Methods:** We examined the efficacy and safety of Isa20 and Isa20+D using the medical records of RRMM patients aged ≥ 80 years, who were treated at our hospital between 2021 and 2023. The response was evaluated according to the International Myeloma Working Group Uniform Response Criteria. Median overall survival (OS) and time to next treatment (TTNT) were estimated using the Kaplan–Meier method. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria version 5.0. The study was approved by the ethics committee of Yamanashi Prefectural Central Hospital and was conducted in accordance with the principles of the Declaration of Helsinki. **Results:** Fifteen patients received either Isa20 (n = 3) or Isa20+D (n = 12). The patient characteristics at diagnosis were: a median age of 83 years (range, 80–92), a male to female ratio of 8:7, and International Staging System stages I/II/III = 3:5:7 patients. The median number of prior treatments was three. Five patients had creatinine clearance < 30 mL/min, eight patients had high-risk cytogenetic abnormalities (at least one of t[4;14], t[14;16], del 17p, or 1q21 gain/amplification), and eleven patients had previously received daratumumab. All patients were classed as frail according to the International Myeloma Working Group Frailty Criteria. The reason for choosing Isa20 or Isa20+D treatment was intolerance to previous treatment (because of chronic heart failure, three patients; appetite loss, two patients; cytopenia, two patients; infection, two patients; renal dysfunction, one patient; liver dysfunction, one patient) and the need to maintain a treatment response (four patients). The disease control rate (i.e., stable disease or better) was 80%. After a median follow-up period of 10 months, the median TTNT was 7.5 months. The median OS was not reached. At the time of analysis, eight patients had discontinued treatment. The main reason for treatment discontinuation was disease progression. Regarding adverse events, an infusion reaction was extremely rare and no unexpected adverse events were identified in this study. **Conclusions:** Isa20 and Isa20+D remain useful and feasible treatment options in a real-world setting, even in frail older adult patients with RRMM.

P-274

Efficacy and safety of elranatamab in Japanese patients with relapsed/refractory multiple myeloma (RRMM): a pooled analysis from the MagnetisMM studies

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Introduction: This was a pooled analysis of Japanese patients (pts) with RRMM enrolled in the MagnetisMM studies MM-2 (NCT04798586) and MM-3 (NCT04649359) that evaluated the efficacy and safety of elranatamab. **Methods:** MagnetisMM-2 was a single-arm, open-label, multicenter, phase 1 study to evaluate elranatamab monotherapy of 1000 µg/kg SC weekly, with a 600 µg/kg SC priming dose, in Japanese pts with RRMM who received ≥3 prior therapies (≥1 proteasome inhibitor (PI), ≥1 immunomodulatory drug (IMiD), and ≥1 anti-CD38 antibody). MagnetisMM-3 is an ongoing open-label, multicenter, non-randomized, phase 2 study in pts with RRMM refractory to ≥1 PI, ≥1 IMiD and ≥1 anti-CD38 antibody, with elranatamab administered SC at a fixed dose of 76 mg weekly. Pts received SC elranatamab in 28-d cycles with step-up doses of 12 mg on C1D1 and 32 mg on C1D4 followed by 76 mg QW beginning C1D8. **Results:** In total, 16 pts (MM-2, n=4; MM-3, n=12) were included, 62.5% were male and median age was 68.5 y (range, 47–83). At baseline, pts had an ECOG PS of 0

the most frequent were keratopathy (83% and 83%), blurred vision (57% and 66%), dry eye (35% and 37%), and keratitis (20% and 23%). Among pts with ≥4 months of follow-up, mean time to first ocular AE was 39 (SD: 34) days. Most ocular AEs were managed by therapy hold (69%; of which 73% restarted belamaf) and/or AE treatment (63%). The median dose hold due to ocular AEs was 43 days (physician-reported keratopathy: mild, 21 days; moderate/severe, 56 days). In all pts, 39 (21%) had a derived tumor response based on serum free light chain levels, (partial response: 74%, very good partial response: 51%). For all pts, the estimated median DoR was 9.1 months, PFS 4.5 months, and OS 7.9 months. The 6-month DoR, PFS and OS rates were 57%, 46%, and 58%, respectively. **Conclusions:** Overall, belamaf was effective in the real-world setting in heavily pre-treated pts with RRMM and limited therapy options. The AE profile was consistent with DREAMM-2. Ocular AEs were manageable and despite their occurrence, a high percentage of pts remained on treatment, suggesting belamaf may fill an unmet need for triple-class refractory pts with RRMM.

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Introduction: Isatuximab monotherapy (20 mg/kg div, Isa20) or combination therapy with dexamethasone (Isa20+D) has proven effective and safe in patients with relapsed/refractory multiple myeloma (RRMM). Because of the low incidence of severe adverse events, these treatments have been used for disease control in older adult patients who are intolerant to prior treatment and/or to maintain the efficacy of prior treatment in our hospital. In this study, we retrospectively evaluated the efficacy and safety of Isa20 and Isa20+D in older adult patients. **Methods:** We examined the efficacy and safety of Isa20 and Isa20+D using the medical records of RRMM patients aged ≥ 80 years, who were treated at our hospital between 2021 and 2023. The response was evaluated according to the International Myeloma Working Group Uniform Response Criteria. Median overall survival (OS) and time to next treatment (TTNT) were estimated using the Kaplan–Meier method. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria version 5.0. The study was approved by the ethics committee of Yamanashi Prefectural Central Hospital and was conducted in accordance with the principles of the Declaration of Helsinki. **Results:** Fifteen patients received either Isa20 (n = 3) or Isa20+D (n = 12). The patient characteristics at diagnosis were: a median age of 83 years (range, 80–92), a male to female ratio of 8:7, and International Staging System stages I/II/III = 3:5:7 patients. The median number of prior treatments was three. Five patients had creatinine clearance < 30 mL/min, eight patients had high-risk cytogenetic abnormalities (at least one of t[4;14], t[14;16], del 17p, or 1q21 gain/amplification), and eleven patients had previously received daratumumab. All patients were classed as frail according to the International Myeloma Working Group Frailty Criteria. The reason for choosing Isa20 or Isa20+D treatment was intolerance to previous treatment (because of chronic heart failure, three patients; appetite loss, two patients; cytopenia, two patients; infection, two patients; renal dysfunction, one patient; liver dysfunction, one patient) and the need to maintain a treatment response (four patients). The disease control rate (i.e., stable disease or better) was 80%. After a median follow-up period of 10 months, the median TTNT was 7.5 months. The median OS was not reached. At the time of analysis, eight patients had discontinued treatment. The main reason for treatment discontinuation was disease progression. Regarding adverse events, an infusion reaction was extremely rare and no unexpected adverse events were identified in this study. **Conclusions:** Isa20 and Isa20+D remain useful and feasible treatment options in a real-world setting, even in frail older adult patients with RRMM.

P-274

Efficacy and safety of elranatamab in Japanese patients with relapsed/refractory multiple myeloma (RRMM): a pooled analysis from the MagnetisMM studies

Tadao Ishida[1], Hisayuki Yokoyama[2], Kenshi Suzuki[1], Satoshi Ito[3], Yuya Nagai[4], Hiroshi Handa[5], Shigeki Ito[6], Yoichi Kamei[7], Masatoshi Nakamura[7], Andrea Viqueira[8], Jane Liang White[9], Kazumi Take[10], Toyoki Moribe[10], Shinsuke Iida[11]

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Introduction: This was a pooled analysis of Japanese patients (pts) with RRMM enrolled in the MagnetisMM studies MM-2 (NCT04798586) and MM-3 (NCT04649359) that evaluated the efficacy and safety of elranatamab. **Methods:** MagnetisMM-2 was a single-arm, open-label, multicenter, phase 1 study to evaluate elranatamab monotherapy of 1000 µg/kg SC weekly, with a 600 µg/kg SC priming dose, in Japanese pts with RRMM who received ≥3 prior therapies (≥1 proteasome inhibitor (PI), ≥1 immunomodulatory drug (IMiD), and ≥1 anti-CD38 antibody). MagnetisMM-3 is an ongoing open-label, multicenter, non-randomized, phase 2 study in pts with RRMM refractory to ≥1 PI, ≥1 IMiD and ≥1 anti-CD38 antibody, with elranatamab administered SC at a fixed dose of 76 mg weekly. Pts received SC elranatamab in 28-d cycles with step-up doses of 12 mg on C1D1 and 32 mg on C1D4 followed by 76 mg QW beginning C1D8. **Results:** In total, 16 pts (MM-2, n=4; MM-3, n=12) were included, 62.5% were male and median age was 68.5 y (range, 47–83). At baseline, pts had an ECOG PS of 0

the most frequent were keratopathy (83% and 83%), blurred vision (57% and 66%), dry eye (35% and 37%), and keratitis (20% and 23%). Among pts with ≥4 months of follow-up, mean time to first ocular AE was 39 (SD: 34) days. Most ocular AEs were managed by therapy hold (69%; of which 73% restarted belamaf) and/or AE treatment (63%). The median dose hold due to ocular AEs was 43 days (physician-reported keratopathy: mild, 21 days; moderate/severe, 56 days). In all pts, 39 (21%) had a derived tumor response based on serum free light chain levels, (partial response: 74%, very good partial response: 51%). For all pts, the estimated median DoR was 9.1 months, PFS 4.5 months, and OS 7.9 months. The 6-month DoR, PFS and OS rates were 57%, 46%, and 58%, respectively. **Conclusions:** Overall, belamaf was effective in the real-world setting in heavily pre-treated pts with RRMM and limited therapy options. The AE profile was consistent with DREAMM-2. Ocular AEs were manageable and despite their occurrence, a high percentage of pts remained on treatment, suggesting belamaf may fill an unmet need for triple-class refractory pts with RRMM.

P-273

Isatuximab monotherapy or combination therapy with dexamethasone in older adult patients with relapsed/refractory multiple myeloma: a single institution experience

Masaki Iino[1], Takahiro Mikawa[1], Shinji Kido[1], Ken Fujimori[1]

[1]Yamanashi Prefectural Central Hospital

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P-274

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(50.0%) or 1 (50.0%); 37.5% had high risk cytogenetics; 25.0% had extramedullary disease. Pts received a median of 7.0 (2–11) prior lines of therapy, all pts were triple-class refractory and 8 pts (50.0%) were penta-drug refractory, and 15 pts (93.8%) were refractory to the last line of therapy. After a median follow-up of 11.1 mo (2.4–13.1), 43.8% of pts remained on treatment; the most common reason for permanent treatment discontinuation was progressive disease (37.5%). The objective response rate by investigator was 50.0% (95% CI 24.7–75.3), although not yet mature at the time of analysis; 37.5% and 50.0% achieved complete response or better and very good partial response or better, respectively. Among responders, the median duration of response was not reached (95% CI 9.2, NE) and the probability of maintaining the response at 9 months was 100% (95% CI: 100, 100). Dose reduction or interruption due to AEs occurred in 87.5% of pts and 1 pt permanently discontinued due to AEs (neutropenia, thrombocytopenia). 15 (93.8%) of pts reported G3/4 AEs. The most common TEAEs (≥50% of pts) were neutropenia (13 (81.3%) [G3/4, 13 (81.3%)]) and CRS (11 (68.8%) [G3/4, 1 (6.3%)]). No pt had ICANS. Overall, 5 (31.3%) pts died; 4 (25%) due to disease progression, 1 (6.3%) unknown. **Conclusions:** Deep and durable responses to elranatamab monotherapy were observed in Japanese pts with heavily pre-treated refractory MM. The safety profile was manageable and no new safety signals were identified. These results support the continued development of elranatamab for the treatment of RRMM in Japanese pts.

P-275

CARTITUDE-1 final results: phase 1b/2 study of ciltacabtagene autoleucel in heavily pretreated patients with relapsed/refractory multiple myeloma

Sundar Jagannath[1], Thomas Martin[2], Saad Usmani[3], Jesus Berdeja[4], Andrzej Jakubowiak[5], Mounzer Agha[6], Adam Cohen[17], Abhinav Deol[8], Myo Htut[9], Alexander Lesokhin[3], Nikhil Munshi[10], Elizabeth O'Donnell[11], Carolyn Jackson[12], Tzu-min Yeh[12], Arnob Banerjee[13], Enrique Zudaire[13], Deepu Madduri[12], Christopher DelCorral[14], Lida Pacaud[14], Yi Lin[15]

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Introduction: Heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM) treated with standard of care therapy have median overall survival (OS) of ~9-12 months. In the single-arm, phase 1b/2 CARTITUDE-1 study (NCT03548207), patients received a single infusion of ciltacabtagene autoleucel (cilta-cel), a chimeric antigen receptor-T cell therapy targeting B-cell maturation antigen. At the final protocol-specified analysis (27.7-month median follow-up), overall response rate (ORR) was 98%, with 83% stringent complete response; 27-month rates of progression-free survival (PFS) and OS were 55% and 70%, respectively. Here, we report CARTITUDE-1 study close out efficacy and safety results. **Methods:** Informed consent was obtained prior to study entry. Enrolled patients had received ≥3 prior lines of therapy (LOT) or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD); and had received prior PI, IMiD, and anti-CD38 antibody therapy. Primary endpoint was ORR and safety; secondary endpoints included PFS, OS, and minimal residual disease (MRD)-negativity at 10^{-5}. **Results:** 97 patients received cilta-cel (59% male; median age 61 years; median of 6 prior LOT; 42% penta-drug refractory; 88% triple-class refractory; 99% refractory to last LOT). As of October 14, 2022, median follow-up was 33.4 months (range, 1.5–45.2). Median duration of response was 33.9 month (95% CI, 25.5–not estimable). Median PFS was 34.9 months (95% CI, 25.2–NE), with an estimated 47.5% of patients progression free and alive at 36 months. Median OS was not reached, with an estimated 62.9% survival at 36 months. Of 49 MRD-evaluable patients, 26 had MRD-negativity sustained for ≥12 months, of which 20 had sustained MRD-negative complete response (CR) or better. Median PFS was not reached in subgroups with ≥CR and/or sustained MRD negativity. Eighteen patients were MRD-negative with ≥CR at 24-months post infusion. No new neurotoxicity events were reported since the 27.7-month median follow-up. Six new cases of second primary malignancy were reported, including 2 cases of basal cell carcinoma and 1 case each of myelodysplastic syndrome, B-cell lymphoma, melanoma, and prostate cancer. Five additional deaths occurred (progressive disease [PD], n=3; pneumonia and sepsis, n=1 each [both unrelated to cilta-cel]), for a total of 35 deaths (PD, n=17; unrelated to cilta-cel, n=12; related, n=6). **Conclusions:** Longer median PFS was observed after a single infusion of cilta-cel than any previously reported therapy in heavily pretreated patients with RRMM. Achieving CR and/or sustained MRD-negativity was associated with prolonged PFS. Patients continue to be followed for safety and survival in the 15-year CARTINUE long-term study (NCT05201781; MMY4002). Data previously presented at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting.

P-276

Healthcare resource utilization and costs among patients with relapsed/refractory multiple myeloma treated with chimeric antigen receptor-T (CAR-T) cell therapy

Sundar Jagannath[1], Akshay Kharat[2], Alex Fu[3,4], Stephen Huo[2], Monal Kohli[5], Shayna Adams[5], Emeka Umeh[5], Miran Foster[5]

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P-275

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P-276

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P-275

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P-276

Healthcare resource utilization and costs among patients with relapsed/refractory multiple myeloma treated with chimeric antigen receptor-T (CAR-T) cell therapy

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Introduction: Chimeric antigen receptor-T (CAR-T) therapies have advanced treatment of multiple myeloma (MM); however, healthcare resource utilization (HCRU) and costs are not well characterized for patients with relapsed/refractory MM (RRMM) who receive commercial CAR-T therapy. The study aim was to describe real-world HCRU and costs in patients with RRMM who received commercial CAR-T treatment. **Methods:** This longitudinal, retrospective, observational study identified patients with RRMM treated with commercial CAR-T using the US national all-payer claims database that covers approximately 80% of the nationally insured population. Adults were eligible if they had ≥1 inpatient or outpatient claim with MM diagnosis and ≥1 claim for commercial CAR-T (idecabtagene vicleucel or ciltacabtagene autoleucel) from March 1, 2021, to September 30, 2022, with ≥12 months continuous enrollment before CAR-T infusion and if they were not enrolled in a clinical trial during the study period. All-cause HCRU and costs (in 2022 US $) were evaluated starting from the day of CAR-T infusion up to day 30 and from day 31 to 100 and day 101 to 180 post-infusion. **Results:** Of the 196 patients who received commercial CAR-T therapy, the mean age was 64.2 years, 58.2% were male, 130 (66.3%) received bridging therapy before CAR-T infusion, and 179 (91.3%) received inpatient CAR-T infusion. Including the day of CAR-T infusion up to 30-day follow-up (n=153), mean (standard deviation [SD]) total all-cause cost per patient per month (PPPM) was $586,801 ($250,128) inclusive of CAR-T drug costs and infusion encounter costs (mean [SD], $522,920 [$201,557]). Mean (SD) total cost PPPM from day 31 to 100 (n=94) and day 101 to 180 (n=50) post-infusion was $11,780 ($13,738) and $6,701 ($17,559), respectively. Including CAR-T infusion day to 30-day follow-up, mean (SD) number of inpatient admissions was 1.8 (2.3) PPPM with a mean (SD) length of stay (LOS) of 14.6 (8.1) days PPPM; 5.2% had ≥1 emergency room (ER) visit; and mean (SD) number of outpatient visits PPPM was 9.1 (5.8). From 31 to 100 days post-infusion, mean (SD) number of outpatient visits PPPM was 2.7 (2.5); 8.5% had ≥1 ER visit; and mean (SD) inpatient admissions PPPM was 0.4 (1.1) with a mean (SD) LOS of 1.1 (3.5) days PPPM. From 101 to 180 days post-infusion, mean (SD) number of outpatient visits PPPM was 1.7 (2.8); 2.0% had ≥1 ER visit; and mean (SD) number of inpatient admissions PPPM was 0.1 (0.5) with a mean (SD) LOS of 0.4 (1.1) days PPPM. **Conclusions:** Patients with RRMM who received CAR-T incurred ~$632,000 in all-cause healthcare costs through 180 days post-infusion, inclusive of CAR-T drug costs. HCRU and costs tapered beyond 30 days to 180 days post-infusion.

P-277

Venetoclax versus bortezomib, in combination with daratumumab and dexamethasone, in patients with t(11;14)-positive relapsed or refractory multiple myeloma

Jonathan Kaufman[1], Hang Quach[2], Rachid Baz[3], Annette Juul Vangsted[4], Shir-Jing Ho[5], Niels Abildgaard[6], Jacob Laubach[7], Vincent Ribrag[8], Simon Gibbs[9], Eva Medvedova[10], Peter Voorhees[11], Muhammad Jalaluddin[12], Jiewei Zeng[12], Jeremy Ross[12], Xifeng Wang[12], Leanne Lash Fleming[12], Orlando Bueno[12], Yan Luo[12], Nizar Bahlis[13]

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Introduction: Venetoclax (Ven) plus daratumumab and dexamethasone (VenDd) has demonstrated preliminary antitumor activity in patients (pts) with t(11;14)+ relapsed/refractory multiple myeloma (RRMM; Phase 1/2). Here, we report updated safety and efficacy from this Phase1/2 trial of VenDd at 400 and 800 mg Ven dose levels, versus bortezomib plus Dd (DVd) in pts with t(11;14)+ RRMM. **Methods:** Parts 1 (nonrandomized) and 3 (randomized among 400 mg VenDd, 800 mg VenDd and DVd arms) in this Phase 1/2 multicenter study evaluated VenDd versus DVd in pts with t(11;14)+ RRMM, who had ≥1 prior line of therapy (LOT), including proteasome inhibitor and immunomodulatory drug exposure (NCT03314181). Pts in the investigational arm (VenDd, 28 day [D] cycles [C]) received oral Ven once daily (400 mg or 800 mg) with daratumumab (either 16 mg/kg IV or 1800 mg subcutaneous [C1–2: D1, {D2 if split dosing in C1 for IV daratumumab}, 8, 15, 22; C3–6: D1 and 15; C7+: D1]) and dexamethasone (40 mg weekly; oral/IV); pts in the DVd arm were dosed per label recommendations. Overall response rate (ORR) was defined as ≥partial response per IMWG criteria. Minimal residual disease negativity (MRD–) was assessed in bone marrow using next-generation sequencing. This trial was designed to compare safety and preliminary efficacy of VenDd (at 400 or 800 mg Ven doses) with DVd (control). **Results:** Part 1 enrolled 5 pts (400 mg VenDd) and 19 pts (800 mg VenDd). Part 3 enrolled 21, 10, and 26 pts in the 400 mg VenDd, 800 mg VenDd and DVd arms. As of Mar 10, 2023, 80 total pts were enrolled (Parts 1 and 3 combined); 55 pts received VenDd (11% del17p, 13% 1q21abn; 53% 1 prior LOT, 2% prior anti-CD38 mAb); and 24 received DVd (21% del17p; 38% 1 prior LOT, 4% anti-CD38 mAb). Median (range) follow-up and treatment exposure (months) were longer with VenDd than Dvd (28.2 [1.0–

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P-277

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55.7] and 23.3 [1.2–56.3] with VenDd vs 16.9 [0.0–34.1] and 9.6 [0.5–33.9] with DVd). The most common AEs (>30%) with DVd were diarrhea, insomnia, and fatigue, and with VenDd were those plus nausea, upper respiratory tract infection, and COVID-19. SAE rates were 51% (VenDd) and 25% (DVd). Discontinuation due to AEs occurred with 6% of pts with VenDd (none with DVd). VenDd achieved 96% ORR, 93% ≥VGPR, 67% ≥CR, 35% MRD– at 10^{-5} and median PFS not reached (95% CI: 35.0–NE). DVd achieved: 65% ORR, 39% ≥VGPR, 19% ≥CR, 8% MRD– at 10^{-5}, and median PFS 15.5 months (7.5–NE). The 33-month PFS rate was 73.4% (95% CI: 56.4–84.6) vs 38.8% (16.3–61.1) for VenDd vs DVd. Of 8 VenDd-treated pts assessed for duration of MRD–, 6 had MRD– >6 months, of whom 2 had MRD– >12 months. No DVd-treated pts had durable MRD– >6 months. **Conclusions:** VenDd produced deep and durable responses, improved outcomes compared with DVd, and had a manageable safety profile in pts with t(11;14)+ RRMM. Data supporting Venetoclax dose selection will be presented.

P-278

Estimating the size of patients with relapsed/refractory multiple myeloma treated with 1-3 and 4 or more prior lines of therapy in the United States

Doris Hansen[1], Akshay Kharat[2], Ravi Potluri[3], Sanjog Patidar[3], Stephen Huo[2], Jack Khouri[4]

[1]Moffiitt Cancer Center; [2]Janssen Pharmaceuticals; [3]Putnam Associates; [4]Taussig Cancer Institute, Cleveland Clinic

Introduction: Approximately 35,000 new cases of multiple myeloma (MM) are diagnosed in the United States every year. Multiple therapies are available for the treatment of MM across the proteasome inhibitor (PI), immunomodulatory drug (IMiD), and anti-CD38 antibody classes. However, evidence suggests that the number of patients eligible for treatment declines after exposure to these classes. The objective of this study was to build an MM disease progression model to estimate the size of the MM patient population with a historically high risk of progression stratified by (1) 1-3 prior lines of therapy (LOT) and (2) ≥4 prior LOT in the United States. **Methods:** A disease model was developed starting with the annual incidence of MM and applying different treatment pathways to generate patient buckets based on treatments received in prior LOT. Patients were classified as having 1-3 prior LOT if they received 1-3 prior LOT and were PI- and IMiD-exposed and refractory to lenalidomide in at least 1 prior line. Patients were classified as having ≥4 prior LOT if they received ≥4 prior LOT including a PI, IMiD, and anti-CD38 monoclonal antibody (ie, triple-class exposed). Claims databases representative of the US MM population and public sources including the SEER*Stat epidemiologic database were used to obtain inputs for the model. Overall, the model estimated the number of patients in the US with 1-3 and ≥4 prior LOT by calendar year and stratified by race/ethnicity and payer-type subgroups. **Results:** An estimated 25,096 patients would have had 1-3 prior LOT, and 15,772 would have had ≥4 prior LOT in 2024. In 2026, the population size is an estimated 22,848 patients with 1-3 prior LOT and 9,643 with ≥4 prior LOT. By race/ethnicity subgroups, the estimated population in 1-3 and ≥4 prior LOT combined would include 30,217 White (74%), 8,857 Black (22%), 956 Hispanic (2%), and 838 Asian (2%) patients in 2024 and 24,023 White (74%), 7,041 Black (22%), 760 Hispanic (2%), and 666 Asian (2%) patients in 2026. The estimated population in 1-3 and ≥4 prior LOT combined by payer type would be 28,016 Medicare (69%) and 12,852 commercial (31%) patients in 2024 and would include 22,702 Medicare (70%) and 9,789 commercial (30%) patients in 2026. **Conclusions:** The data from this MM disease progression model indicate that fewer patients are anticipated to move into the 1-3 prior LOT, PI-exposed, and lenalidomide-refractory relapsed/refractory MM (RRMM) and ≥4 prior LOT triple-class exposed RRMM settings in 2026 versus 2024.

P-279

Efficacy and safety of carfilzomib, lenalidomide, and dexamethasone versus ixazomib, lenalidomide, and dexamethasone in real world patients with relapsed/refractory multiple myeloma: KMM2004 study

Do Young Kim[1], Ho-Jin Shin[1], Chang-Ki Min[2], Hyeon-Seok Eom[3], Jongheon Jung[4], Kihyun Kim[5], Jae Hoon Lee[6], Kwai Han Yoo[6], Ji Yun Lee[7], Ja Min Byun[8], Sung-Hyun Kim[9], Ji Hyun Lee[10], Hee Jeong Cho[11], Sang Min Lee[12], Young Rok Do[13], Sungwoo Park[14], Junglim Lee[15], Seung-Shin Lee[16], Hye Jin Kang[17], Young Hoon Park[18], Sung-Nam Lim[19]

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P-278

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Introduction: Approximately 35,000 new cases of multiple myeloma (MM) are diagnosed in the United States every year. Multiple therapies are available for the treatment of MM across the proteasome inhibitor (PI), immunomodulatory drug (IMiD), and anti-CD38 antibody classes. However, evidence suggests that the number of patients eligible for treatment declines after exposure to these classes. The objective of this study was to build an MM disease progression model to estimate the size of the MM patient population with a historically high risk of progression stratified by (1) 1-3 prior lines of therapy (LOT) and (2) ≥4 prior LOT in the United States. **Methods:** A disease model was developed starting with the annual incidence of MM and applying different treatment pathways to generate patient buckets based on treatments received in prior LOT. Patients were classified as having 1-3 prior LOT if they received 1-3 prior LOT and were PI- and IMiD-exposed and refractory to lenalidomide in at least 1 prior line. Patients were classified as having ≥4 prior LOT if they received ≥4 prior LOT including a PI, IMiD, and anti-CD38 monoclonal antibody (ie, triple-class exposed). Claims databases representative of the US MM population and public sources including the SEER*Stat epidemiologic database were used to obtain inputs for the model. Overall, the model estimated the number of patients in the US with 1-3 and ≥4 prior LOT by calendar year and stratified by race/ethnicity and payer-type subgroups. **Results:** An estimated 25,096 patients would have had 1-3 prior LOT, and 15,772 would have had ≥4 prior LOT in 2024. In 2026, the population size is an estimated 22,848 patients with 1-3 prior LOT and 9,643 with ≥4 prior LOT. By race/ethnicity subgroups, the estimated population in 1-3 and ≥4 prior LOT combined would include 30,217 White (74%), 8,857 Black (22%), 956 Hispanic (2%), and 838 Asian (2%) patients in 2024 and 24,023 White (74%), 7,041 Black (22%), 760 Hispanic (2%), and 666 Asian (2%) patients in 2026. The estimated population in 1-3 and ≥4 prior LOT combined by payer type would be 28,016 Medicare (69%) and 12,852 commercial (31%) patients in 2024 and would include 22,702 Medicare (70%) and 9,789 commercial (30%) patients in 2026. **Conclusions:** The data from this MM disease progression model indicate that fewer patients are anticipated to move into the 1-3 prior LOT, PI-exposed, and lenalidomide-refractory relapsed/refractory MM (RRMM) and ≥4 prior LOT triple-class exposed RRMM settings in 2026 versus 2024.

P-279

Efficacy and safety of carfilzomib, lenalidomide, and dexamethasone versus ixazomib, lenalidomide, and dexamethasone in real world patients with relapsed/refractory multiple myeloma: KMM2004 study

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Medicine, Ewha Womans University, Seoul, South Korea; [19]Inje University College of Medicine, Haeundae Paik Hospital

Introduction: The recent influx of novel agents with different mechanisms of action has led to rapid changes in treatment strategies and outcomes of multiple myeloma. However, in South Korea, where national health insurance service strongly influences drug selection, the lenalidomide based triplet remains the most effective treatment option for RRMM. The approval of KRd in 2018, followed by IRd in 2020, has raised questions about the most effective treatment strategies for patients with RRMM. **Methods:** We retrospectively reviewed the medical records of 182 RRMM patients treated with KRd (112) or IRd (70) at 17 centers in South Korea from May 2020 to April 2021. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were overall survival (OS), overall response rate (ORR), and safety. **Results:** Median age (65 vs 66 yrs; p=0.38) and R-ISS at diagnosis (I: 13.3 vs 21.7%, II: 54.3 vs 48.3% and III: 32.4 vs 30.0%, p=0.38) were not significantly different between the two groups. The trial feasibility to participate in the clinical trial was similar in both groups (83.0 vs 87.1%, p=0.46). Prior treatment history and response to prior therapy were also similar in both groups. Approximately 92% of patients were treated as a second line and the number of patients who had received ASCT was the same at 49% in both groups. Patients with high risk cytogenetics were more likely to be treated with KRd (43.8 vs 18.0%, p=0.003) and the time from diagnosis to XRd treatment was longer in the IRd gorup (20.5 vs 33.7 mo, p=0.08). Patients in the KRd group received 13 cycles of treatment and patients in the IRd group received 15 cycles of treatment (median, p=0.1), with more dose modifications in the IRd group (30.1 vs 41.1%, p=0.023). ORR was not significantly different at 89.1 vs 87.0% (p=0.67), but CRR was better in the KRd group (45.5 vs 30.4%, p=0.046). Median PFS (19.1 vs 28.4 mo, p=0.08) showed a trend towards better outcomes in the IRd group, although not statistically significant, and median OS (31.6 vs not reached, p=0.02) was statistically significantly better in the IRd group. In subgroup analysis, patients with older than 65 years (HR 0.41, p=0.006), normal renal function (HR 0.52, p=0.045), ISS I or II (HR 0.5, p=0.03), extramedullary plasmacytoma (HR 0.35, p=0.02), and PR acheieved (HR 0.59, p=0.04) showed better PFS outcomes with IRd. In the safety analysis, hematologic toxicity, infection, and cardiac events were more frequent in the KRd group, and GI toxicity and skin rash were relatively more frequent in the IRd group. **Conclusions:** Our data showed the treatment outcomes of KRd and IRd in the real-world. Contrary to predictions based on clinical trials, the IRd group showed better survival data. Clinicians tended to choose KRd in the high risk group and it actually showed a deeper response. In contrast, the IRd group did not acheieve a deeper response, but the treatment response was found to be sustainted for a longer period of time.

P-280

A single-center treatment sequencing analysis in patients with relapsed/refractory multiple myeloma (RRMM)

Swarup Kumar[1], Jackson Clark[1], Alvaro Alvarez-Soto[1], Samantha El Warrak[1], Shruthi Kumar[1], Julie Braish[1], Aswanth Reddy[2]

[1]University of Connecticut, UCONN Health; [2]Mercy Health

Introduction: Despite novel therapeutics, multiple myeloma remains incurable with multiple relapses throughout the disease course. In relapsed/refractory multiple myeloma (RRMM), there are several medication classes approved in varying combinations, including anti-CD38 monoclonal antibodies, immunomodulatory drugs (IMiDs), and proteasome inhibitors (PIs), alkylating agents (ALK) amongst others. Despite these advances, there remains a lack of evidence for optimal treatment sequencing in RRMM. **Methods:** This is a single center, IRB approved retrospective study of patients with RRMM evaluated at our facility who received at least one treatment regimen for RRMM between the years 2016 and 2023. Data on patient characteristics, treatment regimens and responses were abstracted from the medical record. Responses were recorded by IMWG treatment response criteria as complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD) and Progressive Disease (PD). Suspected complete response (stCR) was also recorded when bone marrow information was not available. Statistical analyses were conducted using R v4.3 software for computing. **Results:** 48 patients met inclusion criteria and were included in the analysis, 12 of whom had high risk cytogenetics, with 4 ultra-high risk (>1 high risk factor). 20 patients were International Staging System (ISS) stage I, 34 were stage II, and 4 were stage III. Any treatment line that was administered for relapsed disease post induction, autologous SCT consolidation and/or maintenance therapy or primary refractory disease were included. The top four combinations in addition to dexamethasone administered were anti-CD38 drugs combined with IMiD (CD38/IMiD; n=17), anti-CD38 drugs and PIs (CD38/PI; n=16), IMiDs and PIs (IMiD/PI; n=18), and PIs with alkylating agents (PI/ALK; n=19). Overall response rate (ORR; PR or better) was 64.7% (CD38/IMiD), 56.25% (CD38/PI), 65% (IMiD/PI), and 45% (PI/ALK); (p=0.451,chi -square). CR/stCR rates were: 23.5% (CD38/IMiD), 6.25% (CD38/PI), 25% (IMiD/PI), and 5% (PI/ALK); (p=0.144, chi-square). Median Time to next treatment (TNTT) was 43 weeks (CD38/IMiD), 25.5 weeks (CD38/PI), 67 weeks (IMiD/PI), and 45.5 weeks (PI/ALK); p = 0.198, Kruskal-Wallis). When comparing any doublet to triplet regimens, there was no statistical difference in either ORR, 57.69% vs. 52.8%, (p=0.593, chi-square) or CR/stCR rates, 11.53% vs. 13.48%, respectively (p=0.122,chi-square). **Conclusions:** Whilst no significant differences were observed between specific treatment combinations in our RRMM population, there were notable trends toward improved response rates and TNTT in CD38/IMiD and IMiD/PI groups when compared to CD38/PI group. Further, no statistically significant response rate in doublet vs. triplet regimens was observed, raising the question of selecting truly synergistic drug combinations as well as optimal number of drugs in a treatment

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P-280

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regimen for improved efficacy and decreased treatment related toxicity.

P-281

Comparison of daratumumab-based regimens as second-line therapy in relapsed/refractory MM

Charalampos Charalampous[1], Utkarsh Goel[1], Prashant Kapoor[1], Moritz Binder[1], Francis Buadi[1], Joselle Cook[1], David Dingli[1], Angela Dispenzieri[1], Amie Fonder[1], Morie Gertz[1], Wilson Gonsalves[1], Suzanne Hayman[1], Miriam Hobbs[1], Yi Hwa[1], Taxiarchis Kourelis[1], Martha Lacy[1], Nelson Leung[1], Yi Lin[1], Rahma Warsame[1], Robert Kyle[1], Vincent Rajkumar[1], Shaji Kumar[1]

[1]Mayo Clinic

Introduction: The introduction of anti-CD38 antibodies (daratumumab) in the treatment landscape of multiple myeloma (MM) has increased the outcomes of patients with relapsed disease in recent years. However, the ideal combination of these drugs (Dara-IMiD vs. Dara-PI) in patients with relapsed MM is unclear. **Methods:** We reviewed MM patients treated with daratumumab as second-line therapy at our institution from January 1st, 2016, to June 31st, 2022, to assess the outcomes with the different combination therapies. We used the Kaplan-Meier method to estimate PFS from the first relapse. **Results:** We identified 404 patients with a median age of 63.6 years (range: 27.1 – 90.4). Most patients received triplet induction therapy (94%) and upfront transplant (69%) as primary therapy. At the time of Dara initiation, 40% were refractory to IMiDs, 23% to PIs, 19% to both, and 19% to neither drug. Patients treated with Dara-IMiD had significantly better PFS than Dara-PI (28.7 months vs. 13.5 months, p< 0.01, respectively). When stratifying patients based on FISH classification, we found that both high-risk patients (25.3 vs. 8.1 months, p=0.01, respectively) and standard-risk patients (45.5 vs. 17 months, p< 0.01, respectively) benefited significantly from the Dara-IMiD regimen. Among patients treated with Dara-IMiD, those already refractory to IMiDs from the first line had significantly shorter PFS than those without IMiD resistance (14.6 vs. 43.3 months, p< 0.01, respectively). In addition, the lenalidomide-based combination resulted in significantly better PFS compared to pomalidomide in our cohort (39.4 vs. 22.4 months, p< 0.01, respectively). However, no difference was found in the IMiD refractory population (14.2 vs. 17.8 months, respectively). Finally, no significant differences were seen between Dara-IMiD and Dara-PI in patients only refractory to IMiD (16.2 vs. 12.8 months, p=NS, respectively). **Conclusions:** While further studies are required to adjudicate the best combination, we conclude that Dara-IMiD might be more effective in patients with relapsed MM, especially for patients not refractory to IMiDs at first relapse.

P-282

Ranking importance of prognostic factors for relapsed/refractory multiple myeloma (RRMM): international physician panel consensus following a systematic review of the literature

Shaji Kumar[1], Xavier Leleu[2], Katja Weisel[3], Rakesh Popat[4], Beatrice Suero[5], Samantha Craigie[5], Paul Spin[5], Christian Hampp[6], Wenzhen Ge[6], Qiufei Ma[6], Sundar Jagannath[7]

[1]Mayo Clinic, Rochester, MN, US; [2]Hospital La Mileterie, Poitiers, France; [3]University Medical Center of Hamburg-Eppendorf, Hamburg, Germany; [4]NIHR UCLH Clinical Research Facility; [5]EVERSANA; [6]Regeneron; [7]Mount Sinai Medical Center, New York, NY, USA

Introduction: Multiple myeloma (MM) is a highly heterogenous and incurable malignancy. Nearly all patients eventually relapse and/or become refractory to treatment. Patients with relapsed and/or refractory MM (RRMM) typically have poor outcomes, and prognosis worsens with exposure and/or refractoriness to multiple therapies. There is a high unmet need among RRMM patients and there is no single standard of care. Real-world data (RWD) can be used to understand outcomes with currently available therapies and to establish benchmarks for clinical trials. When comparing outcomes in single-arm trials to RWD, it is best practice to pre-specify confounders for adjustment. A systematic, evidence-based, and clinically validated method to identify and rank prognostic factors for pre-specification in comparative RRMM studies is currently lacking. The objective of this study was to identify and rank prognostic factors relevant to treatment outcomes in RRMM based on physician panel consensus. **Methods:** A systematic literature review (SLR; Kumar 2023, PROSPERO CRD42022330369) identified prognostic factors in RRMM that were significantly associated (p< 0.05) with outcomes. Factors associated with objective response rate (ORR) and/or overall survival (OS) and were reported in at least two studies were validated by a clinical expert and included in the ranking process. A panel of five international (United States, France, Germany, UK) MM clinical experts was assembled to confirm the variables identified in the SLR and to rank the prognostic factors. The panel was asked to organize the factors into five groups, with each group representing the level of importance of in terms of predicting outcomes in RRMM. Initial rankings were performed independently. Pooled rankings were calculated by averaging across the experts' rankings on a scale of 1 (least important) – 5 (most important). The pooled rankings and rank differences were presented to the panel for discussion. There were two rounds of panel voting. If 50% of the panel disagreed with the pooled rankings, another round of individual ranking was conducted. The final rankings were determined via consensus based on all (100%) panelists agreeing or strongly agreeing with the pooled rankings. **Results:** The SLR identified 29 factors associated with OS and/or ORR that were reported in at least two studies. Six factors were excluded for redundancy and two were added based on clinical expert opinion. A total of 25 factors were included in the ranking process. The six most important prognostic factors in RRMM were cytogenetic risk, age, refractory status, disease stage,

regimen for improved efficacy and decreased treatment related toxicity.

P-281

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Introduction: The introduction of anti-CD38 antibodies (daratumumab) in the treatment landscape of multiple myeloma (MM) has increased the outcomes of patients with relapsed disease in recent years. However, the ideal combination of these drugs (Dara-IMiD vs. Dara-PI) in patients with relapsed MM is unclear. **Methods:** We reviewed MM patients treated with daratumumab as second-line therapy at our institution from January 1st, 2016, to June 31st, 2022, to assess the outcomes with the different combination therapies. We used the Kaplan-Meier method to estimate PFS from the first relapse. **Results:** We identified 404 patients with a median age of 63.6 years (range: 27.1 – 90.4). Most patients received triplet induction therapy (94%) and upfront transplant (69%) as primary therapy. At the time of Dara initiation, 40% were refractory to IMiDs, 23% to PIs, 19% to both, and 19% to neither drug. Patients treated with Dara-IMiD had significantly better PFS than Dara-PI (28.7 months vs. 13.5 months, p< 0.01, respectively). When stratifying patients based on FISH classification, we found that both high-risk patients (25.3 vs. 8.1 months, p=0.01, respectively) and standard-risk patients (45.5 vs. 17 months, p< 0.01, respectively) benefited significantly from the Dara-IMiD regimen. Among patients treated with Dara-IMiD, those already refractory to IMiDs from the first line had significantly shorter PFS than those without IMiD resistance (14.6 vs. 43.3 months, p< 0.01, respectively). In addition, the lenalidomide-based combination resulted in significantly better PFS compared to pomalidomide in our cohort (39.4 vs. 22.4 months, p< 0.01, respectively). However, no difference was found in the IMiD refractory population (14.2 vs. 17.8 months, respectively). Finally, no significant differences were seen between Dara-IMiD and Dara-PI in patients only refractory to IMiD (16.2 vs. 12.8 months, p=NS, respectively). **Conclusions:** While further studies are required to adjudicate the best combination, we conclude that Dara-IMiD might be more effective in patients with relapsed MM, especially for patients not refractory to IMiDs at first relapse.

P-282

Ranking importance of prognostic factors for relapsed/refractory multiple myeloma (RRMM): international physician panel consensus following a systematic review of the literature

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Introduction: Multiple myeloma (MM) is a highly heterogenous and incurable malignancy. Nearly all patients eventually relapse and/or become refractory to treatment. Patients with relapsed and/or refractory MM (RRMM) typically have poor outcomes, and prognosis worsens with exposure and/or refractoriness to multiple therapies. There is a high unmet need among RRMM patients and there is no single standard of care. Real-world data (RWD) can be used to understand outcomes with currently available therapies and to establish benchmarks for clinical trials. When comparing outcomes in single-arm trials to RWD, it is best practice to pre-specify confounders for adjustment. A systematic, evidence-based, and clinically validated method to identify and rank prognostic factors for pre-specification in comparative RRMM studies is currently lacking. The objective of this study was to identify and rank prognostic factors relevant to treatment outcomes in RRMM based on physician panel consensus. **Methods:** A systematic literature review (SLR; Kumar 2023, PROSPERO CRD42022330369) identified prognostic factors in RRMM that were significantly associated (p< 0.05) with outcomes. Factors associated with objective response rate (ORR) and/or overall survival (OS) and were reported in at least two studies were validated by a clinical expert and included in the ranking process. A panel of five international (United States, France, Germany, UK) MM clinical experts was assembled to confirm the variables identified in the SLR and to rank the prognostic factors. The panel was asked to organize the factors into five groups, with each group representing the level of importance of in terms of predicting outcomes in RRMM. Initial rankings were performed independently. Pooled rankings were calculated by averaging across the experts' rankings on a scale of 1 (least important) – 5 (most important). The pooled rankings and rank differences were presented to the panel for discussion. There were two rounds of panel voting. If 50% of the panel disagreed with the pooled rankings, another round of individual ranking was conducted. The final rankings were determined via consensus based on all (100%) panelists agreeing or strongly agreeing with the pooled rankings. **Results:** The SLR identified 29 factors associated with OS and/or ORR that were reported in at least two studies. Six factors were excluded for redundancy and two were added based on clinical expert opinion. A total of 25 factors were included in the ranking process. The six most important prognostic factors in RRMM were cytogenetic risk, age, refractory status, disease stage,

performance status, and extramedullary disease/plasmacytoma. All panelists agreed with the final rankings. **Conclusions:** This is the first prognostic factor ranking study in RRMM based on international physician panel consensus. Results from this prognostic factor ranking can inform the selection of variables in pre-specified comparative analyses especially between clinical trials and RWD.

P-283

Systematic literature review of prognostic factors for relapsed/refractory multiple myeloma

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Introduction: Patients with relapsed and/or refractory multiple myeloma (RRMM) have a poor prognosis that is further reduced when exposed to multiple therapies. Although several studies have identified factors prognostic of outcomes in patients with RRMM, an up-to-date synthesis is lacking. A systematic and evidence-based approach to identify relevant prognostic factors to support RRMM research is needed in a rapidly changing treatment landscape. Our objective was to conduct a systematic literature review (SLR) of prognostic factors associated with response (objective, complete, and partial response rates, duration of response) and survival (overall and progression-free survival) outcomes in patients with RRMM. **Methods:** Ovid MEDLINE and Embase were searched for clinical trials and observational studies published between January 1, 2016 and April 14, 2022. Eligible studies included RRMM patients and an assessment of prognostic significance of any factor on an outcome of interest via multivariate analysis. Two independent reviewers assessed eligibility, with discrepancies resolved by consensus or a third independent reviewer. Data were extracted using standardized templates. Factors statistically significantly associated with an outcome of interest ($p < 0.05$, or confidence interval excluding the null value) were extracted. Study quality was assessed using the Quality in Prognosis Studies (QUIPS) tool. Data were summarized descriptively. **Results:** Of 5,349 records identified, 130 records reporting on 125 unique studies (23 clinical trials and 102 observational studies) were included. The most common limitations in study quality were related to sample representativeness and control of confounders. Ninety-seven factors were significantly associated with at least one outcome in at least one study. The most commonly identified factors were disease stage (n = 27 studies), age (n = 20), prior lines of therapy (n = 20), best response to index therapy (n = 20), cytogenetic risk (n = 19), lactate dehydrogenase (LDH; n = 12), extramedullary disease/plasmacytoma (EMP) (n = 12), and performance status (PS) (n = 10). Worse survival was associated with higher disease stage, older age, more prior lines of therapy, poorer response, high-risk cytogenetics, elevated LDH levels, EMP presence, and worse PS. Worse response was associated with higher disease stage, younger age, more prior lines of therapy, high-risk cytogenetics, and worse PS. Associations between factors and outcomes were largely consistent across studies, although conflicting associations were noted in < 10% of studies; in some studies, poor reporting limited the ability to ascertain the direction of associations. **Conclusions:** To our best knowledge, this is the first SLR to investigate prognostic factors for an RRMM population. This work provides a comprehensive evidence base for factors prognostic of response and survival outcomes in patients with RRMM.

P-284

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P-283

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P-284

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P-283

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P-284

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Introduction: Carfilzomib, the second generation proteasome inhibitor (PI), in combination with lenalidomide land dexamethasone (KRd) significantly improved the survival of relapsed and/or refractory multiple myeloma (RRMM) patients. However, the real-world outcome of KRd in a large cohort of Asian MM patient is still lacking. The aim of this study was to analyze the effectiveness and toxicity profile of KRd regimen especially focused on clinical trial eligibility and high-risk clinical factors in Korean RRMM patients outside of the clinical trial. **Methods:** Retrospective data of 364 RRMM patients who have received KRd regimen between February, 2018 and October, 2020, was collected from 21 centers participating in the Korean multiple myeloma working party (KMMWP). Clinical trial ineligibility was defined by patient- and treatment-related features that were insufficient to meet the eligibility criteria for ASPIRE trial. **Results:** The median age was 63 years (range, 28-85). Forty-nine percent of patients were trial-ineligible. Among the 355 patients whose response were evaluable, overall response rate was 90%, including a very good partial response, a complete response (CR) and a stringent CR of 25%, 32% and 6%. Among the 62 patients who were evaluated for minimal residual disease (MRD) by EuroFlow standard operation procedure, 36% (22 of 62) were Flow MRD-negative. With a median follow-up duration of 34.8 months (range, 0.00-61.5), the median progression-free survival (PFS) and overall survival (OS) were26.4 months (95% confidence interval, CI, 23.1-29.7 months), and not reached. Trial-ineligibility affected to a significant decrease of PFS and OS after KRd treatment. High-risk disease-related factors, high-risk cytogenetics at diagnosis of MM, EMD, doubling of M protein, and symptomatic MM at the time of KRd treatment affected poorly on PFS by univariate and multivariate analysis. Additionally, EMD, doubling of M protein, and symptomatic MM at the time of KRd treatment affected poorly on OS by univariate and multivariate analysis. Hematologic toxicities were more commonly observed than non-hematologic adverse events (AEs). The most common grade 3 or higher toxicities were neutropenia, followed by infections, fatigue, and acute kidney injuries. Grade 3 or higher cardiovascular AEs were observed in less than 5 percent of the patients. **Conclusions:** KRd treatment for real-world Korean RRMM patients was highly effective with a tolerable AE profile. Trial-ineligible characteristics and high-risk disease-related features affected poorly to progression-free and overall survival of RRMM patients treated with KRd regimen, which necessitates more effective and tolerable new agents and combination therapies for those patients. This work was supported by Amgen (Grant number: ISS20217193).

P-285

Real-world clinical outcomes and treatment patterns among patients with triple-class exposed multiple myeloma: an analysis using the Connect® multiple myeloma disease registry

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Introduction: Despite clinical advances in multiple myeloma (MM), most patients are refractory to treatment or relapse and eventually become refractory. Patients who have been exposed to the 3 main drug classes used to treat MM (immunomodulatory imide drug [IMiD] agents, proteasome inhibitors [PI] and anti-CD38 monoclonal antibodies [mAbs]) – i.e. triple-class exposed (TCE) – have generally poor clinical outcomes. As novel agents become available, it is important to understand their potential benefit to patients with TCE MM. This study described the treatment patterns and clinical outcomes in patients with TCE MM in real-world clinical practice in the United States. **Methods:** We analyzed prospectively collected data from the Connect® MM Disease Registry (NCT01081028). The current study was conducted in multiple myeloma patients enrolled in the Connect MM® registry who became TCE from Nov 16, 2015 to Dec 31, 2020 and who had received an index treatment post-TCE status. The earliest available end date of the third treatment class was considered as the date patients became TCE. If patients received a subsequent line of treatment post-TCE date, that first treatment was defined as the index treatment and treatment initiation date was defined as the index date. Data analyzed included demographics, disease characteristics, prior treatment and class exposure/refractoriness, index treatments and classes, response rates (overall, complete, very good partial, and partial), progression-free survival (PFS), overall survival (OS), and time to progression (TTP). **Results:** The Connect MM Disease Registry includes 317 patients with TCE MM, of whom 215 had received an index treatment post-TCE. Median follow-up from the index date was 11.1 months. Median age of index-treated patients was 68 years, 61% were male, 86% were White, 81% were from a community practice setting. Patients received 3 median lines of treatment (range, 1–9) before index treatment; 83% were IMiD agent refractory, 81% were anti-CD38 mAb refractory, 68% were double-class refractory (IMiD agent and PI), 56% were triple-class refractory, and 9% were penta-refractory. Index treatments were varied (101 monotherapy or combination regimens in total) and carfilzomib/dexamethasone (DEX) (7.4%) and daratumumab/pomalidomide/DEX (7.0%) were the most commonly used treatments. Overall response and complete response rates among patients with TCE MM were 31.6% and 5.1%, respectively; median PFS with the index treatment was 4.4 months (95% CI, 3.0–5.6); median OS was 12.5 months (95% CI, 10.2–15.3), and TTP was 6.3 months (95% CI, 4.6–8.6). **Conclusions:** In the real-world prospective Connect MM Disease Registry, patients with TCE MM had poor response and survival outcomes, with TCE occurring at a median of 3 prior lines of therapy. This study highlights the need for more efficacious and accessible novel

Introduction: Carfilzomib, the second generation proteasome inhibitor (PI), in combination with lenalidomide land dexamethasone (KRd) significantly improved the survival of relapsed and/or refractory multiple myeloma (RRMM) patients. However, the real-world outcome of KRd in a large cohort of Asian MM patient is still lacking. The aim of this study was to analyze the effectiveness and toxicity profile of KRd regimen especially focused on clinical trial eligibility and high-risk clinical factors in Korean RRMM patients outside of the clinical trial. **Methods:** Retrospective data of 364 RRMM patients who have received KRd regimen between February, 2018 and October, 2020, was collected from 21 centers participating in the Korean multiple myeloma working party (KMMWP). Clinical trial ineligibility was defined by patient- and treatment-related features that were insufficient to meet the eligibility criteria for ASPIRE trial. **Results:** The median age was 63 years (range, 28-85). Forty-nine percent of patients were trial-ineligible. Among the 355 patients whose response were evaluable, overall response rate was 90%, including a very good partial response, a complete response (CR) and a stringent CR of 25%, 32% and 6%. Among the 62 patients who were evaluated for minimal residual disease (MRD) by EuroFlow standard operation procedure, 36% (22 of 62) were Flow MRD-negative. With a median follow-up duration of 34.8 months (range, 0.00-61.5), the median progression-free survival (PFS) and overall survival (OS) were26.4 months (95% confidence interval, CI, 23.1-29.7 months), and not reached. Trial-ineligibility affected to a significant decrease of PFS and OS after KRd treatment. High-risk disease-related factors, high-risk cytogenetics at diagnosis of MM, EMD, doubling of M protein, and symptomatic MM at the time of KRd treatment affected poorly on PFS by univariate and multivariate analysis. Additionally, EMD, doubling of M protein, and symptomatic MM at the time of KRd treatment affected poorly on OS by univariate and multivariate analysis. Hematologic toxicities were more commonly observed than non-hematologic adverse events (AEs). The most common grade 3 or higher toxicities were neutropenia, followed by infections, fatigue, and acute kidney injuries. Grade 3 or higher cardiovascular AEs were observed in less than 5 percent of the patients. **Conclusions:** KRd treatment for real-world Korean RRMM patients was highly effective with a tolerable AE profile. Trial-ineligible characteristics and high-risk disease-related features affected poorly to progression-free and overall survival of RRMM patients treated with KRd regimen, which necessitates more effective and tolerable new agents and combination therapies for those patients. This work was supported by Amgen (Grant number: ISS20217193).

P-285

Real-world clinical outcomes and treatment patterns among patients with triple-class exposed multiple myeloma: an analysis using the Connect® multiple myeloma disease registry

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P-286

Impact of hypogammaglobulinemia and immunoglobulin replacement therapy on infection rate in patients with RRMM treated with elranatamab: post-hoc analysis from MagnetisMM-3

Xavier Leleu[1], Nizar Bahlis[2], Paula Rodríguez-Otero[3], Hang Quach[4], Cyrille Touzeau[5], Julien Depaus[6], Shinsuke Iida[7], Mathias Hänel[8], Tomasz Wrobel[9], Eric Leip[10], Umberto Conte[10], Sharon Sullivan[10], Andrea Viqueira[11], Alexander Lesokhin[12]

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P-287

Isatuximab plus pomalidomide and dexamethasone in patients with relapsed and/or refractory multiple myeloma in real life context in France: IMAGE subgroup analysis based on subgroups of interest

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≥1 dose of Isa. HR cytogenetics was the detection of at least one of the following: del(17p), t(4;14), and t(14;16). PFS was defined as the time from start of Isa-Pd to date of disease progression, as reported in the medical record, or death. Verbatim terms for adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities, and AEs were not graded for severity. **Results:** The total effectiveness population was 294, while safety population was 299. 83 pts were aged ≥75, 25 pts had renal function < 30 mL/min/1.73m^2, and 40 pts had HR cytogenetics. 120 pts had unknown cytogenetic risk. Majority of pts across all subgroups had International Staging System Stage III disease, and all subgroups had a median 2 prior lines of therapy, except for pts with renal impairment who had a median 3 prior lines of therapy. Similar to the overall effectiveness population, around 70% of pts in all subgroups were refractory to lenalidomide and their last line of therapy. The mPFS was 13.2 (95% CI: 6.8-15.0) mo, 10.0 (95% CI: 2.4-18.6) mo, and 7.6 (95% CI: 2.8-Not reached) mo in pts aged ≥75, with severe renal impairment, and HR cytogenetics, respectively. Overall response and very good partial response rates were 51.8% and 26.5% in elderly pts, 68.0% and 48.0% in pts with severe renal impairment, and 32.5% and 25.0% in pts with HR cytogenetics. In the overall effectiveness population, ORR and VGPR were 46.3% and 27.9%. 28.9% of elderly, 25.0% of HR cytogenetics, and 30.8% of renal impaired pts had at least one AE. 1 elderly pt and 1 pt with HR cytogenetics had an AE leading to permanent discontinuation of Isa. The incidence of neutropenia was 8.3%, 0%, and 7.5% in elderly, renal impaired, and HR cytogenetics pts. Infections and infestations occurred in 3 pts in the overall safety population — 2 in elderly, 1 in renal impaired, and 0 in HR cytogenetics pts. **Conclusions:** The effectiveness and safety profiles across elderly, renal impaired, and HR cytogenetics subgroups were similar to those in the overall effectiveness population. The results of this subgroup analyses continue to support Isa-Pd for treatment of RRMM across subgroups.

P-288

A model to predict the risk of prolonged thrombocytopenia recovery in relapsed/refractory multiple myeloma patients after anti-BCMA CAR-T treatment

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Introduction: Patients with relapsed/refractory multiple myeloma (RRMM) treated with anti-B cell maturation antigen (BCMA) chimeric antigen receptor-T (CAR-T) cell therapy frequently experience the hematologic toxicity of persistent thrombocytopenia. Our aim was to develop a model that distinguishes between patients at high and low risk for prolonged thrombocytopenia, which may be useful for risk-adapted treatment of hematologic toxicity. **Methods:** We retrospectively analyzed data from a phase 1b/2 trial of 103 RRMM patients treated with CT103A, a fully human anti- BCMA CAR -T (NCT05066646). Recovery of thrombocytopenia was defined as a rebound in platelet count (PLT) to 50×10^9/L. Patients were divided into three groups: non-thrombocytopenia (patients whose PLT never decreased to 50×10^9/L post-infusion), non-sustained thrombocytopenia (patients whose PLT recovered to 50×10^9/L within two months post-infusion), and prolonged thrombocytopenia (patients whose PLT never recovered to 50×10^9/L within two months post- infusion). Receiver operating characteristics (ROC) curve was used to determine baseline clinical characteristics associated with the recovery of prolonged thrombocytopenia. Biomarkers with a P value of 0.6, and a concomitant P value of < 0.05 were used for modeling. Multiple thresholds were tested; the final threshold was set as 1 based on the optimal Youden index, and specificity was ≥ 0.75. **Results:** Ultimately, PLT, C reaction protein, plasma cells in bone marrow, hemoglobin, and Ig Ferritin at baseline were determined to be associated with the recovery of thrombocytopenia and were used to establish the model (Table 1). This model allows prediction of recovery from thrombocytopenia based on baseline data. PLT and hemoglobin levels could partially reflect bone marrow reserve, and plasma cells in bone marrow and ferritin indirectly influence tumor burden. High-risk patients with a model score of 5 or higher may require further supportive care after infusion, including

Table 1 Prolonged Thrombocytopenia Recovery Model

Baseline PLT: >161.5/μL (0 Point), 112.5-161.5 /μL (1 Point), <112.5/μL (2 Points)
Baseline CRP: <5.05 mg/L (0 Point), 5.05-23.95 mg/L (1 Point), >23.95 mg/L (2 Points)
Plasma Cell: <5.65% (0 Point), 5.65-51.05% (1 Point), >51.05% (2 Points)
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P-289

The efficacy and safety of prednisone, cyclophosphamide, doxorubicin and carmustine (PCAB) in relapsed/refractory multiple myeloma in the era of novel therapy, including as a bridge to CAR-T therapy

Eric Li[1], Christian Bryant[1], Esther Jones[1], Tracy King[1], Dipti Talaulikar[2], Jun Ng[2], Adam Bryant[3], Zainab Ridha[3], Nicole Wong Doo[4], Silvia Ling[3], Phoebe Joy Ho[1], Douglas Joshua[1]

[1]Royal Prince Alfred Hospital; [2]Canberra Health Services; [3]Liverpool Hospital; [4]Concord Repatriation and General Hospital

Introduction: Polychemotherapy has been replaced by novel therapies in the management of Multiple Myeloma and is now reserved in the salvage setting despite limited published evidence. Commonly used regimens in this setting include D(T)-PACE and DCEP, which are multi-day continuous infusions, usually administered to patients with low comorbidities as inpatients. This study investigates the efficacy and safety of PCAB, a single day polychemotherapy in relapsed/refractory multiple myeloma (RRMM). **Methods:** This multisite retrospective study involved four Australian tertiary hospitals. Patients with RRMM who received PCAB chemotherapy ± one novel agent between 1/1/2012-1/5/2023 were included. PCAB comprises of cyclophosphamide 600mg/m^2, doxorubicin 30mg/m^2 and carmustine 30mg/m^2 day 1, and prednisone 60mg/m^2 day 15, given every 28 days for up to 12 cycles. Baseline clinical characteristics, treatment response, adverse events and hospitalisation duration were recorded. **Results:** Seventy-seven patients, median age 64 years (range 37-79) with median 4 (range 1-8) prior lines of therapy were included. Of these 76.6% had been exposed to both proteasome inhibitor and immunomodulatory drugs, and 63.6% had a previous autograft. Active extramedullary disease (EMD) and high-risk cytogenetics occurred in 35.1% and 58.0% of patients respectively. Forty-eight (62.3%) patients received only PCAB, while 29 (37.7%) received it in combination, most commonly with bortezomib (n=14) or thalidomide (n=7). After a median of 3 cycles (range 1-11), ORR was 38.4% (CR 5.5%) for the whole cohort, and 27.3% for those solely receiving PCAB. ORR in patients with EMD and high-risk cytogenetics were 30.8% and 42.9% respectively. A subsequent therapy was received in 72.7% of patients, including as bridge to CAR-T therapy (n=2), autograft (n=3) and allograft (n=3). Median PFS and OS were 4.0 months and 6.7 months respectively. Rate of any grade 3/4 cytopenia and febrile neutropenia was 76.2% and 44.3% respectively. Treatment-related deaths, all due to infections occurred in 6 patients (7.8%). Patients required inpatient management for a median of 3.6 days per 28 day cycle. Of patients who died, median 20.2% of days alive was spent as inpatient. **Conclusions:** PCAB has retained efficacy in RRMM including those with high-risk cytogenetics and EMD. It may have a role as bridging therapy deliverable in an outpatient setting. Infection related mortalities highlight need for careful monitoring in this heavily pre-treated cohort.

P-290

Updated long-term follow-up results of a phase 1b/2 study (FUMANBA-1) in patients with relapsed/refractory multiple myeloma (RRMM) treated with equecabtagene autoleucel

Chunrui Li[1], Di Wang[1], Baijun Fang[2], He Huang[3], Jianyong Li[4], Bing Chen[5], Jing Liu[6], Hanyun Ren[7], Yujun Dong[7], Kai Hu[8], Peng Liu[9], Xi Zhang[10], Jian-Qing Mi[11], Zhenyu Li[12], Kaiyang Ding[13], Song-bai Cai[14], Hong-yu Gui[14], Wen Wang[14], Lugui Qiu[11]

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P-289

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P-290

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P-290

Updated long-term follow-up results of a phase 1b/2 study (FUMANBA-1) in patients with relapsed/refractory multiple myeloma (RRMM) treated with equecabtagene autoleucel

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Introduction: Equecabtagene Autoleucel (Eque-cel) is a fully human B-cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory multiple myeloma (RRMM). A phase 1b/2 study (FUMANBA-1) was conducted for Eque-cel in RRMM patients (NCT05066646). Here, we report the results of the FUMANBA-1 trial, which was conducted at 14 sites in China and had a median follow-up duration of 18.07 months (range: 0.4, 30.3). **Methods:** Participants were RRMM patients who had received at least three prior lines of therapy (with at least one proteasome inhibitor and one immunomodulator) and whose disease had progressed after the last line of therapy. Patients with prior BCMA CAR -T therapy were also included. On three consecutive days of lymphodepletion (500mg/m^2 cyclophosphamide and 30mg/m^2 fludarabine), patients received a single infusion of Eque-cel at a dose of 1×10^6 cells/kg. **Results:** As of December 31, 2022, 105 patients received Eque-cel with a

median of 4 lines of prior therapy (range 3-23). 32.4% of patients had high-risk cytogenetic abnormalities (defined as at least one of del (17), t (4:14) and t (14:16) is positive), 13.3% had extramedullary disease (EMD), 11.4% had received prior BCMA CAR-T therapy, and 52.4% belonged to IgG-type MM. Of the 103 patients whose efficacy could be evaluated, 96.1% achieved a response, 77.7% achieved a complete response (CR) or a stringent CR. The 12-month PFS rate was 80.0% (95% CI: 70.33, 86.76). Patients without prior CAR-T therapy, patients who had already received three lines of treatment, and patients who were not IgG MM, achieved deeper responses, and the sCR/ CR rates were 82.4%, 96.3%, and 91.8%, respectively. Patients without high-risk cytogenetic abnormalities and without prior CAR-T therapy had better PFS rate, and 12-m PFS rates were 92.0% (95% CI: 80.07, 96.92) and 85.5% (95% CI: 75.75, 91.51), respectively. Ninety-seven of 103 (94.2%) evaluable patients achieved MRD-negativity, including all ≥ CR patients. 90.0% of patients achieved ≥CR were persistently MRD-negative for ≥12 months. CRS occurred in 93.3% (98/105) of patients, and only one was ≥ grade 3. The median time to onset was six days (range: 1-13), and the median duration was 5 days (range: 2-30). ICANS occurred in 2 patients who had either grade 1 or 2. Eque-cel expansion in peripheral blood peaked at 88001.13 copies/µg gDNA, and the median time to peak level was 12 days post-infusion. CAR Transgenes were still detectable in 50% (32/64) of patients 12 months and in 40% (4/10) of patients 24 months after infusion. Anti-CAR antibodies developed in only 20 (19.2%) patients after infusion. **Conclusions:** A profound and durable response can be achieved in RRMM patients treated with Eque-cel with a median follow-up of 18.07 months. Factors like prior CAR-T therapy, more prior lines of therapy and IgG-type MM could adversely impact the depth of response, and factors like prior CAR-T therapy or high-risk cytogenetic abnormalities might also reduce the PFS.

P-291

Outcomes of third-line therapy in multiple myeloma patients: a report from the Canadian myeloma research group (CMRG)

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Introduction: Multiple myeloma (MM) is an incurable plasma cell neoplasm characterized by multiple relapses. Typically, each subsequent line of therapy is associated with a shorter progression-free survival (PFS). There is paucity of data regarding the use and outcomes of third-line (3L) therapy. Our study assessed the regimens utilized and their long-term outcomes with 3L therapy in CMRG centres. **Methods:** This Canadian multicentre retrospective study utilized the CMRG database to track real-world outcomes of patients treated at major Canadian institutions. Eligibility included adult myeloma patients initiating 3L therapy between 1-Jan-2015 to 31-Dec-2020. **Results:** 1126 of 7911 patients fulfilled eligibility criteria and were included in the study. At MM diagnosis 205 (24%) had high-risk (HR) cytogenetics. Prior to 3L therapy, 482 (43%) had received ASCT, 998 (88%) lenalidomide (len), 996 (88%) bortezomib (bort), 109 (10%) CD38 monoclonal antibody (MoAb) and 53 (5%) pomalidomide. 106 of 1126 (9.4%) were triple-class exposed and/or refractory. At 3L, 548 patients (49%) received a triplet combination. 184 (16%) participated in clinical trials. Daratumumab (dara)-len-dex showed the best outcome with median duration of treatment (DOT) of 12.3 months and median time to next therapy (TTNT) of 32.2 followed by dara-bort-dex with DOT of 6 months and TTNT of 9.0. CD38 MoAb ± steroid, DOT=11 and TTNT=18.5. Outcomes with doublet combinations of IMiD (DOT= 5.7; TTNT=7.5) or proteasome inhibitors (PI) (DOT= 5.9; TTNT=8.9) were similar to dara-bort-dex. TTNT of 32 months was significantly better than 9 (p< 0.0001) and 18 months (p=0.001). Median PFS (mPFS) and OS from the start of 3L were stratified according to cytogenetics, previous ASCT, age, prior PI, len, pomalidomide, or CD38 MoAb. Overall mPFS was 7.5 (95%CI 6.5-8.5) months; dara-len-dex produced the best PFS: 21.4 (95%CI 16.0-28.7) months although HR patients in this group had a PFS of 10.7 [95%CI,4.4- 22.7] versus 21.4 (95%CI 16.0- 28.4) months for standard-risk. For those receiving doublets, mPFS was 6.7 (95% CI 5.6 -8.2) months. Median OS for all patients was 29.7 (95%CI 26.4-32.8) months. There was no significant difference between subgroups and type of treatment; however standard-risk dara-len-dex patients experienced a mOS of 42.9 (95%CI 34.8- 55.0) versus 29.1 (95%CI 13.2- 45.0) months in HR patients (p=0.100). Those without prior exposure to PI that were given triplets containing IMiD ± PI at 3L had the best OS: 37.3 (95%CI 27.2-48.7) months. Prior CD38 MoAb exposure negatively impacted 3L OS: 14.5 (95%CI 9.2-19.6) versus 32.6 (95% CI 28.8-36.0) months. The most common reason for discontinuation of 3L was MM progression (39%) followed by toxicity and death, each 9%. **Conclusions:** In Canadian myeloma centres, 3L patients have been preferably treated with triplet IMiD-based combinations with dara-len-dex showing the best outcomes. The time period assessed in this study reflects previous limited access to dara-based regimens at 2L in Canada.

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P-291

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P-292

Ongoing phase 1 study of HPN217, a half-life extended tri-specific T cell activating construct (TriTAC®) targeting B cell maturation antigen (BCMA) for relapsed/refractory multiple myeloma (MM)

Sumit Madan[1], Caitlin Costello[2], Brea Lipe[3], Eva Medvedova[4], Andrew Cowan[5], Jens Hillengass[6], Leif Bergsagel[7], Xavier Leleu[8], Cyrille Touzeau[9], Daniel Morillo[10], Albert Oriol[11], Raya Mawad[5], Henning Schade[12], Salomon Manier[13], Yifah Yaron[14], Patrick Ng[14], Al-Ola Abdallah[15]

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Introduction: HPN217 is a B Cell Maturation Antigen (BCMA)-targeting tri-specific T cell engager (TCE). HPN217 contains three binding domains including anti-BCMA for MM cell binding, anti-albumin for half-life extension, and anti-CD3 for T cell engagement and activation. HPN217 is under investigation in patients (pts) with heavily pretreated relapsed/refractory MM (RRMM). **Methods:** This dose escalation study is evaluating both fixed and step dose regimens to assess the safety/pharmacology and early clinical activity of HPN217. Pts with RRMM who received at least 3 prior therapies including a proteasome inhibitor, immunomodulatory drug, and CD38 targeted therapy are eligible. Prior exposure to BCMA-targeting agent is permitted. Primary objectives include evaluation of safety, tolerability, pharmacokinetics, and determination of the Recommended Phase 2 Dose(s). Secondary objectives include preliminary efficacy. HPN217 is administered IV once weekly or once every 2 weeks. AEs are graded by CTCAE 5.0, and ASTCT for cytokine release syndrome (CRS). Clinical activity is assessed per IMWG Response Criteria. **Results:** As of 01May2023, 84 pts were treated with HPN217 across 14 dose escalation cohorts and 3 backfill cohorts; dose escalation up to 24 mg is complete; the target dose MTD has not been reached. Further dose/regimen optimization is ongoing in cohorts with doses of 12 mg QW and 24 mg (QW & Q2W). Across all cohorts, pts received a median (range) of 6 (2-19) prior lines of treatment (70% transplantation, 94% triple-exposed, 76% penta-exposed, 16% BCMA targeted therapy). Median age was 69 (38-85). 34 pts remain on treatment. The most common (≥25%) treatment emergent adverse events (TEAEs) were anemia (45%), fatigue (36%), cough and CRS (30%), diarrhea (27%), and nausea (25%). All CRS events were G1-G2 except one event of G3 CRS at 24 mg. Responses were observed at doses ≥ 2.15 mg. The 12 mg cohorts (n=19) have completed enrollment and follow-up is ongoing. At the 12 mg dose level, TEAEs reported in ≥25% of pts were fatigue and cough (47%), anemia (42%), hypokalemia (37%), hypophosphatemia (32%) and diarrhea (26%). CRS was reported in 16% of pts (all G1-2). Responses of PR or better have been reported in 11 (58%) pts, including 2 pts treated with prior BCMA CAR-T. Eight pts (42%) reported a best response of VGPR or better. Treatment is ongoing in 9 responders. **Conclusions:** Dose escalation of HPN217, a novel half-life extended BCMA-targeting TCE, has been completed; target dose MTD was not reached. The 12 mg QW regimen is well tolerated with a manageable adverse event profile, low rates of CRS (16%) and robust early clinical activity (58% ORR). Evaluation of regimens using 24 mg QW and Q2W is ongoing to inform the choice of an RP2D(s). NCT04184050.

P-293

Real-world treatment patterns and outcomes in lenalidomide refractory multiple myeloma patients in Europe: a real-world survey

Joaquín Martínez-López[1], João Mendes[2], Emily Luke[3], Caspian Kluth[3], Phoebe Salmon[3], Abigail Bailey[3], Amanda Ribbands[3], Francesca Gay[4]

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Introduction: Lenalidomide (LEN) is a standard treatment (tx) for multiple myeloma (MM), given in earlier tx lines until disease progression, with many patients (pts) becoming refractory (Ref) to LEN. Real-world data on tx patterns and outcomes in LEN Ref MM pts in earlier lines of therapy (LOT) is limited. **Methods:** Data were drawn from the Adelphi MM Disease Specific Programme™, a cross-sectional survey with retrospective data collection of haematologists/haem-oncologists conducted in Europe between May-Nov 2021. Physicians completed online record forms for their next 8 consulting adult pts with a confirmed diagnosis of MM and actively receiving tx. This included pts receiving: first line (1L) or second line (2L); third line (3L); fourth line and beyond (4L+); and tri-exposed (exposed to a proteasome inhibitor [PI], an immunomodulatory [IMiD], and an anti-CD38 targeted drug). Full tx history was collected, and only pts exposed to LEN who had received 1-3 prior LOT were analysed. Two patient populations were analysed: (1) LEN Ref status (LEN Ref and non-LEN Ref) at time of data collection and (2) LOT pts first became LEN Ref. Bivariate comparisons were made between the LOT pts first became LEN Ref. LEN Ref is defined by the International Myeloma Working Group, as progressive disease during LEN tx or within 60 days of discontinuation. **Results:** Of 1163 pts exposed to LEN who received 1-3 prior LOT, 528 (45%) were LEN Ref. Mean age was 71.1 years, 56% were male, and 77% were retired. 26% of LEN Ref and 30% of non-LEN Ref pts previously received an autologous stem cell transplant (ASCT). Of all LEN Ref pts, 41% had exposure to a PI and IMiD at 1L, 93% before 3L. 71% of LEN Ref pts with prior ASCT (n=137) received a PI and IMiD at 1L, 96% before 3L. For non-ASCT LEN Ref pts (n=391), 30% received a PI and IMiD at 1L, 90% before 3L. Of the LEN Ref pts, 24% (n=129) first became Ref after 1L, 63%

P-292

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P-293

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[1]Hematología Hospital 12 de Octubre, Madrid, Spain; [2]Janssen-Cilag, Porto Salvo, Portugal; [3]Adelphi Real World, Bollington, UK; [4]Division of Hematology 1, Clinical trial unit AOU città della salute e della scienza, University of Torino

Introduction: Lenalidomide (LEN) is a standard treatment (tx) for multiple myeloma (MM), given in earlier tx lines until disease progression, with many patients (pts) becoming refractory (Ref) to LEN. Real-world data on tx patterns and outcomes in LEN Ref MM pts in earlier lines of therapy (LOT) is limited. **Methods:** Data were drawn from the Adelphi MM Disease Specific Programme™, a cross-sectional survey with retrospective data collection of haematologists/haem-oncologists conducted in Europe between May-Nov 2021. Physicians completed online record forms for their next 8 consulting adult pts with a confirmed diagnosis of MM and actively receiving tx. This included pts receiving: first line (1L) or second line (2L); third line (3L); fourth line and beyond (4L+); and tri-exposed (exposed to a proteasome inhibitor [PI], an immunomodulatory [IMiD], and an anti-CD38 targeted drug). Full tx history was collected, and only pts exposed to LEN who had received 1-3 prior LOT were analysed. Two patient populations were analysed: (1) LEN Ref status (LEN Ref and non-LEN Ref) at time of data collection and (2) LOT pts first became LEN Ref. Bivariate comparisons were made between the LOT pts first became LEN Ref. LEN Ref is defined by the International Myeloma Working Group, as progressive disease during LEN tx or within 60 days of discontinuation. **Results:** Of 1163 pts exposed to LEN who received 1-3 prior LOT, 528 (45%) were LEN Ref. Mean age was 71.1 years, 56% were male, and 77% were retired. 26% of LEN Ref and 30% of non-LEN Ref pts previously received an autologous stem cell transplant (ASCT). Of all LEN Ref pts, 41% had exposure to a PI and IMiD at 1L, 93% before 3L. 71% of LEN Ref pts with prior ASCT (n=137) received a PI and IMiD at 1L, 96% before 3L. For non-ASCT LEN Ref pts (n=391), 30% received a PI and IMiD at 1L, 90% before 3L. Of the LEN Ref pts, 24% (n=129) first became Ref after 1L, 63%

(n=330) after 2L and 13% (n=69) after 3L. Pts that became LEN Ref before 3L (87%) were less likely to receive triplet regimens on the LOT they became Ref vs non-LEN Ref (1L: 61% vs 82%, p< 0.0001; 2L: 56% vs 65%, p=0.0039). LEN Ref pts, compared to non-LEN Ref, had a longer mean [SD] duration of therapy (DoT) (1L: 14.1 vs 8.4 months, p< 0.0001; 2L: 17.74 vs 12.9, p< 0.0001) on the line they first became LEN Ref or were exposed to LEN (non-LEN Ref). After pts became LEN Ref, DoT (after 1L: 10.1 vs 15.1, p=0.0007; after 2L: 13.2 vs 13.9, p=0.544) and time to relapse (after 1L: 11.4 vs 18.4, p=0.0005; after 2L: 8.4 vs 11.0, p=0.0418) worsens compared to non-LEN Ref pts. **Conclusions:** This analysis shows most LEN Ref pts were exposed to a PI and IMiD, while also becoming refractory to LEN before they reach 3L. These LEN Ref pts had significantly faster progression and were less likely to receive treatment with triplets, showing shorter DoT and time to relapse compared to pts non-LEN Ref. There is an unmet need for new and effective tx for LEN-ref pts as early as the 2L.

P-294

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Introduction: Teclistamab, the only approved BCMA×CD3 bispecific antibody with a personalized, weight-based, and flexible dosing schedule for the treatment (tx) of triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM), has shown promising efficacy in the phase 1/2 MajesTEC-1 study (NCT03145181/NCT04557098). As MajesTEC-1 is a single-arm study, we assessed the comparative effectiveness of teclistamab vs real-world physician's choice of therapy (RWPC) in pts with TCE RRMM from the real-world, prospective, noninterventional studies, LocoMMotion (NCT04035226; enrolled Aug 2019–Oct 2020; clinical cut-off [CCO] Oct 27, 2022) and MoMMent (NCT05160584; enrolled Nov 2021–July 2022; CCO Oct 27, 2022). MoMMent was initiated as a complement to LocoMMotion to assess practice changes in recent years. **Methods:** Pts treated with the recommended phase 2 dose of teclistamab (1.5 mg/kg tx doses) from MajesTEC-1 (N=165; CCO Jan 4, 2023) were compared with an external control arm from LocoMMotion alone (N=248) or from pooled LocoMMotion + MoMMent (N=302). Inverse probability of tx weighting estimating the average tx effect in the treated population was used to adjust for imbalances in baseline covariates of prognostic significance: refractory status, ISS stage, time to progression on prior line of therapy [LOT], extramedullary disease, number of prior LOTs, time since diagnosis, average duration of prior LOTs, age, hemoglobin, lactate dehydrogenase, creatinine clearance, ECOG performance status, gender, MM type, and prior transplant. Relative effect of teclistamab vs RWPC for rates of overall response (ORR), very good partial response or better (≥VGPR), and complete response or better (≥CR) was estimated with an odds ratio using weighted logistic regression transformed into a response-rate ratio (RR) and 95% CI. A weighted Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% CIs for duration of response (DOR), progression-free survival (PFS), and overall survival (OS). **Results:** Baseline characteristics were well balanced between the 3 cohorts after reweighting external control arms. Pts treated with teclistamab had significantly improved outcomes vs RWPC in LocoMMotion: ORR (RR [95% CI], 2.32 [1.71–3.15]; P< 0.0001), ≥VGPR (RR, 5.60 [3.64–8.62]; P< 0.0001), ≥CR (RR, 183.80 [14.89–2268.30]; P< 0.0001), DOR (HR, 0.35 [0.21–0.56]; P< 0.0001), PFS (HR, 0.47 [0.35–0.64]; P< 0.0001), and OS (HR, 0.64 [0.47–0.88]; P=0.0051). Teclistamab vs RWPC in LocoMMotion + MoMMent also had significantly improved outcomes: ORR (RR [95% CI], 2.38 [1.78–3.19]; P< 0.0001), ≥VGPR (RR, 6.02 [4.00–9.08]; P< 0.0001), ≥CR (RR, 178.55 [18.88–1688.40]; P< 0.0001), DOR (HR, 0.38 [0.23–0.63]; P=0.0002), PFS (HR, 0.48 [0.35–0.65]; P< 0.0001), and OS (HR, 0.67 [0.49–0.91]; P=0.0117). **Conclusions:** Teclistamab demonstrated significantly improved effectiveness over RWPC in LocoMMotion alone and pooled LocoMMotion + MoMMent, emphasizing its clinical benefit as a highly effective tx for pts with TCE RRMM.

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P-294

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P-295

Efficacy, survival and safety of selinexor, bortezomib and dexamethasone (SVd) in patients with lenalidomide-refractory multiple myeloma: subgroup data from the BOSTON trial

María-Victoria Mateos[1], Monika Engelhardt[2], Xavier Leleu[3], Mercedes Gironella Mesa[4], Michele Cavo[5], Meletios Dimopoulos[6], Martina Bianco[7], Giovanni Marino Merlo[7], Charles La Porte[7], Philippe Moreau[8]

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Introduction: Lenalidomide (LEN) is commonly used in frontline therapy for newly diagnosed MM, and there is a need for effective treatment options for patients (pts) with MM refractory to LEN. Selinexor is a first-in-class, oral XPO1 inhibitor with a unique mechanism of action. SVd is indicated in adults with relapsed and refractory MM (RRMM) who have received at least one prior therapy. Initial results of the BOSTON phase 3 trial demonstrated significant improvements in median progression-free survival (mPFS) and overall response rate (ORR) with SVd vs bortezomib and dexamethasone (Vd) in previously treated MM (Grosicki et al. Lancet 2020). We analyzed data from the phase 3 BOSTON trial (NCT03110562) to determine the impact of refractoriness to LEN on SVd efficacy (both PFS and overall survival [OS]) and safety. **Methods:** Eligible pts with RRMM and 1-3 prior therapies were randomized to SVd (selinexor 100 mg QW, bortezomib 1.3 mg/m^2 QW and dexamethasone 20 mg BIW) or standard Vd BIW. We performed a post-hoc stratified analysis of PFS, OS (with crossover adjustment using the two-stage method), response rates and safety in subgroups by refractory status to LEN. **Results:** Of 402 pts, 106 were classified as LEN-refractory (SVd=53, Vd=53). Sixteen pts (30.2%) in the SVd arm became LEN-refractory after 1 prior line of therapy (LOT) and 69.8% after 2 or more LOT; in the Vd group 26.4% became LEN-refractory after 1 prior LOT; 73.6% after 2 or more LOT. Median age was 65 ys (range 40-87) in the SVd arm and 66 y (range 45-85) in the Vd arm. At the time of the analyses, median follow-up was 28.7 mo for SVd arm and 28.6 mo for Vd arm. mPFS was 10.2 mo (95% CI 5.8-NR) with SVd vs 7.1 mo (95% CI 3.5-9.8) with Vd (HR 0.52; 95% CI 0.31-0.88, p=0.012). mOS was 26.7 mo (95% CI 19.9-NR) with SVd vs 18.6 mo (95% CI 13.9-29.0) with Vd, resulting in a statistically significant and clinically meaningful improvement in OS (HR 0.53; 95% CI 0.30-0.95, p=0.03). Response rates for SVd and Vd were as follows: ORR 67.9% vs 47.2% and VGPR or better 35.8% vs 24.5%, respectively. The most common (≥25%) treatment-emergent adverse events with SVd vs Vd in 105 LEN-refractory pts included in the safety population were thrombocytopenia (71.7% vs 40.4%), nausea (50.9% vs 11.5%), fatigue (45.3% vs 21.1%), diarrhea (43.4% vs 19.2%), anemia (39.6% vs 25.0%), and peripheral neuropathy (30.2% vs 38.5%). **Conclusions:** Subgroup data from the BOSTON trial show a statistically significant and clinically meaningful improvement in OS and PFS and higher ORR and VGPR or better with SVd vs Vd in LEN-refractory RRMM pts. The safety profile in the subgroups was similar to that observed in the overall BOSTON population. The statistically significant 47% reduction in risk of death with SVd vs Vd shows an advantage of having a regimen built on two drugs with different mechanisms of action in the difficult-to-treat population of LEN-refractory RRMM pts.

P-296

Lighthouse: melflufen, daratumumab, and dexamethasone versus daratumumab in relapsed/refractory multiple myeloma refractory to an imid and a proteasome inhibitor or with ≥3 prior lines of therapy

María-Victoria Mateos[1], Monika Szarejko[2], Jelena Bila[3], Fredrik Schjesvold[4], Ivan Špička[5], Vladimir Maisnar[6], Artur Jurczyszyn[7], Zhanet Grudeva-Popova[8], Roman Hájek[9], Hanna Usenko[10], Marcus Thuresson[11], Stefan Norin[11], Sara Jarefors[11], Paul Richardson[12], Ludek Pour[13]

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P-295

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P-296

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phase 1/2 ANCHOR study (Ocio EM, et al. ASH 2020, abstract 417), and was further assessed in the phase 3 LIGHTHOUSE study (NCT04649060). **Methods:** Pts with RRMM, refractory to an IMiD and a proteasome inhibitor (PI) or with ≥3 prior LoTs including an IMiD and a PI, were randomized (1:1) to 28-day cycles (C) of intravenous melflufen (30 mg on day 1 per cycle) + oral dex (40 mg weekly; 20 mg if aged ≥75 y) + subcutaneous Dara (1800 mg on days 1, 8, 15, and 22 in C1-2, day 1 and 15 in C3-6, and day 1 in C7+) or Dara monotherapy (regimen as in the melflufen arm) until disease progression or unacceptable toxicity. Prior anti-CD38 monoclonal antibody therapy was allowed, but no pts had received it. Pts with confirmed disease progression in the Dara arm could cross over to melflufen + Dd. Primary endpoint: progression-free survival (PFS). Key secondary endpoints: overall response rate (ORR) and safety. Financial considerations after a partial clinical hold issued by the FDA for all melflufen studies led to premature study closure (23 Feb 2022; data cutoff date). **Results:** From 21 Dec 2020 to 7 Jul 2021, 54 of 240 planned pts were randomized (melflufen + Dd, n=27; Dara, n=27); 2 pts crossed over to melflufen + Dd. With melflufen + Dd vs Dara, median age was 65 y vs 68 y, 11 (41%) vs 13 (48%) had no prior ASCT, and 3 (11%) vs 2 (7%) had a TTP >36 mo after a prior ASCT, respectively. Median PFS was not reached (NR) with melflufen + Dd vs 4.9 mo with Dara (hazard ratio [HR], 0.18 [95% CI, 0.05-0.65]; P=0.0032). ORR was 59.3% with melflufen + Dd vs 29.6% with Dara (P=0.0300). OS was immature, with 2 events with melflufen + Dd vs 4 events with Dara (HR, 0.47 [95% CI, 0.09-2.57]; P=0.3721). Among pts with no prior ASCT or with a TTP >36 mo after a prior ASCT (melflufen + Dd, n=14; Dara, n=15), median PFS was NR with melflufen + Dd (1 event) vs 3.9 mo with Dara (11 events; HR, 0.06 [95% CI, 0.01-0.49]; P=0.0005), ORR was 64.3% vs 13.3% (P=0.0055), and 1 vs 4 OS events occurred (P=0.0369), respectively. With melflufen + Dd vs Dara, the most common grade ≥3 treatment-emergent adverse events were neutropenia (50% vs 12%), thrombocytopenia (50% vs 8%), and anemia (32% vs 19%), respectively. **Conclusions:** Melflufen + Dd showed superior PFS and ORR vs Dara, including in pts with no prior ASCT or with a TTP >36 mo after a prior ASCT, which resembles the population with confirmed benefit from OCEAN. The safety profile of melflufen + Dd was consistent with previous reports of melflufen.

P-297

Selinexor, bortezomib, and dexamethasone in patients with previously treated multiple myeloma: updated results of BOSTON trial by prior therapies

María-Victoria Mateos[1], Monika Engelhardt[2], Xavier Leleu[3], Mercedes Gironella Mesa[4], Michele Cavo[5], Meletios Dimopoulos[6], Martina Bianco[7], Giovanni Marino Merlo[7], Charles La Porte[7], Philippe Moreau[8]

[1]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; [2]Interdisciplinary Cancer Center, University of Freiburg; [3]Hospital La Mileterie, Poitiers, France; [4]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [5]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Università degli Studi di Bologna, Bologna, Italy; [6]National and Kapodistrian University of Athens; [7]Stemline Therapeutics/Menarini Group; [8]University Hospital Hôtel-Dieu, Nantes, France

Introduction: Increasing use of daratumumab + lenalidomide + dexamethasone (DRd) in the frontline setting for multiple myeloma (MM) has led to more patients (pts) with proteasome inhibitor (PI)-naïve early relapse. ESMO Guidelines endorse a PI-based combination including selinexor, bortezomib, and dexamethasone (SVd) in MM pts with PI-naïve early relapse. Selinexor is a first-in-class, oral XPO1 inhibitor with a unique mechanism of action. SVd is indicated for relapsed and refractory MM (RRMM) in adults who have received at least one prior therapy. We analyzed longer follow-up data from the phase 3 BOSTON trial (NCT03110562) to determine the impact of prior therapies, including PI, on SVd efficacy and safety. **Methods:** Eligible pts with RRMM and 1-3 prior therapies were randomized to selinexor QW (100 mg), bortezomib QW (1.3 mg/m^2) and dexamethasone BIW (20 mg) (Vd) or standard BIW Vd. A stratified efficacy analysis and safety analysis were performed in subgroups by prior PI therapy and number of prior regimens. Efficacy analyses were based on Feb 2021 data cut and safety analyses on Jun 2022 data cut. **Results:** Of 402 pts, 198 received 1 prior line of treatment (LOT) (SVd=99; Vd=99; median ages 67 and 69 y, respectively); 95 were PI-naïve (SVd=47; Vd=48; median ages 68 and 67.5 y, respectively); 123 were bortezomib naïve (SVd=61; Vd=62; median ages 68 y both arms). In pts with 1 prior LOT, mPFS was 21.0 vs 10.7 months for SVD vs Vd (HR 0.62; 95% CI 0.41-0.95, p=0.028). In PI naïve pts mPFS was 29.5 vs 9.7 months for SVd vs Vd (HR 0.29; 95% CI 0.14-0.63, p< 0.001). In bortezomib naïve pts mPFS was 29.5 vs 9.7 months for SVd vs Vd (HR 0.35; 95% CI 0.18-0.68, p=0.002). Overall response rates (ORR) were higher with SVd vs Vd in all subgroups: 1 prior LOT 80.8% vs 66.7%; PI-naïve 76.6% vs 70.8%; bortezomib-naïve ORR 75.4% vs 69.4%. Most common (≥25%) treatment-emergent adverse events (AEs) with SVd vs Vd in pts with 1 prior LOT were thrombocytopenia (61.6% vs 28.6%), nausea (52.5% vs 11.2%), fatigue (45.4% vs 17.3%), peripheral neuropathy (38.4% vs 52.0%), diarrhea (34.3% vs 24.5%), and anemia (30.3% vs 26.5%). Safety findings were similar in the PI naïve and bortezomib naïve subgroups. **Conclusions:** Stratified subgroup data from longer follow-up in the BOSTON trial confirm the PFS benefit of SVd over Vd in pts without prior PI or bortezomib exposure as well as pts who have received 1 prior LOT. There was a statistically significant and clinically meaningful ~20 mo median PFS improvement of SVd over Vd in RRMM pts that had no prior exposure to PI and bortezomib, as well as a significant ~10 mo PFS improvement in pts with 1 prior LOT. These outcomes coupled with generally manageable AE profile emphasize the synergy between selinexor and bortezomib and the importance of a double mode of action switch, further supporting SVd use in 1) PI-naïve RRMM pts, 2) bortezomib-naïve RRMM pts, and 3) pts at first relapse.

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P-297

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P-298

Retrospective study of treatment patterns and clinical outcomes by race in patients with triple-class-exposed multiple myeloma treated in a real-world setting

Aster Meche[1], Felix Rondeau[2], Samy Gallienne[2], Patrick Hlavacek[1], Jinma Ren[1], Karen Repetny[1], Sarasa Johnson[2], Alexander Schepart[1], Marco DiBonaventura[1]

[1]Pfizer Inc; [2]Statlog

Introduction: Disparities in access to treatment and clinical outcomes are experienced by multiple myeloma (MM) patients from different racial groups. The objective of this study was to describe differences in treatment patterns and clinical outcomes of real-world (RW) triple-class-exposed (TCE) MM patients (i.e., exposed to ≥1 PI, ≥1 IMiD, ≥1 anti-CD38) by race. **Methods:** Data from two US electronic health record databases (COTA and Flatiron Health) were pooled with duplicate patients removed for this analysis. TCE MM patients initiating a subsequent line of therapy (LOT) (i.e., index LOT) following documentation of exposure to all three classes of drug, who were ≥18 years, and had race information captured within these databases were identified. Patients were categorized as White, Black, Asian, or Other race. Patient and disease characteristics, treatment history and patterns, and clinical outcomes (i.e., response, progression, treatment switch, and death) were described for each racial group using descriptive statistics. Progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) were calculated using Kaplan-Meier methods. **Results:** A total of 1,383 patients were identified (White 1,010 (73%); Black 213 (15%); Asian 36 (3%); Other 124 (9%)). Patient characteristics were similar though Other patients were more likely to identify as Hispanic (41% vs 2-8%, p<.05) and the distribution of some comorbidities also differed (e.g., renal disease: White 10%, Black 17%, Asian 14%, Other 14%, p<.05). Disease characteristics and treatment history were also comparable regardless of race, including exposure to different treatments (e.g., stem cell transplant 47-53%, p=.38) and time from MM diagnosis to index LOT (36.3-41.5 median (m) months, p=.62). However, a significantly higher proportion of Asian patients had the t(4;14) cytogenetic marker (25% vs 8-11%, p<.05). Treatments received in the index LOT were comparable, though White patients were more likely to receive an investigational agent (5% vs 0-2%, p<.05) and Asian patients were more likely to receive treatment combinations including carfilzomib (50% vs 27-31%, p<.05). Response rates did not differ significantly based on race (White 27%, Black 27%, Asian 44%, Other 30%, p=.15). Time-to-event outcome results (months) were as follows: mPFS - White 9.9, Black 8.3, Asian 15.9, Other 12.7; mTTNT – White 7.6, Black 8.9, Asian 10.9, Other 7.8; mOS – White 21.1, Black 17.4, Asian 37.5, Other 27.4. **Conclusions:** No clear health disparity trends were observed among TCE MM patients based on race. This suggests that when patients have equal access to treatment options, differences in outcomes are not necessarily observed. Known health disparities by race may therefore arise earlier in a patient's journey. As such, research exploring if certain race groups are less likely to reach TCE status, while considering other barriers, is needed.

P-299

Survival outcomes in older patients with relapsed/refractory multiple myeloma treated with either IMiD- or non-IMiD-based regimens after triple-class exposure in the PREAMBLE registry

Philippe Moreau[1], Ravi Vij[2], Hartmut Goldschmidt[3], David Kuter[4], David Cella[5], Sujith Dhanasiri[6], Jin Gu[7], Jiaqi Fang[7], Thomas Marshall[7], Susan Fish[7], Karthik Ramasamy[8]

[1]University Hospital Hôtel-Dieu, Nantes, France; [2]Division of Oncology, Washington University School of Medicine, St Louis, MO, USA; [3]Internal Medicine V, GMMG Study Group at University Hospital Heidelberg, Heidelberg, Germany; [4]Center for Hematology, Massachusetts General Hospital, Boston, MA, USA; [5]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [6]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [7]Bristol Myers Squibb, Princeton, NJ, USA; [8]Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Introduction: A significant proportion of patients with multiple myeloma (MM) eventually relapse or become refractory to treatment. Age is an independent prognostic factor in MM, but there is limited information on real-world treatment patterns and clinical outcomes in older patients with relapsed/refractory MM (RRMM) who have been exposed to three prior therapy classes (triple-class exposed [TCE]). The aim of this analysis was to describe the patient characteristics and outcomes (progression-free survival [PFS] and overall survival [OS]) in older patients with TCE RRMM treated with immunomodulatory agents (IMiDs) or non-IMiD agents in the real-world setting. **Methods:** Prospectively collected data were extracted from the multicenter Prospective REsearch Assessment in Multiple Myeloma: An oBservational Evaluation (PREAMBLE) registry, which enrolled patients with newly diagnosed MM and RRMM in Europe and the US from 2012 to 2020. Included patients were ≥70 years of age, TCE (previously treated with an IMiD [lenalidomide (Rev), pomalidomide (Pom), thalidomide (Tha)], an anti-CD38 antibody, and a proteasome inhibitor [PI]), and started a subsequent IMiD (Rev/Pom) or non-IMiD (non-Rev/Pom/Tha) line of therapy at their physician's discretion. All analyses were descriptive; Kaplan-Meier curves were used for PFS and OS analyses. Index date was the date of initiation of post-TCE IMiD or non-IMiD therapy. **Results:** Among 190 TCE patients who initiated a subsequent line of therapy, 91 patients were ≥70 years of age (median age 75 years). At index, 43 of these patients (47.3%) received an IMiD regimen and 48 (52.7%) received a non-IMiD regimen. Baseline demographics were broadly similar between groups. A high proportion of patients were previously refractory to IMiDs in both the IMiD and non-IMiD groups (36/43 [83.7%] and 43/48 [89.6%], respectively). In the IMiD group, the index treatments were: retreatment with IMiD only (14.0%), IMiD+PI (14.0%), IMiD + anti-CD38 (30.2%), and IMiD + other (41.9%). In the non-IMiD group, the index treatments were: PI only (33.3%), anti-CD38 containing regimens (25.0%), and other (41.7%). A total of 19 (44.2%) IMiD-treated patients received a subsequent line of therapy after index compared with 23 (47.9%) non-IMiD treated patients. Overall, the median

P-298

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P-299

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(95% CI) PFS in this group of patients aged ≥70 years was 5.2 (3.0–8.3) months, with 5.9 (2.9–9.3) months in IMiD-treated patients compared with 4.6 (2.3–8.3) months in non-IMiD treated patients. The overall median (95% CI) OS was 19.7 (13.0–NA) months – 16.0 (8.7–NA) in IMiD-treated patients compared with 19.7 (13.0–NA) in non-IMiD treated patients. **Conclusions:** In this study of an older population with TCE RRMM, subsequent treatment regimens were heterogeneous. Survival outcomes appeared to be similar with IMiD- and non-IMiD–based regimens. As this was a relatively small and descriptive study, future analyses are required to further elucidate these findings.

P-300

Targeting DNMT3B impairs multiple myeloma cell proliferation and clonogenic capacity and enhances sensitivity to standard of care agents

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Introduction: In about half of the MM patients, genetic defects and/or abnormal expression are observed in epigenetic modifiers (epiplayers) at the time of diagnosis and this further increases at relapse, indicating an important role for epiplayers in MM cell drug resistance (DR). However, so far, only for two epiplayers, MMSET and EZH2, a clear role in MM cell DR has been formally established. Using RNASeq data from the MMRF CoMMpass study, we found that the epiplayer DNMT3B is significantly increased in the relapsed setting, suggesting a role in MM relapse. Here, we explored the role of DNMT3B in MM cell biology and drug response. **Methods:** Both the DNMT3B specific inhibitor Nanaomycin A (NA) and genetic knockdown using a doxycycline inducible shRNA against DNMT3B (shDNMT3B) were used to specifically target DNMT3B. RNA sequencing was performed upon genetic knockdown in AMO-1 (high DNMT3B levels) and XG-2 (intermediate DNMT3B levels) human myeloma cell lines (HMCL). Viability and apoptosis were assessed using a CellTiter-Glo assay and AnnexinV/7AAD stainings. Cell proliferation was measured by BrdU incorporation and cell cycle analysis, while the clonogenic capacity was evaluated by a colony formation assay. **Results:** Here, we report that high DNMT3B mRNA expression correlates with a worse disease outcome in both newly diagnosed and relapsed patients, indicating a role for DNMT3B in MM progression and DR. Targeting DNMT3B in HMCL using either shDNMT3B or NA resulted in a strong and significant increase in cell death. NA treatment also strongly reduced viability of primary human MM cells, while human BMSC were much less affected. RNA sequencing identified 794 genes differentially expressed upon DNMT3B depletion, with 394 genes upregulated and 400 genes downregulated in DNMT3B-depleted cells compared to non-depleted cells (Fold change > 1.5; FDR ≤ 0.05). Gene set enrichment analysis (GSEA) of the upregulated genes identified significant enrichment of genes involved in histone methylation and stem cells, whereas downregulated genes are mainly involved in cell cycle, apoptosis, stem cells and MM proliferating molecular subgroup. In line, cell cycle analysis upon DNMT3B silencing and NA treatment revealed impaired cell proliferation due to an arrest in the G1 phase. In addition, a strong and significant reduction in the number of colonies was observed upon DNMT3B targeting, thus supporting a role for DNMT3B in MM cell clonogenicity and thus potentially also in MM stemness. Importantly, combining NA with either Bortezomib (Bz) or Melphalan (Mel) resulted in a synergistic inhibition of MM cell viability and further increase in the anti-clonogenic activity. Furthermore, NA was also able to resensitize both Mel and Bz resistant XG-2 cells. **Conclusions:** Together, our findings provide for the first time evidence that DNMT3B could be a novel promising epigenetic target to overcome or delay relapse in MM.

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(95% CI) PFS in this group of patients aged ≥70 years was 5.2 (3.0–8.3) months, with 5.9 (2.9–9.3) months in IMiD-treated patients compared with 4.6 (2.3–8.3) months in non-IMiD treated patients. The overall median (95% CI) OS was 19.7 (13.0–NA) months – 16.0 (8.7–NA) in IMiD-treated patients compared with 19.7 (13.0–NA) in non-IMiD treated patients. **Conclusions:** In this study of an older population with TCE RRMM, subsequent treatment regimens were heterogeneous. Survival outcomes appeared to be similar with IMiD- and non-IMiD–based regimens. As this was a relatively small and descriptive study, future analyses are required to further elucidate these findings.

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patient is still receiving therapy, whereas the median number of lines post treatment with belantamab mafodotin is 1 (range 0-8) and 26% of patients are currently alive. The ORR (overall response rate, PR or better) in this cohort was 52%, whereas the DCR (disease control rate, SD or better) was 89%. The median PFS for the entire group was 2 months (95%CI: 0-7), whereas the median PFS among the responders was 12 months (95%CI: 6-18). Interestingly, the median PFS was 10 months (95%CI: 0-22) for patients who started belantamab mafodotin due to biochemical relapse, as compared to a median PFS of only 0.9 months (95%CI: 0.5-1.2) for patients with symptomatic myeloma relapse. The median OS was 89 months (95%CI: 48-129) from MM diagnosis, whereas the landmark median OS was 16 months (95%CI: 2-30) from belantamab mafodotin initiation. The landmark median OS for the responders was 40 months (95%CI: 24-56). Regarding the toxicity profile, the most common toxicity was eye toxicity in 44% of the patients. More specifically, keratopathy grade 2-3 was reported in 33.3% of the patients. Keratopathy was resolved in all patients, however one patient had to discontinue treatment due to corneal ulcer. Reduction in visual acuity was reported in 26% of the patients. Other toxicities included infections gr 2-3 in five patients, thrombocytopenia gr 3 in two patients and fatigue gr 2 in four patients. **Conclusions:** Belantamab mafodotin showed a safety and efficacy profile consistent with the results of the DREAMM-2 study in triple-class refractory patients with MM in terms of survival benefit and tolerability in the real-world practice.

P-302

Anchor (OP-104): melflufen plus dexamethasone and daratumumab or bortezomib in relapsed/refractory multiple myeloma (RRMM) – final efficacy and safety results

Enrique Ocio[1], Yvonne Efebera[2], Roman Hájek[3], Jan Straub[4], Vladimir Maisnar[5], Jean-Richard Eveillard[6], Lionel Karlin[7], María-Victoria Mateos[8], Albert Oriol[9], Vincent Ribrag[10], Paul Richardson[11], Stefan Norin[12], Jakob Obermüller[12], Nicolaas Bakker[12], Ludek Pour[13]

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Introduction: Melphalan flufenamide (melflufen), a first-in-class peptide-drug conjugate (PDC), plus dexamethasone (dex) is approved for use in Europe in patients (pts) with triple-class refractory RRMM who have received ≥3 prior lines of therapy (LoTs) and progressed >36 mo after a prior autologous stem cell transplant if received. Here, we report the final data for the phase 1/2a ANCHOR study of melflufen with bortezomib + dex (Vd) or daratumumab + dex (Dd) (NCT03481556). **Methods:** Pts had RRMM refractory/intolerant to an IMiD and/or a proteasome inhibitor (PI) and 1-4 prior LoTs. Vd arm: PI in prior LoT (but not refractoriness in the last LoT) was allowed. Dd arm: prior anti-CD38 monoclonal antibody therapy prohibited. All pts received intravenous (IV) melflufen (30 or 40 mg, day 1 per cycle). Vd arm: bortezomib 1.3 mg/m^2 subcutaneous, days 1, 4, 8, and 11 + oral dex (20 mg on days 1, 4, 8, and 11 and 40 mg on days 15 and 22; dose reduced if aged ≥75 y). Dd arm: daratumumab 16 mg/kg IV once per wk (2 cycles), every 2 wk (4 cycles), then every 4 wk + oral dex (40 mg on days 1, 8, 15, and 22). Primary objectives: determine the optimal melflufen dose in each combination (phase 1); assess overall response rate (ORR; phase 2). **Results:** As of 9 Feb 2022 (data cutoff date), 23 pts received melflufen (30 mg, n=15; 40 mg, n=8) +Vd and 33 melflufen (30 mg, n=6; 40 mg, n=27) +Dd. The partial clinical hold issued by the US Food and Drug Administration led to premature study termination on 23 Feb 2022. Vd arm: Median (range) treatment duration was 8.3 mo (2.8-40.0) in the 30-mg cohort and 12.0 mo (2.1-34.7) in the 40-mg cohort. ORR for the pooled cohorts was 78% (2 complete response or better [≥CR], 5 very good partial response [VGPR], 11 partial response [PR]). At a median follow-up of 21 mo, the median progression-free survival (PFS) was 14.7 mo (95% CI, 8.5-33.5); overall survival (OS) was immature with 17 pts (74%) alive at data cutoff. Grade ≥3 treatment-emergent adverse events (TEAEs) were most commonly cytopenias and infrequently nonhematologic; thrombocytopenia led to treatment discontinuation in 3 pts. No dose-limiting toxicities (DLTs) and 3 fatal AEs (1 cardiac failure chronic, 2 COVID-19 pneumonia) occurred. Dd arm: Median (range) treatment duration was 24.1 mo (0.9-44.6) in the 30-mg cohort and 6.2 mo (0.9-41.2) in the 40-mg cohort. ORR was 73% (3 ≥CR, 8 VGPR, 13 PR). Median (95% CI) PFS was 12.9 mo (7.7-15.4) and OS was 26.1 mo (16.4-not estimable), at a median follow-up of 30.0 and 32.8 mo, respectively. Thrombocytopenia and neutropenia were the most common grade ≥3 TEAEs and TEAEs leading to treatment discontinuation. Grade ≥3 nonhematologic TEAEs were infrequent. No DLTs and 4 fatal AEs (2 sepsis, 1 cardiac failure chronic, 1 general physical health deterioration) occurred. **Conclusions:** Melflufen + Vd or Dd showed encouraging activity in RRMM with 1-4 prior LoTs. Safety and efficacy analyses determined melflufen 30 mg to be the recommended dose in triplet regimens.

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P-303

Belantamab mafodotin in patients with relapsed/refractory multiple myeloma who are triple-refractory: a retro-prospective Italian observational study

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Introduction: Recent therapeutic advances in multiple myeloma (MM) patients have dramatically improved patients' outcomes. But drug resistance is an emerging challenge resulting in a poor survival with the urgent need for effective therapies, mostly in triple-refractory MM. Belantamab mafodotin (belamaf), the first-in-class antibody-drug conjugate (ADC) targeting B-cell maturation antigen (BCMA), demonstrated efficacy in monotherapy in DREAMM-2 trial and was approved for relapsed/refractory MM (rrMM) patients with at least four previous lines of therapy (LOT). **Methods:** Being belamaf real-world data scarce, we designed a retro-prospective study aiming to evaluate its efficacy and safety in rrMM patients treated in compassionate use programmes as Named Patient Program (NPP) and Expanded Access Program (EAP) in Italy, under the aegis of European Myeloma Network (EMN). The primary endpoint was the rate of patients achieving a clinical benefit (at least minimal response according to IMWG criteria). Secondary endpoints were safety, ORR (at least PR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS). Eligible criteria were: ≥18 years of age, MM diagnosis according to IMWG criteria, triple-refractoriness (at least one PI, one IMID and one anti-CD38 mAb) and at least 4 prior LOTs. **Results:** Overall, 67 patients have been enrolled by 18 Italian centers, with a median age of 66 years (range 42-82), a median of 6 prior LOT (4-10), ECOG 65, p=0.094 and ECOG≥2, p=0.012 **Conclusions:** In conclusion, our cohort had fewer previous LOTs but similar median age than DREAMM-2 population. We found similar ORR, OS and safety profile, but median PFS and DOR seem to be longer. PFS seems to be not affected by classical disease prognostic factors but by baseline patient characteristics.

P-304

Triple class refractory multiple myeloma: eficacy of the new immunotherapies and new unmet medical need

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Introduction: The prognosis of triple class refractory (TCR) multiple myeloma (MM) patients is dismal, mainly due to the lack of rescue therapies. Newer immunotherapy approaches such us chimeric antigen receptor T (CAR-T) cells and bispecific monoclonal antibodies (BiAbs) directed against BCMA, GPRC5D or FcRH5 have been effective in the TCR setting. However, there are not studies that compared the effectiveness of CAR-T and BiAbs, as well as which is the prognosis of patients who relapsed to these treatments. **Methods:** An observational retrospective study was conducted to indirectly compare the efficacy of CAR-T and BiAbs in 68 TCR patients treated within clinical trials between December 2018 and February 2023. **Results:** Sixty-eight patients were included in this study, 31 were treated with CAR-T and 37 with BiABs (directed against BCMA in 23, GPRC5D in 11 and FcRH5 in 3 patients). No differences were observed except that the BiAbs group had higher proportion of patients >65 years, with more extramedullary disease at relapse and more pretreated compared to the CAR-T group. The overall rate response (at least partial response) was significantly better in the CAR-T group than the BiAbs group (odds ratio 22.1 [95% confidence interval (CI), 2.7-179.9]; P=0.004). In addition, patients treated with CAR-T reached more frequently complete response or better (66.7% vs. 43.2%; P=0,056). After a median of follow-up

P-303

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of 14.6 months (m) (interquartile range, 3,7-54,1), no differences in the progression-free survival (PFS) were observed between the CAR-T and the BiAbs groups (14.1 vs. 12,1 m; P=0.110), but patients receiving CAR-T achieved longer overall survival (OS) (43.0 vs. 18.2 m, hazard ratio 2.3 [95% CI, 1.1-5.2]; P=0.050). Thirty-two patients (12 in the CAR-T and 20 in the BiAbs group) were rescued after progression. Overall, these rescue therapies were very heterogeneous, but 66.7% of the CAR-T group and 25% of the BiAbs group were treated with BiAbs in the subsequent treatment. Patients treated with BiAbs at relapsed showed a trend toward better response. Patients in the CAR-T group who were treated with BiAbs (with a different target than the BCMA) presented the longest PFS 2 (29.1 m), significantly more prolonged than patients in this group rescued with other schemes, (7,9 m, P< 0.001), as well as patients of the BiAbs group regardless of the treatment used at relapse (BiAbs: 7,3 m, P< 0.001; and other therapies: 8.4 m, P=0.002). **Conclusions:** The present study showed that CAR-T and BiAbs are effective treatment in TCR MM patients. In this scenario, CAR-T resulted in better responses, but no differences were observed in PFS compared to BiAbs. However, patients of the CAR-T group presented superior OS showing the importance of treatment sequence and how BiAbs could be useful after CAR-T to improve survival in TCR patients. The identification of sequence approach as well as the development of novel drugs represent the new unmet medical need in the relapse of patients TCR after the new immunotherapy.

P-305

DREAMM-20: a study to investigate the safety and efficacy of belantamab for the treatment of multiple myeloma (MM) when used as monotherapy and in combination treatments

Hang Quach[1], Shang-Yi Huang[2], Hsuan-Yu Lin[3], Dok Hyun Yoon[4], Giulia Fulci[5], Nirav Ratia[5], John Clements[5], Eric Lewis[5], Wei Sun[5], Malika Ahras[5], Sarantos Kaptanis[5], Seema Shafi-Harji[5], Brandon Kremer[5], Chang-Ki Min[6]

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Introduction: MM is an incurable malignant clonal plasma cell disorder and accounts for 1% of all cancers and 10% of all hematologic malignancies. Treatments include combinations of proteasome inhibitors (PIs), immunomodulatory drugs, monoclonal antibodies, alkylating agents, and corticosteroids as well as the newer chimeric antigen receptor T-cell therapies, antibody-drug conjugates (ADCs), and bispecific antibodies. As relapse usually occurs, there is a high unmet need for effective treatments with better safety profiles, given the toxicity of current and emerging treatments. B-cell maturation antigen (BCMA), a cell surface receptor, is upregulated on MM cells. Belantamab (GSK2857914) is a humanized afucosylated immunoglobulin G1 monoclonal antibody targeting BCMA. Belantamab shares the same antibody structure as the ADC belantamab mafodotin but without the conjugated monomethyl auristatin-F payload. Based on preclinical data, belantamab mediates antibody-dependent cellular cytotoxicity through increased FcγRIII binding and antibody-dependent cellular phagocytosis, and blocks BCMA-activated prosurvival and proliferative signaling. Preclinical evidence supports clinical investigation of belantamab for MM. **Methods:** Part 1 of DREAMM-20 is a phase 1/2, open-label, multicenter, dose-escalation study of patients with relapsed or refractory MM to determine the safety, tolerability, and recommended part 2 dose for belantamab. Inclusion criteria include patients aged ≥18 years with confirmed MM (defined by the International Myeloma Working Group [IMWG]), measurable disease, Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate organ system function. Patients must have received ≥3 prior lines of therapy, which included an immunomodulatory agent, a PI, and an anti-CD38 antibody (unless contraindicated or unavailable). Prior receipt of BCMA-targeted agents is allowed. Key exclusion criteria include current corneal epithelial disease except nonconfluent superficial punctate keratitis, meningeal or central nervous system involvement with MM, uncontrolled hypertension, and evidence of clinically significant untreated arrhythmias. Patients will receive belantamab via intravenous infusion on days 1 and 15 of 28-day cycles. Dose escalation is conducted using the modified toxicity probability interval method. The primary endpoint is the incidence of adverse events, including dose-limiting toxicities, which will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Secondary endpoints include pharmacokinetics, incidence of antidrug antibodies, and overall response rate (assessed per the 2016 IMWG criteria). Exploratory endpoints include quality of life, pharmacodynamics (including longitudinal soluble BCMA and M-protein levels), and other biomarker assessments. The trial is sponsored by GSK and registered at ClinicalTrials.gov (NCT05714839).

P-306

Final results of a Phase 1b study of subcutaneous isatuximab administration by an on-body delivery system (OBDS) plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma (RRMM)

Hang Quach[1], Gurdeep Parmar[2], Enrique Ocio[3], H. Miles Prince[4], Albert Oriol[5], Nobuhiro Tsukada[6], Kazutaka Sunami[7], Pierre Bories[8], Sumit Madan[9], Dorothee Semiond[10], Disa Yu[10], Sandrine Macé[11], Florence Suzan[11], Philippe Moreau[12]

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of 14.6 months (m) (interquartile range, 3,7-54,1), no differences in the progression-free survival (PFS) were observed between the CAR-T and the BiAbs groups (14.1 vs. 12,1 m; P=0.110), but patients receiving CAR-T achieved longer overall survival (OS) (43.0 vs. 18.2 m, hazard ratio 2.3 [95% CI, 1.1-5.2]; P=0.050). Thirty-two patients (12 in the CAR-T and 20 in the BiAbs group) were rescued after progression. Overall, these rescue therapies were very heterogeneous, but 66.7% of the CAR-T group and 25% of the BiAbs group were treated with BiAbs in the subsequent treatment. Patients treated with BiAbs at relapsed showed a trend toward better response. Patients in the CAR-T group who were treated with BiAbs (with a different target than the BCMA) presented the longest PFS 2 (29.1 m), significantly more prolonged than patients in this group rescued with other schemes, (7,9 m, P< 0.001), as well as patients of the BiAbs group regardless of the treatment used at relapse (BiAbs: 7,3 m, P< 0.001; and other therapies: 8.4 m, P=0.002). **Conclusions:** The present study showed that CAR-T and BiAbs are effective treatment in TCR MM patients. In this scenario, CAR-T resulted in better responses, but no differences were observed in PFS compared to BiAbs. However, patients of the CAR-T group presented superior OS showing the importance of treatment sequence and how BiAbs could be useful after CAR-T to improve survival in TCR patients. The identification of sequence approach as well as the development of novel drugs represent the new unmet medical need in the relapse of patients TCR after the new immunotherapy.

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P-306

Final results of a Phase 1b study of subcutaneous isatuximab administration by an on-body delivery system (OBDS) plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma (RRMM)

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Introduction: Intravenous (IV) administration of isatuximab (Isa) plus pomalidomide-dexamethasone (Pd) is approved for patients (pts) with RRMM. Subcutaneous (SC) delivery allows a shorter duration of administration, with the aim to optimize convenience of administration and enhance patient comfort. Prior investigations in a Phase 1b study (NCT04045795) determined the recommended phase 2 dose (RP2D) for SC Isa at 1400 mg, and showed safety and efficacy for SC Isa + Pd comparable to IV Isa + Pd in the pivotal ICARIA-MM trial in RRMM pts. We now present the final safety and efficacy study results. **Methods:** This multicenter Phase 1b study evaluated SC vs IV Isa + Pd in RRMM pts with ≥2 prior treatment lines including lenalidomide and a proteasome inhibitor. Pts were randomized to SC by infusion pump (IP)1000 mg or IV 10 mg/kg and to IP1400 mg or IV. In the expansion cohort, SC Isa was administered at the RP2D via OBDS, a wearable bolus injector applied to the abdomen by a healthcare professional. Safety and PK were the primary endpoints; the main secondary endpoints were overall response rate (ORR) and progression-free survival (PFS). **Results:** Of the 56 randomized pts, 25% (3/12) IV, 25% (3/12) IP1000, 30% (3/10) IP1400 and 32% (7/22) of OBDS pts remained on treatment as of 15 Apr 2023. Median follow-up was 33 mo for IV, 39 mo for IP1000, 33 mo for IP1400 and 19 mo for the OBDS cohort due to the sequential accrual. ≥50% of pts had received ≥3 prior treatment lines. In the IV, IP1000, IP1400 and OBDS cohorts, serious treatment-related AEs occurred in 17%, 25%, 50% and 14% of pts; any ≥G3 infections were reported in 25%, 25%, 30% and 36% of pts including 0%, 8%, 0% and 14% ≥G3 Covid-19, respectively. Median duration of OBDS injections was 10 min (6.6-49.5); all injections were completed successfully with no interruption and no infusion reactions (IRs). Local tolerability was good: 7 (32%) pts had 10 injection site reactions, all G1, in 581 administrations (1.7%), mainly erythemas. The relative dose intensity of Isa at the SC RP2D was ≥90% (97%, 95%, 91% and 93% in the IV, IP1000, IP1400 and OBDS cohorts, respectively). ORR was 66.7% in the IV, 66.7% in the IP1000, 80% in the IP1400, and 72.7% in the OBDS cohorts (75% at the RP2D). Median PFS was 22.0 mo, 17.4 mo, not reached and 20.6 mo, respectively (20.6 mo at the RP2D). Minimal residual disease negativity (by NGS) at 10-5 sensitivity was achieved by 1/12 (8%) IV, 0/12 IP1000, 2/10 (20%) IP1400 and 2/22 (9%) OBDS pts (4 CR, 1 VGPR pts) (13% at the RP2D). The incidence of anti-drug antibodies appeared comparable after administration of Isa SC or IV (9.1% vs 8.3%). **Conclusions:** Final study results with SC Isa administration via OBDS at the 1400 mg RP2D + Pd show an efficacy and safety profile consistent with IV administration, with no IRs, and excellent local tolerability. A non-inferiority Phase 3 trial (NCT05405166) evaluating SC Isa via OBDS versus IV Isa is ongoing.

P-307

Efficacy and safety of elranatamab monotherapy in patients with relapsed/refractory multiple myeloma: a post-hoc subgroup analysis from MagnetisMM-3 with modified eligibility criteria

Marc Raab[1], Salomon Manier[2], H. Miles Prince[3], Ajay Nooka[4], Rayan Kaedbey[5], Jens Hillengass[6], Tadao Ishida[7], Sharon Sullivan[8], Umberto Conte[8], Eric Leip[8], Andrea Viqueira[9], Noopur Raje[10]

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Introduction: Results from the Phase 2 MagnetisMM-3 trial (NCT04649359) demonstrated elranatamab (BCMA x CD3 bispecific monoclonal antibody [bsAb]) monotherapy as an effective treatment for patients (pts) with RRMM with a manageable safety profile. Eligibility criteria in MagnetisMM-3 were sufficiently broad to allow for the enrollment of a representative real-world pt population. Here, we present a subgroup analysis of MagnetisMM-3 with modified eligibility criteria reflective of the pt population enrolled in other recent clinical trials of BCMA-directed bsAb. **Methods:** The following modified inclusion/exclusion criteria were applied to the pt population of MagnetisMM-3 Cohort A (BCMA-naïve): ECOG PS ≤1, no CNS involvement, no prior treatment with bi-specific antibodies, platelets ≥75,000 (or ≥50,000 if ≥50% bone marrow plasma cell involvement), eGFR ≥40 mL/min/1.73 m^2. All other eligibility criteria and analysis endpoints remained the same as previously reported (Bahlis et al., ASH 2022). Data cutoff was ~15 mo after last pt's initial dose. **Results:** With the modified criteria, 33 (26.8%) pts were excluded from the original analysis population of MagnetisMM-3 Cohort A. For the 90 pts meeting the modified eligibility criteria, median age was 69 y (range, 36–88), 52.2% were male; median number of prior lines of therapy was 4.0 (2–11); 97.8% and 38.9% of pts were triple-class- and penta-drug refractory, respectively. High-risk cytogenetics [t(4;14), t(14;16),or del(17p)] were present in 24.4% of pts, 27.8% of pts had extramedullary disease by BICR and 11.1% had an R-ISS of III at baseline. At data cutoff, the median follow-up was 15.1 mo (range, 0.2–25.1) and the median treatment duration was 8.4 mo (range, 0.03–24.4); 36.7% of pts remained on treatment. Most common reason for permanent treatment discontinuation was progressive disease (37.8%). Objective response rate per BICR was 67.8% (95% CI, 57.1, 77.2), with 38.9% CR or sCR, 24.4% VGPR, and 4.4% PR. Median duration of response (DOR) has not been reached (95% CI, NE–NE) and DOR rate at 15 mo was 67.1% (95% CI, 52.7, 78.0), median progression-free survival was 13.9 mo (95% CI, 9.8, NE). Most common Grade 3/4 treatment-emergent AEs were hematologic (75.6%), among these the most frequent (≥30%) were neutropenia (46.7%) and anemia (31.1%). Grade 3/4 infections were reported in 41.1% of pts, most common (≥10%) was COVID-19 pneumonia (13.3%); 5 (5.6%) pts had Grade 5 infections. CRS and ICANS occurred in 58.9% and 5.6% of pts respectively. There were no Grade ≥3 CRS or ICANS events. **Conclusions:** In this post-hoc subgroup analysis of pts with RRMM in MagnetisMM-3 with modified eligibility criteria that resemble recent clinical trials of BCMA-directed bsAb, elranatamab monotherapy remained efficacious with a manageable safety profile. Results were comparable

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P-308

Superiority of daratumumab plus lenalidomide and dexamethasone in first and second relapse in multiple myeloma patients: a real-world single centre retrospective analysis

Jolien Raddoux[1], Anneleen Vanhellemont[1], Michel Delforge[1]

[1]University Hospital Leuven, Leuven, Belgium

Introduction: The anti-CD38 antibody daratumumab is an important part of the treatment strategy in newly diagnosed and relapsed/refractory multiple myeloma (MM) patients. Data proving the benefit of daratumumab-based over non-daratumumab based regimens in the real-world setting are still limited. The aim of this real-world data analysis was to evaluate the clinical benefit of the use of daratumumab in 2nd and 3rd line treatment in a large cohort of anti-CD38 naïve patients with relapsed MM treated in the University Hospital Leuven, Belgium. **Methods:** Data from the UZ Leuven patient database were analysed through the Augmenting THerapeutic Effectiveness through Novel Analytics (ATHENA) platform. The UZ Leuven Multiple Myeloma database was transformed to the OMOP-Common Data Model 5.3.1 as part of the ATHENA project. Patient data were collected until April 12, 2022. Different cohorts were identified based on daratumumab or non-daratumumab treatment in 2nd line treatment (DARA-2 versus non-DARA-2) and 3rd line treatment (DARA-3 versus non-DARA-3). We analysed the time to next treatment and overall survival from 2nd line treatment (TTNT2; OS2) and from 3rd line treatment (TTNT3; OS3). **Results:** A total of 217 patients were included in this retrospective analysis. The cohorts contained respectively 107 patients in DARA-2, 39 patients in non-DARA-2, 39 patients in DARA-3 and 74 patients in non-DARA-3. In the DARA-2 cohort, 73 patients were treated with daratumumab-lenalidomide-dexamethasone (DRd) and 34 patients with daratumumab-bortezomib-dexamethasone (DVd). The median TTNT2 was 11,0 months in the DVd group versus not been reached (NR) in the DRd group (HR: 3,75; 95% CI: 2,1-6,68; p < 0,001). In the DVd group, median OS2 was 21, 8 months versus not been reached in the DRd group (HR: 2,99; 95%CI: 1,38-6,48; p=0,005). The median TTNT2 was significantly longer in the DRd group compared to the non-DARA-2 cohort (NR vs 20,5 months; HR: 0,44; 95% CI: 0,25-0,76; p=0,003). In the DARA-3 cohort, 29 patients were treated with DRd and 10 patients with DVd. The median TTNT3 was longer for the DRd group compared to the DVd group (20,7 vs 5,4 months; HR: 4,41; 95% CI 1,94-9,98; p< 0,001). The longest OS3 was also observed in the DRd group (41,9 months), compared to the DVd group (18,9 months) (HR: 2,82; 95% CI: 1,08-7,32; p=0,03). The median TTNT3 was significantly longer in the DRd group compared to the non-DARA-3 cohort (20,7 vs 5,8 months; HR: 0,49; 95% CI: 0,29-0,82; p=0,006). **Conclusions:** This single centre real-world data analysis shows the clinical benefit of dara-based over non-dara based regimens in first and second relapse. In addition, compared with DVd, DRd is associated with significantly longer TTNT and survival.

P-309

ZnDDC, a novel CELMoD-like agent binding to DDB1-CRBN complex demonstrates significant synergism with BTZ and IMiDs and overcomes IMiDs resistance in myeloma cell lines and primary samples

Gowtham Rajendran[1], Vinodh Kannappan[1], Karim Azar[1], Elyas Khan[2], Q. Ping Dou[2], Supratik Basu[1], Weiguang Wang[1]

[1]University of Wolverhampton; [2]Wayne State University

Introduction: Although immunomodulatory imide drugs (IMiDs), also called CRBN E3 ligase modulatory drugs (CELMoDs), e.g., lenalidamide (LEN), pomalidomide (POM) and proteasome inhibitor [bortezomib (BTZ)] improved the survival rate of multiple myeloma (MM), all MM patients are relapsed due to drug resistance. Therefore, development of new IMiDs is of clinical urgency. Due to the time (15 years) and costs (£1.5 billion/drug) for new drug development, repositioning of old drugs for new indications is an emerging economical strategy. Disulfiram (DS), an anti-alcoholism drug used in clinic for over 60 years, demonstrates excellent specific anticancer activity with no/low toxicity to normal tissues. DS chelates copper (Cu) and zinc (Zn) to form copper-diethyldithiocarbamate (CuDDC) and zinc-diethyldithiocarbamate (ZnDDC) which are the active anticancer compounds. Although the anticancer activity of DS has been known for more than three decades, its application in cancer clinic has been limited by its very short half-life in the bloodstream (< 4 min). In the recent years, we developed long half-life injectable DS showing strong anticancer efficacy in numerous cancer animal models. In this study, we developed a novel PEGylated liposome encapsulated ZnDDC (PEG-Lipo/ZnDDC) which shows stronger immunomodulatory and anti-MM effect than currently available IMiDs (LEN and POM) and reverses resistance, and synergistically enhances the anti-MM activity of IMiDs and BTZ. **Methods:** MTT assay, RT-PCR, Western blot, Fluorescence imaging, Flow cytometry, Magnetic bead primary MM cell isolation and culture, HPLC, isobologram analysis, Nano formulation techniques, computer docking and modelling. **Results:** We successfully developed PEG-Lipo/ZnDDC with satisfied drug loading content and controlled releasing. ZnDDC showed strong cytotoxicity in MM cell lines and patient-derived MM cells (IC50s: 5-10μM) in normoxic and hypoxic conditions. ZnDDC synergistically enhanced the cytotoxicity of IMiDs and BTZ and reversed their chemoresistance in normoxic and hypoxic conditions. Although ZnDDC had no effect on mRNA expression of cereblon (CRBN), IKZF1, IKZF3 and IRF4, a significant downregulation of IKZF1, IKZF3, IRF4 and cMyc proteins was observed after treating the MM cell lines with sub-cytotoxic concentrations of ZnDDC (2-5 μM). After exposure to low concentration of ZnDDC, levels of both IL-2 mRNA and protein were significantly boosted in T lymphocytes. Computer modelling through molecular docking using the AutoDock Vina software demonstrated a very strong

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Jolien Raddoux[1], Anneleen Vanhellemont[1], Michel Delforge[1]

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Introduction: The anti-CD38 antibody daratumumab is an important part of the treatment strategy in newly diagnosed and relapsed/refractory multiple myeloma (MM) patients. Data proving the benefit of daratumumab-based over non-daratumumab based regimens in the real-world setting are still limited. The aim of this real-world data analysis was to evaluate the clinical benefit of the use of daratumumab in 2nd and 3rd line treatment in a large cohort of anti-CD38 naïve patients with relapsed MM treated in the University Hospital Leuven, Belgium. **Methods:** Data from the UZ Leuven patient database were analysed through the Augmenting THerapeutic Effectiveness through Novel Analytics (ATHENA) platform. The UZ Leuven Multiple Myeloma database was transformed to the OMOP-Common Data Model 5.3.1 as part of the ATHENA project. Patient data were collected until April 12, 2022. Different cohorts were identified based on daratumumab or non-daratumumab treatment in 2nd line treatment (DARA-2 versus non-DARA-2) and 3rd line treatment (DARA-3 versus non-DARA-3). We analysed the time to next treatment and overall survival from 2nd line treatment (TTNT2; OS2) and from 3rd line treatment (TTNT3; OS3). **Results:** A total of 217 patients were included in this retrospective analysis. The cohorts contained respectively 107 patients in DARA-2, 39 patients in non-DARA-2, 39 patients in DARA-3 and 74 patients in non-DARA-3. In the DARA-2 cohort, 73 patients were treated with daratumumab-lenalidomide-dexamethasone (DRd) and 34 patients with daratumumab-bortezomib-dexamethasone (DVd). The median TTNT2 was 11,0 months in the DVd group versus not been reached (NR) in the DRd group (HR: 3,75; 95% CI: 2,1-6,68; p < 0,001). In the DVd group, median OS2 was 21, 8 months versus not been reached in the DRd group (HR: 2,99; 95%CI: 1,38-6,48; p=0,005). The median TTNT2 was significantly longer in the DRd group compared to the non-DARA-2 cohort (NR vs 20,5 months; HR: 0,44; 95% CI: 0,25-0,76; p=0,003). In the DARA-3 cohort, 29 patients were treated with DRd and 10 patients with DVd. The median TTNT3 was longer for the DRd group compared to the DVd group (20,7 vs 5,4 months; HR: 4,41; 95% CI 1,94-9,98; p< 0,001). The longest OS3 was also observed in the DRd group (41,9 months), compared to the DVd group (18,9 months) (HR: 2,82; 95% CI: 1,08-7,32; p=0,03). The median TTNT3 was significantly longer in the DRd group compared to the non-DARA-3 cohort (20,7 vs 5,8 months; HR: 0,49; 95% CI: 0,29-0,82; p=0,006). **Conclusions:** This single centre real-world data analysis shows the clinical benefit of dara-based over non-dara based regimens in first and second relapse. In addition, compared with DVd, DRd is associated with significantly longer TTNT and survival.

P-309

ZnDDC, a novel CELMoD-like agent binding to DDB1-CRBN complex demonstrates significant synergism with BTZ and IMiDs and overcomes IMiDs resistance in myeloma cell lines and primary samples

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Introduction: Although immunomodulatory imide drugs (IMiDs), also called CRBN E3 ligase modulatory drugs (CELMoDs), e.g., lenalidamide (LEN), pomalidomide (POM) and proteasome inhibitor [bortezomib (BTZ)] improved the survival rate of multiple myeloma (MM), all MM patients are relapsed due to drug resistance. Therefore, development of new IMiDs is of clinical urgency. Due to the time (15 years) and costs (£1.5 billion/drug) for new drug development, repositioning of old drugs for new indications is an emerging economical strategy. Disulfiram (DS), an anti-alcoholism drug used in clinic for over 60 years, demonstrates excellent specific anticancer activity with no/low toxicity to normal tissues. DS chelates copper (Cu) and zinc (Zn) to form copper-diethyldithiocarbamate (CuDDC) and zinc-diethyldithiocarbamate (ZnDDC) which are the active anticancer compounds. Although the anticancer activity of DS has been known for more than three decades, its application in cancer clinic has been limited by its very short half-life in the bloodstream (< 4 min). In the recent years, we developed long half-life injectable DS showing strong anticancer efficacy in numerous cancer animal models. In this study, we developed a novel PEGylated liposome encapsulated ZnDDC (PEG-Lipo/ZnDDC) which shows stronger immunomodulatory and anti-MM effect than currently available IMiDs (LEN and POM) and reverses resistance, and synergistically enhances the anti-MM activity of IMiDs and BTZ. **Methods:** MTT assay, RT-PCR, Western blot, Fluorescence imaging, Flow cytometry, Magnetic bead primary MM cell isolation and culture, HPLC, isobologram analysis, Nano formulation techniques, computer docking and modelling. **Results:** We successfully developed PEG-Lipo/ZnDDC with satisfied drug loading content and controlled releasing. ZnDDC showed strong cytotoxicity in MM cell lines and patient-derived MM cells (IC50s: 5-10μM) in normoxic and hypoxic conditions. ZnDDC synergistically enhanced the cytotoxicity of IMiDs and BTZ and reversed their chemoresistance in normoxic and hypoxic conditions. Although ZnDDC had no effect on mRNA expression of cereblon (CRBN), IKZF1, IKZF3 and IRF4, a significant downregulation of IKZF1, IKZF3, IRF4 and cMyc proteins was observed after treating the MM cell lines with sub-cytotoxic concentrations of ZnDDC (2-5 μM). After exposure to low concentration of ZnDDC, levels of both IL-2 mRNA and protein were significantly boosted in T lymphocytes. Computer modelling through molecular docking using the AutoDock Vina software demonstrated a very strong

binding of ZnDDC to the DDB1-CRBN complex, similar to that of LEN and POM. ZnDDC also reversed hypoxia-induced IMiDs and BTZ resistance in tested MM cell lines. **Conclusions:** ZnDDC demonstrates CELMoD like property with synergistic effect when used in combination with clinically available IMiDs and BTZ; The effect of ZnDDC is potentially CRL4CRBN-IKZF1/3-IRF4 pathway dependent; Further study is ongoing which could translate this work into MM clinic in a fast track.

P-310

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Paula Rodríguez-Otero[1], Christine Michaels-Igbokwe[2], Hannah Collacott[3], Julia Braverman[4], Thomas Marshall[4], Antoine Tinel[5], Devender Dhanda[4]

[1]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain; [2]Evidera, Montréal, QC, Canada; [3]Evidera, Bethesda, MD, USA; [4]Bristol Myers Squibb, Princeton, NJ, USA; [5]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland

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P-311

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P-311

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among the three periods of time (7 vs 9 vs 7 months, p=0.722). Patients who received ≤3 prior lines of therapy had a significantly longer OS from T0 than patients who had received more than 3 lines (median 9 vs. 5 months, p=0.005). On the contrary, there was no difference in OS between patients treated only with conventional chemotherapy or those exposed to novel drugs (median 7 vs 7 months, p=NS). **Conclusions:** The median OS of patients who start palliative treatment with CP is 7 months. This survival has remained similar over the last 50 years and is not influenced by the period of time or previous exposure to novel drugs. However, the number of prior lines of therapy has a significant impact on OS, being shorter for those patients who start palliative treatment after more than 3 prior lines.

P-312

Impact of the IF system using HYDRASHIFT® on response evaluation for patients under treatment with the IgG-κ monoclonal antibody, Isatuximab

Yuko Shirouchi[1], Kazumi Kaihara[1], Tsunaki Sekita[1], Naoko Amano[2], Konosuke Nakayama[1], Kazunori Miyake[1], Hitoshi Abe[1], Dai Maruyma[1]

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Introduction: Isatuximab is an anti-CD38 monoclonal antibody (mAb) that improves outcomes and depth of response in patients with relapsed or refractory multiple myeloma (MM). Serum Immunofixation (IF) is referenced in the IMWG guidelines for assessing complete response (CR) in MM. Isatuximab is an IgG-κ mAb detected by IF, which interferes with interpretation of CR. To avoid this interference and assist in accurate clinical assessment and therapeutic monitoring of MM patients, the HYDRASHIFT 2/4 Isatuximab (HYDRASHIFT Isa IF assay) was developed by Sebia with Sanofi. It has been utilized in determining final CR in the IKEMA study (Lancet 2021, Blood Cancer J 2023). The HYDRASHIFT Isa IF assay, intended for use on the HYDRASYS system, was evaluated for providing accurate M-protein detection and CR assessment in MM. We used different IF systems in analyzing the sera of MM patients who are being given treatments containing Isatuximab in order to examine differences in M-protein detection ability and CR assessment. **Methods:** Samples from 5 patients whose treatments included isatuximab were tested and monitored with IF on the HYDRASYS system (Sebia) using HYDRASHIFT 2/4 Isatuximab kit (Sebia) and with IF on the Epalyzer2 system (Helena). Serum FLCs and immunoglobulins (IGs) concentration were also measured. **Results:** The median age of 5 patients (3 males and 2 females) was 73 years (range; 49-79). The HYDRASHIFT Isa IF assay completely removed the Isatuximab-based IgG-κ band from the gamma region and changed 2 of 5 patients on the response evaluations to CR. Three patients showed M-proteins, IgG-κ, IgG-λ, IgA-κ, and free kappa (BJP-κ) that originated from MM. One patient with serious renal impairment having high serum FLC (κ: 1585 mg/L and λ: 6.9 mg/L), was found to have an IgA-κ and two BJP-κ monoclonal bands by HYDRASHIFT Isa IF assay. In this patient, the Epalyzer2 detected only the IgG-κ from Isatuximab, an IgA band with no associated light chain, and one weak BJP-κ. During monitoring by the HYDRASHIFT Isa IF assay, one of the two CR patients had a weak IgA-κ detected, indicating disease progression. However, the Epalyzer2 couldn't detect this IgA-κ and only detected IgG-κ originating from Isatuximab. **Conclusions:** The HYDRASYS system and HYDRASHIFT Isa IF assay was shown to have high sensitivity and specificity, providing accurate CR assessment, and also correctly identified serum BJP and a small M-protein. These results suggest that the response and CR assessments of patients can differ depending on the IF system used. In the clinical practice of MM in patients being treated with isatuximab, the use of the HYDRASHIFT Isa IF assay showed good performance regarding the proper CR and M-protein interpretation. These studies suggest that a "proper" CR assessment of isatuximab-treated patients would be increased by use of HYDRASHIFT Isa IF assay.

P-313

ALLG MM25 (VIBER-M): a phase Ib/II study of venetoclax, iberdomide and dexamethasone for patients in first or second relapse of multiple myeloma with t(11;14)

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Introduction: Translocation t(11;14) is an initiating lesion that is seen in approximately 20% of patients with multiple myeloma (MM). It is considered an intermediate-risk lesion and is associated with inferior outcomes amongst the intermediate risk-group. This is the only cytogenetic lesion in MM that is amenable to targeted treatment with Bcl2-inhibition. Venetoclax (Ven) is a Bcl2-inhibitor that induces cell death, and has been shown to be highly efficacious in patients with relapsed/refractory myeloma (RRMM) who harbour t(11;14) and high Bcl2 levels. Given that there is a significant attrition rate in patient numbers with each subsequent line of therapy, there is a need to move Bcl2-inhibitors to earlier lines of treatment to optimise clinical outcomes. In the current era where lenalidomide (len) maintenance is used in first line, there is a need for a len-free regimen at relapse. Iberdomide is a potent cereblon E3 ligase modulator (CELMod) that has been shown in pre-clinical studies to have direct anti-myeloma and immunostimulatory activity, including in len- and pomalidomide-resistant cell lines. Early studies in heavily pre-treated RRMM have demonstrated good response rates when iberdomide is combined with standard-of-care therapy. We hypothesize that the combination of Ven, iberdomide (Iber) and dexamethasone (Dex) will be highly synergistic and have better utility in rescuing MM patients with t(11;14) at first or second relapse. **Methods:** Treatment will be administered as an all oral regimen in a 28-day cycle: Ven on Days 1-28; Iber on Days 1-21; and weekly Dex. An adverse-event adapted trial design is used in anticipation of overlapping haematological toxicities between Ven and Iber, mainly

among the three periods of time (7 vs 9 vs 7 months, p=0.722). Patients who received ≤3 prior lines of therapy had a significantly longer OS from T0 than patients who had received more than 3 lines (median 9 vs. 5 months, p=0.005). On the contrary, there was no difference in OS between patients treated only with conventional chemotherapy or those exposed to novel drugs (median 7 vs 7 months, p=NS). **Conclusions:** The median OS of patients who start palliative treatment with CP is 7 months. This survival has remained similar over the last 50 years and is not influenced by the period of time or previous exposure to novel drugs. However, the number of prior lines of therapy has a significant impact on OS, being shorter for those patients who start palliative treatment after more than 3 prior lines.

P-312

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Yuko Shirouchi[1], Kazumi Kaihara[1], Tsunaki Sekita[1], Naoko Amano[2], Konosuke Nakayama[1], Kazunori Miyake[1], Hitoshi Abe[1], Dai Maruyma[1]

[1]Cancer Institute Hospital, Japanese Foundation for Cancer Research; [2]SEBIA JAPAN

Introduction: Isatuximab is an anti-CD38 monoclonal antibody (mAb) that improves outcomes and depth of response in patients with relapsed or refractory multiple myeloma (MM). Serum Immunofixation (IF) is referenced in the IMWG guidelines for assessing complete response (CR) in MM. Isatuximab is an IgG-κ mAb detected by IF, which interferes with interpretation of CR. To avoid this interference and assist in accurate clinical assessment and therapeutic monitoring of MM patients, the HYDRASHIFT 2/4 Isatuximab (HYDRASHIFT Isa IF assay) was developed by Sebia with Sanofi. It has been utilized in determining final CR in the IKEMA study (Lancet 2021, Blood Cancer J 2023). The HYDRASHIFT Isa IF assay, intended for use on the HYDRASYS system, was evaluated for providing accurate M-protein detection and CR assessment in MM. We used different IF systems in analyzing the sera of MM patients who are being given treatments containing Isatuximab in order to examine differences in M-protein detection ability and CR assessment. **Methods:** Samples from 5 patients whose treatments included isatuximab were tested and monitored with IF on the HYDRASYS system (Sebia) using HYDRASHIFT 2/4 Isatuximab kit (Sebia) and with IF on the Epalyzer2 system (Helena). Serum FLCs and immunoglobulins (IGs) concentration were also measured. **Results:** The median age of 5 patients (3 males and 2 females) was 73 years (range; 49-79). The HYDRASHIFT Isa IF assay completely removed the Isatuximab-based IgG-κ band from the gamma region and changed 2 of 5 patients on the response evaluations to CR. Three patients showed M-proteins, IgG-κ, IgG-λ, IgA-κ, and free kappa (BJP-κ) that originated from MM. One patient with serious renal impairment having high serum FLC (κ: 1585 mg/L and λ: 6.9 mg/L), was found to have an IgA-κ and two BJP-κ monoclonal bands by HYDRASHIFT Isa IF assay. In this patient, the Epalyzer2 detected only the IgG-κ from Isatuximab, an IgA band with no associated light chain, and one weak BJP-κ. During monitoring by the HYDRASHIFT Isa IF assay, one of the two CR patients had a weak IgA-κ detected, indicating disease progression. However, the Epalyzer2 couldn't detect this IgA-κ and only detected IgG-κ originating from Isatuximab. **Conclusions:** The HYDRASYS system and HYDRASHIFT Isa IF assay was shown to have high sensitivity and specificity, providing accurate CR assessment, and also correctly identified serum BJP and a small M-protein. These results suggest that the response and CR assessments of patients can differ depending on the IF system used. In the clinical practice of MM in patients being treated with isatuximab, the use of the HYDRASHIFT Isa IF assay showed good performance regarding the proper CR and M-protein interpretation. These studies suggest that a "proper" CR assessment of isatuximab-treated patients would be increased by use of HYDRASHIFT Isa IF assay.

P-313

ALLG MM25 (VIBER-M): a phase Ib/II study of venetoclax, iberdomide and dexamethasone for patients in first or second relapse of multiple myeloma with t(11;14)

Shirlene Sim[1], Ann Solterbeck[2], Cecily Forsyth[3], Jay Hocking[4], Ian Kerridge[5], Hock-Choong Lai[6], Olga Motorna[7], Hang Quach[1]

[1]St Vincent's Hospital Melbourne, VIC, Australia; [2]Statistical Revelations; [3]Gosford Hospital, NSW, Australia; [4]Austin Health, VIC, Australia; [5]Royal North Shore Hospital, NSW, Australia; [6]Townsville University Hospital, QLD, Australia; [7]Eastern Health, VIC, Australia

Introduction: Translocation t(11;14) is an initiating lesion that is seen in approximately 20% of patients with multiple myeloma (MM). It is considered an intermediate-risk lesion and is associated with inferior outcomes amongst the intermediate risk-group. This is the only cytogenetic lesion in MM that is amenable to targeted treatment with Bcl2-inhibition. Venetoclax (Ven) is a Bcl2-inhibitor that induces cell death, and has been shown to be highly efficacious in patients with relapsed/refractory myeloma (RRMM) who harbour t(11;14) and high Bcl2 levels. Given that there is a significant attrition rate in patient numbers with each subsequent line of therapy, there is a need to move Bcl2-inhibitors to earlier lines of treatment to optimise clinical outcomes. In the current era where lenalidomide (len) maintenance is used in first line, there is a need for a len-free regimen at relapse. Iberdomide is a potent cereblon E3 ligase modulator (CELMod) that has been shown in pre-clinical studies to have direct anti-myeloma and immunostimulatory activity, including in len- and pomalidomide-resistant cell lines. Early studies in heavily pre-treated RRMM have demonstrated good response rates when iberdomide is combined with standard-of-care therapy. We hypothesize that the combination of Ven, iberdomide (Iber) and dexamethasone (Dex) will be highly synergistic and have better utility in rescuing MM patients with t(11;14) at first or second relapse. **Methods:** Treatment will be administered as an all oral regimen in a 28-day cycle: Ven on Days 1-28; Iber on Days 1-21; and weekly Dex. An adverse-event adapted trial design is used in anticipation of overlapping haematological toxicities between Ven and Iber, mainly

among the three periods of time (7 vs 9 vs 7 months, p=0.722). Patients who received ≤3 prior lines of therapy had a significantly longer OS from T0 than patients who had received more than 3 lines (median 9 vs. 5 months, p=0.005). On the contrary, there was no difference in OS between patients treated only with conventional chemotherapy or those exposed to novel drugs (median 7 vs 7 months, p=NS). **Conclusions:** The median OS of patients who start palliative treatment with CP is 7 months. This survival has remained similar over the last 50 years and is not influenced by the period of time or previous exposure to novel drugs. However, the number of prior lines of therapy has a significant impact on OS, being shorter for those patients who start palliative treatment after more than 3 prior lines.

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neutropenia. There will be intra-patient dose escalation over the first three cycles; if there is no Grade 3 neutropenia with fever or Grade 4 neutropenia lasting more than 5 days, Grade 4 thrombocytopenia or ≥Grade 3 treatment-related non-haematological toxicities, doses will be escalated (Cycle 1: Iber 1.3mg/Ven 200mg; Cycle 2: Iber 1.3mg/Ven 400mg; Cycle 3 onwards: Iber 1.6mg/Ven 400mg). Three safety assessments will be carried out after five patients have completed cycle 1, 2 and 3 respectively. Treatment will be until disease progression. Primary endpoint is achievement of very good partial response or better. Total study duration will be 4.5 years, with recruitment over 24 months, median expected time on treatment of 24 months, and follow up until 6 months after the last patient has had their last dose of treatment. This research is a cooperative trial group study lead by the Australasian Leukaemia and Lymphoma Group (ALLG), as ALLG MM25. This study is supported by AbbVie Inc. and Bristol-Myers Squibb Company. **Conclusions:** We anticipate that combination Ven-Iber-Dex will be well tolerated and result in deep and durable remission in MM patients with t(11;14) in first or second relapse.

P-314

Bendamustine salvage for relapsed – refractory multiple myeloma: a retrospective analysis of outcomes in heavily pretreated patients

Aakanksha Singh[1], Narendra Agrawal[1], Rohan Haldar[1], Dinesh Bhurani[1], Jyoti Shankar Raychoudhari[1]

[1]Rajiv Gandhi Cancer institute and Research Center

Introduction: Multiple myeloma in first-line or second-line setting are exposed and hence become refractory to IMIDs, PIs and monoclonal antibodies. The response rates of bendamustine in relapsed/ refractory multiple myeloma ranged from 20 to 30% for monotherapy to >80% for triple-drug combinations. **Methods:** From Jan 2016 to July 2022, 50 patients of RRMM after two or more lines of therapy were included. ORR (overall response rate) defined as a partial response or more after two cycles to a maximum of 6 cycles. Bendamustine in combination with Pomalidomide/ Carfilzomib/Bortezomib/Daratumumab/PAD chemotherapy and dexamethasone was given. **Results:** All patients had prior PI (including Carfilzomib) and IMid (including Pomalidomide) exposure. 28.0% patients had prior Daratumumab exposure. 48.0% patients had prior ASCT, 26.0% patients were Triple Refractory and 20.0% were Penta-Refractory. 46.0% patients had Plasmacytoma (Paraskeletal- 13, Extramedullary-10), 14% Circulating plasma cells, 16% Secondary amyloidosis and 22% High Risk cytogenetics. In total, 25 (50%) patients responded and included: CR-8.0%, VGPR-12.0% and PR-30.0%. No difference in ORR observed for presence or absence of Extra Medullary Disease (40% vs 46%), circulating plasma cells (57 % vs 48%), high risk cytogenetics (50% vs 52%) and RISS Stage III vs RISS Stage I/II (47.6% vs 52.4%) respectively. The response rates were similar in patients who relapsed after ASCT versus not (48% vs 52%), triple refractory (44% vs 56%) and penta refractory (42% vs 55%), respectively with p value>0.05. While Bendamustine/ Daratumumab and Bendamustine/ PAD showed impressive ORR of 87.5% and 75.0% respectively, the Bendamustine/ Pomalidomide, Bendamustine/ Carfilzomib and Bendamustine/ Bortezomib also showed an ORR of 42.9%, 37.5% and 47.1% respectively. Bendamustine/ Dexamethasone had a dismal ORR-16.7%. Patients /=3 cycles of chemotherapy (HR 1.29, 95% CI 1.01 – 1.80, p- 0.046). At a median follow-up of 11.5 months, median PFS and OS were 4 (95% CI: 2.25-5.00) months and 9.00 (95% CI: 5.25- not reached) months respectively. 32 (64%) of patients died on follow up. Patients with < CR in all prior lines of therapy had inferior OS, HR 1.39 (95% CI: 1.15-2.00, p=0.050) and PFS (HR 1.39, 95% CI: 1.15-1.99, p-0.050). Triple refractory myeloma (HR 1.32, 95% CI: 1.17-1.62, p-0.001) and Penta refractory (HR 1.21, 95% CI: 1.10-1.46, p< 0.001) had an inferior PFS. 8% patients had Grade 3/4 hematological toxicity requiring dose reduction. **Conclusions:** Bendamustine showed encouraging responses across all risk groups, high burden disease and heavily pretreated patients post exposure to novel agents, making an excellent bridging therapy to bispecifics, off the shelf allogenic CARs and NK- CARs.

P-315

Elranatamab exposure-safety analysis in patients with relapsed/refractory multiple myeloma: analysis from MagnetisMM studies

Pooneh Soltantabar[1], Donald Irby[1], Jennifer Hibma[1], Diane Wang[1], Jason Williams[1], Akos Czibere[1], Andrea Viqueira[2], Anne Hickman[1], Mohamed Elmeliegy[1]

[1]Pfizer Inc.; [2]Pfizer SLU, Madrid, Spain

Introduction: Elranatamab was demonstrated to be an effective treatment for patients (pts) with RRMM with a manageable safety profile based on the results from the Phase 2 (Ph2) MagnetisMM-3 trial (NCT04649359). This analysis explored the exposure-response (ER) for infections, neutropenia and peripheral neuropathy. **Methods:** The ER-safety analysis of elranatamab was performed using pooled data from 4 studies: MagnetisMM-1 (first-in-human Ph1, NCT03269136), MagnetisMM-2 (Japan Ph1, NCT04798586), MagnetisMM-3 (Ph2), and MagnetisMM-9 (Ph1/2, NCT05014412). These studies included a dose range of 0.1 to 50 µg/kg IV and 80 to 1000 µg/kg (6 to 76 mg) QW SC. Binomial logistic regression was used. The safety endpoints were Grade ≥ 3 (G3+) neutropenia, G3+ infections and Grade ≥ 2 (G2+) peripheral neuropathy. Base models explored free (ie, unbound) and total (ie, free and sBCMA-bound) elranatamab PK on the probability of developing each of the selected safety endpoints. Average exposure up to the event (Cave,event) was used as the PK metric in this analysis. A Full model was developed for each safety endpoint to explore the influence of clinical and laboratory covariates and PK. Stepwise backward elimination (α =0.01) was used for covariate selection and final model development. **Results:** Out of 324 participants treated with elranatamab monotherapy, 47%, 35% and 9% experienced G3+ neutropenia, G3+ infection and G2+ peripheral neuropathy. The median (range) time to first event of G3+ neutropenia and G3+ infection was 43.00 (4 - 312) and 79.5 (4 - 428) days, respectively. Given the distribution of the time to first instance of these events, C_ave,event was used as the exposure metric. For neutropenia, base

neutropenia. There will be intra-patient dose escalation over the first three cycles; if there is no Grade 3 neutropenia with fever or Grade 4 neutropenia lasting more than 5 days, Grade 4 thrombocytopenia or ≥Grade 3 treatment-related non-haematological toxicities, doses will be escalated (Cycle 1: Iber 1.3mg/Ven 200mg; Cycle 2: Iber 1.3mg/Ven 400mg; Cycle 3 onwards: Iber 1.6mg/Ven 400mg). Three safety assessments will be carried out after five patients have completed cycle 1, 2 and 3 respectively. Treatment will be until disease progression. Primary endpoint is achievement of very good partial response or better. Total study duration will be 4.5 years, with recruitment over 24 months, median expected time on treatment of 24 months, and follow up until 6 months after the last patient has had their last dose of treatment. This research is a cooperative trial group study lead by the Australasian Leukaemia and Lymphoma Group (ALLG), as ALLG MM25. This study is supported by AbbVie Inc. and Bristol-Myers Squibb Company. **Conclusions:** We anticipate that combination Ven-Iber-Dex will be well tolerated and result in deep and durable remission in MM patients with t(11;14) in first or second relapse.

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Introduction: Elranatamab was demonstrated to be an effective treatment for patients (pts) with RRMM with a manageable safety profile based on the results from the Phase 2 (Ph2) MagnetisMM-3 trial (NCT04649359). This analysis explored the exposure-response (ER) for infections, neutropenia and peripheral neuropathy. **Methods:** The ER-safety analysis of elranatamab was performed using pooled data from 4 studies: MagnetisMM-1 (first-in-human Ph1, NCT03269136), MagnetisMM-2 (Japan Ph1, NCT04798586), MagnetisMM-3 (Ph2), and MagnetisMM-9 (Ph1/2, NCT05014412). These studies included a dose range of 0.1 to 50 µg/kg IV and 80 to 1000 µg/kg (6 to 76 mg) QW SC. Binomial logistic regression was used. The safety endpoints were Grade ≥ 3 (G3+) neutropenia, G3+ infections and Grade ≥ 2 (G2+) peripheral neuropathy. Base models explored free (ie, unbound) and total (ie, free and sBCMA-bound) elranatamab PK on the probability of developing each of the selected safety endpoints. Average exposure up to the event (Cave,event) was used as the PK metric in this analysis. A Full model was developed for each safety endpoint to explore the influence of clinical and laboratory covariates and PK. Stepwise backward elimination (α =0.01) was used for covariate selection and final model development. **Results:** Out of 324 participants treated with elranatamab monotherapy, 47%, 35% and 9% experienced G3+ neutropenia, G3+ infection and G2+ peripheral neuropathy. The median (range) time to first event of G3+ neutropenia and G3+ infection was 43.00 (4 - 312) and 79.5 (4 - 428) days, respectively. Given the distribution of the time to first instance of these events, C_ave,event was used as the exposure metric. For neutropenia, base

model results indicated that total C_ave,event was not significantly associated (P-value=0.4307) with G3+ neutropenia, however, free C_ave,event was significant (P-value=0.0272). For infections, total C_ave,event was not significantly associated with G3+ infections (P-value=0.1918), however, free C_ave,event was significant (P-value=0.0362). Neither the exposure metrics nor the clinical or laboratory covariates were retained in the final models after backward elimination. For peripheral neuropathy, the analysis dataset included a total of 29 events of G2+ peripheral neuropathy which did not allow for a statistical analysis. However, there was no apparent ER relationship by visual inspection of diagnostic plots and exposure in participants with G2+ peripheral neuropathy was within the range of those without events. **Conclusions:** No statistically significant relationship was observed between elranatamab exposure (free or total Cave,event) and the incidence of G3+ AEs of neutropenia/infection and G2+ peripheral neuropathy. Elranatamab demonstrated a relatively flat exposure-safety profile. This finding together with the meaningful clinical benefit observed in the MagnetisMM-3 study indicates a favorable benefit-risk for elranatamab at the 76 mg QW/Q2W regimen.

P-316

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Kazuhito Suzuki[1], Morio Matsumoto[2], Naoki Takezako[3], Yasushi Hiramatsu[4], Yotaro Tamai[5], Shingo Yano[1], Kenshi Suzuki[6]

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P-317

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P-317

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P-317

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of severe side effects (5%, 10%, 20%); (3) how pts live with MM Tx (living without Tx, living with Tx at home, living with Tx at a hospital); (4) scientific innovation, defined as a Tx that is either first-in-class or leads to future development of better MM Tx (yes, no); and (5) monthly OOP cost ($100, $500, $1000, $1500). A Tx that provides the opportunity to live without Tx and/or offers scientific innovation was deemed innovative. Subsequently, discrete choice experiment surveys were conducted. Choice data were analyzed using mixed logit (ML) models. **Results:** Forty-seven pts participated in this interim analysis. The average age was 62.4 years; most were female (n=29, 62%) and had experienced relapse (n=30, 64%). The ML model revealed that pts preferred increased PFS, less severe side effects, a Tx that offered life without Tx, scientific innovation, and lower OOP cost. PFS had the highest conditional relative importance (37%) from the pts' perspective, followed by the OOP cost (27%) and how they live with MM Tx (17%). Of the 30 HCPs, 50% were physicians (n=15), 30% were nurses (n=9), and 20% were pharmacists (n=6). The findings of the ML model were consistent with the pt survey. PFS had the highest conditional relative importance from the HCPs' perspective (31%), followed by how pts live with MM Tx (22%) and scientific innovation (19%). **Conclusions:** Our findings show that pts and HCPs positively valued innovative MM Tx that provided the opportunity to live without Tx and/or offered scientific innovation. Not accounting for the value of innovation would result in underestimation of its value and potentially lead to less access to innovation and less R&D investment for future innovation.

P-318

The real-world use and efficacy of pomalidomide for relapsed and refractory multiple myeloma in the era of CD38 antibodies

Agoston Gyula Szabo[1], Jonathan Thorsen[2], Katrine Fladeland Iversen[3], Mette Bøegh Levring[4], Carsten Helleberg[5], Emil Hermansen[5], Søren Thorgaard Bønløkke[6], Katrine Nielsen[6], Elena Manuela Teodorescu[7], Eva Kurt[8], Casper Nørgaard Strandholdt[9], Annette Juul Vangsted[5]

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Introduction: Pomalidomide-dexamethasone (Pd) has been a standard of care treatment for myeloma since 2013. Due to the current treatment algorithms, pomalidomide is mostly used in patients already exposed to a CD38 antibody. However, the clinical performance of pomalidomide in the era of CD38 antibodies is largely unknown. **Methods:** Here we describe the real-world use and efficacy of pomalidomide in a complete Danish, nationwide cohort of daratumumab-exposed patients. We conducted a nationwide retrospective review of the clinical course of all patients treated with a daratumumab-containing regimen prior to 1.1.2019. Treatment data were updated until 1.1.2021. **Results:** We identified 328 patients that were treated with pomalidomide. Of these, 137 received Pd, 65 daratumumab-pomalidomide-dexamethasone (DPD), 43 pomalidomide-cyclophosphamide-dexamethasone (PCD), 19 carfilzomib-pomalidomide-dexamethasone (KPD), 11 pomalidomide-bortezomib-dexamethasone (PVD) and 52 pomalidomide in other combinations. Patients treated with Pd had a partial response or better rate (>=PR) of 35.8% and median time to next treatment (mTNT) of 4.9 months, almost identical to previous prospective clinical trials. Although treatment with the various pomalidomide-containing triplet regimens resulted in higher >=PR rates (PCD: 46.5%, PVD: 63.6%, DPD: 55.4%, KPD: 63.2%), the achieved mTNT was not significantly better than what was achieved with Pd (PCD: 5.4, PVD: 5.3, DPD: 4.7 months). The exemption to this was KPD (mTNT 7.4 months), but this regimen was used earlier in the course of the disease. The most important predictor of outcomes, rather than the choice of index regimen (p=0.72), was prior exposure (p=0.0116). Compared to CD38 antibody-naïve patients, patients previously treated with a CD38 antibody had reduced partial response or better rate (38.0% vs 47.3%), shorter median TNT (4.0 vs 5.9 months), and shorter median OS (12.4 vs 24.2 months) on pomalidomide treatment. **Conclusions:** In this large real-world cohort, the clinical performance of Pd was almost identical to the results of prospective clinical trials. Although treatment with the various pomalidomide-containing triplet regimens resulted in higher response rates, the achieved TNT was not better than what was achieved with Pd. Compared to CD38 antibody-naïve patients, patients previously treated with a CD38 antibody achieved worse outcomes with pomalidomide.

P-319

Efficacy and safety of daratumumab with ixazomib and dexamethasone in lenalidomide-exposed patients after one prior line of therapy: final results of the Phase 2 study DARIA

Evangelos Terpos[1], Ioannis Ntanasis-Stathopoulos[1], Maria Gavriatopoulou[1], Eirini Katodritou[2], Evdoxia Hatjiharissi[3], Panagiotis Malandrakis[1], Evgenia Verrou[2], Alexandros Leonidakis[4], Magdalini Migkou[1], Sosana Delimpasi[5], Argiris Symeonidis[6], Efstathios Kastritis[1], Meletios Dimopoulos[1]

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Efficacy and safety of daratumumab with ixazomib and dexamethasone in lenalidomide-exposed patients after one prior line of therapy: final results of the Phase 2 study DARIA

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of severe side effects (5%, 10%, 20%); (3) how pts live with MM Tx (living without Tx, living with Tx at home, living with Tx at a hospital); (4) scientific innovation, defined as a Tx that is either first-in-class or leads to future development of better MM Tx (yes, no); and (5) monthly OOP cost ($100, $500, $1000, $1500). A Tx that provides the opportunity to live without Tx and/or offers scientific innovation was deemed innovative. Subsequently, discrete choice experiment surveys were conducted. Choice data were analyzed using mixed logit (ML) models. **Results:** Forty-seven pts participated in this interim analysis. The average age was 62.4 years; most were female (n=29, 62%) and had experienced relapse (n=30, 64%). The ML model revealed that pts preferred increased PFS, less severe side effects, a Tx that offered life without Tx, scientific innovation, and lower OOP cost. PFS had the highest conditional relative importance (37%) from the pts' perspective, followed by the OOP cost (27%) and how they live with MM Tx (17%). Of the 30 HCPs, 50% were physicians (n=15), 30% were nurses (n=9), and 20% were pharmacists (n=6). The findings of the ML model were consistent with the pt survey. PFS had the highest conditional relative importance from the HCPs' perspective (31%), followed by how pts live with MM Tx (22%) and scientific innovation (19%). **Conclusions:** Our findings show that pts and HCPs positively valued innovative MM Tx that provided the opportunity to live without Tx and/or offered scientific innovation. Not accounting for the value of innovation would result in underestimation of its value and potentially lead to less access to innovation and less R&D investment for future innovation.

P-318

The real-world use and efficacy of pomalidomide for relapsed and refractory multiple myeloma in the era of CD38 antibodies

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Introduction: Pomalidomide-dexamethasone (Pd) has been a standard of care treatment for myeloma since 2013. Due to the current treatment algorithms, pomalidomide is mostly used in patients already exposed to a CD38 antibody. However, the clinical performance of pomalidomide in the era of CD38 antibodies is largely unknown. **Methods:** Here we describe the real-world use and efficacy of pomalidomide in a complete Danish, nationwide cohort of daratumumab-exposed patients. We conducted a nationwide retrospective review of the clinical course of all patients treated with a daratumumab-containing regimen prior to 1.1.2019. Treatment data were updated until 1.1.2021. **Results:** We identified 328 patients that were treated with pomalidomide. Of these, 137 received Pd, 65 daratumumab-pomalidomide-dexamethasone (DPD), 43 pomalidomide-cyclophosphamide-dexamethasone (PCD), 19 carfilzomib-pomalidomide-dexamethasone (KPD), 11 pomalidomide-bortezomib-dexamethasone (PVD) and 52 pomalidomide in other combinations. Patients treated with Pd had a partial response or better rate (>=PR) of 35.8% and median time to next treatment (mTNT) of 4.9 months, almost identical to previous prospective clinical trials. Although treatment with the various pomalidomide-containing triplet regimens resulted in higher >=PR rates (PCD: 46.5%, PVD: 63.6%, DPD: 55.4%, KPD: 63.2%), the achieved mTNT was not significantly better than what was achieved with Pd (PCD: 5.4, PVD: 5.3, DPD: 4.7 months). The exemption to this was KPD (mTNT 7.4 months), but this regimen was used earlier in the course of the disease. The most important predictor of outcomes, rather than the choice of index regimen (p=0.72), was prior exposure (p=0.0116). Compared to CD38 antibody-naïve patients, patients previously treated with a CD38 antibody had reduced partial response or better rate (38.0% vs 47.3%), shorter median TNT (4.0 vs 5.9 months), and shorter median OS (12.4 vs 24.2 months) on pomalidomide treatment. **Conclusions:** In this large real-world cohort, the clinical performance of Pd was almost identical to the results of prospective clinical trials. Although treatment with the various pomalidomide-containing triplet regimens resulted in higher response rates, the achieved TNT was not better than what was achieved with Pd. Compared to CD38 antibody-naïve patients, patients previously treated with a CD38 antibody achieved worse outcomes with pomalidomide.

P-319

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Introduction: The use of lenalidomide in frontline therapy for patients with newly diagnosed multiple myeloma (MM) has increased the number of those who become refractory to lenalidomide at second line. In this context, we assessed the efficacy of daratumumab in combination with ixazomib and dexamethasone (Dara-Ixa-dex). **Methods:** DARIA was a prospective, open-label, multicenter, phase 2 study. Eligible adult patients had relapsed/refractory MM (RRMM) after one prior line with a lenalidomide-based regimen and a Karnofsky Performance Status (KPS) score of ≥70. Treatment with Dara-Ixa-dex comprised an induction phase of nine 28-days cycles and a maintenance phase. During induction, patients received Dara at the approved schedule, 4mg oral ixazomib (days 1, 8, and 15 of each cycle) and 40mg oral dexamethasone weekly. In maintenance, Dara-Ixa were administered every 4 weeks until disease progression or unacceptable toxicity, with dexamethasone being discontinued. The primary endpoint was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), the toxicity profile of Dara-Ixa-dex, and the effects of the combination on serum bone metabolism markers (C-terminal telopeptide of type 1 collagen [CTX], tartrate-resistant acid phosphatase isoform 5b [TRACP-5b], bone-specific alkaline phosphatase [bALP], and osteocalcin [OC]) from baseline until disease progression. **Results:** Overall, 50 patients were enrolled (median age: 69 (range 50-89) years; males: 28 [56%]). At screening, 38 (76%) patients had a KPS score ≥90, and most were at revised ISS stage I and II (n=47, 94%). 32 (64%) patients were refractory to lenalidomide, and 17 (34%) had prior ASCT. ORR was 64% (n=32); 1 (2%) patient had a complete response, 16 (32%) a very good partial response (VGPR), and 15 (30%) patients had a PR. The median (range) time from first treatment dose until first response (≥PR) was 1.0 (0.9-17.6) month. After a median (range) follow-up of 23.4 (1.1-47.6) months, the median PFS was 8.1 months (95%CI: 5.2-15.8) and the median OS was 39.2 months (95%CI: 17.4-39.3). Regarding bone metabolism indices, the median changes from baseline for CTX, TRACP-5b, bALP and OC were significant ($p< 0.05$) and became evident as early as at 6 months. At the end of the study, 13 (26%) patients were still on treatment; reasons for treatment discontinuation were progressive disease (n=29, 58%), physician's decision and fatal serious adverse event [SAE] (n=3, 6% each), and adverse event [AE] (n=2, 4%). Overall, 20 (40%) patients had ≥1 grade 3/4 AE, the most common being thrombocytopenia (n=10, 20%). 14 (28%) patients had ≥1 SAE, the most common being acute kidney injury and pneumonia (n=2, 4% each). Four fatal SAEs due to infections were reported. **Conclusions:** In conclusion, second-line treatment with Dara-Ixa-dex in patients with RRMM pre-treated with a lenalidomide-based regimen resulted in rapid (< 2 months) and satisfactory responses along with a favorable effect on bone metabolism.

P-320

Iberdomide (IBER) plus dexamethasone (DEX) in patients with relapsed/refractory multiple myeloma (RRMM): a safety analysis from the CC-220-MM-001 trial

Niels van de Donk[1], Darrell White[2], Brea Lipe[3], Abdullah Khan[4], Ruben Niesvizky[5], Albert Oriol[6], Mercedes Gironella Mesa[7], Faiz Anwer[8], Manisha Bhutani[9], Brian McClune[10], Seema Singhal[11], Yiming Cheng[12], Izumi Hamada[12], Kexin Jin[12], Thomas Solomon[12], Kevin Hong[12], Alpesh Amin[12], Paulo Maciag[12], Sagar Lonial[13]

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Introduction: IBER is a novel, oral cereblon (CRBN) E3 ligase modulator (CELMoD™) with enhanced antimyeloma effects compared with immunomodulatory drugs (IMiDs®). In the phase 1/2 CC-220-MM-001 trial (NCT02773030), IBER+DEX showed meaningful clinical activity (overall response rate 32.2% in Cohort B [dose escalation], 26.2% in Cohort D [dose expansion]) in heavily pretreated RRMM; treatment-emergent adverse events (TEAEs) were mostly hematologic, consistent with the profile of a CRBN-modulating drug. Here we report the safety profile of IBER+DEX in Cohorts B and D. **Methods:** Patients (pts) received IBER on days (D) 1–21 at a dose range of 0.3–1.6mg (Cohort B) or at 1.6mg (Cohort D) with weekly DEX (40mg; 20mg if >75 years of age) of each 28-day cycle. Following a dose interruption, the IBER dose may be maintained if neutropenia was the only IBER-related toxicity and granulocyte-colony stimulating factor (G-CSF) was used. Primary endpoints were to determine recommended phase 2 dose (Cohort B) and efficacy (Cohort D); safety was a secondary endpoint. Pharmacokinetics (PK) samples were collected on D8, 15, and 22 in cycles 1–4 and a population PK model was developed to estimate IBER PK exposure, which was correlated with efficacy and safety endpoints to assess exposure–response (ER) relationships. **Results:** As of June 2, 2021, 197 pts had received IBER+DEX (90 in Cohort B, 107 in Cohort D). The most frequent grade (Gr) 3/4 TEAEs were neutropenia (38 [42.2%] pts), anemia (24 [26.7%] pts), and infections (23 [25.6%] pts) in Cohort B, and neutropenia (48 [44.9%] pts), anemia (30 [28.0%] pts), and infections (29 [27.1%] pts) in Cohort D. Excluding infections, Gr 3/4 non-hematologic TEAEs were low. Venous thromboembolism occurred in 4 (4.4%) pts in Cohort B and 5 (4.7%) pts in Cohort D. Seventy-four (82.2%) pts in Cohort B and 95 (88.8%) pts in Cohort D experienced at least 1 TEAE related to IBER. Median

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P-320

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onset of neutropenia, anemia, and thrombocytopenia was < 1 mo (both Cohorts); median time to resolution was ≤0.26 mo (Cohort B) and ≤0.46 mo (Cohort D). TEAEs led to IBER dose interruptions in 47 (52.2%) and 56 (52.3%) pts in Cohorts B and D, and dose reductions in 22 (24.4%) and 20 (18.7%) pts in Cohorts B and D, respectively. Epoetin was used in 15 (16.7%) and 13 (12.1%) pts in Cohorts B and D, and G-CSF was used for neutropenia in 33/44 (75.0%) and 40/66 (60.6%) pts in Cohorts B and D, respectively. TEAEs led to IBER discontinuation in 6 (6.7%) and 5 (4.7%) pts in Cohorts B and D; of these, 3 (3.3%) and 1 (0.9%) pt(s) discontinued due to hematologic TEAEs, respectively. ER analysis showed that a higher IBER PK exposure was associated with a higher probability and earlier occurrence of Gr ≥3 neutropenia (P<0.05) and Gr ≥3 thrombocytopenia (P<0.05). **Conclusions:** The all-oral regimen of IBER+DEX showed a tolerable safety profile in pts with RRMM. TEAEs were manageable with dose modifications, dose interruptions, and G-CSF, and few pts discontinued IBER due to TEAEs.

P-321

Real-world outcomes in myeloma patients with t(11;14): a matched comparison using the Canadian myeloma research group national clinical database

Julia Varghese[1], Christopher Venner[2], Martha Louzada[3], Donna Reece[4], Darrell White[5], Jiandong Su[6], Michael Chu[7], Victor Jimenez-Zepeda[8], Arleigh McCurdy[9], Kevin Song[10], Hira Mian[11], Michael Sebag[12,13], Debra Bergstrom[14], Julie Stakiw[15], Anthony Reiman[16], Rami Kotb[17], Muhammad Aslam[18], Rayan Kaedbey[12], Engin Gul[19], Richard LeBlanc[20]

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Introduction: In myeloma, t(11;14) confers a unique biology including a lymphoplasmacytic phenotype and an association with plasma cell leukemia. Some studies report a favourable while others a worse prognosis, compared to non-t(11;14) cases. Dependence of t(11;14) cells on the BCL-2 pathway offers a potential therapeutic target. We performed a matched comparison of real-world outcomes in patients with and without t(11;14) as a benchmark for future therapy targeting BCL-2 **Methods:** Using the Canadian Myeloma Research Group Database, we identified patients with a t(11;14) diagnosed from 2004-22. Patients were matched with a non-t(11;14) cohort based on age at line 1 of therapy, gender, year of diagnosis and history of ASCT. Outcomes were examined over the first 4 therapy lines. Differences in baseline characteristics, response, and drug exposure were assessed by McNemar's test and Wilcoxon Signed Rank test. Progression-free (PFS) and overall survival (OS) were calculated by the Kaplan-Meier product-limit method **Results:** 234 t(11;14) patients were matched 1:1 with a non-t(11;14) cohort. Baseline characteristics were similar aside from more patients with light chain myeloma (20.0% vs 8.85%; p < 0.05), hyposecretory/oligosecretory/non-IgA/G subtypes (17.0% vs 7.96%; p< 0.05), and del17p (17.7% vs 7.08%; p< 0.05) in the t(11;14) cohort. Comparing the t(11;14) vs non-t(11;14) groups, the majority of patients received bortezomib-based treatment in line 1 (87.4% vs 84.5%; p=0.767) and 62.8% in each arm underwent ASCT. The most common regimens in line 2 were lenalidomide-based (59.2% vs 77.0%; p=0.24) followed by bortezomib-based treatment (39.8% vs 21.1%; p=0.57). In line 2, daratumumab-based treatment was used in 20.3% vs 30.9% (p< 0.05) respectively. Further regimen details will be presented at the meeting. The median PFS in t(11;14) vs non-t(11;14) patients respectively were 44 vs 46 mo (p< 0.05) after line 1, 18 vs 32 mo (p< 0.05) for line 2, 6 vs 13 mo (p=0.79) for line 3 and 3 vs 6 mo (p=0.83) for line 4 treatment. The median OS in t(11;14) vs non-t(11;14) patients respectively were 99 mo vs 128 mo (p=0.47) after line 1, 77 mo in each cohort (p=0.82) after line 2, 43 vs 26 mo (p=0.44) after line 3 and 34 vs 15 mo after line 4 (p=0.82) **Conclusions:** Compared with non-t(11;14), those with t(11;14) had a shorter PFS in lines 1 and 2. Although not yet translating into a worse OS, this merits longer follow up. The t(11;14) group had more high-risk patients that may account for the shorter PFS. A higher-risk molecular subset with concurrent mutated CCND1 may also be present. The PFS difference was most notable in line 2 where heterogenous immunomodulatory-based therapy was used suggesting a differential effect in t(11;14). Daratumumab use was also higher for non-(11;14) cases in line 2. Our large matched comparison in real-world t(11;14) myeloma serves as an important benchmark for studies looking at targeted BCL-2 inhibitors in these patients.

P-322

Real world outcomes of belantamab mafodotin from the UK and Ireland: updated results

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P-321

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Introduction: In myeloma, t(11;14) confers a unique biology including a lymphoplasmacytic phenotype and an association with plasma cell leukemia. Some studies report a favourable while others a worse prognosis, compared to non-t(11;14) cases. Dependence of t(11;14) cells on the BCL-2 pathway offers a potential therapeutic target. We performed a matched comparison of real-world outcomes in patients with and without t(11;14) as a benchmark for future therapy targeting BCL-2 **Methods:** Using the Canadian Myeloma Research Group Database, we identified patients with a t(11;14) diagnosed from 2004-22. Patients were matched with a non-t(11;14) cohort based on age at line 1 of therapy, gender, year of diagnosis and history of ASCT. Outcomes were examined over the first 4 therapy lines. Differences in baseline characteristics, response, and drug exposure were assessed by McNemar's test and Wilcoxon Signed Rank test. Progression-free (PFS) and overall survival (OS) were calculated by the Kaplan-Meier product-limit method **Results:** 234 t(11;14) patients were matched 1:1 with a non-t(11;14) cohort. Baseline characteristics were similar aside from more patients with light chain myeloma (20.0% vs 8.85%; p < 0.05), hyposecretory/oligosecretory/non-IgA/G subtypes (17.0% vs 7.96%; p< 0.05), and del17p (17.7% vs 7.08%; p< 0.05) in the t(11;14) cohort. Comparing the t(11;14) vs non-t(11;14) groups, the majority of patients received bortezomib-based treatment in line 1 (87.4% vs 84.5%; p=0.767) and 62.8% in each arm underwent ASCT. The most common regimens in line 2 were lenalidomide-based (59.2% vs 77.0%; p=0.24) followed by bortezomib-based treatment (39.8% vs 21.1%; p=0.57). In line 2, daratumumab-based treatment was used in 20.3% vs 30.9% (p< 0.05) respectively. Further regimen details will be presented at the meeting. The median PFS in t(11;14) vs non-t(11;14) patients respectively were 44 vs 46 mo (p< 0.05) after line 1, 18 vs 32 mo (p< 0.05) for line 2, 6 vs 13 mo (p=0.79) for line 3 and 3 vs 6 mo (p=0.83) for line 4 treatment. The median OS in t(11;14) vs non-t(11;14) patients respectively were 99 mo vs 128 mo (p=0.47) after line 1, 77 mo in each cohort (p=0.82) after line 2, 43 vs 26 mo (p=0.44) after line 3 and 34 vs 15 mo after line 4 (p=0.82) **Conclusions:** Compared with non-t(11;14), those with t(11;14) had a shorter PFS in lines 1 and 2. Although not yet translating into a worse OS, this merits longer follow up. The t(11;14) group had more high-risk patients that may account for the shorter PFS. A higher-risk molecular subset with concurrent mutated CCND1 may also be present. The PFS difference was most notable in line 2 where heterogenous immunomodulatory-based therapy was used suggesting a differential effect in t(11;14). Daratumumab use was also higher for non-(11;14) cases in line 2. Our large matched comparison in real-world t(11;14) myeloma serves as an important benchmark for studies looking at targeted BCL-2 inhibitors in these patients.

P-322

Real world outcomes of belantamab mafodotin from the UK and Ireland: updated results

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onset of neutropenia, anemia, and thrombocytopenia was < 1 mo (both Cohorts); median time to resolution was ≤0.26 mo (Cohort B) and ≤0.46 mo (Cohort D). TEAEs led to IBER dose interruptions in 47 (52.2%) and 56 (52.3%) pts in Cohorts B and D, and dose reductions in 22 (24.4%) and 20 (18.7%) pts in Cohorts B and D, respectively. Epoetin was used in 15 (16.7%) and 13 (12.1%) pts in Cohorts B and D, and G-CSF was used for neutropenia in 33/44 (75.0%) and 40/66 (60.6%) pts in Cohorts B and D, respectively. TEAEs led to IBER discontinuation in 6 (6.7%) and 5 (4.7%) pts in Cohorts B and D; of these, 3 (3.3%) and 1 (0.9%) pt(s) discontinued due to hematologic TEAEs, respectively. ER analysis showed that a higher IBER PK exposure was associated with a higher probability and earlier occurrence of Gr ≥3 neutropenia (P<0.05) and Gr ≥3 thrombocytopenia (P<0.05). **Conclusions:** The all-oral regimen of IBER+DEX showed a tolerable safety profile in pts with RRMM. TEAEs were manageable with dose modifications, dose interruptions, and G-CSF, and few pts discontinued IBER due to TEAEs.

P-321

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Western Hospitals NHS Foundation Trust; [9]Royal Berkshire NHS Foundation Trust; [10]University Hospital of Wales; [11]North Tees and Hartlepool NHS Foundation Trust; [12]The Clatterbridge Cancer Centre; [13]Manchester University NHS Foundation Trust; [14]University Hospital Waterford; [15]Belfast City Hospital; [16]Worcestershire Acute Hospitals NHS Trust; [17]NHS Greater Glasgow and Clyde; [18]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK; [19]University of Glasgow

Introduction: Belantamab mafodotin (belamaf) is an antibody-drug conjugate therapy for myeloma that targets BCMA on malignant plasma cells. Its role in relapsed/refractory myeloma was demonstrated in the DREAMM-2 trial, where it associated with an overall response rate (ORR) of 31% and frequent ocular toxicity – outcomes that have been replicated in retrospective studies across Europe and the USA. Belamaf monotherapy is available in the UK and Ireland through the named-patient programme (NPP), typically as fifth or higher-line therapy and often after disease progression on pomalidomide; however, outcome data for this population are lacking in the literature. **Methods:** We conducted a multicentre retrospective study across the UK and Ireland of patients receiving belamaf monotherapy within the NPP. Belamaf was administered as per the summary of product characteristics, starting at 2.5 mg intravenously every three weeks. Contributors entered data from routine patient notes into a secure online form. Case registration ran from January 2022 to June 2022 (extending to March 2023 for one centre). Data were cleaned in Microsoft Excel and the Tidyverse for R. Analysis was performed on Stata. The primary endpoint was ORR. Secondary end points included progression-free survival (PFS), duration of response (DOR), overall survival (OS) and adverse events (AEs). The Kaplan-Meier method was used for survival analysis. **Results:** 81 patients were registered across thirteen contributing centres. The median age was 65 years (IQR 58 to 72), with 43% female. Median Charlson co-morbidity index was 2. Where data were available, 26% patients had ISS-III and 65% high-risk cytogenetics. Median lines prior therapy was 5 (IQR 4 to 6), with median time from diagnosis to belamaf of 73 months. 70% patients had had prior autologous stem cell transplant. Unexpectedly, 10% were anti-CD38 naïve. At an interim analysis, with median follow-up of 6.6 months and 4 cycles administered (IQR 2 to 6), 48% (n = 39) had discontinued therapy (PD 40%, death 6%, toxicity 1%, unknown 1%). ORR was 56% with at least VGPR in 30%. Median PFS was 9.3 months (95% CI 3.7 to 13.1); median DOR was 15.9 months (4.1 to not reached); and median OS 17.8 months (7.6 to not reached). Data collection for extended survival analysis is ongoing. Toxicity data were available for 76 patients. 83% experienced any grade AE, the most common being keratopathy, infection and thrombocytopenia, affecting 58%, 36% and 20% of patients, respectively. These were also the most frequent ≥ grade 3 AEs; infection affected 30% of patients (with 4% COVID-related deaths), thrombocytopenia 11%, and keratopathy 7%. AE-associated dose delays or reductions occurred in 43% of patients. **Conclusions:** We report an ORR of 56% in our cohort of UK and Ireland patients receiving belamaf monotherapy under the NPP. We will present at the meeting extended follow-up results and an analysis across clinically relevant covariates to compare these outcomes with other studies of belamaf monotherapy.

P-323

A Phase 3 randomized, open-label trial of selinexor, pomalidomide, and dexamethasone versus elotuzumab, pomalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma

Katja Weisel[1], Ohad Benur[2], Dane Van Domelen[2], Mario Boccadoro[3], Pieter Sonneveld[4]

[1]University Medical Center of Hamburg-Eppendorf, Hamburg, Germany; [2]Karyopharm; [3]Hematology Division, Department of Molecular Biotechnologies and Health Sciences, Cattedra Ematologia, Torino; [4]Erasmus MC Cancer Institute

Introduction: Trial in progress. Increased use of lenalidomide, proteasome inhibitors (PIs) and anti-CD38 monoclonal antibodies (αCD38 mAbs) in early lines of therapy for multiple myeloma (MM) leaves an unmet need for treatments with different mechanisms of action for patients (pts) who develop relapsed and/or refractory MM (RRMM). Selinexor (S), an oral XPO1 inhibitor, and elotuzumab (Elo), a mAb targeting SLAMF7, have novel mechanisms of action and have been evaluated with pomalidomide and dexamethasone (Pd). Results from the phase 1/2 STOMP (NCT02343042) and XPORT-MM-028 (NCT04414475) trials suggest once weekly (QW) SPd was effective in RRMM at S doses of 40mg (SPd-40) or 60mg (SPd-60). SPd-60 had an overall response rate (ORR) of 65% (13/20) and median progression-free survival (mPFS) of 9.5 months (mos). SPd-40 yielded an ORR of 50% (14/28) and mPFS was not reached after a median follow-up time of 12.2 mo. Hematologic adverse events (AEs) included neutropenia, anemia, and thrombocytopenia. Non-hematologic AEs included nausea, fatigue, and weight decrease, all primarily grades 1-2 in severity, with lower rates in SPd-40. In previous studies, EloPd in pts with at least 2 prior lines of therapy yielded an ORR of 53% and mPFS of 10.3 mos. While there are no known prospective randomized studies of EloPd in pts who previously received an aCD38mAb, retrospective studies have reported reduced efficacy. **Methods:** Study design: A Phase 3 randomized, open-label, multicenter trial (NCT05028348) of SPd versus EloPd in pts with RRMM. Select eligibility includes 1-4 prior lines of therapy, including lenalidomide, a PI, and treatment with a regimen that included an αCD38 mAb in the immediate prior line of therapy, but naïve to P, S, and Elo. Randomization stratification factors include number of prior lines, Revised International Staging System (R-ISS) stage, and triple-class refractoriness. The primary objective is to compare the PFS of SPd vs EloPd. The trial consists of two parts. Part 1 assessed the safety and tolerability of S (40 or 60 mg QW) with P (4mg QD on days 1-21) + d (40mg QW) or Elo with Pd to determine the optimal S dose for Part 2. As the study was ongoing, updated data from STOMP and XPORT-MM-028 indicated SPd-40 showed generally comparable efficacy to SPd-60 but with lower AE rates. Thus, SPd-40 was identified as the dose for Part 2. In part 2, ~222 pts will be randomized 1:1 to SPd-40 or EloPd (both administered in 28-day cycles). All pts in the SPd-40 arm will receive dual anti-emetic prophylaxis, such as a 5-HT3 antagonist and olanzapine. Assuming mPFS of 8 mos for SPd vs. 4.8 mos for EloPd (hazard ratio = 0.6), 138 PFS events will provide 85% power to detect superiority at one-sided alpha = 0.025. Secondary

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endpoints include ORR, overall survival, safety and tolerability, and patient-reported quality of life outcomes. Study treatment may continue until progressive disease and all pts will be followed for survival for 3 years.

P-324

LocoMMotion: a prospective, observational, multinational study of real-life current standards of care in patients with relapsed/refractory multiple myeloma–final analysis at 2-year follow-up

Katja Weisel[1], Philippe Moreau[2], Valerio De Stefano[3], Hartmut Goldschmidt[4], Michel Delforge[5], Mohamad Mohty[6], Joanne Lindsey-Hill[7], Dominik Dytfeld[8], Emanuele Angelucci[9], Laure Vincent[10], Aurore Perrot[11], Reuben Benjamin[12], Niels van de Donk[13], Enrique Ocio[14], Ester in't Groen-Damen[15], Tito Roccia[16], Jordan Schecter[17], Imène Haddad[18], Vadim Strulev[19], Lada Mitchell[20], Jozefien Buyze[19], Silva Saarinen[21], Octavio Costa Filho[22], Hermann Einsele[23], María-Victoria Mateos[24]

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P-325

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endpoints include ORR, overall survival, safety and tolerability, and patient-reported quality of life outcomes. Study treatment may continue until progressive disease and all pts will be followed for survival for 3 years.

P-324

LocoMMotion: a prospective, observational, multinational study of real-life current standards of care in patients with relapsed/refractory multiple myeloma–final analysis at 2-year follow-up

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Introduction: The prospective, non-interventional, multinational LocoMMotion study (NCT04035226) demonstrated suboptimal outcomes in patients (pts) with TCE RRMM (Mateos, Leukemia 2022; data cut-off, May 21, 2021). As a complement to LocoMMotion, the prospective, non-interventional, multinational MoMMent study (NCT05160584) was recently initiated to assess the evolving SOC in pts with TCE RRMM. We report the first pooled analysis of the LocoMMotion (final) and MoMMent studies (data cut-off, Oct 27, 2022). **Methods:** Data were pooled from LocoMMotion, with median follow-up (mFU) of 26.4 months (mo; range, 0.1–35.0) in 248 pts enrolled Aug 2019–Oct 2020, and MoMMent, with mFU of 5.1 mo (range, 0.4–10.9) in 54 pts enrolled Nov 2021–Jul 2022. Both studies have similar designs; statistical heterogeneity was investigated using Cochran Q and I-square. Eligible pts received ≥3 prior lines of therapy (LOT; LocoMMotion allowed < 3 prior LOT if pts were double refractory to a PI and IMiD), were TCE, had measurable disease and documented progressive disease since their last LOT, and had an ECOG performance status (PS) score of 0 or 1 at screening. All pts provided informed consent. The primary endpoint was overall response rate (ORR), evaluated per IMWG criteria by the same review committee. Continuous variables were summarized using descriptive statistics, and ORR was reported with 95% exact CIs. Time-to-event data were summarized by Kaplan-Meier methods. **Results:** Pooled analysis included 302 pts with a mFU of 24.4 mo (range, 0.1–35.0). At baseline, median age was 69 years (y), 54% of pts were male, 75.7% had an ECOG PS of 1, and median time since diagnosis was 6.3 y. Pts received a median of 4 prior LOT (range, 2–13), 73.5% were triple-class refractory, and 17.9% were penta-drug refractory. Prior exposure to BCMA-targeting therapies was higher in MoMMent vs LocoMMotion (11% vs 5%). Overall, 102 unique regimens were used as SOC, and 63.9% of pts received regimens comprising ≥3 drugs. Belantamab mafodotin (22% vs 3%) and idecabtagene vicleucel (6% vs 0%) were more common in MoMMent vs LocoMMotion. In the pooled analysis, ORR was 30.8% (95% CI, 25.6–36.3), median progression-free survival (mPFS) was 4.9 mo (95% CI, 4.2–5.7), and median overall survival was 13.83 mo (95% CI, 10.8–16.9). In MoMMent, ORR was 25.9% (95% CI, 15.0–39.7) and mPFS was 4.9 mo (95% CI, 3.1–6.3), consistent with the LocoMMotion results. Overall, 264 (87.4%) pts reported ≥1 any grade treatment-emergent adverse event (TEAE), with 187 (61.9%) reporting ≥1 grade ≥3 TEAE. 23 (7.6%) deaths due to TEAEs occurred on study, mostly due to infection (n=15). **Conclusions:** These initial results suggest that outcomes in pts with TCE RRMM remain poor. A high unmet need remains for pts with TCE RRMM, as evidenced by the observation that bispecific antibody and CAR-T cell therapies are not yet widely utilized. Increased adoption of these novel immunotherapies into SOC is key to improving outcomes. Additional MoMMent data at 9.2 mo mFU will be presented.

P-326

Genome-wide CRISPR screen identifies SPOP as a modulator of IMiDs sensitivity in multiple myeloma

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Introduction: The development of novel agents including immunomodulatory drugs (IMiDs) lenalidomide (Len) and pomalidomide (Pom) has led to improved patient outcomes in multiple myeloma (MM); however, MM patients inevitably experience relapse and drug resistance. The expression level of CRBN, CRBN-binding proteins, and CRL4CRBN ubiquitin ligase is considered to be associated with IMiDs resistance. Clinical studies have shown that MM patients can exhibit IMiDs resistance even without CRBN abnormalities, suggesting the molecular mechanisms of intrinsic resistance to IMiDs are not fully understood. **Methods:** To delineate the molecular mechanisms underlying IMiDs resistance, we performed genome-wide knockout (KO) screening in IMiDs-sensitive MM cells. For in vitro work, we used the MM cell lines MM1S, and H929. We used sgRNA to KO SPOP and BRD4 in MM cells. **Results:** After performing a CRISPR KO screen in MM cells, we discovered that in addition to CRBN and its associated genes, sgRNAs targeting SPOP (speckle-type POZ protein, a speckled zinc finger protein) were highly enriched after treatment with Poma. Importantly, SPOP KO MM cell lines acquire significant resistance to Pom and Len treatment. To examine whether SPOP

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Introduction: The prospective, non-interventional, multinational LocoMMotion study (NCT04035226) demonstrated suboptimal outcomes in patients (pts) with TCE RRMM (Mateos, Leukemia 2022; data cut-off, May 21, 2021). As a complement to LocoMMotion, the prospective, non-interventional, multinational MoMMent study (NCT05160584) was recently initiated to assess the evolving SOC in pts with TCE RRMM. We report the first pooled analysis of the LocoMMotion (final) and MoMMent studies (data cut-off, Oct 27, 2022). **Methods:** Data were pooled from LocoMMotion, with median follow-up (mFU) of 26.4 months (mo; range, 0.1–35.0) in 248 pts enrolled Aug 2019–Oct 2020, and MoMMent, with mFU of 5.1 mo (range, 0.4–10.9) in 54 pts enrolled Nov 2021–Jul 2022. Both studies have similar designs; statistical heterogeneity was investigated using Cochran Q and I-square. Eligible pts received ≥3 prior lines of therapy (LOT; LocoMMotion allowed < 3 prior LOT if pts were double refractory to a PI and IMiD), were TCE, had measurable disease and documented progressive disease since their last LOT, and had an ECOG performance status (PS) score of 0 or 1 at screening. All pts provided informed consent. The primary endpoint was overall response rate (ORR), evaluated per IMWG criteria by the same review committee. Continuous variables were summarized using descriptive statistics, and ORR was reported with 95% exact CIs. Time-to-event data were summarized by Kaplan-Meier methods. **Results:** Pooled analysis included 302 pts with a mFU of 24.4 mo (range, 0.1–35.0). At baseline, median age was 69 years (y), 54% of pts were male, 75.7% had an ECOG PS of 1, and median time since diagnosis was 6.3 y. Pts received a median of 4 prior LOT (range, 2–13), 73.5% were triple-class refractory, and 17.9% were penta-drug refractory. Prior exposure to BCMA-targeting therapies was higher in MoMMent vs LocoMMotion (11% vs 5%). Overall, 102 unique regimens were used as SOC, and 63.9% of pts received regimens comprising ≥3 drugs. Belantamab mafodotin (22% vs 3%) and idecabtagene vicleucel (6% vs 0%) were more common in MoMMent vs LocoMMotion. In the pooled analysis, ORR was 30.8% (95% CI, 25.6–36.3), median progression-free survival (mPFS) was 4.9 mo (95% CI, 4.2–5.7), and median overall survival was 13.83 mo (95% CI, 10.8–16.9). In MoMMent, ORR was 25.9% (95% CI, 15.0–39.7) and mPFS was 4.9 mo (95% CI, 3.1–6.3), consistent with the LocoMMotion results. Overall, 264 (87.4%) pts reported ≥1 any grade treatment-emergent adverse event (TEAE), with 187 (61.9%) reporting ≥1 grade ≥3 TEAE. 23 (7.6%) deaths due to TEAEs occurred on study, mostly due to infection (n=15). **Conclusions:** These initial results suggest that outcomes in pts with TCE RRMM remain poor. A high unmet need remains for pts with TCE RRMM, as evidenced by the observation that bispecific antibody and CAR-T cell therapies are not yet widely utilized. Increased adoption of these novel immunotherapies into SOC is key to improving outcomes. Additional MoMMent data at 9.2 mo mFU will be presented.

P-326

Genome-wide CRISPR screen identifies SPOP as a modulator of IMiDs sensitivity in multiple myeloma

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Introduction: The development of novel agents including immunomodulatory drugs (IMiDs) lenalidomide (Len) and pomalidomide (Pom) has led to improved patient outcomes in multiple myeloma (MM); however, MM patients inevitably experience relapse and drug resistance. The expression level of CRBN, CRBN-binding proteins, and CRL4CRBN ubiquitin ligase is considered to be associated with IMiDs resistance. Clinical studies have shown that MM patients can exhibit IMiDs resistance even without CRBN abnormalities, suggesting the molecular mechanisms of intrinsic resistance to IMiDs are not fully understood. **Methods:** To delineate the molecular mechanisms underlying IMiDs resistance, we performed genome-wide knockout (KO) screening in IMiDs-sensitive MM cells. For in vitro work, we used the MM cell lines MM1S, and H929. We used sgRNA to KO SPOP and BRD4 in MM cells. **Results:** After performing a CRISPR KO screen in MM cells, we discovered that in addition to CRBN and its associated genes, sgRNAs targeting SPOP (speckle-type POZ protein, a speckled zinc finger protein) were highly enriched after treatment with Poma. Importantly, SPOP KO MM cell lines acquire significant resistance to Pom and Len treatment. To examine whether SPOP

KO-induced IMiDs resistance was CRBN-pathway dependent, we assessed CRBN and its downstream interacting protein levels. SPOP KO showed no effect on CRBN expression; moreover, IMiDs can still trigger IKZF1 and IKZF3 degradation, associated with the downregulation of IRF4, suggesting that SPOP mediates sensitivity to IMiDs in a mechanism independent of CRBN-IKZF1/3 axis. Compared to plasma cells from normal donors, we found that the expression levels of SPOP were significantly decreased in MGUS patients, smoldering myeloma patients, newly diagnosed MM patients, and refractory relapsed MM patients (p-values: 2.4e-2, 2.0e-4, 9.9e-3, 3.17e-6, respectively). SPOP is the adaptor protein of the Cullin3-RING ubiquitin ligase complex. Therefore, the function of SPOP is determined by the characteristics of the substrates it recruits. We performed immunoprecipitation with overexpressed SPOP in MM cells, followed by mass spectrometry analysis, and identified BRD4 as a candidate protein binding to SPOP in MM, which was confirmed by Co-IP. KO of SPOP upregulated the protein level of BRD4 in MM cells. In SPOP KO MM cells, KO of BRD4 resulted in the restoration of MM cell sensitivity to IMiDs treatment. BRD4 plays a significant role in the development and progression of various tumors. The BRD4 inhibitor JQ1 has been shown to exhibit anti-tumor effects in multiple types of cancer. We found that combination treatment with JQ-1 and IMiDs reversed IMiDs resistance of SPOP KO MM cell lines and primary MM cells from relapsed patients. **Conclusions:** Our data show that SPOP is a CRBN-independent modulator of IMiDs sensitivity by regulating BRD4 and provides the preclinical rationale for combining IMiDs with BRD4 inhibitors to overcome IMiDs resistance and improve patient outcomes.

P-327

Hyposecretory progression pattern indicates inferior survival of multiple myeloma

Jingyu Xu[1], Wenqiang Yan[1], Huishou Fan[2], Lugui Qiu[1], Gang An[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [2]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union Medical College

Introduction: Almost all MM patients will eventually progress and relapse either asymptomatically or with end-organ damage. At progression patients always present different features with different levels of M protein and plasma cells in bone marrow (BMPC). Interestingly, some patients who are secretory MM types at diagnosis show higher BMPC percentage but lower M protein when PD. The recognition of this subgroup is still unclear.We evaluated the effect of different progression patterns on the survival according to M protein and BMPC percentage. **Methods:** We analyzed baseline and progression features of 211 patients between January 1, 2013 to June 1, 2021 in our hospital. We classify the PD patterns as 3 groups according to the M protein and clonal PCs in bone marrow: a. hyposecretory progression (HypoP) means > 10% increase of the absolute percentage of BMPCs but serum M-protein increase < 5g/L; b. extramedullary progression (EMP) means appearance of a new extramedullary lesion; c. classic progression (ClaP) means any one or more of the other PD criteria according to IMWG criteria. HRCA is defined as the presence of t (4;14), t (14;16) or del (17p) by FISH. Time from the first relapse to death as overall survival after relapse (rel-OS). **Results:** We retrospectively analyzed 12 patients (5.7%) and 30 (14.2%) patients who met the new definition of HypoP and EMP, respectively, and 169 (80.1%) patients can be classified as ClaP group. Interestingly, different to other 2 groups, female patients shared more percentage (66.7%) and IgA (50.0%) as well as light chain (41.7%) were the two most common M protein types in HypoP group. As for the clinical features, HypoP patients were more likely to suffer from hypercalcemia, renal dysfunction and lower serum M protein level both at diagnosis and progression. Also, there were more percentage patients in EMP (50.0% and 53.3%) and HypoP (41.7% and 66.7%) presenting HRCA both at diagnosis and progression. The median follow-up is 42.9m (7.8-99.7m). Patients in ClaP and EMP groups experienced similar PFS whereas HypoP patients had significantly shorter median PFS (P=0.001, 20.6m vs. 22.8m vs. 12.9m). We also found that compared to ClaP and EMP groups, patients with HypoP feature had inferior median OS (P< 0.001, 68.4m vs. 47.2m vs. 25.9m) and rel-OS (P< 0.001, 31.2m vs. 16.6m vs. 8.9m). Besides, a Cox-regression multivariate analysis showed ISS-III (HR 0.471, 95% CI 0.312-0.712; P=0.001), higher LDH (HR 0.519, 95% CI 0.310-0.869, P=0.04), EMP (HR 0.547, 95% CI 0.331-0.904. P=0.019) and HypoP (HR 0.241, 95% CI 0.107-0.543. P=0.001) were associated with shorter OS. **Conclusions:** In conclusion, our results indicate that the patients at progression presenting increased BMPC but lower M protein are inclined to have aggressive features such as hypercalcemia, renal dysfunction and lower serum M protein level both at diagnosis and progression. Also, the hyposecretory progression pattern is a valuable indicator of inferior survival compared to other progression patterns.

P-328

Talquetamab vs real-world physician's choice of therapy (RWPC): comparative efficacy in patients (pts) with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM)

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KO-induced IMiDs resistance was CRBN-pathway dependent, we assessed CRBN and its downstream interacting protein levels. SPOP KO showed no effect on CRBN expression; moreover, IMiDs can still trigger IKZF1 and IKZF3 degradation, associated with the downregulation of IRF4, suggesting that SPOP mediates sensitivity to IMiDs in a mechanism independent of CRBN-IKZF1/3 axis. Compared to plasma cells from normal donors, we found that the expression levels of SPOP were significantly decreased in MGUS patients, smoldering myeloma patients, newly diagnosed MM patients, and refractory relapsed MM patients (p-values: 2.4e-2, 2.0e-4, 9.9e-3, 3.17e-6, respectively). SPOP is the adaptor protein of the Cullin3-RING ubiquitin ligase complex. Therefore, the function of SPOP is determined by the characteristics of the substrates it recruits. We performed immunoprecipitation with overexpressed SPOP in MM cells, followed by mass spectrometry analysis, and identified BRD4 as a candidate protein binding to SPOP in MM, which was confirmed by Co-IP. KO of SPOP upregulated the protein level of BRD4 in MM cells. In SPOP KO MM cells, KO of BRD4 resulted in the restoration of MM cell sensitivity to IMiDs treatment. BRD4 plays a significant role in the development and progression of various tumors. The BRD4 inhibitor JQ1 has been shown to exhibit anti-tumor effects in multiple types of cancer. We found that combination treatment with JQ-1 and IMiDs reversed IMiDs resistance of SPOP KO MM cell lines and primary MM cells from relapsed patients. **Conclusions:** Our data show that SPOP is a CRBN-independent modulator of IMiDs sensitivity by regulating BRD4 and provides the preclinical rationale for combining IMiDs with BRD4 inhibitors to overcome IMiDs resistance and improve patient outcomes.

P-327

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Introduction: Almost all MM patients will eventually progress and relapse either asymptomatically or with end-organ damage. At progression patients always present different features with different levels of M protein and plasma cells in bone marrow (BMPC). Interestingly, some patients who are secretory MM types at diagnosis show higher BMPC percentage but lower M protein when PD. The recognition of this subgroup is still unclear.We evaluated the effect of different progression patterns on the survival according to M protein and BMPC percentage. **Methods:** We analyzed baseline and progression features of 211 patients between January 1, 2013 to June 1, 2021 in our hospital. We classify the PD patterns as 3 groups according to the M protein and clonal PCs in bone marrow: a. hyposecretory progression (HypoP) means > 10% increase of the absolute percentage of BMPCs but serum M-protein increase < 5g/L; b. extramedullary progression (EMP) means appearance of a new extramedullary lesion; c. classic progression (ClaP) means any one or more of the other PD criteria according to IMWG criteria. HRCA is defined as the presence of t (4;14), t (14;16) or del (17p) by FISH. Time from the first relapse to death as overall survival after relapse (rel-OS). **Results:** We retrospectively analyzed 12 patients (5.7%) and 30 (14.2%) patients who met the new definition of HypoP and EMP, respectively, and 169 (80.1%) patients can be classified as ClaP group. Interestingly, different to other 2 groups, female patients shared more percentage (66.7%) and IgA (50.0%) as well as light chain (41.7%) were the two most common M protein types in HypoP group. As for the clinical features, HypoP patients were more likely to suffer from hypercalcemia, renal dysfunction and lower serum M protein level both at diagnosis and progression. Also, there were more percentage patients in EMP (50.0% and 53.3%) and HypoP (41.7% and 66.7%) presenting HRCA both at diagnosis and progression. The median follow-up is 42.9m (7.8-99.7m). Patients in ClaP and EMP groups experienced similar PFS whereas HypoP patients had significantly shorter median PFS (P=0.001, 20.6m vs. 22.8m vs. 12.9m). We also found that compared to ClaP and EMP groups, patients with HypoP feature had inferior median OS (P< 0.001, 68.4m vs. 47.2m vs. 25.9m) and rel-OS (P< 0.001, 31.2m vs. 16.6m vs. 8.9m). Besides, a Cox-regression multivariate analysis showed ISS-III (HR 0.471, 95% CI 0.312-0.712; P=0.001), higher LDH (HR 0.519, 95% CI 0.310-0.869, P=0.04), EMP (HR 0.547, 95% CI 0.331-0.904. P=0.019) and HypoP (HR 0.241, 95% CI 0.107-0.543. P=0.001) were associated with shorter OS. **Conclusions:** In conclusion, our results indicate that the patients at progression presenting increased BMPC but lower M protein are inclined to have aggressive features such as hypercalcemia, renal dysfunction and lower serum M protein level both at diagnosis and progression. Also, the hyposecretory progression pattern is a valuable indicator of inferior survival compared to other progression patterns.

P-328

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P-327

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P-328

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Introduction: In MonumenTAL-1 (NCT03399799/NCT04634552), talquetamab, a G protein–coupled receptor family C group 5 member D × CD3 bispecific antibody, had an overall response rate of >71% in TCE pts with RRMM who received ≥3 prior lines of therapy (LOT). To assess the relative effectiveness of both recommended phase 2 doses (RP2Ds) of talquetamab vs RWPC, adjusted comparisons were performed using individual patient-level data from MonumenTAL-1 and the Flatiron Health MM cohort database study (Flatiron). **Methods:** An external control arm for MonumenTAL-1 was created from eligible pts in the Flatiron database (data cut-off [DCO] Aug 2022) who met key MonumenTAL-1 eligibility criteria (N=629 with 1169 eligible LOT). Individual patient-level data from MonumenTAL-1 were included for pts who received subcutaneous (SC) talquetamab 0.4 mg/kg weekly (QW; n=143) and SC talquetamab 0.8 mg/kg every other week (Q2W; n=145) utilizing a Jan 17, 2023 DCO. In the base model, baseline characteristics of prognostic variables (refractory status, cytogenetic risk, International Staging System stage, time to disease progression on last LOT, number of prior LOT, time since diagnosis, age, and hemoglobin) were adjusted using inverse probability of treatment weighting. The full model was adjusted for the base model variables as well as prior stem cell transplant, ECOG performance status, race, sex, and MM type. Efficacy outcomes were progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS). A weighted Cox proportional hazards model was used to derive hazard ratios (HRs) and 95% CIs for time-to-event endpoints; a weighted Kaplan-Meier method was used to derive median time-to-events. Sensitivity analyses assessed the impact of alternative statistical methods and variable adjustment. **Results:** After weighting, baseline characteristics were balanced across cohorts, with standardized mean differences < 0.2. In the base case analysis, compared with RWPC, pts treated with both RP2Ds of talquetamab had significantly improved PFS (QW: 7.5 vs 4.0 months [mo], HR=0.55, 95% CI 0.44–0.69, P< 0.0001; Q2W: 14.2 vs 4.0 mo, HR=0.40, 95% CI 0.31–0.53, P< 0.0001), TTNT (QW: 9.1 vs 5.1 mo, HR=0.59, 95% CI 0.47–0.74, P< 0.0001; Q2W: 13.3 vs 5.1 mo, HR=0.45, 95% CI 0.35–0.59, P< 0.0001), and OS (QW: not reached vs 16.5 mo, HR=0.56, 95% CI 0.40–0.78, P=0.0007; Q2W: not reached vs 15.9 mo, HR=0.48, 95% CI 0.33–0.70, P=0.0002). The fully adjusted models and sensitivity analyses remained in favor of talquetamab for both RP2Ds, consistent with the base case. **Conclusions:** Both RP2Ds of talquetamab significantly improved effectiveness vs RWPC across all outcomes. These data highlight the potential of talquetamab as an effective treatment option in pts with TCE RRMM and support the rationale of planned prospective trials to compare talquetamab with standard of care regimens in this patient population.

P-329

A phase II study of daratumumab with weekly carfilzomib, pomalidomide, and dexamethasone in relapsed and refractory multiple myeloma

Andrew Yee[1], Omar Nadeem[2], Jacalyn Rosenblatt[3], Adam Sperling[2], Giada Bianchi[4], Nikhil Munshi[5], Elizabeth O'Donnell[1], Andrew Branagan[1], David Avigan[3], Jessica Liegel[3], Cynthia Harrington[1], Emerentia Agyemang[1], Kathleen Lively[1], Lisette Packer[1], Samuel Han[1], Cole Minsky[1], Manal Riadi[1], Cailin McVey[2], Kaleigh Donnelly[2], Caitlin Smith[3], Mackenna Katzeff[2], Amy Goguen[2], Nora Horick[1], Paul Richardson[2], Noopur Raje[1]

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Introduction: Daratumumab (dara), carfilzomib (K), pomalidomide (P), and dexamethasone (d) are established therapies in relapsed multiple myeloma (MM) with activity in 3-drug combinations including: dara Kd; dara Pd; and KPd. The paradigm in MM is moving towards more intensive and well-tolerated combinations to achieve deeper and more durable responses while ensuring tolerability. Quadruplet regimens are now becoming standard in newly diagnosed MM, and we explored a 4-drug regimen in relapsed disease. A phase 2 study of dara KPd with a twice/week schedule of K showed an ORR of 89% in pts with a median of 1 prior line (Derman B et al., Blood Adv 2023). Here we report an ongoing study of dara with weekly KPd (dara wKPd) to improve the schedule and tolerability of this regimen. **Methods:** This phase 2 study (NCT04176718) enrolled pts with relapsed/refractory MM who received at least 1 prior therapy, including both lenalidomide and a proteasome inhibitor. Prior therapy with dara, K, or P was permitted except for K and P given together as last line of therapy. Dara wKPd was given on a 28-day schedule, and dara was given according to the dara Pd schedule. An initial cohort (N=16) received dara 16 mg/kg iv (with 1st dose split over two days); the trial was amended to dara 1800 mg sc. K 56 mg/m^2 iv was given weekly on days 1, 8, 15 for cycles 1-12 and days 1, 15 for cycles 13+; for C1D1, dose was 20 mg/m^2. P 4 mg was given po on days 1-21. Dex 40 mg was given weekly with the dose split over two days. Treatment was until progression or unacceptable toxicity. The primary endpoints were overall response and the safety profile of dara wKPd. Secondary endpoints included PFS. **Results:** We enrolled 44 pts, and accrual is complete. Median age was 66 (range 42-73), and median number of prior lines was 2 (range 1-5). All pts were refractory to their last line of therapy and all had prior lenalidomide and proteasome inhibitor. Prior therapies included: pomalidomide (48%), bortezomib (93%), carfilzomib (16%), ixazomib (43%), daratumumab (9%), auto SCT (34%), and ide-cel (2%). High risk FISH: del 17p (20%); t(14;16) (5%); gain of 1q (45%). Median follow up was 10.9 months. 3 pts came off study due to neutropenia leading to delay in treatment. Overall response rate was 98% (PR 27%, VPGR 50%, CR 20%). Median PFS was 30.9 months (95% CI 30.5-not

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Introduction: In MonumenTAL-1 (NCT03399799/NCT04634552), talquetamab, a G protein–coupled receptor family C group 5 member D × CD3 bispecific antibody, had an overall response rate of >71% in TCE pts with RRMM who received ≥3 prior lines of therapy (LOT). To assess the relative effectiveness of both recommended phase 2 doses (RP2Ds) of talquetamab vs RWPC, adjusted comparisons were performed using individual patient-level data from MonumenTAL-1 and the Flatiron Health MM cohort database study (Flatiron). **Methods:** An external control arm for MonumenTAL-1 was created from eligible pts in the Flatiron database (data cut-off [DCO] Aug 2022) who met key MonumenTAL-1 eligibility criteria (N=629 with 1169 eligible LOT). Individual patient-level data from MonumenTAL-1 were included for pts who received subcutaneous (SC) talquetamab 0.4 mg/kg weekly (QW; n=143) and SC talquetamab 0.8 mg/kg every other week (Q2W; n=145) utilizing a Jan 17, 2023 DCO. In the base model, baseline characteristics of prognostic variables (refractory status, cytogenetic risk, International Staging System stage, time to disease progression on last LOT, number of prior LOT, time since diagnosis, age, and hemoglobin) were adjusted using inverse probability of treatment weighting. The full model was adjusted for the base model variables as well as prior stem cell transplant, ECOG performance status, race, sex, and MM type. Efficacy outcomes were progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS). A weighted Cox proportional hazards model was used to derive hazard ratios (HRs) and 95% CIs for time-to-event endpoints; a weighted Kaplan-Meier method was used to derive median time-to-events. Sensitivity analyses assessed the impact of alternative statistical methods and variable adjustment. **Results:** After weighting, baseline characteristics were balanced across cohorts, with standardized mean differences < 0.2. In the base case analysis, compared with RWPC, pts treated with both RP2Ds of talquetamab had significantly improved PFS (QW: 7.5 vs 4.0 months [mo], HR=0.55, 95% CI 0.44–0.69, P< 0.0001; Q2W: 14.2 vs 4.0 mo, HR=0.40, 95% CI 0.31–0.53, P< 0.0001), TTNT (QW: 9.1 vs 5.1 mo, HR=0.59, 95% CI 0.47–0.74, P< 0.0001; Q2W: 13.3 vs 5.1 mo, HR=0.45, 95% CI 0.35–0.59, P< 0.0001), and OS (QW: not reached vs 16.5 mo, HR=0.56, 95% CI 0.40–0.78, P=0.0007; Q2W: not reached vs 15.9 mo, HR=0.48, 95% CI 0.33–0.70, P=0.0002). The fully adjusted models and sensitivity analyses remained in favor of talquetamab for both RP2Ds, consistent with the base case. **Conclusions:** Both RP2Ds of talquetamab significantly improved effectiveness vs RWPC across all outcomes. These data highlight the potential of talquetamab as an effective treatment option in pts with TCE RRMM and support the rationale of planned prospective trials to compare talquetamab with standard of care regimens in this patient population.

P-329

A phase II study of daratumumab with weekly carfilzomib, pomalidomide, and dexamethasone in relapsed and refractory multiple myeloma

Andrew Yee[1], Omar Nadeem[2], Jacalyn Rosenblatt[3], Adam Sperling[2], Giada Bianchi[4], Nikhil Munshi[5], Elizabeth O'Donnell[1], Andrew Branagan[1], David Avigan[3], Jessica Liegel[3], Cynthia Harrington[1], Emerentia Agyemang[1], Kathleen Lively[1], Lisette Packer[1], Samuel Han[1], Cole Minsky[1], Manal Riadi[1], Cailin McVey[2], Kaleigh Donnelly[2], Caitlin Smith[3], Mackenna Katzeff[2], Amy Goguen[2], Nora Horick[1], Paul Richardson[2], Noopur Raje[1]

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P-330

The third-generation genetic engineered mouse model of late-stage multiple myeloma

Jianhong Lin[1], Mohsin Maqbool[1], Kylin Emhoff[1], Tyler Alban[1], Hanna Hong[2], Eric Irons[1], Wanying Zhang[1], Rie Maeda[2], Sarah Ondrejka[3], Megan Nakashima[3], Faiz Anwer[4], Jason Valent[4], Jennifer Yu[1], Timothy Chan[1], Justin Lathia[1], Jianjun Zhao[1]

[1]Cleveland Clinic Lerner Research Institute; [2]Cleveland Clinic Lerner College of Medicine; [3]Cleveland Clinic; [4]Cleveland Clinic Taussig Cancer Institute

Introduction: There exists, as of yet, no genetically engineered mouse model (GEMM) with which to simultaneously investigate multiple genetic perturbations in vivo. This is due to (i) lack of a non-leaky germinal center B cell specific Cre mouse, and (ii) lack of an inducible Cre mouse that can simultaneously induce dysregulation of multiple genes in the adult animal. Many genes of interest in MM are either embryonically lethal or cause other neoplasia development in AID-Cre, KRASG12D mice and in Cγ1-Cre, NRASQ61R mice leading, in the latter, to death prior to overt MM development. For these reasons, studies of MM tumorigenesis in the conditional transgenic mouse have been severely restricted by the "leakiness" of AID-Cre mice and Cγ1-Cre mice currently in use. There is therefore an urgent need for a newer system with which to activate genetic mutations or their expression simultaneously in the germinal-center B-cells only in adult mice. **Methods:** We recently created the brand new AIDCreERT2 +/-, EYFP LSL/-, P53 L/L, KrasG12D LSL/-, cMYCLSL/- (AEY-PKM) mouse model, with germinal center B cell restricted overexpression of KrasG12D and cMYC, along with homozygous deletion of P53. Unlike AID-Cre+/- mice, AIDCreERT2 +/- mice express Cre recombinase under the control of an AID promoter and tamoxifen. **Results:** Mice carrying a combination of these traits developed clonal expansion of clonal CD138+ MM cells in the bone marrow and experienced MGUS and MM as they aged (100% of mice after 6 months of age). These studies are the first demonstration of the driving impact of this combination of genes in MM development. AEY-P(K/Q/V)M mice required only ~5 months to develop MGUS and then MM. By comparing the WGS data from these murine MM cell lines, we found most of them to consist of missense mutations and C to T mutations indicative of the germinal center AID process in these cell lines. Fewer secondary genetic mutations are needed for transformation in AEY-PKM and AEY-PM cells to MM cells in comparation with VK*MYC MM cell lines. We also identified similar common mutations in all four mouse myeloma cells lines, including for example Sp140, which was also found in recently published MM patients' data. In our 10X scRNA seq studies using bone marrow samples from 3 AEY-PM, 3 AEY-PKM, 3 AEY-PQM and 3 AEY-PVM bone marrow cells to identify distinct gene signatures from different immune cell populations. We stratified bone marrow immune cells from MM patients into 19 cell clusters. By means of scRNA seq analysis, we then identified the topmost upregulated and downregulated genes in each immune cell cluster. In combination with 5'BCR and 5'TCR seq, we also verified that all the MM tumor developed from AEY-PM, AEY-PKM, AEY-PQM, and AEY-PVM were IgG1 type. **Conclusions:** Our newly generated third generation AEY-PK/V/QM mice with short latency and high penetrance are feasible for preclinical studies without the need of transplantation avoided potential Graft vs. Host Disease (GVHD) from different mice.

P-331

Targeting gut microbial nitrogen recycling and cellular uptake of ammonium to improve bortezomib resistance in multiple myeloma

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Introduction: Gut microbe alterations are closely related to the tumorigenesis and development of cancers. However, the relationship between gut microbe and drug resistance of multiple myeloma (MM) has not been reported. **Methods:** The feces and serum samples of healthy donors (HD), newly diagnosed MM patients (ND) and relapsed MM patients (RM) come from multiple clinical institutions (License number: 202305359). The 5TGM1 MM mouse models were prepared to examine the effect of nitrogen-recycling bacteria on MM in vivo (License number: D2022058). **Results:** To probe the difference in gut microbe between HD and MM patients, we performed shotgun metagenomic sequencing of fecal samples from a cohort of HD, ND and RM, and found that ND and RM show a significantly higher alpha diversity and Citrobacter freundii (CFr) was significantly enriched in RM. Owing

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P-330

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P-330

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to CFr is a nitrogen-recycling bacteria, we detected the concentration of NH4+ in MM patient's feces and serum, and found that NH4+ increased significantly in RM, and the relative abundance of CFr was positively correlated with NH4+ in feces and serum of RM. Subsequently, we confirmed that NH4+ can promote the drug resistance of MM cells to bortezomib (BTZ) through in vitro and in vivo experiments. Meanwhile, we constructed a CFr deaminase gene deletion (CFr-KO) strain, and found that CFr produces a large fraction of NH4+ by expressing deaminases, and NH4+ molecules produced in the intestinal tract subsequently enter the circulation and eventually travel to the bone marrow, causing MM cells to become resistant to BTZ. Finally, we treated MM cells with NH4+ and detected the expression of resistance related protein. It was found that NH4+ can upregulate the expression of NEK2, and NH4+ can increase the acetylation of NEK2 and reduce its ubiquitin degradation, thus maintaining its protein stability. SLC12A2 as the key transmembrane transporter that mediates the uptake of NH4+ by MM cells, we discovered that furosemide sodium (Fus) can downregulate the expression of SLC12A2 in MM cells. Fus inhibits NH4+ uptake in MM cells and reduces the BTZ resistance-promoting effects of NH4+ supplementation in vitro and in vivo. Next, we analyzed the effect of Fus treatment in MM patients, finding that the MM patients treated with Fus achieved longer progression-free survival and higher curative effect scores. Finally, to explore additional strategies for tackling drug resistance in MM, we performed single Clostridium butyricum (CBu) and triple probiotic (TPro) transplantation by gavage, and we found that in keeping with the effect of CBu transplantation, TPro, an FDA-approved clinical drug, exhibited consistent efficacy in alleviating BTZ resistance. **Conclusions:** In summary, we identify, for the first time, CFr and NH4+ as key modulators of MM relapse, unveil novel molecular mechanisms for drug resistance in MM patients, and provide new therapeutic strategies for the intervention of MM progression and drug resistance.

P-332

Challenge accepted: copy number detection by digitalMLPA on small DNA quantities and low tumour content

Lilit Atanesyan[1], Charlotte Enright[1], Suvi Savola[1]

[1]MRC Holland

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P-333

Multi-omic analysis of multiple myeloma subtypes reveals epigenetic programs of high-risk disease

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to CFr is a nitrogen-recycling bacteria, we detected the concentration of NH4+ in MM patient's feces and serum, and found that NH4+ increased significantly in RM, and the relative abundance of CFr was positively correlated with NH4+ in feces and serum of RM. Subsequently, we confirmed that NH4+ can promote the drug resistance of MM cells to bortezomib (BTZ) through in vitro and in vivo experiments. Meanwhile, we constructed a CFr deaminase gene deletion (CFr-KO) strain, and found that CFr produces a large fraction of NH4+ by expressing deaminases, and NH4+ molecules produced in the intestinal tract subsequently enter the circulation and eventually travel to the bone marrow, causing MM cells to become resistant to BTZ. Finally, we treated MM cells with NH4+ and detected the expression of resistance related protein. It was found that NH4+ can upregulate the expression of NEK2, and NH4+ can increase the acetylation of NEK2 and reduce its ubiquitin degradation, thus maintaining its protein stability. SLC12A2 as the key transmembrane transporter that mediates the uptake of NH4+ by MM cells, we discovered that furosemide sodium (Fus) can downregulate the expression of SLC12A2 in MM cells. Fus inhibits NH4+ uptake in MM cells and reduces the BTZ resistance-promoting effects of NH4+ supplementation in vitro and in vivo. Next, we analyzed the effect of Fus treatment in MM patients, finding that the MM patients treated with Fus achieved longer progression-free survival and higher curative effect scores. Finally, to explore additional strategies for tackling drug resistance in MM, we performed single Clostridium butyricum (CBu) and triple probiotic (TPro) transplantation by gavage, and we found that in keeping with the effect of CBu transplantation, TPro, an FDA-approved clinical drug, exhibited consistent efficacy in alleviating BTZ resistance. **Conclusions:** In summary, we identify, for the first time, CFr and NH4+ as key modulators of MM relapse, unveil novel molecular mechanisms for drug resistance in MM patients, and provide new therapeutic strategies for the intervention of MM progression and drug resistance.

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Challenge accepted: copy number detection by digitalMLPA on small DNA quantities and low tumour content

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P-334

Fluorescence in situ hybridization (FISH) t(11;14) testing practices over time in patients with newly diagnosed multiple myeloma (MM) in the USA in the Flatiron Health database

Linda Baughn[1], Sophia Li[2], Rongrong Wang[2], Faiza Zafar[2], Archibong Yellow-Duke[2], Vivek Chopra[2], Allicia Girvan[3], Shaji Kumar[1]

[1]Mayo Clinic, Rochester, MN, US; [2]Genentech, Inc., South San Francisco, CA, US; [3]AbbVie, Inc. North Chicago, IL, US

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P-335

Small nucleotide, copy number and structural variants cooperate to hijack driver genes in extramedullary progression of myeloma

Nicholas Bingham[1], Jaynish Shah[1], Antonia Reale[1], Daniel Wong[1], Tiffany Khong[1], Sridurga Mithraprabhu[1], Andrew Spencer[1]

[1]Alfred Health-Monash University, Melbourne, VIC, Australia

Introduction: Extramedullary disease (EMD) affects up to 30% of multiple myeloma (MM) patients, predicting poor overall survival due to aggressive disease kinetics and multi-drug resistance. Elucidating EMD genomics may inform targeted treatment approaches. **Methods:** We obtained EMD samples from 15 patients (n=8 fresh and n=7 formalin-fixed, paraffin embedded). Second EMD biopsies were taken in n=3, with n=1 having 3 sequential EMD biopsies. Germline variants were excluded using buccal swab DNA. DNA was extracted using QIAGEN DNeasy kit prior to whole genome sequencing (WGS) (30x; xGen PRISM library preparation; Illumina Novaseq). Bioinformatics identified short

Sequencing was performed on short-read instruments (Illumina) and aligned to the GRCh38 genome with Bismark. DNAm values were obtained at 5x coverage at 16,374,655 CpGs in 90% of samples with an average coverage of 24x. Data were compared to WGBS from the BluePrint project. CoMMpass samples had 100% matching germline and somatic genetic data and 93% had matching RNA-seq. **Results:** Analysis of newly diagnosed MM samples (N=370/415) showed median DNAm was 45% (23-77%), which was significantly less than 69% in normal plasma cells. MM-specific hypomethylation occurred in large, late-replicating domains of the genome. In contrast, normal plasma cells and other B cell malignancies (CLL), showed no reduction in DNAm at late replicating regions. Cross-sectional analysis of RNA and DNAm in cis found 170,777 loci associated with expression, with most (98%) positively associated with transcription and found in gene bodies. Unsupervised t-SNE analysis of DNAm data grouped samples by expression subtype with the NSD2/MMSET (MS) and Proliferation (PR) subtypes more clearly defined by DNAm than RNA-seq. The MS and PR subtypes had 2,075,489 and 418,474 differentially methylated loci (DML), respectively. However, the MS subtype had more DNAm (92% of DML being higher) whereas the PR subtype had less DNAm (99.95% of DML being lower) as compared to other subtypes. Ablation of NSD2 resulted in reduced DNAm, indicating MS subtype hypermethylation was specific to NSD2 expression and excessive H3K36me2. In contrast, no individual gene could be ascribed to PR subtype hypomethylation, but hypomethylation of these loci were prognostic of outcome and lost DNAm between paired baseline and relapse samples. **Conclusions:** While MM is characterized by a profound loss of DNAm, the DNAm retained in actively transcribed gene bodies suggests a role in expression. MM subtypes have distinct epigenetic programs with the high-risk MS and PR subtypes having divergent epigenetic programs. Higher levels of DNAm in the MS subtype are specific to NSD2 overexpression and may result from excessive H3K36me2 being recognized by the PWWP domains of DNA methyltransferases. Lower levels of DNAm in the PR subtype better defined this subtype than RNA and likely result from the replication-dependent loss of DNAm, suggesting DNAm at these loci serve as a readout of the mitotic clock in MM.

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Introduction: t(11;14) is an important biomarker of MM prognosis and response to therapy, including the BCL-2 inhibitor venetoclax. As MM management evolves with emerging targeted therapies and risk-stratification measures, FISH testing for t(11;14) is needed. We assessed testing practices in MM to understand biomarker testing trends and equitable practices in the USA using the Flatiron Health database. **Methods:** This retrospective study included patients aged ≥ 18 years, diagnosed with MM as their first and only malignancy in the nationwide Flatiron Health electronic health-record derived, de-identified database, between January 2011–July 2022, with ≥ 2 clinic encounters 6 months after diagnosis. Clinical trial participants were excluded. FISH testing rates at diagnosis (≤ 30 days prior to or 90 days post-diagnosis) were evaluated across three timeframes: start of study period to R-ISS publication (Palumbo et al. 2015) (January 2011–August 2015), R-ISS to updated NCCN guidelines (V.1.2020) which include venetoclax for t(11;14)+ MM (September 2015–May 2020), and updated NCCN guidelines to end of study period (June 2020–July 2022). Time to FISH test from diagnosis was assessed. **Results:** Amongst 12,284 eligible patients, at diagnosis, median (interquartile range [IQR]) age was 70 (61–77) years, 46% were female, and 68.8% (n = 8,451) had a FISH test. Testing rates at diagnosis increased yearly, from 50.1% in 2011 to 75.1% by 2022, and during the three defined timeframes (starting from earliest) were 60.2%, 72.1%, and 74.6% ($p < 0.001$). For FISH tests beyond diagnosis (≤ 30 days prior or any time post-diagnosis), 75% (n = 9,157) had ≥ 1 test and median (IQR) time to test was 13 (4–24) days. Testing rates were similar regardless of care setting (community/academic), race/ethnicity, gender, and socioeconomic status index, but decreased with older age (75 years: 66.3% [n = 2,550/3,845]). All subgroups had a median time from diagnosis to FISH test of < 30 days. Despite 17.8% (n = 1,627/9,157) of tested patients having t(11;14), first treatment choice was not impacted, with similar first-line regimens reported for patients with/without t(11;14). **Conclusions:** FISH testing at diagnosis has increased since 2011 alongside changes in MM management guidelines. Though the Flatiron Health database shows minimal testing disparities, other studies indicate real-world survival imbalances; thus there is still a need to identify and address disparities pre- and post-MM diagnosis.

P-335

Small nucleotide, copy number and structural variants cooperate to hijack driver genes in extramedullary progression of myeloma

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Introduction: Extramedullary disease (EMD) affects up to 30% of multiple myeloma (MM) patients, predicting poor overall survival due to aggressive disease kinetics and multi-drug resistance. Elucidating EMD genomics may inform targeted treatment approaches. **Methods:** We obtained EMD samples from 15 patients (n=8 fresh and n=7 formalin-fixed, paraffin embedded). Second EMD biopsies were taken in n=3, with n=1 having 3 sequential EMD biopsies. Germline variants were excluded using buccal swab DNA. DNA was extracted using QIAGEN DNeasy kit prior to whole genome sequencing (WGS) (30x; xGen PRISM library preparation; Illumina Novaseq). Bioinformatics identified short

nucleotide variants (SNVs), copy number variations (CNVs) and structural variants (SV) using the Broad Institute GATK best practice pipeline, CNVpytor and Manta, respectively. Droplet digital PCR was used to confirm SNV and CNV findings. **Results:** The median age at diagnosis of MM was 52 years (n=4 primary EMD, n=11 secondary EMD). 46% were hyperdiploid. Driver mutations (DM) in the MAPK pathway were seen in 80%, primarily at codon 61 of NRAS and KRAS (n=5, n=3); only two non-p.Q61 mutations were seen (NRAS p.G13R and KRAS p.A146V). Three patients had activating BRAF mutations (two p.V600E, one p.G469A). Variant allele frequencies (VAF) of DM suggested clonal rather than subclonal level. A quarter of patients (26.6%) had loss of function TP53 mutations. In those with no MAPK DM identified, the median whole genome SNV was 77,142 with a tumour mutational burden (TMB) of 15 mutations/Mb, compared to 20,543 and 3.2 in DM patients. The median SNV and TMB increased with relapse or progression of EMD.CNV/SV analysis identified gain(3q), gain(1q), del(1p) and monosomy 13/ del(13q) in 93%, 86%, 46% and 73% respectively. Gains of BRAF (66%) and MYC (53%) and loss of TP53 (40%) were frequent; with SNV, 20% had biallelic loss. Secondary translocations were seen in 40% of patients, involving MYC, FGFR3, CCND2 and CCND3 in 20%, 13%, 6% and 6%, respectively, and partnered with IGH, IGL and TXNDC5. There was a median of 44 SV per patient. The majority of SV had not been previously identified in these patients and frequently involved published MM driver genes or known super-enhancers such as H1FX. Sequential biopsies of EMD demonstrated temporospatial persistence of DM, with the same DM detected at different anatomical sites and at separate timepoints. There were increased numbers of CNV/SV with relapsed EMD after therapy, consistent with a role in disease progression and drug resistance. **Conclusions:** The MAPK DM, high TMB and persistent genomic instability suggest roles for MAPK-targeted therapies, immunotherapies and DNA damage repair pathway inhibitors, respectively, in EMD. Recurrent codon 61 mutations in RAS suggest a specific role in EMD progression.

P-336

Prognostic relevance of NOTCH-driven matrisome-associated genes in multiple myeloma

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Introduction: Multiple myeloma (MM) originates from a B cell undergoing B-cell receptor affinity maturation in the germinal center. Errors during class switch recombination and ectopic somatic hypermutation generate immunoglobulin (Ig) gene translocations that are presumptive originating events present in the earliest stages of plasma cell neoplasia. Secondary somatic mutations, including MYC rearrangements, NFkB and RAS/mTORC1 pathway activation, contribute to tumor progression and subclonal heterogeneity. Here, we explore the multi-step progression occurring spontaneously in a murine model of MM driven by MYC dysregulation. **Methods:** We performed WGS, WES and RNAseq on 15 de novo, 58 transplantable lines and 25 tumor lines capable of growth in vitro. In established Vk*MYC transplantable lines, the transgene was excised by tamoxifen driven CRE recombinase. **Results:** We confirmed that MYC expression is sufficient to initiate the progression of a benign monoclonal gammopathy, but full malignancy requires additional somatic events that are spontaneously acquired and selected over time in tumors that have undergone significant Ig somatic hypermutation (average 4.6 mutation/100bp). Notably, there is a convergence between mice and men in the signaling pathways dysregulated during tumor progression, although the genomic mechanisms can be species specific. As in human MM, we noted activation of the NFkB pathway in half of the tumors mostly driven by structural rearrangements in Map3k14, including insertional mutagenesis by endogenous retroelements. This is consistent with a key role for NFkB pathway in MM progression, as demonstrated in two recent murine models of MM driven by IKK2 activation. While activation of RAS/MTORC1 in human MM is mostly driven by mutations of N- and K-RAS, unique to the mouse is the complete inactivation of Pten in a third of cases due to deletion and point mutations mediated by a transcription linked mutational process with a preference for thymidine. As in human MM, we detected frequent alteration (one third) of chromatin modifiers, most commonly Kdm6a and Ncor1. Like in human MM, Trp53 inactivation is almost universal in tumors capable of growing in vitro. Similar to human MM, we noted a progressive reduction of Ig transcription with disease progression, ranging from >50% of the transcriptome in early stages to ~1% in cell lines growing in vitro, that inversely correlates with proliferation. Despite the acquisition of these various progression events, the tumors remain dependent of continuous MYC transgene expression, identifying tumor specific vulnerability. **Conclusions:** By forcing progression of monoclonal gammopathy through MYC dysregulation, the Vk*MYC model spontaneously acquires a diverse array of mutations associated with progression in human MM. This genomic diversity is captured in 58 transplantable tumors lines that can be passaged in vivo into immunocompetent non-irradiated, syngeneic C57Bl/6 recipients, and 25 cell lines capable of in vitro growth.

P-338

Differential DNA mutation profiles in multiple myeloma patients: implications of PET/CT findings

Hee Jeong Cho[1], Ju-Hyung Kim[1], Donghyeon Lee[2], Dong Won Baek[1], Sang-Kyun Sohn[1], Jong Gwang Kim[1], Joon Ho Moon[1]

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Introduction: The presence of focal lesions in positron emission tomography/computed tomography (PET/CT) scans is well-established as a predictive marker in patients with multiple myeloma (MM). However, there is a lack of knowledge regarding the genetic backgrounds of patients with focal lesions in PET/CT. This study aimed to investigate the DNA sequencing analysis in patients with MM and compare the differences in mutation profiles based on PET/CT results. **Methods:** PET/CT results were determined by the number of focal lesions and the presence of diffuse lesions in the skeletal bone, assessed using the Deauville score. Positive PET/CT findings were defined as metabolic uptake higher than the liver background. Targeted DNA sequencing of 80 mutations was performed to analyze MM cells extracted from the bone marrow using next-generation sequencing (NGS). **Results:** Sixteen newly diagnosed MM patients were enrolled in this study. The median age of the patients was 66 years (range: 49-76). Four patients had ISS stage I, six had stage II, and six had stage III. High-risk cytogenetics, including t(4;14), t(14;16), and del(17p), were identified in six patients (37.5%). Additionally, six patients exhibited amp(1q). Eight patients (50.0%) had more than three focal lesions on PET/CT (FL > 3), while five patients (31.2%) showed positive findings for diffuse lesions on PET/CT. Two patients encountered issues with trimming the fastq file, resulting in a final sequencing analysis of 14 patients using the Genome Analysis Tool Kit (GATK). The analysis revealed a total of 152 somatic mutations with an allele frequency (AF) >1%. The top 10 frequently identified genes were KMT2C (57%), NCOR1 (57%), PABPC1 (50%), ATM (36%), RPS3A (36%), EP300 (29%), HUWE1 (29%), TET2 (29%), TP53 (29%), and ACTG1 (21%). Notably, PABPC1 (6/8, 75%) and KMT2C (6/8, 75%) mutations were more common in patients with FL > 3, whereas patients with FL ≤ 3 exhibited a higher frequency of ATM gene (4/6, 67%) mutations. In patients without diffuse lesions, NCOR1 mutations were frequently observed. **Conclusions:** We found that mutation distribution varied according to PET/CT results, with patients exhibiting FL > 3 showing a higher frequency of PABPC1 and KMT2C mutations. Further studies are warranted to gain a better understanding of the genetic background associated with positive PET/CT findings in MM.

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P-339

Longitudinal genetically detectable minimal residual disease by interphase fluorescence in situ hybridization confers a poor prognosis in multiple myeloma

Jian Cui[1], Tengteng Yu[2], Wenqiang Yan[2], Jingyu Xu[2], Jiahui Liu[1], Huishou Fan[1], Lugui Qiu[2], Gang An[2]

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Introduction: Deeper depth of response (DpR) after induction therapy, especially gain of negative minimal residual disease (MRD), has been linked to prolonged survival in multiple myeloma (MM). However, flow-MRD examination focuses on the numbers, but not on the biological characteristics of residual plasma cells (PCs). To explore whether the genetic features of residual tumor cells affect the survival time of patients with MM, we investigated the clonality of cytogenetic abnormalities (CAs) of the residual PCs using fluorescence in situ hybridization (iFISH) in the National Longitudinal Cohort of Hematological Diseases in China (NCT04645199). **Methods:** A total of 396 patients diagnosed with newly diagnosed MM (NDMM) between January 2014 and March 2020 were included in this study. EDTA-anticoagulated BM aspirate samples were collected at diagnosis for all 396 patients included in this study, and clonal PCs were enriched by CD138+ magnetic beads (Miltenyi Biotec, Paris, France). iFISH was then performed with probes specific for CAs as follows: 13q14, 17p13, 1q21, 14q32 (5'IGH, 3'IGH), t(4;14)(p16;q32), t(11;14)(q13;q32), and t(14;16)(q32;q23), and a total of 200 interphase nuclei were analyzed. **Results:** Persistent CAs after induction therapy were detected in about half of the patients (118/269, 43%), and patients with undetectable CAs showed significantly improved survival compared with those with genetically detectable MRD (median progression-free survival [mPFS]: 59.7 months vs. 35.7 months, P < 0.001; median overall survival [mOS]: 97.1 months vs. 68.8 months, p = 0.011). Additionally, different patterns of therapy-induced clonal evolution were observed by comparing the clonal structure of residual PCs with paired baseline samples. Patients who maintained at high-risk during follow-up had the worst survival (mPFS: 23.0 months; mOS:40.4 months), while those returned to lower risk or had iFISH- at both time points had the best survival (mPFS: 59.7 months; mOS: 97.2 months). **Conclusions:** These foundings highlighted the prognostic value of genetic testing in residual tumor cells after induction therapy, which may provide a deep understanding of clonal evolution and guide the clinical therapeutic strategies.

P-340

Minor clone of del(17p) provides a reservoir for relapse in multiple myeloma

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Introduction: As a secondary high-risk cytogenetic abnormality, The deletion of chromosome 17p [del(17p)], especially in high subclonal fraction, is associated with poor prognosis in multiple myeloma. Although del(17p) is detected in approximately 5-10% of newly diagnosed multiple myeloma (NDMM) patients, its prevalence increases to more than 10% in patients at relapse, mainly due to the emergence of new clones with acquired del(17p) during follow-up. However, the impact of del(17p) at relapse on survival at different clonal sizes remains unclear, despite the fact that patients who acquire del(17p) during follow-up have significantly shorter overall survival (OS) compared to controls. Furthermore, the patterns of clonal evolution of del(17p) between diagnosis and relapse and its prognostic value have not been fully understood. **Methods:** The present study was based on the National Longitudinal Cohort of Hematological Diseases in China (NCT04645199). A total of 995 patients in the diagnosis dataset and 293 patients in the relapse dataset have been identified with the required cytogenetic data (tested for chr1q gain, del(17p), del(13q), and IgH rearrangement). Among these patients, 197 had paired iFISH data at diagnosis and first relapse. **Results:** We found a higher frequency of high-risk cytogenetic abnormalities (CAs) and more CAs in MM at relapse than those at diagnosis. Minor clone (present in 10%-50% of malignant PCs) of del(17p) at relapse (hazard ratio = 1.86) but not at diagnosis (hazard ratio = 1.39) was associated with a poor prognosis in MM. Our analysis of paired iFISH results revealed that 56 and 12 patients developed one or more than one new CAs at relapse, with the majority being secondary cytogenetic events, such as del(17p) and gain/amp(1q). We then classified patients into six groups based on the change patterns in clonal size of del(17p) between the two time points. Patients in group A, who experienced the loss of del(17p) at relapse, as well as those in group B, who had a decreasing clonal size from the major to the minor clone at relapse, and those in group C, who did not have del(17p) at both time points, all had similarly superior outcomes (with a second OS of 50.3 months, 16.6 months, and 26.9 months, respectively). In contrast, patients in group D, who newly acquired del(17p) at relapse, had a relatively worse survival (with a second OS of 20.2 months). Of the remaining 16 patients, those with a stable clone of del(17p) between two time points (group E) and those with an obvious increase in clonal size of del(17p) (group F) both had the poorest outcomes (with a second OS of 12.5 months and 12.8 months, respectively). **Conclusions:** In conclusion, our data confirmed the adverse impact of a minor clone

P-339

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of del(17p) at relapse and highlighted the importance of designing optimal therapeutic strategies to eliminate high-risk CAs.

P-341

Use of optical genome mapping in the cytogenetic diagnosis of multiple myeloma

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Introduction: Prognosis of patients with multiple myeloma (MM) is highly heterogeneous. Most of them present genetic alterations and chromosomal abnormalities, with translocations persisting throughout the disease. Cytogenetic studies are usually performed using specific fluorescence in situ hybridization (FISH) probes on selected CD138+ plasma cells. Recently, a new diagnostic technique based on the optical mapping of the genome (Optical Genome Mapping, OGM) is available, which allows the detection of both structural alterations and copy number changes at the whole genome level in a single assay. The main objective of this work was to evaluate and compare OGM performance in total bone marrow (BM) with FISH conducted in selected plasma cells. **Methods:** A total of 10 patients diagnosed with MM were included in this study. All cases were analyzed by FISH on selected CD138+ plasma cells. In parallel, high molecular weight DNA was extracted from total BM, fluorescently marked with the DLE-1 enzyme, and charged in a Shapyr chip for analysis in a Shapyr system (Bionano, San Diego, CA, USA). **Results:** The median age of the patients was 56.5 years old (range, 31–83). Seven were R-ISS stage II and three R-ISS III. Median BM infiltration by plasma cells was 22.5% (range, 6–85%). FISH detected alterations in 8 patients, was negative in 1 patient and non-assessable in 1 case. All patients included in the study were assessable by OGM. In patients #1 and #10, FISH and OGM were concordant, but OGM detected more chromosomal alterations, including multiple losses and gains of material, translocations, and monosomies. Regarding patient #2, with a negative FISH panel, OGM detected multiple CNV and a t(8;18) resulting in a potential TCF4::MYC fusion gene. OGM resolved the case with non-assessable FISH (patient #3) and detected multiple CNV, including a deletion of TP53. Patients #4, #5, #8, and #9 with positive FISH results had a negative result by OGM, likely in the context of low infiltration of plasma cells in BM. Likewise, cases #6 and #7 had a non-concordant result between FISH and OGM, given that OGM did not detect the alterations found by FISH. **Conclusions:** In this study, we analyzed the potential use of OGM in cytogenetic diagnosis of MM using total BM. Our preliminary data suggest that OGM is useful to detect chromosomal alterations and CNV in cases with negative and non-assessable FISH, particularly in patients with high BM infiltration of plasma cells. However, we observed that OGM was negative and non-concordant with FISH for some patients with low plasma cell infiltration and further, refining CD138+ selection will be needed to extend OGM to patients with low BM infiltration.

P-342

Genomic profiling of treated high-risk smoldering multiple myeloma

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Introduction: Early intervention for High-Risk Smoldering Multiple Myeloma (HR-SMM) achieves deeper and more prolonged responses compared to newly diagnosed MM (NDMM). It is unclear if this benefit is due to treatment of a less complex entity or inaccuracy in clinical HR-SMM definition. **Methods:** To gain biologic insight into treatment outcomes, we performed the first whole genome sequencing (WGS) analysis of treated HR-SMM for 27 patients treated with carfilzomib, lenalidomide, and dexamethasone (KRd) and R maintenance (NCT01572480). We pooled genomic features with 24 patients with HR-SMM treated with Elotuzumab (Elo)R+/-d; (E-PRISM) and compared to 701 patients with NDMM from CoMMpass. **Results:** After a median follow-up of 24.6 months, median PFS was unreached. After 8 cycles of KRd, 21 (78%) achieved negativity for minimal residual disease (Flow-MRD; LOD 10-5). At 1 year of maintenance, 48% sustained MRD-negativity and 7% lost MRD-negativity. Accrual began in 2012. 3 patients would today be reclassified as MM per 2014 IMWG criteria. One such patient had the only biochemical progression. Otherwise, 11% were HR by Mayo2008 criteria, 52% by Mayo 20/2/20, 67% by PETHEMA, and 78% by RLM criteria (Rajkumar et al. Blood. 2015). 67% met criteria by 2 or more scores and the median 5-year risk of progression per Pangea was 19% (range 5-82). Across pooled HR-SMM, frequency of HR IgH translocations was similar (t(4;14), t(14;16), t(14;20); $p>0.05$) as compared to NDMM from CoMMpass. Driver genes (Rustad et al. Blood Can Disc. 2020) were interrogated together with copy number variation at their loci. Mutations of RAS pathway genes (KRAS, NRAS, and BRAF) were diminished in SMM (22% vs. 48%; $p = < 0.001$), as were gains at the MYC locus (8q24; 6% vs 25%; $p < 0.001$) and gains/amps at 1q (19% vs 33%; $p = 0.039$). Aberrations at key tumor suppressors were less common in HR-SMM ($p < 0.05$): CDKN2C (4 vs 15%), CYLD (8% vs 28%), MAX (8% vs 25.0%), NFKBIA (4% vs 15%), RB1 (20% vs 49%), TENT5C (12% vs 29%), TP53 (4% vs 14%) and TRAF3 (4% vs 20%). There was no biallelic inactivation of TRAF3 as compared to 10% in NDMM ($p = 0.010$).

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P-341

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P-342

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In a genome-corrected comparison, APOBEC (SBS2+SBS13) mutational signatures were diminished in KRd WGS compared to 60 dara-KRd-treated NDMM (Maura et al., ASH 2022; 37% vs 87%, p < 0.001) and in E-PRISM vs CoMMpass (17% vs 45%, p = 0.006). Finally, pooling the HR-SMM treated with KRd and Elo-R+/-d, gain/amp1q was associated with a composite of MRD-positivity, loss of MRD-negativity at 1 year, and progressive disease (39% vs 11%; p = 0.047). **Conclusions:** In patients treated on 2 parallel clinical trials for HR-SMM, we found a uniform and relative simplicity in genomic features, which may explain the superior outcomes of contemporary trials. These results support the use of genomics to contextualize advantages of early intervention in SMM (i.e., to avoid overtreatment of non-progressors and to better identify cases likely to progress without therapy).

P-343

Evaluation of single nucleotide variants in BRCA1, CDKN1A, TP53BP, and XRCC1 in multiple myeloma patients undergoing hematopoietic stem cell transplantation: association with clinical outcomes

David Garrido[1], Sergio Lopresti[2], Flavia Stella[2], Camila Galvano[3], Ana Inés Catalán[4], Carolina Ottati[4], Ariela Fundia[3], Daniela Lens[4], Irma Slavutsky[3], Eloísa Riva[5]

[1]Hospital de Clínicas Dr. Manuel Quintela; [2]Hospital Prof. Dr. Alejandro Posadas; [3]Institute of Experimental Medicine CONICET-Academia Nacional de Medicina; [4]Departamento Básico de Medicina, Hospital de Clínicas Dr. Manuel Quintela; [5]Hospital Británico. Montevideo, Uruguay

Introduction: High-dose melphalan (HDM) followed by autologous hematopoietic stem cell transplantation (ASCT) remains the standard upfront treatment for transplant-eligible multiple myeloma (MM) patients. However, clinical responses to this strategy are highly variable. We hypothesize that single nucleotide variants (SNVs) in DNA repair genes may influence clinical outcomes in the transplant setting. Aims: To determine the association of SNV in CDKN1A (rs1801270), TP53BP1 (rs560191), BRCA1 (rs4986850, rs1799949, and rs799917), and XRCC1 (rs25487) genes, with the response and progression-free survival (PFS) in patients with MM treated with HDM as pre-transplant conditioning **Methods:** An observational, analytic, and retrospective study, including adult patients with active MM, diagnosed at the Hospital de Clínicas (HC), Uruguay, and Hospital Posadas, Argentina, who received HDM and ASCT as consolidation therapy either frontline or second-line. Evaluated outcomes included response rate and PFS. DNA was purified from peripheral blood or bone marrow. Genotyping of SNVs was performed by conventional PCR and Sanger sequencing. Statistical analysis was performed with SPSS v.26 at p< 0.05. **Results:** We included 34 MM patients with a median age of 53.5 years at diagnosis, 64.7% males, and 35.3% females. The frequency of MM types was 61.8% IgG, 23.6% IgA, and 14.7% light chain myeloma. Risk groups included 26.5% ISS1, 44.1% ISS2, and 29.4% ISS3. Bortezomib-based regimens were used in 97.1%. Six patients received ASCT as second-line consolidation therapy. The median PFS for the whole group was 29.2 months. In patients receiving ASCT as first-line consolidation therapy, a ≥CR after transplantation, and ISS-1 were associated with improved PFS, achieving 48.9 months (p< 0.01) and 54.1 months (p< 0.01), respectively. The frequency of ≥CR before and after ASCT was 26.5% and 52.9%, respectively. The allele frequencies found were rs25487 G 75%, A 25%; rs799917 C 56.4%, T 43.6%; rs4986850 G 89.7%, A 10.3%; rs1799949 G 63.2%, A 36.8%; rs1801270 C 73.5%, A 26.5%; and rs560191 G 77.9%, C 22.1%. No significant differences were found between observed genotype frequencies and those predicted from the Hardy-Weinberg equilibrium. Higher CR rates after the first ASCT were associated with CDKN1A rs1801270 CC (73.3%) and TP53BP1 rs560191 GC/CC (70%) genotypes. Patients with homozygous genotype for BRCA1 rs799917 TT had a significantly lower median PFS compared to CT/CC carriers (p< 0.01) which was similar in patients receiving ASCT only as first-line consolidation (48.9 months vs 16.7 months, p=0.1) **Conclusions:** These preliminary results would indicate that homozygosity for the alternative BRCA1 rs799917 T allele would be associated with treatment failure. To our knowledge, this is the first study evaluating the impact of single nucleotide variants (SNVs) in DNA repair genes in the HDM-ASCT clinical outcomes in Latin America, Further studies are required to validate our results.

P-344

Multiomics profiling of extramedullary multiple myeloma tumors and their microenvironment

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Introduction: Extramedullary disease (EMD) is an aggressive manifestation of multiple myeloma (MM), where MM plasma cells (PCs) become independent of the bone marrow (BM) microenvironment and infiltrate other tissues and organs. The incidence of EMD is increasing and is associated with worse prognosis and drug resistance. Unfortunately, the molecular processes underpinning the pathogenesis of extramedullary form of MM that could help better tailor treatment, are poorly understood. Therefore, we performed the most comprehensive multiomics study

In a genome-corrected comparison, APOBEC (SBS2+SBS13) mutational signatures were diminished in KRd WGS compared to 60 dara-KRd-treated NDMM (Maura et al., ASH 2022; 37% vs 87%, p < 0.001) and in E-PRISM vs CoMMpass (17% vs 45%, p = 0.006). Finally, pooling the HR-SMM treated with KRd and Elo-R+/-d, gain/amp1q was associated with a composite of MRD-positivity, loss of MRD-negativity at 1 year, and progressive disease (39% vs 11%; p = 0.047). **Conclusions:** In patients treated on 2 parallel clinical trials for HR-SMM, we found a uniform and relative simplicity in genomic features, which may explain the superior outcomes of contemporary trials. These results support the use of genomics to contextualize advantages of early intervention in SMM (i.e., to avoid overtreatment of non-progressors and to better identify cases likely to progress without therapy).

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Introduction: High-dose melphalan (HDM) followed by autologous hematopoietic stem cell transplantation (ASCT) remains the standard upfront treatment for transplant-eligible multiple myeloma (MM) patients. However, clinical responses to this strategy are highly variable. We hypothesize that single nucleotide variants (SNVs) in DNA repair genes may influence clinical outcomes in the transplant setting. Aims: To determine the association of SNV in CDKN1A (rs1801270), TP53BP1 (rs560191), BRCA1 (rs4986850, rs1799949, and rs799917), and XRCC1 (rs25487) genes, with the response and progression-free survival (PFS) in patients with MM treated with HDM as pre-transplant conditioning **Methods:** An observational, analytic, and retrospective study, including adult patients with active MM, diagnosed at the Hospital de Clínicas (HC), Uruguay, and Hospital Posadas, Argentina, who received HDM and ASCT as consolidation therapy either frontline or second-line. Evaluated outcomes included response rate and PFS. DNA was purified from peripheral blood or bone marrow. Genotyping of SNVs was performed by conventional PCR and Sanger sequencing. Statistical analysis was performed with SPSS v.26 at p< 0.05. **Results:** We included 34 MM patients with a median age of 53.5 years at diagnosis, 64.7% males, and 35.3% females. The frequency of MM types was 61.8% IgG, 23.6% IgA, and 14.7% light chain myeloma. Risk groups included 26.5% ISS1, 44.1% ISS2, and 29.4% ISS3. Bortezomib-based regimens were used in 97.1%. Six patients received ASCT as second-line consolidation therapy. The median PFS for the whole group was 29.2 months. In patients receiving ASCT as first-line consolidation therapy, a ≥CR after transplantation, and ISS-1 were associated with improved PFS, achieving 48.9 months (p< 0.01) and 54.1 months (p< 0.01), respectively. The frequency of ≥CR before and after ASCT was 26.5% and 52.9%, respectively. The allele frequencies found were rs25487 G 75%, A 25%; rs799917 C 56.4%, T 43.6%; rs4986850 G 89.7%, A 10.3%; rs1799949 G 63.2%, A 36.8%; rs1801270 C 73.5%, A 26.5%; and rs560191 G 77.9%, C 22.1%. No significant differences were found between observed genotype frequencies and those predicted from the Hardy-Weinberg equilibrium. Higher CR rates after the first ASCT were associated with CDKN1A rs1801270 CC (73.3%) and TP53BP1 rs560191 GC/CC (70%) genotypes. Patients with homozygous genotype for BRCA1 rs799917 TT had a significantly lower median PFS compared to CT/CC carriers (p< 0.01) which was similar in patients receiving ASCT only as first-line consolidation (48.9 months vs 16.7 months, p=0.1) **Conclusions:** These preliminary results would indicate that homozygosity for the alternative BRCA1 rs799917 T allele would be associated with treatment failure. To our knowledge, this is the first study evaluating the impact of single nucleotide variants (SNVs) in DNA repair genes in the HDM-ASCT clinical outcomes in Latin America, Further studies are required to validate our results.

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P-343

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P-344

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of EMD cells to date combining the whole exome sequencing (WES), bulk RNA sequencing (RNA-seq) and single cell RNA sequencing (scRNA-seq) data from the largest cohort of EMD samples ever sequenced (N=15) collected between 2017-2023. **Methods:** WES was performed for 15 EMD samples and 8 paired NDMM samples using Twist Comprehensive Human Exome. RNAseq was performed for 15 EMD, 8 paired NDMM, 7 unpaired NDMM and 15 unrelated RRMM samples using SMARTer Stranded Total RNA-Seq Kit v2. scRNAseq was performed for 5 EMD samples using Cedhromium 3' library kit. All sequencing was performed on Illumina platform. Only FACS/MACS sorted aberrant PCs were used in case bulk DNA/RNA sequencing. Chromosomal aberrations were evaluated using the combination of FISH and WES. **Results:** We show that combination of genomic lesions 1q21 gain/amplification and at least one mutated gene in MAPK signaling are the most frequent mutations in EMD, present in 14/15 (93%) and 13/15 (87%) EMD samples, respectively. Analyses of bulk RNAseq data showed up-regulation of pathways connected to cell proliferation and upregulation of potent growth factor IL6. Interestingly, CXCR4 gene, important for a homing of plasma cells in bone marrow, was significantly downregulated as well as production of immunoglobulins, with IGL being more prevalent than IGH. We focused on expression of molecular targets for modern immunotherapy, which could be effective in EMD. However, we observed decrease in expression of CD38, GPRC5D, SLAMF7 in EMD cells and lower expression of HLA molecules, which are important for action of immunotherapeutics. Intriguingly, our data suggested novel EMD targets with elevated expression of genes EZH2 and CD70, that are already in use in non-myeloma oncology. In addition, we identified CD8+ T and NK cells as the most abundant immune subsets in EMD microenvironment. **Conclusions:** We performed the largest genomic study of EMD tumors to date and revealed that combination of 1q21 gain/amp and mutations in MAPK pathway are presumably defining genomic features of EMD. Next, transcriptomic profiling of EMD cells suggested high proliferative potential, decreased BM homing, decreased IG production, autocrine growth regulation and decreased expression of some key therapeutically relevant molecules. Finally, for the first time, we dissected the microenvironment of EMD tumors. Overall, our findings represent a significant contribution to understanding of biology and resistance of EMD.

P-345

Connecting 1q amplification and PHF19 expression in high-risk myeloma clones

Travis Johnson[1], Parvathi Sudha[2], Enze Liu[2], Vivek Chopra[3], Cedric Dos Santos[3], Michael Nixon[3], Kun Huang[1], Rafat Abonour[4], Mohammad Abu Zaid[2], Brian Walker[2]

[1]Department of Biostatistics and Health Data Science, School of Medicine, Indiana University; [2]Melvin and Bren Simon Comprehensive Cancer Center, Division of Hematology and Oncology, School of Medicine, Indiana University; [3]Genentech Inc.; [4]Indiana University School of Medicine, Indianapolis, IN, USA

Introduction: Myeloma is a plasma cell malignancy in which a high-risk set of patients can be defined by genomic markers including cytogenetic groups such as loss of 1p, gain or amplification (gain/amp) 1q, and TP53 abnormalities. Increasingly, other markers are also being identified that are associated with progression such as PHF19. **Methods:** Bone marrow aspirates from smoldering multiple myeloma (SMM; n=10), newly diagnosed multiple myeloma (NDMM; n=22), and relapsed/refractory multiple myeloma (RRMM; n=17) patients were collected. Samples underwent CD138+ sorting and single cell multiomic sequencing (RNA-seq and ATAC-seq; 10X Genomics). The multiomic single cell data were integrated using Seurat via weighted nearest neighbors (WNN). Copy number variants (CNVs) were generated using InferCNV. The transcription factor (TF) databases, hTFtarget and TF2DNA were used to identify TFs regulating genes of interest. Previously published paired ChIP-seq and RNA-seq from myeloma cell lines were used to determine TF binding sites. Finally, differences in TF, cell cycle inhibitors, and epigenetic regulator chromatin accessibility and expression in subclones within patient samples with high-risk CNVs were evaluated. **Results:** We previously reported a subset of myeloma cells present primarily in RRMM patients that we denoted relapse/refractory plasma cells (RRPC) that express PHF19 ($P < 0.0001$) and are enriched for amp(1q) ($P < 0.0001$). To determine how PHF19 expression is controlled we examined TF binding sites and identified 92 TFs predicted to bind to the promoter region. Given the association of the RRPCs with amp(1q) we identified seven TF loci encoded on 1q including ZNF648, ATF3, KDM5B, PBX1, RBBP5, RFX5, and USF1 of which PBX1 ($log2FC=0.78$, $P < 0.0001$), RFX5 ($log2FC=0.81$, $P < 0.0001$), and RBBP5 ($log2FC=0.93$, $P < 0.0001$) were significantly up-regulated in RRPCs. ChIP-seq and RNA-seq data were available for PBX1 in MM1S and U266 cell lines, and indicated PBX1 binding at the promoter of PHF19 which was in the top 4% of MM1S ChIP-seq peaks and the top 8% of U266 ChIP-seq peaks. Silencing PBX1 via shRNA significantly decreased PHF19 expression in both cell lines. In our single cell data PBX1 ($log2FC=0.78$, $P < 0.0001$), PHF19 ($log2FC=2.43$ $P < 0.0001$), and FOXM1, a previously identified target of PBX1 in myeloma, ($log2FC=3.64$, $P < 0.0001$) were upregulated in RRPCs. PHF19 expression was detectable in 47% of RRPCs compared to only 9% of cells in other clusters (5.22 fold increase) and PBX1 expression was detectable in 22% of RRPCs compared to only 10% of cells in other clusters (2.44 fold increase). **Conclusions:** Here we show a link between amp(1q), increased expression of the transcription factor PBX1 which leads to increased expression of the high-risk marker PHF19. This link gives further strength and biological meaning to the impact of amp(1q) on high-risk disease.

P-346

Internal tandem duplications of the BCMA transmembrane domain are common in hyperdiploid multiple myeloma and associated with constitutive NF-kB signaling

Bryce Turner[1], Daniel Enriquez[1], Christophe Legendre[1], Felix Madrid[1], Shari Kyman[1], Jennifer Rogers[2], George Mulligan[2], Sagar Lonial[3], Jonathan Keats[1,4]

of EMD cells to date combining the whole exome sequencing (WES), bulk RNA sequencing (RNA-seq) and single cell RNA sequencing (scRNA-seq) data from the largest cohort of EMD samples ever sequenced (N=15) collected between 2017-2023. **Methods:** WES was performed for 15 EMD samples and 8 paired NDMM samples using Twist Comprehensive Human Exome. RNAseq was performed for 15 EMD, 8 paired NDMM, 7 unpaired NDMM and 15 unrelated RRMM samples using SMARTer Stranded Total RNA-Seq Kit v2. scRNAseq was performed for 5 EMD samples using Cedhromium 3' library kit. All sequencing was performed on Illumina platform. Only FACS/MACS sorted aberrant PCs were used in case bulk DNA/RNA sequencing. Chromosomal aberrations were evaluated using the combination of FISH and WES. **Results:** We show that combination of genomic lesions 1q21 gain/amplification and at least one mutated gene in MAPK signaling are the most frequent mutations in EMD, present in 14/15 (93%) and 13/15 (87%) EMD samples, respectively. Analyses of bulk RNAseq data showed up-regulation of pathways connected to cell proliferation and upregulation of potent growth factor IL6. Interestingly, CXCR4 gene, important for a homing of plasma cells in bone marrow, was significantly downregulated as well as production of immunoglobulins, with IGL being more prevalent than IGH. We focused on expression of molecular targets for modern immunotherapy, which could be effective in EMD. However, we observed decrease in expression of CD38, GPRC5D, SLAMF7 in EMD cells and lower expression of HLA molecules, which are important for action of immunotherapeutics. Intriguingly, our data suggested novel EMD targets with elevated expression of genes EZH2 and CD70, that are already in use in non-myeloma oncology. In addition, we identified CD8+ T and NK cells as the most abundant immune subsets in EMD microenvironment. **Conclusions:** We performed the largest genomic study of EMD tumors to date and revealed that combination of 1q21 gain/amp and mutations in MAPK pathway are presumably defining genomic features of EMD. Next, transcriptomic profiling of EMD cells suggested high proliferative potential, decreased BM homing, decreased IG production, autocrine growth regulation and decreased expression of some key therapeutically relevant molecules. Finally, for the first time, we dissected the microenvironment of EMD tumors. Overall, our findings represent a significant contribution to understanding of biology and resistance of EMD.

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Introduction: Myeloma is a plasma cell malignancy in which a high-risk set of patients can be defined by genomic markers including cytogenetic groups such as loss of 1p, gain or amplification (gain/amp) 1q, and TP53 abnormalities. Increasingly, other markers are also being identified that are associated with progression such as PHF19. **Methods:** Bone marrow aspirates from smoldering multiple myeloma (SMM; n=10), newly diagnosed multiple myeloma (NDMM; n=22), and relapsed/refractory multiple myeloma (RRMM; n=17) patients were collected. Samples underwent CD138+ sorting and single cell multiomic sequencing (RNA-seq and ATAC-seq; 10X Genomics). The multiomic single cell data were integrated using Seurat via weighted nearest neighbors (WNN). Copy number variants (CNVs) were generated using InferCNV. The transcription factor (TF) databases, hTFtarget and TF2DNA were used to identify TFs regulating genes of interest. Previously published paired ChIP-seq and RNA-seq from myeloma cell lines were used to determine TF binding sites. Finally, differences in TF, cell cycle inhibitors, and epigenetic regulator chromatin accessibility and expression in subclones within patient samples with high-risk CNVs were evaluated. **Results:** We previously reported a subset of myeloma cells present primarily in RRMM patients that we denoted relapse/refractory plasma cells (RRPC) that express PHF19 ($P < 0.0001$) and are enriched for amp(1q) ($P < 0.0001$). To determine how PHF19 expression is controlled we examined TF binding sites and identified 92 TFs predicted to bind to the promoter region. Given the association of the RRPCs with amp(1q) we identified seven TF loci encoded on 1q including ZNF648, ATF3, KDM5B, PBX1, RBBP5, RFX5, and USF1 of which PBX1 ($log2FC=0.78$, $P < 0.0001$), RFX5 ($log2FC=0.81$, $P < 0.0001$), and RBBP5 ($log2FC=0.93$, $P < 0.0001$) were significantly up-regulated in RRPCs. ChIP-seq and RNA-seq data were available for PBX1 in MM1S and U266 cell lines, and indicated PBX1 binding at the promoter of PHF19 which was in the top 4% of MM1S ChIP-seq peaks and the top 8% of U266 ChIP-seq peaks. Silencing PBX1 via shRNA significantly decreased PHF19 expression in both cell lines. In our single cell data PBX1 ($log2FC=0.78$, $P < 0.0001$), PHF19 ($log2FC=2.43$ $P < 0.0001$), and FOXM1, a previously identified target of PBX1 in myeloma, ($log2FC=3.64$, $P < 0.0001$) were upregulated in RRPCs. PHF19 expression was detectable in 47% of RRPCs compared to only 9% of cells in other clusters (5.22 fold increase) and PBX1 expression was detectable in 22% of RRPCs compared to only 10% of cells in other clusters (2.44 fold increase). **Conclusions:** Here we show a link between amp(1q), increased expression of the transcription factor PBX1 which leads to increased expression of the high-risk marker PHF19. This link gives further strength and biological meaning to the impact of amp(1q) on high-risk disease.

P-346

Internal tandem duplications of the BCMA transmembrane domain are common in hyperdiploid multiple myeloma and associated with constitutive NF-kB signaling

Bryce Turner[1], Daniel Enriquez[1], Christophe Legendre[1], Felix Madrid[1], Shari Kyman[1], Jennifer Rogers[2], George Mulligan[2], Sagar Lonial[3], Jonathan Keats[1,4]

of EMD cells to date combining the whole exome sequencing (WES), bulk RNA sequencing (RNA-seq) and single cell RNA sequencing (scRNA-seq) data from the largest cohort of EMD samples ever sequenced (N=15) collected between 2017-2023. **Methods:** WES was performed for 15 EMD samples and 8 paired NDMM samples using Twist Comprehensive Human Exome. RNAseq was performed for 15 EMD, 8 paired NDMM, 7 unpaired NDMM and 15 unrelated RRMM samples using SMARTer Stranded Total RNA-Seq Kit v2. scRNAseq was performed for 5 EMD samples using Cedhromium 3' library kit. All sequencing was performed on Illumina platform. Only FACS/MACS sorted aberrant PCs were used in case bulk DNA/RNA sequencing. Chromosomal aberrations were evaluated using the combination of FISH and WES. **Results:** We show that combination of genomic lesions 1q21 gain/amplification and at least one mutated gene in MAPK signaling are the most frequent mutations in EMD, present in 14/15 (93%) and 13/15 (87%) EMD samples, respectively. Analyses of bulk RNAseq data showed up-regulation of pathways connected to cell proliferation and upregulation of potent growth factor IL6. Interestingly, CXCR4 gene, important for a homing of plasma cells in bone marrow, was significantly downregulated as well as production of immunoglobulins, with IGL being more prevalent than IGH. We focused on expression of molecular targets for modern immunotherapy, which could be effective in EMD. However, we observed decrease in expression of CD38, GPRC5D, SLAMF7 in EMD cells and lower expression of HLA molecules, which are important for action of immunotherapeutics. Intriguingly, our data suggested novel EMD targets with elevated expression of genes EZH2 and CD70, that are already in use in non-myeloma oncology. In addition, we identified CD8+ T and NK cells as the most abundant immune subsets in EMD microenvironment. **Conclusions:** We performed the largest genomic study of EMD tumors to date and revealed that combination of 1q21 gain/amp and mutations in MAPK pathway are presumably defining genomic features of EMD. Next, transcriptomic profiling of EMD cells suggested high proliferative potential, decreased BM homing, decreased IG production, autocrine growth regulation and decreased expression of some key therapeutically relevant molecules. Finally, for the first time, we dissected the microenvironment of EMD tumors. Overall, our findings represent a significant contribution to understanding of biology and resistance of EMD.

P-345

Connecting 1q amplification and PHF19 expression in high-risk myeloma clones

Travis Johnson[1], Parvathi Sudha[2], Enze Liu[2], Vivek Chopra[3], Cedric Dos Santos[3], Michael Nixon[3], Kun Huang[1], Rafat Abonour[4], Mohammad Abu Zaid[2], Brian Walker[2]

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Introduction: Myeloma is a plasma cell malignancy in which a high-risk set of patients can be defined by genomic markers including cytogenetic groups such as loss of 1p, gain or amplification (gain/amp) 1q, and TP53 abnormalities. Increasingly, other markers are also being identified that are associated with progression such as PHF19. **Methods:** Bone marrow aspirates from smoldering multiple myeloma (SMM; n=10), newly diagnosed multiple myeloma (NDMM; n=22), and relapsed/refractory multiple myeloma (RRMM; n=17) patients were collected. Samples underwent CD138+ sorting and single cell multiomic sequencing (RNA-seq and ATAC-seq; 10X Genomics). The multiomic single cell data were integrated using Seurat via weighted nearest neighbors (WNN). Copy number variants (CNVs) were generated using InferCNV. The transcription factor (TF) databases, hTFtarget and TF2DNA were used to identify TFs regulating genes of interest. Previously published paired ChIP-seq and RNA-seq from myeloma cell lines were used to determine TF binding sites. Finally, differences in TF, cell cycle inhibitors, and epigenetic regulator chromatin accessibility and expression in subclones within patient samples with high-risk CNVs were evaluated. **Results:** We previously reported a subset of myeloma cells present primarily in RRMM patients that we denoted relapse/refractory plasma cells (RRPC) that express PHF19 ($P < 0.0001$) and are enriched for amp(1q) ($P < 0.0001$). To determine how PHF19 expression is controlled we examined TF binding sites and identified 92 TFs predicted to bind to the promoter region. Given the association of the RRPCs with amp(1q) we identified seven TF loci encoded on 1q including ZNF648, ATF3, KDM5B, PBX1, RBBP5, RFX5, and USF1 of which PBX1 ($log2FC=0.78$, $P < 0.0001$), RFX5 ($log2FC=0.81$, $P < 0.0001$), and RBBP5 ($log2FC=0.93$, $P < 0.0001$) were significantly up-regulated in RRPCs. ChIP-seq and RNA-seq data were available for PBX1 in MM1S and U266 cell lines, and indicated PBX1 binding at the promoter of PHF19 which was in the top 4% of MM1S ChIP-seq peaks and the top 8% of U266 ChIP-seq peaks. Silencing PBX1 via shRNA significantly decreased PHF19 expression in both cell lines. In our single cell data PBX1 ($log2FC=0.78$, $P < 0.0001$), PHF19 ($log2FC=2.43$ $P < 0.0001$), and FOXM1, a previously identified target of PBX1 in myeloma, ($log2FC=3.64$, $P < 0.0001$) were upregulated in RRPCs. PHF19 expression was detectable in 47% of RRPCs compared to only 9% of cells in other clusters (5.22 fold increase) and PBX1 expression was detectable in 22% of RRPCs compared to only 10% of cells in other clusters (2.44 fold increase). **Conclusions:** Here we show a link between amp(1q), increased expression of the transcription factor PBX1 which leads to increased expression of the high-risk marker PHF19. This link gives further strength and biological meaning to the impact of amp(1q) on high-risk disease.

P-346

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[1]TGen; [2]MMRF; [3]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [4]City of Hope

Introduction: Recent reports have highlighted a number of genetic resistance events in patients who have progressed on BCMA and GPRC5D targeted immunotherapies. We have leveraged the multi-dimensional data in the MMRF CoMMpass study to define the incidence of target allele loss in patients. Moreover, the usage of multiple advanced mutation callers identified recurrent internal tandem duplications (ITD) in TNFRSF17/BCMA reminiscent of the FLT3 ITD seen in AML. **Methods:** Whole genome, exome, and RNA sequencing results from IA22 of the MMRF CoMMpass study were processed through an updated pipeline with alignment to the GRCh38 reference genome. Small variant calling was performed with 5 independent variant callers; Mutect2, Strelka2, Octopus, VarDict, and Lancet. Copy number was determined using GATK CNV with an optimized diploid centering model, structural events were identified using Manta and gene expression estimates were determined using Salmon. **Results:** Integration of the available gene expression, copy number and mutational data facilitated the comprehensive evaluation of the current antibody, bispecific or CAR-T target antigens. At diagnosis all patients expressed the target genes and none had bi-allelic loss of a target loci, however, single copy loss was detected for FCRL5 (0.8%), CD38 (5.6%), GPRC5D (13.2%), and BCMA (3.4%). Four hyperdiploid patients had very high expression of BCMA, which were associated with high level amplifications (5, 12, or 30 copies) or an IgH translocation. High confidence mutation calls (>=3 callers) identified eight patients with SNV or INDEL mutations in BCMA. Two patients had inactivating nonsense or frameshift mutations while the remaining five had large 37-58 nucleotide ITD. Since large insertions are one of the most difficult events to identify we curated the single variant caller results and identified three additional patients with ITD of 46-73 nucleotides. Interestingly, all of these patients have a hyperdiploid karyotype and the ITD occur within the transmembrane domain with a minimal duplication of amino acids 61-66. The ITD are predicted to be gain-of-function events, as each patient was characterized by a high NF-kB gene expression index, exceeding the 90th percentile observed in the cohort in all cases. **Conclusions:** As we begin to prioritize the use of different immune-based therapies it will be important to consider the relative risk each patient has to develop resistance based on the preexisting loss of one target gene copy, as some targets are frequently lost (GPRC5D) while others are rarely lost (FCRL5). Some hyperdiploid patients have hyperactivation of NF-kB signaling as a result of BCMA overexpression by high level copy number gains and immunoglobulin translocations or ITD. These patients are likely dependent on BCMA mediated signaling and would likely be exquisitely sensitive to BCMA targeted therapies. It will be essential to determine if current BCMA directed therapies can still bind these BCMA ITD isoforms.

P-347

Longitudinal profiling identifies genetic mechanisms of resistance to four different drug classes in a t(4;14) positive patient

Jonathan Keats[1,2], Azra Borogovac[2], Shari Kyman[1], Jessica Molnar[1], Shukmei Wong[1], Daniel Enriquez[1], Bryce Turner[1], Christophe Legendre[1], Danielle Metz[1], Murali Janakiram[2], Scott Goldsmith[2], Myo Htut[2], Flavia Pichiorri[2], Amrita Krishnan[2]

[1]TGen; [2]City of Hope National Comprehensive Cancer Center

Introduction: Myeloma patients have many therapeutic options available but multiple relapses remains a common scenario. Genomic profiling may help us better understand resistance mechanisms and ultimately select optimal therapies. We present a t(4;14) patient treated with radiation therapy and CyBorD followed by VRd induction, HDT+ASCT, and 27 months of proteasome inhibitor based maintenance therapy (CR). At relapse they received daratumumab based salvage in combination with lenalidomide and then pomalidomide. Subsequent progression was treated with a BCMA directed bispecific with initial sCR but progression occurred seven months later. Subsequent therapy with Isa-Kd resulted in a short PR before progressing two months later and being unresponsive to SVd. The first profiled bone marrow was collected during leukapheresis for cilta-cel but due to progressive disease the patient received an FCRL5 directed bispecific, and a second sample was collected at progression after a brief sCR to this agent. Unfortunately, the patient did not respond to subsequent therapy including a GPRC5D directed bispecific and the stored cilta-cel product. **Methods:** Plasma cells were enriched from bone marrow and peripheral blood using the human CD138+ Positive Selection Kit on an Applied Cells MARS CS Flex Cell Separator. PCR-free short read WGS and mRNA sequencing libraries were sequenced on a NovaSeq 6000. Long-read WGS libraries were sequenced on PromethION R10.4.1 flow cells. **Results:** WGS confirmed the presence of t(4;14), gain(1q21) and del(13q14). Additional events detected included: t(8;22)-IgL::MYC, chromothripsis within and between chromosomes 4 and 17, plus bi-allelic deletions of BCL2L11/BIM, RB1, and CDKN2A/CDKN2B suggesting an apoptosis resistant and proliferative tumor. Therapeutic resistance to anti-CD38 agents and IMiDs started with one copy deletions of CD38 and IKZF3 created by the chromothripsis event. Convergent evolution occurred to inactivate the second CD38 allele with three clones having different interstitial deletions. The second IKZF3 allele was inactivated by a frameshift mutation. This sample also had bi-allelic loss of TNFRSF17/BCMA with eleven different deletions overlapping TNFRSF17/BCMA and a 3 bp deletion in the extracellular domain (Ser30), indicating the presence of multi-clonal resistance. A significant clonal selection was evident in the second timepoint with single inactivation events detected in BIM, CD38, and BCMA. Interestingly, the three copies of FCRL5 detected initially were fully intact even after evaluation with long read sequencing but the expression of FCRL5 was almost undetectable by RNAseq (0.6 TPM) compared to the median seen in the MMRF CoMMpass cohort (243 TPM). **Conclusions:** This case represents the first known bi-allelic loss of CD38 and acquired loss of FCRL5

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P-347

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expression. These events, along with the loss of BCMA highlight the need for more advanced clinical testing to assess the actionability of the diverse therapeutic targets available to treat patients today.

P-348

ADAR1-regulated cytoplasmic dsRNA-immune sensing pathway is a novel mechanism of lenalidomide resistance in multiple myeloma

Mun Yee Koh[1], Tae-Hoon Chung[1], Sabrina Hui Min Toh[1], Nicole Xin Ning Tang[1], Jianbiao Zhou[1], Leilei Chen[1,2], Wee Joo Chng[3], Phaik Ju Teoh[1,4,5]

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Introduction: Immunomodulatory drugs (IMiDs) such as lenalidomide and pomalidomide are one of the main cornerstone treatments in multiple myeloma (MM). However, acquired resistance to IMiDs commonly underlies relapse, rendering MM generally incurable. IMiDs bind directly to cereblon (CRBN), the substrate adaptor of the CRL4(CRBN) E3 ubiquitin ligase, and promote the proteasomal degradation of IKZF1 and IKZF3, resulting in MM cell growth inhibition. While resistance to IMiDs has been commonly associated with abnormalities in CRBN and the corresponding factors within the same pathway, the underlying mechanisms in the majority of the cases remain unclear. Adenosine-to-inosine RNA editing, a post-transcriptional modification of dsRNA, catalysed by ADAR1, has shown biological and clinical relevance in MM. ADAR1 is important in the regulation of innate immune response via the dsRNA sensing pathway. Nevertheless, how ADAR1 expression and its aberrant RNA editing could affect cancer immunogenicity and importantly, in regulating IMiDs responses in MM, remain largely unexplored. This study elucidates the role of ADAR1 in mediating MM responses to IMiDs, specifically lenalidomide. **Methods:** A combination of public MM patients' dataset analyses (MMRF CoMMpass, APEX, HOVON, UAMS), generation of isogenic lenalidomide-resistant (LenR) cells and MM models with differential ADAR1 expression were utilised to assess the functional role of ADAR1, its effect in regulating lenalidomide responses in MM and the plausible biological mechanism of actions. **Results:** We observed a close association between ADAR1 expression with lenalidomide sensitivity in a panel of MM cells and in CoMMpass patients' (n=776 len-treated patients of a total of 911), which portends clinical significance. MM cells with ADAR1 knockdown demonstrated enhanced lenalidomide sensitivity, associated with the accumulation of endogenous dsRNAs, activation of the dsRNA-sensing pathways and increased interferon (IFN) responses. Conversely, ADAR1 overexpression reduced lenalidomide sensitivity in an RNA-editing dependent manner, which was observed concomitantly with suppression of the dsRNA-sensing pathway. Assessment of the LenR cells versus len-sensitive revealed higher ADAR1 expression, in association with increased RNA editing frequency, impediment of dsRNAs accumulation and suppression of the dsRNA-sensing pathway. Importantly, we identified the MDA5 as the predominant dsRNA sensor stimulating MM immunogenicity to lenalidomide, with ADAR1 as the upstream regulator. Concordantly, these in vitro findings were supported by our in vivo observations. **Conclusions:** In summary, we identified ADAR1-mediated suppression of dsRNA-sensing pathway as a novel mechanism regulating lenalidomide resistance. Our study harbours crucial translational value as ADAR1 is located at chromosome 1q21 which is frequently amplified in the MM patients. Further studies involve investigating the association of ADAR1 with CRBN pathway.

P-349

A retrospective assessment of biologically relevant genomic perturbations and variants of unknown significance in a cohort of plasma cell disorder at our institution; a single center experience

Swarup Kumar[1], Kaylyn Kirk[1], Katharine Hooper[1], Ritika Vankina[1]

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Introduction: Significant advances in understanding genomic profiles of plasma cell disorder patients have been made recently. However, the spectrum of genomic variants of uncertain significance (VUS) including their frequency and malignant transformation potential has not been well studied. In our cohort, we assessed the prevalence of biologically relevant variants and VUS using the Tempus xT® platform which is a targeted panel of 648 genes identified by DNA next-generation sequencing (NGS) enriched for clinically relevant and cancer driver genes and genes of emerging or uncertain clinical significance. We also assessed MSigDb (Human Molecular Signatures Database) hallmark gene set pathways that can be impacted by genomic VUS using a web-based tool Enrich R® providing various types of visualization summaries of collective functions of gene lists. **Methods:** Genomic data from bone marrow aspirate samples of sixty-four patients in our institution with monoclonal gammopathies (MGUS), smoldering myeloma (SM), multiple myeloma (MM), AL amyloidosis (AMY) and Waldenstrom's macroglobulinemia (WM) was abstracted using the Tempus xT® NGS platform and compared. Enrich-R® was then used to identify the top 3 Hallmark 2020 MSigDb pathways that were relevant amongst VUS. **Results:** Amongst all patients, 55 biologically relevant mutations and 292 VUS mutations were identified. Twenty-seven of the biologically relevant mutations (49%) were in MM (24/64) with the median number per patient being 1 (0-4). The most frequently observed mutations were that of DNMT3A LOF (6, 22.22%) and KRAS GOF (3, 11.11%). 132 VUS mutations with median of 5 (0-23) mutations per patient were also identified of which KMT2D LOF (5, 3.79%) and NOTCH1 GOF (4, 3.03%) were the most frequently identified. Amongst patients with MGUS (17/64), 6 (12%) biologically relevant mutations were identified whilst 70 VUS mutations with median 4 (1-8) mutations per patient

expression. These events, along with the loss of BCMA highlight the need for more advanced clinical testing to assess the actionability of the diverse therapeutic targets available to treat patients today.

P-348

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P-349

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Swarup Kumar[1], Kaylyn Kirk[1], Katharine Hooper[1], Ritika Vankina[1]

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Introduction: Significant advances in understanding genomic profiles of plasma cell disorder patients have been made recently. However, the spectrum of genomic variants of uncertain significance (VUS) including their frequency and malignant transformation potential has not been well studied. In our cohort, we assessed the prevalence of biologically relevant variants and VUS using the Tempus xT® platform which is a targeted panel of 648 genes identified by DNA next-generation sequencing (NGS) enriched for clinically relevant and cancer driver genes and genes of emerging or uncertain clinical significance. We also assessed MSigDb (Human Molecular Signatures Database) hallmark gene set pathways that can be impacted by genomic VUS using a web-based tool Enrich R® providing various types of visualization summaries of collective functions of gene lists. **Methods:** Genomic data from bone marrow aspirate samples of sixty-four patients in our institution with monoclonal gammopathies (MGUS), smoldering myeloma (SM), multiple myeloma (MM), AL amyloidosis (AMY) and Waldenstrom's macroglobulinemia (WM) was abstracted using the Tempus xT® NGS platform and compared. Enrich-R® was then used to identify the top 3 Hallmark 2020 MSigDb pathways that were relevant amongst VUS. **Results:** Amongst all patients, 55 biologically relevant mutations and 292 VUS mutations were identified. Twenty-seven of the biologically relevant mutations (49%) were in MM (24/64) with the median number per patient being 1 (0-4). The most frequently observed mutations were that of DNMT3A LOF (6, 22.22%) and KRAS GOF (3, 11.11%). 132 VUS mutations with median of 5 (0-23) mutations per patient were also identified of which KMT2D LOF (5, 3.79%) and NOTCH1 GOF (4, 3.03%) were the most frequently identified. Amongst patients with MGUS (17/64), 6 (12%) biologically relevant mutations were identified whilst 70 VUS mutations with median 4 (1-8) mutations per patient

expression. These events, along with the loss of BCMA highlight the need for more advanced clinical testing to assess the actionability of the diverse therapeutic targets available to treat patients today.

P-348

ADAR1-regulated cytoplasmic dsRNA-immune sensing pathway is a novel mechanism of lenalidomide resistance in multiple myeloma

Mun Yee Koh[1], Tae-Hoon Chung[1], Sabrina Hui Min Toh[1], Nicole Xin Ning Tang[1], Jianbiao Zhou[1], Leilei Chen[1,2], Wee Joo Chng[3], Phaik Ju Teoh[1,4,5]

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Introduction: Immunomodulatory drugs (IMiDs) such as lenalidomide and pomalidomide are one of the main cornerstone treatments in multiple myeloma (MM). However, acquired resistance to IMiDs commonly underlies relapse, rendering MM generally incurable. IMiDs bind directly to cereblon (CRBN), the substrate adaptor of the CRL4(CRBN) E3 ubiquitin ligase, and promote the proteasomal degradation of IKZF1 and IKZF3, resulting in MM cell growth inhibition. While resistance to IMiDs has been commonly associated with abnormalities in CRBN and the corresponding factors within the same pathway, the underlying mechanisms in the majority of the cases remain unclear. Adenosine-to-inosine RNA editing, a post-transcriptional modification of dsRNA, catalysed by ADAR1, has shown biological and clinical relevance in MM. ADAR1 is important in the regulation of innate immune response via the dsRNA sensing pathway. Nevertheless, how ADAR1 expression and its aberrant RNA editing could affect cancer immunogenicity and importantly, in regulating IMiDs responses in MM, remain largely unexplored. This study elucidates the role of ADAR1 in mediating MM responses to IMiDs, specifically lenalidomide. **Methods:** A combination of public MM patients' dataset analyses (MMRF CoMMpass, APEX, HOVON, UAMS), generation of isogenic lenalidomide-resistant (LenR) cells and MM models with differential ADAR1 expression were utilised to assess the functional role of ADAR1, its effect in regulating lenalidomide responses in MM and the plausible biological mechanism of actions. **Results:** We observed a close association between ADAR1 expression with lenalidomide sensitivity in a panel of MM cells and in CoMMpass patients' (n=776 len-treated patients of a total of 911), which portends clinical significance. MM cells with ADAR1 knockdown demonstrated enhanced lenalidomide sensitivity, associated with the accumulation of endogenous dsRNAs, activation of the dsRNA-sensing pathways and increased interferon (IFN) responses. Conversely, ADAR1 overexpression reduced lenalidomide sensitivity in an RNA-editing dependent manner, which was observed concomitantly with suppression of the dsRNA-sensing pathway. Assessment of the LenR cells versus len-sensitive revealed higher ADAR1 expression, in association with increased RNA editing frequency, impediment of dsRNAs accumulation and suppression of the dsRNA-sensing pathway. Importantly, we identified the MDA5 as the predominant dsRNA sensor stimulating MM immunogenicity to lenalidomide, with ADAR1 as the upstream regulator. Concordantly, these in vitro findings were supported by our in vivo observations. **Conclusions:** In summary, we identified ADAR1-mediated suppression of dsRNA-sensing pathway as a novel mechanism regulating lenalidomide resistance. Our study harbours crucial translational value as ADAR1 is located at chromosome 1q21 which is frequently amplified in the MM patients. Further studies involve investigating the association of ADAR1 with CRBN pathway.

P-349

A retrospective assessment of biologically relevant genomic perturbations and variants of unknown significance in a cohort of plasma cell disorder at our institution; a single center experience

Swarup Kumar[1], Kaylyn Kirk[1], Katharine Hooper[1], Ritika Vankina[1]

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Introduction: Significant advances in understanding genomic profiles of plasma cell disorder patients have been made recently. However, the spectrum of genomic variants of uncertain significance (VUS) including their frequency and malignant transformation potential has not been well studied. In our cohort, we assessed the prevalence of biologically relevant variants and VUS using the Tempus xT® platform which is a targeted panel of 648 genes identified by DNA next-generation sequencing (NGS) enriched for clinically relevant and cancer driver genes and genes of emerging or uncertain clinical significance. We also assessed MSigDb (Human Molecular Signatures Database) hallmark gene set pathways that can be impacted by genomic VUS using a web-based tool Enrich R® providing various types of visualization summaries of collective functions of gene lists. **Methods:** Genomic data from bone marrow aspirate samples of sixty-four patients in our institution with monoclonal gammopathies (MGUS), smoldering myeloma (SM), multiple myeloma (MM), AL amyloidosis (AMY) and Waldenstrom's macroglobulinemia (WM) was abstracted using the Tempus xT® NGS platform and compared. Enrich-R® was then used to identify the top 3 Hallmark 2020 MSigDb pathways that were relevant amongst VUS. **Results:** Amongst all patients, 55 biologically relevant mutations and 292 VUS mutations were identified. Twenty-seven of the biologically relevant mutations (49%) were in MM (24/64) with the median number per patient being 1 (0-4). The most frequently observed mutations were that of DNMT3A LOF (6, 22.22%) and KRAS GOF (3, 11.11%). 132 VUS mutations with median of 5 (0-23) mutations per patient were also identified of which KMT2D LOF (5, 3.79%) and NOTCH1 GOF (4, 3.03%) were the most frequently identified. Amongst patients with MGUS (17/64), 6 (12%) biologically relevant mutations were identified whilst 70 VUS mutations with median 4 (1-8) mutations per patient

were also identified. Most frequent VUS were ARID1B LOF (4, 5.71%) and ATM LOF(2, 2.86%). Mean tumor mutational burden (TMB;m/mB) of all disease states was 1.67 in patients with AMY, WM (1.4), and MM (1.32) in comparison to that of MGUS (0.37) and SM (0.23) patients (p 0.08; Mann Whitney U). Identified VUS were input into curated hallmark MSigDb gene sets in EnrichR that identified the following targets in MM patients, E2F Target, G2-M Checkpoint and p53 pathway and in MGUS patents, PI3K/AKT/mTOR signaling, p53 pathway, and Estrogen response late in descending order of importance. **Conclusions:** We herein report the genomic profile of plasma cell disorders using a commercially available assay at the time of diagnosis. Higher TMB and number of VUS per patient trended towards malignant disease states, suggesting that estimation of the known and unknown genomic burden can inform transformation potential. Pathway analysis of VUS genes can also be informative of their biological relevance if truly differentially expressed.

P-350

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Noemie Leblay[1], Remi Tilmont[1], Mansour Poorebrahim[1], Sungwoo Ahn[1], Ranjan Maity[1], Holly Lee[1], Elie Barakat[1], Benjamin Barwick[2], Lawrence Boise[2], Nizar Bahlis[3], Paola Neri[3]

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Introduction: The BCL2 inhibitor venetoclax has shown promising results in multiple myeloma (MM) patients harboring the t(11;14). However, among these patients the responses are not universal, suggesting that several factors influence its response. We have previously demonstrated that MM cells adapt to its selective pressure by transitioning from B cell-like to a mature plasma cell-like transcriptional and epigenetic signatures. In this study, we used MM primary samples and cell lines to functionally validate some of the key factors involved in venetoclax resistance. **Methods:** Serial BM aspirates were collected from 15 relapsed MM patients; 6 harboring t(11;14) and 9 without the translocation, prior to initiation of therapy and at the time of relapse. All t(11;14) patients were treated with venetoclax. Chromatin accessibility and mRNA profiling of isolated CD138+ MM cells were performed using Chromium Single Cell ATAC and 3' Reagent Kits (10x Genomics) respectively. Pairwise sequencing was performed on NexSeq 500 platform. Cell Ranger, Seurat and ArchR were used for sample demultiplexing, barcode processing, single-cell 3' gene counting and data analysis. Overexpression of MCL1, NOXA, and RUNX1 were induced with lentivirus transduction. **Results:** By comparing the epigenome and transcriptome of pre- and post-venetoclax samples from t(11;14) patients, we identified MCL1 as the major event responsible for venetoclax resistance. As such the overexpression of MCL1 in the venetoclax-sensitive KMS12BM induced resistance to venetoclax through the shifting of BIM loading from BCL2 to MCL1. Furthermore, the MCL1 upregulation was associated with downregulation of the apoptotic sensitizer NOXA and low NOXA/MCL1 ratio. Of interest, ectopic expression of NOXA in the venetoclax-resistant U266 led to loss of MCL1 binding to BIM, confirming the important role of NOXA in priming BCL2 dependency. Furthermore, based on scATAC seq data that showed an enrichment of RUNX1 binding in venetoclax-resistant cells we have decided to overexpress RUNX1 in KMS12BM. As expected, we observed a significant reduction in venetoclax-induced cell death in these cells when compared with WT through downregulation of BCL2. Of note, we also observed an enrichment of RUNX1 binding in non-t(11;14) cells when compared with t(11;14). As such, treatment with the RUNX1 inhibitor AI-10-49 in the non-t(11;14) OPM2 cells resulted in overexpression of NOXA and loss of MCL1 binding to BIM confirming the dual effect of RUNX1 on MCL1 dependence by repressing NOXA and BCL2. **Conclusions:** Taken together these data underline the complexity of the mechanisms involved in venetoclax resistance and showed that the loss of BCL2 dependency can be due to NOXA downregulation and upregulation of MCL-1 and RUNX-1. Therefore, the use of agents that can prime BCL2-dependency through upregulation of NOXA and shifting BIM loading to BCL2 (RUNX1 inhibitors) could be explored in combination with venetoclax in MM patients who acquire MCL1 dependence following treatment.

P-351

Are genomic lesions of cereblon pathway genes sufficient to explain clinical relapses from IMiD-based treatment in multiple myeloma (MM)?

Lisa Leypoldt[1,21,3,4], Torsten Steinbrunn[1,2,3,5], Phaik Ju Teoh[1,2,3,6,7], Ricardo de Matos Simoes[1,2,3,8], Ryosuke Shirasaki[1,2,3,8,9], Constantine Mitsiades[1,2,3,8]

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were also identified. Most frequent VUS were ARID1B LOF (4, 5.71%) and ATM LOF(2, 2.86%). Mean tumor mutational burden (TMB;m/mB) of all disease states was 1.67 in patients with AMY, WM (1.4), and MM (1.32) in comparison to that of MGUS (0.37) and SM (0.23) patients (p 0.08; Mann Whitney U). Identified VUS were input into curated hallmark MSigDb gene sets in EnrichR that identified the following targets in MM patients, E2F Target, G2-M Checkpoint and p53 pathway and in MGUS patents, PI3K/AKT/mTOR signaling, p53 pathway, and Estrogen response late in descending order of importance. **Conclusions:** We herein report the genomic profile of plasma cell disorders using a commercially available assay at the time of diagnosis. Higher TMB and number of VUS per patient trended towards malignant disease states, suggesting that estimation of the known and unknown genomic burden can inform transformation potential. Pathway analysis of VUS genes can also be informative of their biological relevance if truly differentially expressed.

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patients (pts) relapse after IMiD-containing regimens. **Methods:** We evaluated the molecular profiling alterations of 42 CRBNPGs (vs. a set of 42 known MM driver genes; defined by prior studies e.g. Ansari-Pour et al Blood 2023) in pts of the MMRF CoMMpass study (IA22) who had genomic or transcriptional analyses in ≥2 paired bone marrow samples before vs. after IMiD-based treatment (baseline, relapse[s]). **Results:** Among 179 pts fulfilling inclusion criteria, 32 pts (17.9%) had at least one mutated CRBNPG at any timepoint (ptsmut). Of 25 CRBNPGs mutated in any pt, FAM83F was most frequently affected (n=4; 12.5%), followed by CRBN and IKZF3 (n=3 each; 9.4%). 19 pts (59.4%) had a CRBNPG mutation at baseline; 13 pts (40.6%) developed a new CRBNPG mutation at relapse; and 2 pts (6.3%) had >1 mutation (2 and 5 genes). Increase in variant allele frequencies (VAF) of at least one CRBNPG mutation occurred in 14 pts (43.8% of ptsmut), but VAF at relapse were < 0.5. Interestingly, preexisting CRBNPG mutations were not detectable at relapse in 9 pts (28.1%) or had decline in VAF in 3 pts. Clinical response (≥partial response) to IMiDs was documented in 11/13 pts (84.6%) who developed a new CRBNPG mutation and 11/14 pts (78.6%) with VAF increase, while 2 and 3 pts, respectively, had stable or progressive disease. Out of 19 pts with a mutation present at baseline, 2 (10.5%) were non-responsive to IMiD treatment. Importantly, no evidence for complete LOF for any CRBNPG (e.g., via combination of mutation, downregulation/alternative splicing, DNA copy number loss, fusion, etc) was identified at relapse or baseline. Most pts received IMiDs+Proteasome inhibitor (PI), but in our preclinical CRISPR studies, KO of CRBNPGs did not cause sensitization (or resistance) to PIs, thus genomic results for CRBNPGs conceivably were not skewed by PI use, e.g. via elimination of cells with complete LOF of CRBNPGs. In this set of pts, mutations in known MM driver genes (e.g., KRAS, BRAF, ARID1A, TP53, IRF4 among the most frequently affected) were detected at relapse in 26 pts (81.3% of ptsmut) with heterogeneous VAF changes at relapse vs. baseline. **Conclusions:** A minority of MM pts relapsing from IMiD-based treatments harbor genomic defects of CRBNPGs but typically not complete LOF for any such gene, and new/enriched mutations in known MM driver genes cannot be excluded as alternative explanations, beyond CRBNPGs, for these relapses. Additional and more complex, genomic or non-genomic, mechanisms may account for resistance to these regimens.

P-352

Enhanced expression of DNp73 promotes drug resistance and immune evasion in multiple myeloma by targeting the MYC and MYCN pathways

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Introduction: Multiple myeloma (MM) remains an incurable malignancy of plasma cells. The complex bone marrow microenvironment promotes resistance to both current anti-myeloma agents and emerging immunotherapies. Among genomic drivers of the disease, alterations of the tumor suppressor TP53 are associated with poor outcomes. DNp73, an inhibitor of the p53 tumor suppressor family, drives drug resistance and cancer progression in several solid malignancies. However, the biological functions and molecular mechanisms of DNp73 in MM remain unclear. In this study, we investigated the role of DNp73 in the drug resistance of MM, and disclosed the corresponding mechanism of how DNp73 promotes the immune escape of MM cells. **Methods:** We constructed DNp73 overexpression and sh-RNA interference plasmids to obtain stable cell lines. The effects of DNp73 on proliferation and drug sensitivity were determined by flow cytometry and xenotransplantation model. RNA-seq and CHIP-seq were performed to detect the mechanisms of drug resistance in MM cells. The DNA damage repair and invasion ability of MM cells were detected by immunofluorescence and transwell assay. To validate the role of DNp73 in immune escape, we performed phagocytosis assays. **Results:** Our previous study reported that miR-15a was downregulated in MM cells and correlated with the inferior outcome of MM patients. Further analysis demonstrated that DNp73 was a direct target of p65, loss of miR-15a led to the activation of NF-κB-p65 pathway in MM cells. In addition, the level of miR-15a was negatively correlated with the expression of DNp73 in MM cells of patients ($r=-0.672$, $p< 0.05$). After DNp73 was down-regulated, cell proliferation and drug resistance were effectively inhibited. Further in vivo study indicated the tumor volume in DNp73 knockdown group was reduced, and increased sensitivity to the carfilzomib, epirubicin and pomalidomide was observed ($p< 0.01$). Of note, RNA-seq analysis indicated that DNp73 expression was positively correlated with MYCN, MYC and CDK7 transcriptional programs in MM. GSEA analysis showed that MYC targets and DNA damage repair pathways were significantly enriched in DNp73-OE cells. Compared to control group, DNp73-OE cells were resistant to irradiation-induced cell death($p< 0.01$). Meanwhile, DNp73 knockdown significantly reduced the migration and invasion of cells($p< 0.01$). CHIP-seq data showed that DNp73 could bind to the promoter region of MYCN. DNp73 overexpression protects MM cells from phagocytosis, treated with anti-human CD47 antibody increased phagocytosis of macrophages($p< 0.01$). **Conclusions:** In the present study, we demonstrated that miR-15a downregulation activated NF-κB, which promoted DNp73 expression at transcription level. DNp73 is a potential oncogene involved in MM pathogenesis, which promotes MM cells growth and immune evasion by targeting MYC and MYCN pathway.

P-353

In vitro functional characterization of a multiple myeloma susceptibility locus

Angelica Macauda[1], Mehrnoosh Shokouhi[1], Rainer Will[1], Romano Liotti[2], Pelin Ünal[1], Jose Manuel Maldonado-Sanchez[1], Federico Canzia[1]

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patients (pts) relapse after IMiD-containing regimens. **Methods:** We evaluated the molecular profiling alterations of 42 CRBNPGs (vs. a set of 42 known MM driver genes; defined by prior studies e.g. Ansari-Pour et al Blood 2023) in pts of the MMRF CoMMpass study (IA22) who had genomic or transcriptional analyses in ≥2 paired bone marrow samples before vs. after IMiD-based treatment (baseline, relapse[s]). **Results:** Among 179 pts fulfilling inclusion criteria, 32 pts (17.9%) had at least one mutated CRBNPG at any timepoint (ptsmut). Of 25 CRBNPGs mutated in any pt, FAM83F was most frequently affected (n=4; 12.5%), followed by CRBN and IKZF3 (n=3 each; 9.4%). 19 pts (59.4%) had a CRBNPG mutation at baseline; 13 pts (40.6%) developed a new CRBNPG mutation at relapse; and 2 pts (6.3%) had >1 mutation (2 and 5 genes). Increase in variant allele frequencies (VAF) of at least one CRBNPG mutation occurred in 14 pts (43.8% of ptsmut), but VAF at relapse were < 0.5. Interestingly, preexisting CRBNPG mutations were not detectable at relapse in 9 pts (28.1%) or had decline in VAF in 3 pts. Clinical response (≥partial response) to IMiDs was documented in 11/13 pts (84.6%) who developed a new CRBNPG mutation and 11/14 pts (78.6%) with VAF increase, while 2 and 3 pts, respectively, had stable or progressive disease. Out of 19 pts with a mutation present at baseline, 2 (10.5%) were non-responsive to IMiD treatment. Importantly, no evidence for complete LOF for any CRBNPG (e.g., via combination of mutation, downregulation/alternative splicing, DNA copy number loss, fusion, etc) was identified at relapse or baseline. Most pts received IMiDs+Proteasome inhibitor (PI), but in our preclinical CRISPR studies, KO of CRBNPGs did not cause sensitization (or resistance) to PIs, thus genomic results for CRBNPGs conceivably were not skewed by PI use, e.g. via elimination of cells with complete LOF of CRBNPGs. In this set of pts, mutations in known MM driver genes (e.g., KRAS, BRAF, ARID1A, TP53, IRF4 among the most frequently affected) were detected at relapse in 26 pts (81.3% of ptsmut) with heterogeneous VAF changes at relapse vs. baseline. **Conclusions:** A minority of MM pts relapsing from IMiD-based treatments harbor genomic defects of CRBNPGs but typically not complete LOF for any such gene, and new/enriched mutations in known MM driver genes cannot be excluded as alternative explanations, beyond CRBNPGs, for these relapses. Additional and more complex, genomic or non-genomic, mechanisms may account for resistance to these regimens.

P-352

Enhanced expression of DNp73 promotes drug resistance and immune evasion in multiple myeloma by targeting the MYC and MYCN pathways

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Introduction: Multiple myeloma (MM) remains an incurable malignancy of plasma cells. The complex bone marrow microenvironment promotes resistance to both current anti-myeloma agents and emerging immunotherapies. Among genomic drivers of the disease, alterations of the tumor suppressor TP53 are associated with poor outcomes. DNp73, an inhibitor of the p53 tumor suppressor family, drives drug resistance and cancer progression in several solid malignancies. However, the biological functions and molecular mechanisms of DNp73 in MM remain unclear. In this study, we investigated the role of DNp73 in the drug resistance of MM, and disclosed the corresponding mechanism of how DNp73 promotes the immune escape of MM cells. **Methods:** We constructed DNp73 overexpression and sh-RNA interference plasmids to obtain stable cell lines. The effects of DNp73 on proliferation and drug sensitivity were determined by flow cytometry and xenotransplantation model. RNA-seq and CHIP-seq were performed to detect the mechanisms of drug resistance in MM cells. The DNA damage repair and invasion ability of MM cells were detected by immunofluorescence and transwell assay. To validate the role of DNp73 in immune escape, we performed phagocytosis assays. **Results:** Our previous study reported that miR-15a was downregulated in MM cells and correlated with the inferior outcome of MM patients. Further analysis demonstrated that DNp73 was a direct target of p65, loss of miR-15a led to the activation of NF-κB-p65 pathway in MM cells. In addition, the level of miR-15a was negatively correlated with the expression of DNp73 in MM cells of patients ($r=-0.672$, $p< 0.05$). After DNp73 was down-regulated, cell proliferation and drug resistance were effectively inhibited. Further in vivo study indicated the tumor volume in DNp73 knockdown group was reduced, and increased sensitivity to the carfilzomib, epirubicin and pomalidomide was observed ($p< 0.01$). Of note, RNA-seq analysis indicated that DNp73 expression was positively correlated with MYCN, MYC and CDK7 transcriptional programs in MM. GSEA analysis showed that MYC targets and DNA damage repair pathways were significantly enriched in DNp73-OE cells. Compared to control group, DNp73-OE cells were resistant to irradiation-induced cell death($p< 0.01$). Meanwhile, DNp73 knockdown significantly reduced the migration and invasion of cells($p< 0.01$). CHIP-seq data showed that DNp73 could bind to the promoter region of MYCN. DNp73 overexpression protects MM cells from phagocytosis, treated with anti-human CD47 antibody increased phagocytosis of macrophages($p< 0.01$). **Conclusions:** In the present study, we demonstrated that miR-15a downregulation activated NF-κB, which promoted DNp73 expression at transcription level. DNp73 is a potential oncogene involved in MM pathogenesis, which promotes MM cells growth and immune evasion by targeting MYC and MYCN pathway.

P-353

In vitro functional characterization of a multiple myeloma susceptibility locus

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Introduction: Several genome-wide association studies (GWAS) have been conducted to identify germline variants predisposing to multiple myeloma (MM). Up to date, 24 loci were found to be associated with MM risk, but very little information is available about their functional role. GWAS design takes advantage of the linkage disequilibrium (LD) structure of the human genome, thus the main GWAS findings are single-nucleotide polymorphisms (SNPs) that show the strongest association with MM risk (measured as the lowest p-values), but they are not necessarily the functionally causal variants. The functional characterization of the causal risk variants would lead to a better understanding of disease development. For these reasons we aimed at exploring in vitro the function of the GWAS-identified rs3747481 SNP through CRISPR-Cass9 knock-in technology in the U266B1 MM cell line. **Methods:** To maximize the probability to capture the casual variant, we focused on chr16 q23.1, the locus with the smallest number of SNPs in high LD (r2>0.8). A cell pool of U266B1 containing the edited locus of interest was generated by the company Synthego (https://www.synthego.com/) with CRISPR-Cas9 knock-in technology. The isogenic cell colonies were then generated using a CloneSelect Single-Cell Printer. Successfully growing colonies with the three possible genotypes at rs3747481 were functionally tested. In particular, we measured: differences in proliferation, migration and gene expression of the nearby gene RNF40. The last test was also performed in 25 MM bone marrow samples with known genotypes at rs3747481. Kruskal-Wallis and T test were used to analyse the statistical significance. **Results:** rs3747481 was of particular functional interest, due to the following reasons: it is a missense variant (protein change: P359L), has a high CADD PHRED score (22.1) and, according to GTEx portal, it is associated with the expression level of the RNF40 gene. We successfully isolated two T/T colonies and one C/T colony for functional testing (T is the MM risk associated allele). A 2.3-fold decrease in proliferation was observed in T/T colonies and 2.9 for colonies with C/T genotype compared to the C/C wild type (p=0.02). The migration assay showed a significant increase in cell migration of 3-fold (p=0.002) for the cells carrying the T allele. A significant increase of the expression of RNF40 was also observed when comparing the 3 genotypes in the cell lines, with the highest expression in T/T cells (p=0.001). A similar difference was observed in the BM patients as well, although not significant. **Conclusions:** We successfully edited the genotypes of interest and observed a decrease in proliferation and an increase in migration in colonies with the MM risk allele, as well as a significant increase in the expression of RNF40. These findings confirmed the functional role of rs3747481. However, further experiments will be needed to better understand the biological mechanism of action of the polymorphism.

P-354

Whole genome sequencing reveals significant genetic admixture in multiple myeloma patients, impacting assessment of etiology

Kylee Maclachlan[1], Patrick Blaney[2], Dylan Gagler[2], Eileen Boyle[3], Benjamin Diamond[4], Urvi Shah[1], Neha Korde[1], Sham Mailankody[1], Malin Hultcrantz[1], Hani Hassoun[1], Carlyn Rose Tan[5], Alexander Lesokhin[5], Nicolas Robine[6], Lara Winterkorn[6], Timothy Chu[6], Zoe Steinsnyder[6], Maria Arcila[5], Faith Davies[2], Ola Landgren[4], Saad Usmani[5], Francesco Maura[4], Gareth Morgan[2]

[1]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City NY, USA; [2]Myeloma Research Program, NYU Langone, Perlmutter Cancer Center; [3]Myeloma Research, UCL Cancer Institute; [4]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami; [5]Memorial Sloan Kettering Cancer Center, New York City NY, USA; [6]New York Genome Center

Introduction: In the U.S. population, having African ancestry (AA) conveys a higher risk of multiple myeloma (MM) than white ancestry (WA), however, published whole genomic sequencing (WGS) data is predominantly from WA populations. The Polyethnic-1000 (P1000) is a multi-institutional initiative with the New York Genome Center, investigating cancers having a higher prevalence in AA populations. We hypothesize that self-described race and ethnicity, according to limited proscribed categories, are insufficient to delineate biological contribution to MM development. Unique biological insights may require comprehensive definition of genetic origin, considering heterogeneity within historically defined groups. **Methods:** We applied Admixture, a composition profile based on SNPs corresponding to geographical reference populations, to both targeted sequencing (MSK-Heme-IMPACT) and WGS. Admixture estimates proportion per patient from 5 super populations (African [AFR], American [AMR], European [EUR], East Asian, South Asian), with WGS allowing resolution of 23 subpopulations. From patients self-identifying as Black or Hispanic, 111 samples had IMPACT and 101 WGS. Results were compared with the CoMMpass dataset and WA WGS, to a total WGS cohort of 1221. **Results:** Genomic complexity hidden by self-reported race and ethnicity was revealed by genetically determined Admixture. IMPACT data estimated that while 42 (38%) had AFR super family contribution ≥0.9, 37 (33%) had 0.5-0.8 and 32 (29%) had < 0.5. 24% self-identifying as Hispanic had ≥0.5 AFR. From WGS, 46/101 had ≥ 0.25 from at least 2/23 subpopulations (consistent with grandparents) with 94 having ≥0.125 from different subpopulations (consistent with great-grandparents). From those with ≥0.25 from different populations, 33 were within AFR while 11 were across super-populations. Hierarchical clustering analysis of the P1000 samples together with 134 CoMMpass samples having AFR > 0.1 produced 3 main patient clusters; 2 with predominantly AFR ancestry, clustering by proportion of AFR contribution, while 1 cluster was highly admixed with EUR and AMR. Clustering based on subpopulations was highly analogous. Considering the entire WGS cohort produced 6 clusters; 5 had a predominant super population, with the majority of AFR collapsed into 1 cluster, while 1 cluster was heterogenous in composition. Self-described WA patients also had significant admixture revealed. **Conclusions:** Self-reported race and ethnicity don't allow consideration of the significant variability of genetic admixture present in our patients, with likely insufficient granularity on inherited risk of MM. Our genomic datasets could benefit from increasing AA and Hispanic representation. Clustering analysis should consider both the entire cohort and separately analyze non-WA samples, to allow adequate resolution of genetic

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P-354

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origin. Ongoing studies will incorporate genetic admixture alongside somatic genomic assessment to accurately investigate progression risk from precursor disease to MM.

P-355

A novel genomewide RNA-Targeting CRISPR/Cas13 screen identifies a plasma cell-specific long non-coding RNA (LncRNA) essential for myeloma cell growth

Domenico Maisano[1], Anil Aktas-Samur[1], Claire Gao[1], Na Liu[1], Vanessa Favasuli[1], Pietro Folino[1], Annamaria Gulla[2], Kenneth Anderson[3], Carl Novina[1], Mariateresa Fulciniti[1], Mehmet Samur[1], Eugenio Morelli[1], Nikhil Munshi[4]

[1]Dana-Farber Cancer Institute; [2]Candiolo Cancer Institute; [3]LeBow Institute for Myeloma Therapeutics and Jerome Lipper Center for Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; [4]Dana-Farber Cancer Institute, Boston, MA, USA, Veterans Affairs Boston Healthcare System/Harvard Medical School

Introduction: Long non-coding RNAs (lncRNAs) are abundant RNA molecules that outnumber protein-coding genes in the human genome. They play significant roles in biological processes by interacting with proteins and other nucleic acids. Our previous work using RNA-seq data and a CRISPRi screen identified a series of lncRNAs as independent predictors of clinical outcome and confirmed their functional significance in promoting MM cell growth. However, CRISPRi focuses just on lncRNAs with defined transcription start sites. **Methods:** To find tumor-promoting lncRNAs in a genomewide unbiased manner, we have exploited the RNA-targeting activity of the CRISPR-Cas13d endonuclease, which enables the selective knockdown of lncRNA transcripts of any genomic origin. We have used it to perform viability screens in five MM cell lines, targeting > 6,000 lncRNAs whose expression was identified using RNA-seq data from CD138+ MM cells from 360 MM patients. We developed a pooled lentiviral library comprising 60,000 sgRNAs, with 9 of them per lncRNA and > 500 non-targeting sgRNAs as negative controls. This library was infected at a low MOI (< 0.3) into five MM cell lines (AMO1, H929, KMS11, OPM2, R8226) expressing Cas13d. After three weeks, we employed MAGeCK robust rank aggregation (RRA) algorithm to identify sgRNAs that displayed either depletion or enrichment within the MM cell population. **Results:** We identified 155 lncRNAs essential for MM cell proliferation. A novel lncRNA named MYND1, was one of the most abundant lncRNAs in MM and normal plasma cells (median TPM>25), whereas it is significantly lower or absent in 54 normal tissues and cell types. RT-qPCR confirmed the plasma-cell specificity of MYND1 and its higher expression in MM cells compared to plasma cells. Furthermore, using subcellular qRT-PCR, we detected MYND1 mostly in the nucleus. Higher MYND1 expression predicted a worse clinical outcome in the newly diagnosed MM patients (n=360) enrolled in the IFM/DFCI clinical trial 2009 (NCT01191060). Knocking down MYND1 using antisense oligonucleotides in three MM cell lines (AMO1, H929, and KMS11) caused significant time-dependent inhibition of MM cell viability. Following MYND1 depletion in AMO1 cells, RNA-seq and GSEA identified significant modulation of expression of splice variants and inhibition of spliceosome-related gene signatures. MYND1 shares half of its sequence with U1 small nuclear RNA, a key component of the spliceosome complex. We confirmed the extensive interaction of MYND1 with spliceosome components HNRNPC, HNRNPH2, and HNRNPH3 in MM cells using ChIRP-MS and in vitro using RPPD-MS. **Conclusions:** The functional impact of modulating MYND1 on spliceosome proteins is currently under investigation. Furthermore, ongoing nucleotide pairing analysis and structure simulations are being conducted to determine the optimal MYND1 targeting strategy. Our preliminary study suggests that MYND1 supports splicing activity, thus promoting MM cell growth and survival, and is a potential therapeutic target.

P-356

Effect of amplification or gain of 1Q21 in patients with multiple myeloma treated with daratumumab

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Introduction: Gain and amplification of 1q21 have been proposed as prognostic markers in patients with multiple myeloma, and there is evidence that these alterations may be associated with worse responses to anti-CD38 monoclonal antibodies (1, 2, 3). In this study, we analyzed the effect of 1q alterations on the prognosis of patients with multiple myeloma treated with isatuximab and daratumumab. **Methods:** We collected retrospective data from 117 patients treated with daratumumab at our center. Patients were considered eligible if they had cytogenetic studies and response evaluation. +1q alterations were classified as gain if 3 copies of the gene were found and amplification if 4 or more copies were present determined by FISH. **Results:** The median age at diagnosis was 66 years, and 54.7% were women. A total of 23.1% had high-risk ISS-R at diagnosis, and 16.2% had extramedullary involvement. Most of the cohort (80 patients, 68.4%) were relapsed or refractory to previous lines, and received daratumumab therapy after a median of 1 previous line (0-6). In the majority of the cases, daratumumab was administered in combination with other anti-myeloma agents, and only 14.5% of patients received it as monotherapy. A total of 26.5% of patients had 1q gain, and 24.7% had amplification. Overall, the progression-free survival (PFS) in the group of patients with 1q gain or amplification was 14 months compared to 28 months in those without any alteration in 1q, showing a hazard ratio (HR) for PFS of 1.75 (CI 1.05-2.88). Analyzing patients with gain and amplification separately, only patients with 1q amplification maintained a statistically significant difference in the risk of progression (12 vs 28 months; p=0.019; HR 1.9, CI 1.06-3.40), while patients with 1q gain showed a non-significant trend towards shorter PFS (19

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Introduction: Long non-coding RNAs (lncRNAs) are abundant RNA molecules that outnumber protein-coding genes in the human genome. They play significant roles in biological processes by interacting with proteins and other nucleic acids. Our previous work using RNA-seq data and a CRISPRi screen identified a series of lncRNAs as independent predictors of clinical outcome and confirmed their functional significance in promoting MM cell growth. However, CRISPRi focuses just on lncRNAs with defined transcription start sites. **Methods:** To find tumor-promoting lncRNAs in a genomewide unbiased manner, we have exploited the RNA-targeting activity of the CRISPR-Cas13d endonuclease, which enables the selective knockdown of lncRNA transcripts of any genomic origin. We have used it to perform viability screens in five MM cell lines, targeting > 6,000 lncRNAs whose expression was identified using RNA-seq data from CD138+ MM cells from 360 MM patients. We developed a pooled lentiviral library comprising 60,000 sgRNAs, with 9 of them per lncRNA and > 500 non-targeting sgRNAs as negative controls. This library was infected at a low MOI (< 0.3) into five MM cell lines (AMO1, H929, KMS11, OPM2, R8226) expressing Cas13d. After three weeks, we employed MAGeCK robust rank aggregation (RRA) algorithm to identify sgRNAs that displayed either depletion or enrichment within the MM cell population. **Results:** We identified 155 lncRNAs essential for MM cell proliferation. A novel lncRNA named MYND1, was one of the most abundant lncRNAs in MM and normal plasma cells (median TPM>25), whereas it is significantly lower or absent in 54 normal tissues and cell types. RT-qPCR confirmed the plasma-cell specificity of MYND1 and its higher expression in MM cells compared to plasma cells. Furthermore, using subcellular qRT-PCR, we detected MYND1 mostly in the nucleus. Higher MYND1 expression predicted a worse clinical outcome in the newly diagnosed MM patients (n=360) enrolled in the IFM/DFCI clinical trial 2009 (NCT01191060). Knocking down MYND1 using antisense oligonucleotides in three MM cell lines (AMO1, H929, and KMS11) caused significant time-dependent inhibition of MM cell viability. Following MYND1 depletion in AMO1 cells, RNA-seq and GSEA identified significant modulation of expression of splice variants and inhibition of spliceosome-related gene signatures. MYND1 shares half of its sequence with U1 small nuclear RNA, a key component of the spliceosome complex. We confirmed the extensive interaction of MYND1 with spliceosome components HNRNPC, HNRNPH2, and HNRNPH3 in MM cells using ChIRP-MS and in vitro using RPPD-MS. **Conclusions:** The functional impact of modulating MYND1 on spliceosome proteins is currently under investigation. Furthermore, ongoing nucleotide pairing analysis and structure simulations are being conducted to determine the optimal MYND1 targeting strategy. Our preliminary study suggests that MYND1 supports splicing activity, thus promoting MM cell growth and survival, and is a potential therapeutic target.

P-356

Effect of amplification or gain of 1Q21 in patients with multiple myeloma treated with daratumumab

Irene Zamanillo[1], Lucia Medina de Alba[1], Rafael Alonso[1], Jose Maria Sanchez[1], Clara Cuellar[1], Manuela Fernandez-Guijarro[2], Joaquín Martínez-López[1]

[1]University Hospital 12 de Octubre; [2]Hospital 12 de Octubre, Instituto de Investigación Hospital 12 de Octubre (i+12), Centro Nacional de Investigaciones Oncológicas (CNIO), Universidad Complutense

Introduction: Gain and amplification of 1q21 have been proposed as prognostic markers in patients with multiple myeloma, and there is evidence that these alterations may be associated with worse responses to anti-CD38 monoclonal antibodies (1, 2, 3). In this study, we analyzed the effect of 1q alterations on the prognosis of patients with multiple myeloma treated with isatuximab and daratumumab. **Methods:** We collected retrospective data from 117 patients treated with daratumumab at our center. Patients were considered eligible if they had cytogenetic studies and response evaluation. +1q alterations were classified as gain if 3 copies of the gene were found and amplification if 4 or more copies were present determined by FISH. **Results:** The median age at diagnosis was 66 years, and 54.7% were women. A total of 23.1% had high-risk ISS-R at diagnosis, and 16.2% had extramedullary involvement. Most of the cohort (80 patients, 68.4%) were relapsed or refractory to previous lines, and received daratumumab therapy after a median of 1 previous line (0-6). In the majority of the cases, daratumumab was administered in combination with other anti-myeloma agents, and only 14.5% of patients received it as monotherapy. A total of 26.5% of patients had 1q gain, and 24.7% had amplification. Overall, the progression-free survival (PFS) in the group of patients with 1q gain or amplification was 14 months compared to 28 months in those without any alteration in 1q, showing a hazard ratio (HR) for PFS of 1.75 (CI 1.05-2.88). Analyzing patients with gain and amplification separately, only patients with 1q amplification maintained a statistically significant difference in the risk of progression (12 vs 28 months; p=0.019; HR 1.9, CI 1.06-3.40), while patients with 1q gain showed a non-significant trend towards shorter PFS (19

origin. Ongoing studies will incorporate genetic admixture alongside somatic genomic assessment to accurately investigate progression risk from precursor disease to MM.

P-355

A novel genomewide RNA-Targeting CRISPR/Cas13 screen identifies a plasma cell-specific long non-coding RNA (LncRNA) essential for myeloma cell growth

Domenico Maisano[1], Anil Aktas-Samur[1], Claire Gao[1], Na Liu[1], Vanessa Favasuli[1], Pietro Folino[1], Annamaria Gulla[2], Kenneth Anderson[3], Carl Novina[1], Mariateresa Fulciniti[1], Mehmet Samur[1], Eugenio Morelli[1], Nikhil Munshi[4]

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P-357

Individualized risk in newly diagnosed multiple myeloma

Francesco Maura[1], Arjun Rajanna[1], Bachisio Ziccheddu[1], Andriy Derkach[2], Alexandra Poos[3,4], Kylee Maclachlan[5], Eileen Boyle[6], Malin Hultcrantz[5], Ariosto Silva[7], Graham Jackson[8], Martin Kaiser[9], Charlotte Pawlyn[9], Gordon Cook[10], Leif Bergsagel[11], Hartmut Goldschmidt[12], Katja Weisel[13], Roland Fenk[14], Elias Mai[2,15], Marc Raab[16], Frits van Rhee[17], Saad Usmani[2], Ken Shain[7], Niels Weinhold[3,4], Gareth Morgan[18], Ola Landgren[19]

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Introduction: Outcomes for newly diagnosed multiple myeloma (NDMM) patients are heterogenous, with overall survival (OS) ranging from months to over 10 years. Though genomic events strongly contribute to clinical outcomes, yet the "one-size-fits-all" treatment paradigm remains dominant for NDMM. **Methods:** To decipher the molecular and clinical heterogeneity at unprecedented depth and develop the first artificial intelligence individualized prediction model for risk in NDMM (IRMMa), we assembled a large training (n=1933) and validation (n=256) set of patients with NDMM with available clinical-, genomic-, and therapeutic data. The training set was composed by the following cohorts: MMRF CoMMpass (n=1062), Myeloma Genome Project (n=492), Moffit AVATAR (n=177), and MSKCC MyTYPE (n=109). The validation set included patients enrolled in the GMMG-HD6 (NCT02495922) clinical trial with available whole genome sequencing (WGS). **Results:** To integrate clinical, demographic, genomic, and treatment data we compared different methods of predicting OS and event-free survival (EFS). Overall the Neural Cox Non-proportional-hazards (NCNPH)-based model emerged as most accurate in predicting EFS and OS, (c-index 0.69 and 0.73, respectively) and was used as the core-engine of IRMMa. IRMMa's accuracy was significantly higher than all existing prognostic models: ISS (EFS: 0.56; OS: 0.61), R-ISS (EFS: 0.54, OS: 0.57), R2-ISS (EFS 0.56; OS: 0.63). Among all 132 genomic features tested, only twenty significantly improved model accuracy for OS, including deletions on 1p, 1q21 gain/amp, TP53 loss, t(4;14)(NSD2;IGH), a high contribution of the APOBEC mutational signature and copy number variation signatures indicating chromothripsis. Importantly, while the inclusion of each feature improved the model accuracy, IRMMa has been developed as a flexible tool able to predict outcomes with incomplete data. Specifically, because genomic profiling is only rarely performed in current clinical practice, IRMMa performance was tested without genomic data. Despite this, IRMMa still outperformed ISS, R-ISS, and R2-ISS with EFS and OS c-index of 0.69 and 0.71, respectively. IRMMa accuracy and superiority compared to other prognostic models were validated on 256 patients enrolled in the GMMG-HD6 (NCT02495922) clinical trial. As a key innovation, IRMMa is able to predict differences in outcomes across different treatment combinations and strategies. For instance, using IRMMa we were able to predict NDMM patients, in whom high-dose melphalan followed by autologous stem cell transplant (HDM-ASCT) provides a significant advantage, and those in whom HDM-ASCT does not impact outcome. **Conclusions:** Integrating clinical, demographic, genomic, and therapeutic data, we have developed the first individualized risk-prediction model enabling personally tailored therapeutic decisions for NDMM patients.

P-358

Myeloma at a younger age presents with distinctive clinical and molecular features

Mateo Mejia Saldarriaga[1], Aubrie Sowa[2], Jorge Contreras[1], David Jayabalan[1], Cara Rosenbaum[1], Roger Pearse[1], Jorge Monge[3], Ruben Niesvizky[4], Mark Bustoros[1]

[1]Weill Cornell Medicine; [2]University College Dublin Medical Schoo; [3]Weill Cornell Medicine Myeloma Center; [4]Division of Oncology & Hematology, Weill Cornell Medicine, New York, NY, USA*

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selected to identify those above the median age and diminish overlap between groups. **Results:** African American (AA) were enriched in the ≤ 45 year groups in both cohorts (WCM 31% vs 13%, MMRF 33% vs 15%, p 45 years at diagnosis (183 patients) as a control in the WCM cohort showed similar results. Lower incidence of deletion 13q and gain 1q in the ≤ 45 years cohort (35% vs 50% p = 0.03, and 22% vs 42% p < 0.01) when compared to the ≥ 63 year cohort was seen. There were no differences in the rate of recurrent translocation, deletion, or mutations in MM. Enrichment of the CD-1 (associated with Cyclin D1) subgroup in the ≤ 45 years subgroup, while the LB (low bone) and HP (associated with hyperdiploidy) were enriched in the older group. Mutational signature analysis was done including all single nucleotide variants, the ≥ 63 year had higher mutational burden (3.8 vs 3.3 mut/Mb, p < 0.01), due to higher count and frequency of clock-like signatures (COSMIC 1 and 5), while there were no differences in other signatures. **Conclusions:** Young MM represents a distinct clinical enriched for AA, lower ISS stage and likely higher functional class and physiologic reserve (higher ASCT and lower ECOG), leading to improved PFS/OS, likely derived from better tolerance to highly active therapies and less attrition after progression. We identified a distinct molecular subgroup enriched for CD-1 signature and lower rates of deletion 13q and gain 1q, with a higher mutational burden due to higher clock-like signatures which suggest a later time of disease onset. There were no differences in the rate of recurrent translocation, hyperdiploidy or mutations. Genomic studies focused in AAs/Hispanics germline and somatic factors associated with MM are required to identify the biological origin for the observed differences.

P-359

Non-paraskeletal extramedullary disease is associated with high rates of high risk cytogenetic alterations and has a distinct transcriptional profile

Mateo Mejia Saldarriaga[1], Caitlin Unkenholz[1], David Jayabalan[1], Jorge Contreras[1], Roger Pearse[1], Cara Rosenbaum[1], Jorge Monge[1], Ruben Niesvizky[1], Mark Bustoros[1]

[1]Weill Cornell Medicine

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P-360

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P-359

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cofactors PHF19 have been associated with inferior overall survival in MM patients. Following this observation, using data from over 1500 MM patients, we investigated the genomic and transcriptomic landscape of the PRC2 complex in high-risk MM patients with a view to identify novel therapeutic targets. We utilized the EZH2 inhibitor Tazemetostat (Taz) to identify MM cell lines sensitive and resistant to PRC2 inhibition. Furthermore, we map key transcriptomic differences in the sensitive lines. Through both chemical and genetic disruption, we investigate phenotypic differences in PRC2 activity in MM cell lines with different genetic backgrounds. **Methods:** The Myeloma Genome Project data was used to map the expression of PRC2 genes in MM patients. A panel of MM cell lines were treated with Taz to determine cells with sensitivity to inhibition of EZH2 methyltransferase. For subsequent experiments, cells were treated with either 1μM Taz or DMSO control for 5 days. RNAseq was performed to identify a gene signature associated with sensitivity to EZH2 inhibition and significant pathways associated with EZH2 inhibition in sensitive and resistant cell lines were identified. Using the MMRF patient dataset, a gene set variance analysis was used to assign a PRC2 associated activity score for each patient. ChIP-seq was performed and histone marks (H3K27ac, H3K27me3 and H3K4me3) were analyzed in differentially express genes. Gene expression in interferon response genes across a panel of MM lines was validated by qPCR. The expression of PRC2 components were modulated in MM cell lines by CRISPR-Cas9. Taz sensitivity and phenotypic differences in apoptosis and cell growth were measured. **Results:** Patients with a PRC2 dependant gene signature were identified by mapping genomic and transcriptomic activity of PRC2 and its interactions across MM patients. In addition, MM cell lines showed varying levels of sensitivity to Taz treatment. RNAseq experiments revealed several pathways significantly altered upon EZH2 inhibition in sensitive cell lines including upregulation of IFN response genes and MYC downregulation. Furthermore, upregulation of H3K27ac and H3K4me3, active histone marks, were identified in promoters of IFN response genes in Taz sensitive cells. These significant transcriptional changes of IFN expression were confirmed across a panel of MM cell lines. **Conclusions:** PRC2 plays a role in IFN-related gene expression and may constitute a therapeutic mechanism in high-risk MM patients.

P-361

Genomic and transcriptomic landscape of hyper-APOBEC multiple myeloma

Marios Papadimitriou[1], Bachisio Ziccheddu[1], Abdessamad Youssfi[1], Marilena Tauro[2], Mark Meads[2], Kylee Maclachlan[3], Saad Usmani[4], Alexandra Poos[5], Marc Raab[6], Niels Weinhold[6], Ken Shain[2], Ola Landgren[7], Francesco Maura[7]

[1]University of Miami; [2]H Lee Moffitt Cancer Center; [3]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City NY, USA; [4]Memorial Sloan Kettering Cancer Center, New York City NY, USA; [5]Department of Hematology, Oncology and Rheumatology, Heidelberg University Hospital; [6]University Hospital Heidelberg; [7]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami

Introduction: APOBEC mutational signatures are among the most important mutational signatures present in the majority of patients with newly diagnosed multiple myeloma (NDMM). APOBEC mutational signatures are primarily caused by two enzymes, APOBEC3A (A3A) and APOBEC3B (A3B). While these genes are expressed in most myeloma cells, their influence on APOBEC mutagenesis appear to be extremely heterogeneous, with some patients having no detectable mutations and others having high contribution (hyper-APOBEC). **Methods:** To decipher the mechanism of APOBEC mutagenesis, we utilized 752 whole genomes from NDMM patients enrolled in the CoMMpass study. 723 and 767 had available whole exome sequencing (WES) and RNA sequencing (RNA-Seq) data, respectively. **Results:** APOBEC activity was identified in 416/723 (57.5%) patients using WES. Of these, 41 (5.8%) had MAF/MAFB translocations. Overall, 48/723 (6.6%) patients were defined as hyper-APOBEC (13 without MAF/MAFB events). We used differential expression (DE) analysis between three groups: hyper-APOBEC with MAF/MAFB (HA_TRA: n=31), hyper-APOBEC without MAF/MAFB (HA_NORM: n=8), and non-hyper-APOBEC without MAF/MAFB (WT: n=510). We identified 534 APOBEC-associated genes which were independent from the MAF/MAFB events. Importantly, A3B was higher in hyper-APOBEC with and without MAF/MAFB, while A3A was mostly expressed in MAF/MAFB samples. Using Spearman's correlation, we identified 50 significantly correlated genes (rho-squared>0.18; $p< 0.00001$) with A3B. Most of the genes belonged to the APOBEC-associated group defined by the DE and showed cell cycle/proliferation activity, suggesting a link between highly proliferative disease and hyper-APOBEC. To validate this finding, we evaluated the link between these genes and hyper-APOBEC among ICGC breast cancers. Overall, 35 of these genes showed similar correlation in hyper-APOBEC breast. Interestingly, most of these genes appear to be negatively controlled by E2F4, and positively controlled by FOXM1 and MYBL2. These three transcription factors are well-established regulators of the DREAM complex, which has been shown to play a key role in APOBEC transcriptional regulation (Roelofs et al., eLife, 2020). Next, we compared 131 genomic events to identify potential differences between the hyper-APOBEC and WT. HA_TRA and HA_NORM showed similarities, including a highly complex genomic profile enriched for 1q gain, 13q and 16q deletions ($p< 0.05$). In terms of gene expression, both groups showed enrichment for GEP70 positivity. Finally, HA_TRA and HA_NORM showed similar poor outcomes compared to WT. **Conclusions:** Patients with hyper-APOBEC NDMM are characterized by a distinct transcriptional profile with high cell proliferation, reduced inhibition by the DREAM complex, and a high level of genomic complexity reflected in poorer clinical outcomes.

P-362

ID2 acts as a novel tumor suppressor in MM by inhibition of TCF3 transcriptional activity

Tommaso Perini[1], Yao Yao[2], Jessica Fong Ng[2], Shuhui Deng[2], Anais Schavgoulidze[2], Moritz Binder[3], Ryan Young[4], Mei Knudson[5], Charles Epstein[5],

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cofactors PHF19 have been associated with inferior overall survival in MM patients. Following this observation, using data from over 1500 MM patients, we investigated the genomic and transcriptomic landscape of the PRC2 complex in high-risk MM patients with a view to identify novel therapeutic targets. We utilized the EZH2 inhibitor Tazemetostat (Taz) to identify MM cell lines sensitive and resistant to PRC2 inhibition. Furthermore, we map key transcriptomic differences in the sensitive lines. Through both chemical and genetic disruption, we investigate phenotypic differences in PRC2 activity in MM cell lines with different genetic backgrounds. **Methods:** The Myeloma Genome Project data was used to map the expression of PRC2 genes in MM patients. A panel of MM cell lines were treated with Taz to determine cells with sensitivity to inhibition of EZH2 methyltransferase. For subsequent experiments, cells were treated with either 1μM Taz or DMSO control for 5 days. RNAseq was performed to identify a gene signature associated with sensitivity to EZH2 inhibition and significant pathways associated with EZH2 inhibition in sensitive and resistant cell lines were identified. Using the MMRF patient dataset, a gene set variance analysis was used to assign a PRC2 associated activity score for each patient. ChIP-seq was performed and histone marks (H3K27ac, H3K27me3 and H3K4me3) were analyzed in differentially express genes. Gene expression in interferon response genes across a panel of MM lines was validated by qPCR. The expression of PRC2 components were modulated in MM cell lines by CRISPR-Cas9. Taz sensitivity and phenotypic differences in apoptosis and cell growth were measured. **Results:** Patients with a PRC2 dependant gene signature were identified by mapping genomic and transcriptomic activity of PRC2 and its interactions across MM patients. In addition, MM cell lines showed varying levels of sensitivity to Taz treatment. RNAseq experiments revealed several pathways significantly altered upon EZH2 inhibition in sensitive cell lines including upregulation of IFN response genes and MYC downregulation. Furthermore, upregulation of H3K27ac and H3K4me3, active histone marks, were identified in promoters of IFN response genes in Taz sensitive cells. These significant transcriptional changes of IFN expression were confirmed across a panel of MM cell lines. **Conclusions:** PRC2 plays a role in IFN-related gene expression and may constitute a therapeutic mechanism in high-risk MM patients.

P-361

Genomic and transcriptomic landscape of hyper-APOBEC multiple myeloma

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Introduction: APOBEC mutational signatures are among the most important mutational signatures present in the majority of patients with newly diagnosed multiple myeloma (NDMM). APOBEC mutational signatures are primarily caused by two enzymes, APOBEC3A (A3A) and APOBEC3B (A3B). While these genes are expressed in most myeloma cells, their influence on APOBEC mutagenesis appear to be extremely heterogeneous, with some patients having no detectable mutations and others having high contribution (hyper-APOBEC). **Methods:** To decipher the mechanism of APOBEC mutagenesis, we utilized 752 whole genomes from NDMM patients enrolled in the CoMMpass study. 723 and 767 had available whole exome sequencing (WES) and RNA sequencing (RNA-Seq) data, respectively. **Results:** APOBEC activity was identified in 416/723 (57.5%) patients using WES. Of these, 41 (5.8%) had MAF/MAFB translocations. Overall, 48/723 (6.6%) patients were defined as hyper-APOBEC (13 without MAF/MAFB events). We used differential expression (DE) analysis between three groups: hyper-APOBEC with MAF/MAFB (HA_TRA: n=31), hyper-APOBEC without MAF/MAFB (HA_NORM: n=8), and non-hyper-APOBEC without MAF/MAFB (WT: n=510). We identified 534 APOBEC-associated genes which were independent from the MAF/MAFB events. Importantly, A3B was higher in hyper-APOBEC with and without MAF/MAFB, while A3A was mostly expressed in MAF/MAFB samples. Using Spearman's correlation, we identified 50 significantly correlated genes (rho-squared>0.18; $p< 0.00001$) with A3B. Most of the genes belonged to the APOBEC-associated group defined by the DE and showed cell cycle/proliferation activity, suggesting a link between highly proliferative disease and hyper-APOBEC. To validate this finding, we evaluated the link between these genes and hyper-APOBEC among ICGC breast cancers. Overall, 35 of these genes showed similar correlation in hyper-APOBEC breast. Interestingly, most of these genes appear to be negatively controlled by E2F4, and positively controlled by FOXM1 and MYBL2. These three transcription factors are well-established regulators of the DREAM complex, which has been shown to play a key role in APOBEC transcriptional regulation (Roelofs et al., eLife, 2020). Next, we compared 131 genomic events to identify potential differences between the hyper-APOBEC and WT. HA_TRA and HA_NORM showed similarities, including a highly complex genomic profile enriched for 1q gain, 13q and 16q deletions ($p< 0.05$). In terms of gene expression, both groups showed enrichment for GEP70 positivity. Finally, HA_TRA and HA_NORM showed similar poor outcomes compared to WT. **Conclusions:** Patients with hyper-APOBEC NDMM are characterized by a distinct transcriptional profile with high cell proliferation, reduced inhibition by the DREAM complex, and a high level of genomic complexity reflected in poorer clinical outcomes.

P-362

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Introduction: Multiple myeloma (MM) is often sustained by chromosomal translocations that involve super-enhancers and transcription factors (TF), thus leading to a profound rewiring of transcriptional circuits. This generates MM specific non-oncogene addictions on TFs, including a strong dependency on the poorly characterized basic helix-loop-helix transcription factor (bHLH) TCF3 (E2A). Here we identify and describe Inhibitor of DNA binding 2 (ID2) as a potent tumor suppressor in MM thanks to its ability to prevent TCF3 activity. **Methods:** We combined genome-wide unpublished CRISPRa and CRISPRi screen and RNA-seq of MM patients to identify deregulation of ID2-TCF3 axis in MM. We manipulated ID2 and TCF3 expression by inducible lentiviral platforms and performed both unbiased (RNA-seq, proteomics, ATAC-seq) and hypothesis driven (analysis of cell cycle, proliferation, EMSA assays) experiments to test its role in MM cell. **Results:** We performed a genome-wide CRISPRa screen in three MM cell lines (AMO1, ANBL6 and JJN3), and identified the Inhibitor of DNA binding (ID) genes among the top hits inhibiting MM cell fitness. Importantly, the ID proteins (ID1, ID2, ID3, and ID4) can inhibit bHLH transcription factors, in particular E proteins like TCF3, by preventing their binding to DNA. We have therefore evaluated their expression in MM patients and found that ID2 is specifically and significantly downregulated in malignant plasma vs. normal plasma cells ($p = 0.0059$). Moreover, data from a genome-wide CRISPRi screen in 16 MM cell lines showed that only ID2 KO confers a proliferative advantage in a subset of MM cell lines (CSS score ≥ 0.5), mainly those with naturally higher ID2 expression. Mechanistically, by co-immunoprecipitation and mass-spectrometry we found that ID2 preferentially binds to TCF3 in MM cells, and we used an EMSA assay to find that ID2 overexpression caused a loss of TCF3 DNA-binding activity. This led to transcriptomic changes that caused cell-cycle arrest in G1 and subsequent senescence, with a complete halt in proliferation in three MM cell lines. Importantly, this anti-myeloma effect was partially rescued by TCF3 overexpression. In summary, we hypothesize that the lower ID2 expression observed in MM cells confers a proliferative advantage by allowing higher TCF3 activity, supporting growth and proliferation. Finally, we demonstrated that soluble factors secreted by bone marrow stromal cells induce further downregulation of ID2 expression at the transcriptional and protein levels, together with an increase in TCF3 binding motifs availability in open chromatin regions. Also in this context, overexpression of ID2 reduces TCF3 binding activity and prevents MM proliferation. **Conclusions:** In conclusion, we identified a novel tumor suppressor role for ID2 in MM and propose a model where MM cells unleash the whole oncogenic/proliferative potential of TCF3 by deregulating its inhibitor with the support of the bone marrow milieu.

P-363

Mitochondrial protease ClpP is a novel immunogenic vulnerability in multiple myeloma

Tommaso Perini[1], Paola Zordan[2], Rossella Del Pizzo[1], Laura Oliva[1], Maria Materozzi[1], Mehmet Samur[3], Ugo Orfanelli[1], Enrico Milan[2], Nikhil Munshi[4], Bellone Matteo[2], Simone Cenci[1]

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Introduction: Mitochondria orchestrate key homeostatic functions in cancer cells. Moreover, due to their bacterial origin, they can release potent immunogenic signals in the cytosol. ClpP, a resident protease of the mitochondrial matrix, has been proposed as a target in OXPHOS-dependent cancer cells, and its ablation is associated with mitochondrial DNA (mtDNA) leakage-driven cGAS-STING activation in fibroblasts. Prompted by the distinctive expression of ClpP in malignant plasma cells (PC) and by the value of activating STING to awaken immunity, we here evaluated ClpP as a possible target with both cell-intrinsic and immunostimulatory effects against multiple myeloma (MM). **Methods:** We manipulated ClpP expression in MM cell lines, by both stable and inducible shRNA-mediated knockdown (KD), and assessed tumor growth in vitro and in vivo. We evaluated the effects of ClpP KD by Seahorse bioenergetic profiling, transcriptomics, proteomics, metabolomics and metabolite tracing experiments. Activation of cGAS-STING and downstream effects on immune cells were evaluated in coculture experiments of MM, dendritic and T cells. **Results:** ClpP mRNA was significantly higher in bone marrow-purified malignant vs. normal PCs, and MM cell lines showed exquisite sensitivity to both acute and inducible KD of ClpP in vitro. Importantly, inducible silencing of ClpP in MM cells delayed tumor growth and prolonged survival in immunodeficient mice. Toxicity proved independent of the currently acknowledged ClpP-controlled mitochondrial functions (mainly OXPHOS surveillance and maintenance of ATP production). Indeed, an integrated proteomic and metabolomic approach revealed derangement in citric acid and urea cycles, together with depletion of the polyamines spermidine, spermine and putrescine upon ClpP KD. Concordantly, inhibition of spermidine biosynthesis or of its usage phenocopied ClpP KD toxicity MM cells. In parallel, unbiased proteomics and RNA-seq, followed by targeted biochemical validation, identified transcriptional upregulation of IFN-stimulated genes and activation of cGAS-STING upon ClpP KD. In line with a downstream secretion of type-I IFNs and proinflammatory molecules, ClpP KD MM cell supernatants significantly boosted maturation and activation of human dendritic cells and enhanced their ability to stimulate IFN-Γ production by CD8+ T cells. **Conclusions:** Overall, our data demonstrate that ClpP is essential to MM cells due to a novel non-bioenergetic function, with both intra- and extra-cellular implications. ClpP manipulation

Annamaria Gulla[6], Eugenio Morelli[2], Raphael Szalat[7], Mehmet Samur[2], Kenneth Anderson[8], Mariateresa Fulciniti[2], Nikhil Munshi[9]

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P-363

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unveils an unprecedented role of mitochondrial homeostasis in regulating polyamine biosynthesis and an unexplored dependency of MM on polyamines for survival and proliferation. Furthermore, ClpP ablation activates cGAS-STING in MM cells, paving the way for the exploration of mitochondria as targets to stimulate otherwise indolent anti-tumoral immunity against myeloma.

P-364

Novel FKBP12 targeting PROTACs enhances BMP-induced apoptosis in multiple myeloma

Ingrid Quist-Løkken[1], Michael Walz[2], Felix Hausch[2], Toril Holien[1]

[1]Norwegian University of Science and Technology; [2]Technische Universität Darmstadt

Introduction: Multiple myeloma is an incurable disease, which grows resistant to all known therapies. Previously it has been shown that targeting FKBP12 with FK506, also known as Tacrolimus, leads to apoptosis in multiple myeloma cells when FK506 is combined with bone morphogenetic proteins (BMPs). To avoid the immunosuppressive effects of FK506 we wanted to find methods of targeting FKBP12 that are non-immunosuppressive. PROteolysis TArgeting Chimeras (PROTACs) are compounds that specifically degrade proteins of interest and have emerged as a potential therapeutic strategy for cancer. There are a few FKBP12 targeting PROTACs commercially available, one of which has been shown to successfully remove FKBP12 in mice liver cells in vivo. Here, we investigated the efficacy of two novel FKBP12 PROTACs on BMP-induced signaling and apoptosis in multiple myeloma. **Methods:** We compared the effect of two novel FKBP12 specific PROTACs (unpublished) with the commercially available RC32 on BMP activity and apoptosis in multiple myeloma cells. FK506 and FKBP12 knock out cells were used as controls. Specifically, multiple myeloma cell lines were treated with PROTACs combined with BMP4 or BMP6 before analysis of FKBP12 and phospho-SMAD1/5/8 protein levels using western blot. Cell viability dose-response curves were made using CellTiter Glo and we used annexin V/propidium staining to show induction of apoptosis. SMAD1/5/8 activity was also investigated using a reporter cell line, INA-6 BRE-luc. To assess potential immunosuppressive effects, we measured the nuclear translocation of NFAT transcription factors by western blot. **Results:** We show that FKBP12 specific PROTACs potently reduced the protein level of FKBP12 without affecting other relevant FKBPs. The reduction in FKBP12 protein level correlated with increased BMP-induced SMAD1/5/8 phosphorylation. The use of FKBP12 specific PROTACs in multiple myeloma cell lines strongly potentiated BMP-induced apoptosis. The effect on apoptosis was similar to what we saw with the drug FK506 and when we knocked out FKBP12 from multiple myeloma cell lines. Out of these three ways of targeting FKBP12, only FK506 is immunosuppressive as measured by inhibition of NFAT nuclear translocation. **Conclusions:** We here show two novel PROTACs that potently reduce FKBP12 protein levels in multiple myeloma cells. The degradation of FKBP12 potentiates apoptosis in multiple myeloma cell lines when combined with BMPs. Further research is needed to verify efficacy and safety in vivo, but our in vitro results indicate a potential of FKBP12 specific PROTACs in multiple myeloma and supports further investigation.

P-365

Genetic profiling and drug response analysis in multiple myeloma: insights for personalized treatment approaches

Aikaterini Rapi[1,2], Alexandra Poos[1,2], Antonia-Eugenia Angeli-Terzidou[1,3], Berit Brinkmann[1,3], Anja Baumann[1,2], Jennifer Rohleder[1,2], Daniel Kazdal[4], Katharina Knoeringer[1], Michael Hundemer[1], Albrecht Stenzinger[5], Sascha Dietrich[3,6], Vassilis Souliotis[7], Niels Weinhold[1,2], Marc Raab[1]

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Introduction: Multiple myeloma (MM) is a genetically complex disease characterized by driver events at diagnosis and precursor stages. Disease progression involves a complex interplay of genetic, epigenetic, and biochemical mechanisms, especially in extensively treated patients. We and others have recently shown that relapsed/refractory MM (RRMM) is characterized by impaired DNA damage response (DDR) and increased genomic instability resulting in drug resistance. To address this challenge, we aimed at exploring the therapeutic vulnerabilities conferred by these mechanistic hallmarks of RRMM using a high-throughput combinatorial drug screening approach in correlation with genetic markers. Additionally, we aimed to explore any potential associations between DDR deregulation and aberrations in the MAPK pathway, considering its known prevalence in drug-refractory MM. **Methods:** Human Myeloma Cell Lines (HMCLs) were used as a disease model. A panel of 26 HMCLs underwent panel Next Generation Sequencing (NGS) to characterize genomic alterations in the MAPK pathway and DDR genes. The high-throughput drug screening was conducted to investigate the single drug response of 29 drugs and 54 drug combinations. The data obtained from the drug screening were analysed using Bayesian Synergy, Synergy finder, and Drug Sensitivity Score (DSS) R packages. **Results:** The molecular characterization of the 26 HMCLs revealed a total of 242 genetic alterations. Mutations in tp53 (71%), KMT2C (42%), CDKN2C (38%), and RAS family proteins (38%) were commonly observed in our study. Three distinct groups were identified based on tumour mutational burden (TMB) scores. Sensitivity to Trametinib (MEK1/2 inhibitor) and SCH772984 (ERK inhibitor) were significantly associated with higher TMB values ($p < 0.05$). Ruxolitinib demonstrated higher effectiveness

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Ingrid Quist-Løkken[1], Michael Walz[2], Felix Hausch[2], Toril Holien[1]

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Introduction: Multiple myeloma is an incurable disease, which grows resistant to all known therapies. Previously it has been shown that targeting FKBP12 with FK506, also known as Tacrolimus, leads to apoptosis in multiple myeloma cells when FK506 is combined with bone morphogenetic proteins (BMPs). To avoid the immunosuppressive effects of FK506 we wanted to find methods of targeting FKBP12 that are non-immunosuppressive. PROteolysis TArgeting Chimeras (PROTACs) are compounds that specifically degrade proteins of interest and have emerged as a potential therapeutic strategy for cancer. There are a few FKBP12 targeting PROTACs commercially available, one of which has been shown to successfully remove FKBP12 in mice liver cells in vivo. Here, we investigated the efficacy of two novel FKBP12 PROTACs on BMP-induced signaling and apoptosis in multiple myeloma. **Methods:** We compared the effect of two novel FKBP12 specific PROTACs (unpublished) with the commercially available RC32 on BMP activity and apoptosis in multiple myeloma cells. FK506 and FKBP12 knock out cells were used as controls. Specifically, multiple myeloma cell lines were treated with PROTACs combined with BMP4 or BMP6 before analysis of FKBP12 and phospho-SMAD1/5/8 protein levels using western blot. Cell viability dose-response curves were made using CellTiter Glo and we used annexin V/propidium staining to show induction of apoptosis. SMAD1/5/8 activity was also investigated using a reporter cell line, INA-6 BRE-luc. To assess potential immunosuppressive effects, we measured the nuclear translocation of NFAT transcription factors by western blot. **Results:** We show that FKBP12 specific PROTACs potently reduced the protein level of FKBP12 without affecting other relevant FKBPs. The reduction in FKBP12 protein level correlated with increased BMP-induced SMAD1/5/8 phosphorylation. The use of FKBP12 specific PROTACs in multiple myeloma cell lines strongly potentiated BMP-induced apoptosis. The effect on apoptosis was similar to what we saw with the drug FK506 and when we knocked out FKBP12 from multiple myeloma cell lines. Out of these three ways of targeting FKBP12, only FK506 is immunosuppressive as measured by inhibition of NFAT nuclear translocation. **Conclusions:** We here show two novel PROTACs that potently reduce FKBP12 protein levels in multiple myeloma cells. The degradation of FKBP12 potentiates apoptosis in multiple myeloma cell lines when combined with BMPs. Further research is needed to verify efficacy and safety in vivo, but our in vitro results indicate a potential of FKBP12 specific PROTACs in multiple myeloma and supports further investigation.

P-365

Genetic profiling and drug response analysis in multiple myeloma: insights for personalized treatment approaches

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Introduction: Multiple myeloma (MM) is a genetically complex disease characterized by driver events at diagnosis and precursor stages. Disease progression involves a complex interplay of genetic, epigenetic, and biochemical mechanisms, especially in extensively treated patients. We and others have recently shown that relapsed/refractory MM (RRMM) is characterized by impaired DNA damage response (DDR) and increased genomic instability resulting in drug resistance. To address this challenge, we aimed at exploring the therapeutic vulnerabilities conferred by these mechanistic hallmarks of RRMM using a high-throughput combinatorial drug screening approach in correlation with genetic markers. Additionally, we aimed to explore any potential associations between DDR deregulation and aberrations in the MAPK pathway, considering its known prevalence in drug-refractory MM. **Methods:** Human Myeloma Cell Lines (HMCLs) were used as a disease model. A panel of 26 HMCLs underwent panel Next Generation Sequencing (NGS) to characterize genomic alterations in the MAPK pathway and DDR genes. The high-throughput drug screening was conducted to investigate the single drug response of 29 drugs and 54 drug combinations. The data obtained from the drug screening were analysed using Bayesian Synergy, Synergy finder, and Drug Sensitivity Score (DSS) R packages. **Results:** The molecular characterization of the 26 HMCLs revealed a total of 242 genetic alterations. Mutations in tp53 (71%), KMT2C (42%), CDKN2C (38%), and RAS family proteins (38%) were commonly observed in our study. Three distinct groups were identified based on tumour mutational burden (TMB) scores. Sensitivity to Trametinib (MEK1/2 inhibitor) and SCH772984 (ERK inhibitor) were significantly associated with higher TMB values ($p < 0.05$). Ruxolitinib demonstrated higher effectiveness

in IL-6 dependent myeloma cell lines ($p < 0.003$). Presence of DDR protein (tp53, ATR, ATM) mutations were associated with higher Drug Sensitivity scores in Nutlin-3a, UMI77, and Doxorubicin ($p< 0.05$). Among the drug combinations evaluated, BTK or PI3K inhibitors combined with PARP inhibitors, as well as DNA damage checkpoint inhibitors with ATM/ATR inhibitors exhibited the highest bayesynergy and Bliss scores for synergistic efficacy. Interestingly, combined BTK/PARP inhibition showed best efficacy in IKZF mutant cell lines, indicating a potential role in IMID-refractory disease. **Conclusions:** Our study underscores the significance of establishing ex vivo drug response panels in addition to NGS and immunochemistry data to advance precision medicine approaches in multiple myeloma. Addressing potential vulnerabilities created by common mechanisms of resistance may be more widely applicable than targeting rare activating mutations in RRMM. Therefore, by leveraging targeted therapy, patients can achieve favourable treatment responses, thus enabling them to gain access to subsequent immunotherapy options and maximize their therapeutic benefits.

P-366

Signaling pathway data analytics of nephropathy and neuropathy from drug toxicities in multiple myeloma

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Introduction: With the emergence of new therapeutic options, it is crucial to gain a comprehensive understanding of the toxicity profile associated with anti-multiple myeloma (MM) drug regimens (AMDRs). Previous studies have indicated that the occurrence of adverse events (AEs) may be influenced by specific genes and genetic factors. This study aims to investigate the link between genes, drug regimens, and AEs in AMDRs. By exploring the genetic evidence of neuro and renal AEs associated with specific regimens, we aim to understand the interplay between genetics and treatment-related toxicity in MM patients. **Methods:** The study used the 1DATA databank to integrate spontaneous reports (401,576 patients) of Human Drug AEs from openFDA, MedDRA, and ATC classification. An empirical Bayes approach converted RR values and variability to empirical Bayes geometric mean (EBGM). The 5th EBGM percentile (EB05) served as the lower bound for confidence intervals. Gene targets from AMDRs were obtained from DGIdb and DisGeNET. A comprehensive MM pharmacovigilance (PV) pharmacogenetics (PG) network was created using STRING and Gephi. The network depicted connections among drugs, genes, and MM through protein interactions. Gene expression data from MM patients and cells were obtained from MMRF CoMMpass and NCI's GDC using QIAGEN Ingenuity Pathway Analysis (QIAGEN IPA). **Results:** The first comparison was associated with the MM cell dataset for patients treated with K vs the control group, and three other MMRF datasets (KRd vs Rd, VRd vs Rd, and KRd vs VRd). We observed peripheral neuropathy was reported in VRd (EBGM = 3.47, EB05 = 3.11) and V (EBGM = 1.47, EB05 = 1.26) with EB05>1 in both regimens. We also found that NF-κB signaling pathway related to peripheral neuropathy was downregulated in MMRF (VRd vs Rd). Next, signaling pathways related to the renal (renal cell carcinoma signaling) and nervous (NF-κB signaling pathway related to peripheral neuropathy) systems were selected from the canonical pathways of four data comparisons (K vs control group, KRd vs Rd, VRd vs Rd, and KRd vs VRd) and we analyzed genes that were significantly altered. PV and PG analytics related to these systems associated with renal, nervous, and respiratory AEs were presented below. **Conclusions:** Doublet and triplet therapies like Rd, VRD, and KRd exhibited higher toxicity than V and K in PV. Dexamethasone-containing combinations showed worsened AE profiles. This novel methodology revealing nephro- and neuro-toxicity associations with specific AMDRs can potentially mitigate AEs and improve treatment tolerability.

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P-367

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P-367

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P-366

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Introduction: Multiple myeloma (MM) is a diverse disease both clinically and genetically. This study aims to analyze the impact of cytogenetic abnormalities detected through fluorescence in situ hybridization (FISH) and the role of co-segregation on prognosis in newly diagnosed MM patients. **Methods:** We have investigated the presence of t(4;14), t(14;16), 17p deletion, +1q (gain/amplification) and 1p deletion by FISH on CD38 purified plasma cells. The cut-off level for considering a positive result was set at 10% for IGH translocations (fusion/break-apart probes), and 20% for gains and deletions. For +1q, gain was defined as 3 copies (1q gain), and 1q amplification as ≥4 copies (amp1q). Statistical analyses were performed to compare different groups and evaluate progression-free survival (PFS) and overall survival (OS). The Cox proportional hazards regression model was employed to estimate hazard ratios and 95% confidence intervals. **Results:** A total of 1304 patients enrolled in 4 trials (GEM05MAS65, GEM05MENOS65, GEM2010, and GEM2012) were included in the study. The frequencies of genetic abnormalities were: del(17p) in 8%, t(4;14) in 12%, t(14;16) in 3%, +1q in 43%, and del(1p) in 8%. The median follow-up was 61 months. The median PFS was 44 months, and the median OS was not yet reached. Patients with t(4;14) had a shorter PFS (median 28 m vs. 45 m, p< 0.001)) and OS (3-year OS 61% vs. 80%. p< 0.001). It was frequently found in association with other genetic alterations (71% of cases), which significantly worsened its negative impact on survival. However, the presence of t(14;16) did not impact survival. Del(17p) was found to be associated with poor prognosis using a cut-off level of ≥20% positive cells. No significant differences in outcome among the other cutoff groups analyzed (≥30% up to ≥70%) were observed. Patients with ≥80% cells with 17p deletion had a particularly poor prognosis, with a median PFS of just over one year. Co-segregation with other genetic abnormalities did not significantly affect the outcome in patients with del(17p). Patients with + 1q had significantly shorter PFS (36.5 m vs. 53 m, p=0.0001) and OS (81 m vs. NR, p=0.0002). In our series, no significant outcome differences were found between 1q gain and amplifications. Del(1p) was also associated with inferior PFS in the overall series, but no differences in OS were observed. Interestingly, upon analyzing patients with +1q ordel(1p) as the sole abnormality its negative prognostic impact disappeared. **Conclusions:** In conclusion, our study confirmed the prognostic significance of high-risk cytogenetic abnormalities in a large cohort of MM patients. We also demonstrated the importance of considering the co-occurrence of high-risk alterations to accurately assess prognosis. Thus, while del(17p) retains its adverse prognosis even as a solitary abnormality, the negative prognosis of 1q gains was mitigated if this abnormality occured as the sole aberration.

P-368

Deep learning-based classifier for malignant plasma cell identification from single-cell RNA-seq data

Sarthak Satpathy[1], William Pilcher[1], Vaishali Prahalad[1], Manoj Bhasin[1]

[1]Emory University

Introduction: Recent characterization of Multiple myeloma (MM) using single-cell profiling has revealed that plasma cells (PCs) exhibit high heterogeneity and are patient-specific. Existing methods for characterizing malignancy in PCs rely on marker-based annotation or CNV detection, which necessitate human intervention and are cumbersome. To overcome this, we have developed an unbiased deep learning (DL)-based method that can automatically identify malignant PCs by analyzing single-cell profiles, leveraging its high accuracy and transferable learning ability. **Methods:** Publicly available single-cell RNA sequencing data of 10,790 MM and 9,329 normal PCs were obtained (GSE193531) for 26 subjects with MM (n=8), smoldering multiple myeloma (SMM) (n=12), and monoclonal gammopathy (MGUS) (n=6), as well as 9 normal bone marrow (NBM) samples. The autoencoder-based DL model was trained and cross-validated on different sets of patients within the training dataset. Model performance was further evaluated on 3,523 normal PCs and 11,656 MM cells from the Human Cell Atlas and studies of MM immune microenvironment characterization. Correlative analysis between predicted malignancy and survival was performed using a Cox regression model. Additionally, gene-regulatory analysis was performed on the gene signature of malignant-classified PCs to gain molecular insights. **Results:** Our autoencoder-based DL model, designed to classify malignant and normal PCs, achieved 100% accuracy on the training and test data. Further independent validation on a different patient set consisting of 6,193 normal and 7,786 malignant cells achieved ~98% accuracy in predicting malignant (F1=0.98) and normal phenotypes (F1=0.98). We applied this model to predict the proportion of malignant PCs in

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Introduction: Multiple myeloma (MM) is a diverse disease both clinically and genetically. This study aims to analyze the impact of cytogenetic abnormalities detected through fluorescence in situ hybridization (FISH) and the role of co-segregation on prognosis in newly diagnosed MM patients. **Methods:** We have investigated the presence of t(4;14), t(14;16), 17p deletion, +1q (gain/amplification) and 1p deletion by FISH on CD38 purified plasma cells. The cut-off level for considering a positive result was set at 10% for IGH translocations (fusion/break-apart probes), and 20% for gains and deletions. For +1q, gain was defined as 3 copies (1q gain), and 1q amplification as ≥4 copies (amp1q). Statistical analyses were performed to compare different groups and evaluate progression-free survival (PFS) and overall survival (OS). The Cox proportional hazards regression model was employed to estimate hazard ratios and 95% confidence intervals. **Results:** A total of 1304 patients enrolled in 4 trials (GEM05MAS65, GEM05MENOS65, GEM2010, and GEM2012) were included in the study. The frequencies of genetic abnormalities were: del(17p) in 8%, t(4;14) in 12%, t(14;16) in 3%, +1q in 43%, and del(1p) in 8%. The median follow-up was 61 months. The median PFS was 44 months, and the median OS was not yet reached. Patients with t(4;14) had a shorter PFS (median 28 m vs. 45 m, p< 0.001)) and OS (3-year OS 61% vs. 80%. p< 0.001). It was frequently found in association with other genetic alterations (71% of cases), which significantly worsened its negative impact on survival. However, the presence of t(14;16) did not impact survival. Del(17p) was found to be associated with poor prognosis using a cut-off level of ≥20% positive cells. No significant differences in outcome among the other cutoff groups analyzed (≥30% up to ≥70%) were observed. Patients with ≥80% cells with 17p deletion had a particularly poor prognosis, with a median PFS of just over one year. Co-segregation with other genetic abnormalities did not significantly affect the outcome in patients with del(17p). Patients with + 1q had significantly shorter PFS (36.5 m vs. 53 m, p=0.0001) and OS (81 m vs. NR, p=0.0002). In our series, no significant outcome differences were found between 1q gain and amplifications. Del(1p) was also associated with inferior PFS in the overall series, but no differences in OS were observed. Interestingly, upon analyzing patients with +1q ordel(1p) as the sole abnormality its negative prognostic impact disappeared. **Conclusions:** In conclusion, our study confirmed the prognostic significance of high-risk cytogenetic abnormalities in a large cohort of MM patients. We also demonstrated the importance of considering the co-occurrence of high-risk alterations to accurately assess prognosis. Thus, while del(17p) retains its adverse prognosis even as a solitary abnormality, the negative prognosis of 1q gains was mitigated if this abnormality occured as the sole aberration.

P-368

Deep learning-based classifier for malignant plasma cell identification from single-cell RNA-seq data

Sarthak Satpathy[1], William Pilcher[1], Vaishali Prahalad[1], Manoj Bhasin[1]

[1]Emory University

Introduction: Recent characterization of Multiple myeloma (MM) using single-cell profiling has revealed that plasma cells (PCs) exhibit high heterogeneity and are patient-specific. Existing methods for characterizing malignancy in PCs rely on marker-based annotation or CNV detection, which necessitate human intervention and are cumbersome. To overcome this, we have developed an unbiased deep learning (DL)-based method that can automatically identify malignant PCs by analyzing single-cell profiles, leveraging its high accuracy and transferable learning ability. **Methods:** Publicly available single-cell RNA sequencing data of 10,790 MM and 9,329 normal PCs were obtained (GSE193531) for 26 subjects with MM (n=8), smoldering multiple myeloma (SMM) (n=12), and monoclonal gammopathy (MGUS) (n=6), as well as 9 normal bone marrow (NBM) samples. The autoencoder-based DL model was trained and cross-validated on different sets of patients within the training dataset. Model performance was further evaluated on 3,523 normal PCs and 11,656 MM cells from the Human Cell Atlas and studies of MM immune microenvironment characterization. Correlative analysis between predicted malignancy and survival was performed using a Cox regression model. Additionally, gene-regulatory analysis was performed on the gene signature of malignant-classified PCs to gain molecular insights. **Results:** Our autoencoder-based DL model, designed to classify malignant and normal PCs, achieved 100% accuracy on the training and test data. Further independent validation on a different patient set consisting of 6,193 normal and 7,786 malignant cells achieved ~98% accuracy in predicting malignant (F1=0.98) and normal phenotypes (F1=0.98). We applied this model to predict the proportion of malignant PCs in

sequential samples of MGUS and SMM patients, and found average malignancies of 12.66% and 77.55%, respectively. Furthermore, from our recently published MM immune microenvironment study, our model predicted significantly higher malignancy for rapid progressors (mean 0.688 ± 0.048) compared to non-progressors (mean 0.371±0.039, Welch's t-test, p 1, p0.25), of which 75 were ribosomal genes. Higher malignancy was also correlated with higher cytogenic risk (p< 0.05) and aneuploidy (p< 0.01) in PCs from the MM patients. **Conclusions:** This DL-based model for predicting malignant PCs could prove to be valuable in the prognosis of MM and in assessing the progression kinetics of precursor stages (i.e., MGUS or SMM) to MM. Further evaluation of the accuracy of malignancy prediction based on blood profiles may lead to the development of a less invasive tool for tracking MM to support better outcomes.

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Single cell multi-omic correlation of single nucleotide variants, copy number variation and surface epitopes for clonal profiling of myeloma

Adam Sciambi[1], Cedric Dos Santos[2], Yang Li[1], Joanne Nguyen[1], Priyam Priyam[1], Vivek Chopra[2], Habib Hamidi[2], Michael Nixon[3], Yann Nouet[4], Todd Druley[1], Herve Avet-Loiseau[5]

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Introduction: Multiple myeloma (MM) is a cancer of plasma cells with approximately 200,000 new diagnoses each year and a 54% 5-year overall survival rate. As myeloma cells expand, clonal genetic differences lead to relapse due to acquired resistance in 100% of patients, mandating regular, long-term surveillance. Improvements in precision medicine for MM have come from monoclonal antibodies and antibody-drug conjugates that specifically target the offending cells. However, while existing diagnostic modalities offer exquisite sensitivity, they are limited in exploring subclonal genetic changes and putative antibody targets on refractory myeloma cells, leaving the clinician to use their best judgment on salvage therapy. Knowing the actual targets on the refractory disease would better facilitate precision medicine. **Methods:** Using cryopreserved, human MM patient samples processed on the Mission Bio Tapestri platform, we were able to simultaneously quantify subclones by single-cell single nucleotide variants (SNV), copy number variants (CNV), and surface protein analysis. We show complex clonal evolution of MM in individual samples as copy gains and losses were sequentially acquired and correlated with expression changes of MM markers. These single time point samples were thawed from frozen bone marrow mononuclear cells previously enriched for CD38, stained with a 45-plex antibody-oligo cocktail to label common heme-specific surface markers for sequencing analysis, and processed with a 733-plex DNA primer panel that combined whole-genome CNV coverage with MM gene hotspots. **Results:** Across the cases analyzed, complex branching phylogenetic trees were reconstructed with as many as five subclones and clear associated shifts in MM-marker expression. When averaged across subclones, each of the samples had CNV profiles that matched patient records, ranging from a single gene-level copy gain to arm-level gains and losses across the majority. The progression of protein expression within different samples could be mapped together on a single plot and correlated with generally higher MM-markers as subclonal genetic variants were acquired, though occasional branches saw reversal. The fraction of other cell phenotypes, such as T-cells and those with low viability, decreased within subclones as mutational burden grew. The drop in low viability implied improved clonal robustness (at least to handling) with disease progression. **Conclusions:** This high-resolution, single cell assay offers a potential new modality for the diagnosis and surveillance of patients with suspected MGUS, SGUS or high-risk MM. We have demonstrated: 1) exceptional results from cryopreserved human specimens, 2) the ability to use genetic lesion profiling to positively identify subclonal MM and, most importantly, 3) correlate cell surface protein expression of potential therapeutic targets with each clonal and subclonal population.

P-370

CoMMsol: a machine learning model for outcome-specific copy number alterations' clonality cut-offs definition in multiple myeloma

Vincenza Solli[1,2], Ajsi Kanapari[1,2], Gaia Mazzocchetti[1,2], Andrea Poletti[1,2], Ilaria Vigliotta[1,2], Marina Martello[1,2], Ignazia Pistis[2], Enrica Borsi[2], Barbara Taurisano[1,2], Silvia Armuzzi[1,2], Lucia Pantani[1,2], Elena Zamagni[1,2], Michele Cavo[2], Carolina Terragna[2]

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the first one with significantly shorter PFS and OS (PFS HR 2.15, CI 1.79-2.58 p< 0001, OS HR 2.37, CI 1.86-3.02 p< 0.0001). The worse prognostic impact was observed even in the absence of both amp1q and del17p, observed in 38/249 (15%) pts (PFS HR 2.57, CI 1.79-3.70 p< 00001, OS HR 2.49, CI 1.57-3.94 p=0.0001), compared to 494pts. The risk of relapse defined by the presence of ≥1 ER-CNAs was independent from those conferred both by R-IIS 3 (HR=1.51 CI 0.17-2.39-2.2; p=0.01) and by low quality (< stable disease) first-line best clinical response (HR=2.59 CI0.33-2.84 p=0.004). Notably, the type of induction therapy was not descriptive in this multivariate model, suggesting that ER is strongly related to pts' baseline genomic architecture, and not to induction therapy they were provided to. **Conclusions:** ML approach allowed to define CNAs-specific dynamic clonality cut-offs, improving the CNAs calls' accuracy to identify MM pts with the highest probability to ER. The use of these ER-related cut-offs pinpointed few CNAs, whose presence at baseline is highly predictive of ER, including amp2p, del2p, del12p, and del19p, whose biological role in MM needs further investigations. As being outcome-dependent, the coMMsol method is dynamic and might be adjusted according to the selected outcome variable of interest (e.g. MRD-negativity) thus providing outcome-specific clonality cut-offs. Thanks to AIRC IG2018_22059, RF-2016-02362532.

P-371

Mutant-specific pharmacological inhibition of KRAS in multiple myeloma and functional genomics studies to identify mechanisms regulating myeloma cell response vs. resistance to KRAS inhibition

Torsten Steinbrunn[1,2,3,4], Ryosuke Shirasaki[1,2,3,5,6], Olga Dashevsky[1,2,3], Huihui Tang[1,2,3,5], Shizuka Yamano[1,2], Phaik Ju Teoh[1,2,3,7,8], Lisa Leypoldt[1,2,3,9], Takeru Sugihara[1,2,3], Rin Mizuno[1,2,3], Mariko Kaji[1], Jeffrey Sorrell[1,2], Brian Glassner[1,2,3], Ricardo de Matos Simoes[1,2,3], James Christensen[10], Constantine Mitsiades[1,2,3,5]

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P-372

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the first one with significantly shorter PFS and OS (PFS HR 2.15, CI 1.79-2.58 p< 0001, OS HR 2.37, CI 1.86-3.02 p< 0.0001). The worse prognostic impact was observed even in the absence of both amp1q and del17p, observed in 38/249 (15%) pts (PFS HR 2.57, CI 1.79-3.70 p< 00001, OS HR 2.49, CI 1.57-3.94 p=0.0001), compared to 494pts. The risk of relapse defined by the presence of ≥1 ER-CNAs was independent from those conferred both by R-IIS 3 (HR=1.51 CI 0.17-2.39-2.2; p=0.01) and by low quality (< stable disease) first-line best clinical response (HR=2.59 CI0.33-2.84 p=0.004). Notably, the type of induction therapy was not descriptive in this multivariate model, suggesting that ER is strongly related to pts' baseline genomic architecture, and not to induction therapy they were provided to. **Conclusions:** ML approach allowed to define CNAs-specific dynamic clonality cut-offs, improving the CNAs calls' accuracy to identify MM pts with the highest probability to ER. The use of these ER-related cut-offs pinpointed few CNAs, whose presence at baseline is highly predictive of ER, including amp2p, del2p, del12p, and del19p, whose biological role in MM needs further investigations. As being outcome-dependent, the coMMsol method is dynamic and might be adjusted according to the selected outcome variable of interest (e.g. MRD-negativity) thus providing outcome-specific clonality cut-offs. Thanks to AIRC IG2018_22059, RF-2016-02362532.

P-371

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Introduction: Extensive research has been conducted to elucidate the molecular mechanisms underlying the pathophysiology of Multiple Myeloma. The role of BMPs (Bone Morphogenetic Proteins) and their downstream gene expression regulators, such as Smad (Small Mother Against Decapentaplegic) transcription factors in the molecular-level imbalance of bone metabolism remains uncertain. Most studies were conducted in preclinical models which did not account the effect of the human microenvironment. In our study, we investigated the transcriptional levels of BMP-2, BMP-6 and Smad6 in human bone marrow aspirates. **Methods:** Our study included 39 patients (19 newly diagnosed patients, 20 refractory/relapsed patients) and 10 controls (patients with other non-Hodgkin lymphomas without bone marrow infiltration). RNA isolation of bone marrow mononuclear cells was conducted using the Omega Biotek® EZNA Total RNA kit, and RNA quantification by using a Nanodrop2000® spectrophotometer. cDNA synthesis was performed using the QuantiTect® Reverse Transcription Kit (50), Qiagen®. The primers for BMP-2, BMP-6, and Smad6 were designed by Qiagen®. B2-microglobulin was the reference gene. The RT-PCR was conducted using the QuantiNova SYBR Green PCR kit from Qiagen®. We validated our PCR products using gel electrophoresis and melt curves. PCR reactions were conducted in duplicate. Differential expression was calculated using the ΔΔCt method and graphs were created using the GraphPad Prism program. **Results:** There was no significant difference in gene expression of BMP-2 between controls and newly diagnosed patients (p=ns), and relapsed patients (p=ns). On the other hand, BMP-6 was found to be increased by 4.8 times in newly diagnosed patients (p = 0.0004) and 2.56 times in relapse patients (p = 0.0226). Finally, for Smad6, no statistically significant difference was found between controls and newly diagnosed patients (p = 0.2861), but it decreased by 1.5 times in relapsed patients (p = 0.012). **Conclusions:** BMPs and, to a lesser extent, Smads have been investigated in the past as potent regulators of bone metabolism in Multiple Myeloma, mostly in preclinical setting. Our findings in bone marrow aspirates of myeloma patients suggest that BMP-2 did not show a significant difference between controls and patients, indicating that it may not have a significant impact on bone metabolism. Conversely, the increased BMP-6 levels may indicate either increased fixation in the matrix and an inability to act through a positive feedback mechanism or involvement in the induction of genes that inhibit apoptosis. Smad6 expression is reduced in R/R patients, suggesting that MM cells have developed mechanisms of dependence on BMPs and induces Smad6 repression through alternative signaling pathways or inhibitors. The role of BMPs and Smads still appears unclear; further experiments may elucidate their role on signaling pathways in MM.

P-373

Functional genomics of genes residing in the minimally deleted chromosome 17p13 region in multiple myeloma: therapeutic implications

Phaik Ju Teoh[1,2,3,4,5], Ricardo de Matos Simoes[1,2,3,4,6], Tae-Hoon Chung[7], Olga Dashevsky[1,2,3], Shizuka Yamano[1,2], Torsten Steinbrunn[1,2,3,8], Lisa Leypoldt[1,2,3,9], Francisca Vazquez[3], Wee Joo Chng[10], Constantine Mitsiades[1,2,3,11]

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Introduction: Chromosome 17p deletion (del(17p)), a high-risk feature in multiple myeloma (MM), is typically monoallelic. Its biological/clinical significance involves complete loss-of-function (LOF) of the tumor suppressor gene (TSG) TP53, through deletion of one TP53 copy and inactivating mutation (double-hit lesion) of the other copy, whereas biallelic loss is rare. While this combined copy number (CN) loss and mutation of TP53 appear to be favored over biallelic deletion of TP53/17p13, the mechanisms for this phenomenon have not been elucidated. We hypothesized that 17p13 contains multiple genes essential for MM cell survival, thereby favoring retention of at least one copy of this region in MM cells. **Methods:** We curated genes residing in chr17p13 through the UCSC Genome Browser and examined their essentiality scores (CHRONOS 22Q2 or CERES scores from DepMap) in 19 MM cell lines (including 3 TP53 wild-type [WT] lines), to identify genes are that "core"/"pan-cancer" dependencies (CERES/CHRONOS scores 90% of tumor lines across all lineages); preferentially essential for MM cells (compared with all non-MM lines) vs recurrently (but not preferentially) essential for MM cells vs non-essential. Functional assessment of key genes was complemented by in silico analyses of MMRF CoMMpass data (IA22, n=1050) and CRISPR-based LOF studies (of individual genes or in pooled format) or cDNA-overexpression studies. **Results:** Of the 108 chr17p13 genes, we identified 7 "core" essential genes (RPL26, AURKB, EIF4A1, MED31, EIF5A, TRAPPC1, ELP5), 2 MM-preferential dependencies (the glycosylation regulator MPDU1, and the purine biosynthesis gene PFAS); and other genes (e.g. CTDNEP1, CTC1) that were recurrent essentiality (e.g. in >3/19 MM lines). Enrichment of CRISPR KO was observed for TP53 in 2 of 3 TP53 WT MM lines; and 1 for candidate TSG, SAT2. This latter gene had enrichment of its CRISPR-KO in a pooled screen in NCI-H929

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cells (not studied in DepMap). Supporting this result, targeted CRISPR-KO and overexpression of SAT2 increased vs decreased, the growth of H929 cells and their sensitivity to bortezomib or lenalidomide treatment. CN losses, all monoallelic, of SAT2 were observed in 11.4% of samples, suggesting that the preference for monoallelic CN loss of 17p13 applies not only for TP53 but also other putative TSGs of this locus. In contrast to 17p13, TSGs with recurrent biallelic deletion (e.g. CDKN2C on chr1p32; CN loss in 12% of pts, with 23/152 [15%] biallelic events) have fewer essential genes and longer genomic distances from them (e.g. MPDU1 is within 85kbp of TP53, while the closest essential gene to CDKN2C (BTF3L4) is >1Mbp away). **Conclusions:** 17p13.1 contains several "core" or MM-preferential (MPDU1, PFAS) dependencies, some located close to TP53. This may explain why monoallelic del(17p) events predominate in MM and suggests that therapies targeting MPDU1, PFAS or other dependencies of this locus may have applications for high-risk 17p(del) MM.

P-374

Stratifying multiple myeloma patients for personalized therapy based on TP53 mutation, deletion, and drug response profiles

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[1]Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University of Helsinki, iCAN Digital Precision Cancer Medicine Flagship, University of Helsinki, Helsinki, Finland; [2]Department of Biology, National University of Ireland, W23 F2K8, Maynooth, Irelan; [3]Department of Haematology, Mater Misericordiae University Hospital, D07 WKW8, Dublin, Ireland; [4]Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center, University of Helsinki, Helsinki, Finland

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P-375

Unraveling signaling pathways in multiple myeloma cardiovascular toxicities from pharmacovigilance and pharmacogenomics data mining

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cells (not studied in DepMap). Supporting this result, targeted CRISPR-KO and overexpression of SAT2 increased vs decreased, the growth of H929 cells and their sensitivity to bortezomib or lenalidomide treatment. CN losses, all monoallelic, of SAT2 were observed in 11.4% of samples, suggesting that the preference for monoallelic CN loss of 17p13 applies not only for TP53 but also other putative TSGs of this locus. In contrast to 17p13, TSGs with recurrent biallelic deletion (e.g. CDKN2C on chr1p32; CN loss in 12% of pts, with 23/152 [15%] biallelic events) have fewer essential genes and longer genomic distances from them (e.g. MPDU1 is within 85kbp of TP53, while the closest essential gene to CDKN2C (BTF3L4) is >1Mbp away). **Conclusions:** 17p13.1 contains several "core" or MM-preferential (MPDU1, PFAS) dependencies, some located close to TP53. This may explain why monoallelic del(17p) events predominate in MM and suggests that therapies targeting MPDU1, PFAS or other dependencies of this locus may have applications for high-risk 17p(del) MM.

P-374

Stratifying multiple myeloma patients for personalized therapy based on TP53 mutation, deletion, and drug response profiles

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expression data. Drug-associated genes were obtained from the Drug Gene Interaction Database. Genes were then imported to the Online Mendelian Inheritance in Man (OMIM) to search for existing AE clinical features. AE clinical features were then linked to the defined Medical Dictionary for Regulatory Activities (MedDRA) hierarchy. Gene-gene interaction was also determined through the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING). **Results:** Our results suggested that gene expression is highly influenced by multiple AMDRs from the combinations of carfilzomib, bortezomib, lenalidomide or dexamethasone. We found multiple pathways were differentially expressed (signaling pathways, such as eNOS, PI3K, NFAT, NFkB and MAPK), when carfilzomib-lenalidomide-dexamethasone, bortezomib-lenalidomide-dexamethasone, and lenalidomide-dexamethasone regimens were involved, raising the possibility of associations between these pathways and specific AE profiles including cardiovascular disorders, neoplasm, or other serious AEs, see Table for pharmacovigilance (PV) and pharmacogenomics (PG). The occurrence of pericardial disorders increased with high confidence when carfilzomib-lenalidomide-dexamethasone was administered. We also found that the carfilzomib-lenalidomide-dexamethasone regimen compared with other treatments such as lenalidomide-dexamethasone or bortezomib-lenalidomide-dexamethasone were more closely associated with multiple pathways such as cardiac hypertrophy signaling, thrombin signaling, coagulation system, and HIF1a signaling which were likely to be the genetic signaling factors concomitant with presentations of heart failure, cardiac arrhythmias or other cardio-toxicities such as pulmonary hypertension, tumor progression and metastasis. **Conclusions:** Understanding the genomic basis of specific drug-AE combinations could reveal the molecular mechanisms underlying drug-gene-AE associations and characterize the causality of AE and drug use. Our study offers insights for predicting treatment responses when considering alternative agents in MM.

Table 1 PV and PG

	Cardiac		Vascular		Neoplasm	
Drug	PV	PG	PV	PG	PV	PG
Carfilzomib-Lenalidomide-Dexamethasone	7 (5)	6 (4)	8 (1)	4 (1)	7 (1)	2
Carfilzomib	6 (5)	2 (2)	9 (4)	–	6	–
Bortezomib-Lenalidomide-Dexamethasone	6 (3)	5 (3)	8 (1)	3	6 (1)	3 (2)
Bortezomib	5	–	7	–	4 (1)	1
Lenalidomide-Dexamethasone	7 (2)	6 (2)	8 (1)	4 (1)	7 (4)	5 (3)
Lenalidomide	7 (2)	–	10 (1)	–	7	2
Dexamethasone	4	4	2	1	4	–

P-376

Genomic and transcriptional profiling stratifies myeloma models into two clusters with distinct risk signatures and drug responses

Evan Flietner[1], Mei Yu[2], Govinda Poudel[1], Anthony Veltri[2], Yun Zhou[1], Adhithi Rajagopalan[1], Yubin Feng[1], Terra Lasho[3], Zhi Wen[4], Yuqian Sun[1], Mrinal Patnaik[3], Natalie S. Callander[1], Fotis Asimakopoulos[5], Demin Wang[2], Jing Zhang[1]

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Introduction: Approximately 15-20% of newly diagnosed multiple myeloma (MM) display high-risk features with a poor response to current treatment options and shorter survival than the standard-risk group. Genetic events are used to stratify high-risk MM (hrMM) (e.g. Amp1q). Two hrMM gene signatures, UAMS-70 and EMC-92 (SKY92), have been independently developed and validated to predict poor clinical outcomes. Within the hrMM group, two ultra hrMM subgroups were identified as double hit hrMM (with >2 high-risk cytogenetic abnormalities) and functional hrMM, who did not have hrMM-associated genomic alterations but were refractory to induction therapy or had early relapse within 12 months. These ultra hrMM had an overall worse prognosis than genetically defined hrMM. Clearly, novel approaches are required for treating hrMM, particularly ultra hrMM. However, the lack of mouse models recapitulating hrMM and ultra-hrMM has been a barrier in these challenging settings. Activation of a human MYC transgene in germinal center B cells induces a highly penetrant, but relatively indolent MM in primary Vk*MYC mice. Subsequent selection via transplantation and bortezomib (Btz) treatment established transplantable t-Vk*MYC lines (e.g. t-Vk12653) that shows reduced response to Btz in vivo. We recently generated a highly malignant MM mouse model driven by GC expression of hMYC transgene and endogenous NRASQ61R (named "VQ mice"). **Methods:** We performed genomic and transcriptomic profiling of MM models using whole exome sequencing, copy number variation analysis, and RNA-Seq. **Results:** We report that Group A VQ MM and t-Vk12653 share similar transcriptome and several hrMM features, including hyperproliferation, extramedullary disease, exhaustion of CD4 and CD8 T cells, and partial response to Btz treatment. In comparison to control plasma cells, they express higher EMC-92 hrMM scores but not UAMS-70 hrMM gene signature. Compared to Group A VQ and t-Vk12653 MM models, Group B VQ expresses additional hrMM and ultra hrMM features, including downregulation of Fam46c, expression of UAMS-70 and EMC-92 hrMM gene signatures and Amp1q-associated PBX1-FOXM1 gene signatures, upregulation of cancer growth pathways associated with functional hrMM, and de novo resistance to venetoclax in vitro and to Btz and anti-TIGIT immune checkpoint blockade in vivo. Our results suggest that Group A VQ MM and t-Vk12653 may represent Revised International Staging System (R-ISS) Stage III MM without ultra hrMM, while Group B VQ represent R-ISS Stage III MM with ultra hrMM features. Interestingly, trametinib (Tra), an FDA-approved MEK inhibitor, is the only single agent we tested so far that significantly prolongs the survival of both Group A and B VQ

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P-376

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mice. Its survival benefit is only observed in immunocompetent but not in immunodeficient NSG mice, suggesting that Tra functions through an intact immune system. **Conclusions:** Our study provides a strong rational to develop Tra-based immunotherapies for treating RAS-driven hrMM and ultra hrMM.

P-377

CD38 targeting in multiple myeloma

Andrea Abel[1], Laia Querol Cano[1], Annemiek van Spriel[1], Roel Hammink[1], Martin ter Beest[1]

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Introduction: Despite recent advances in cancer immunotherapies targeting specific tumor proteins, there is a lack of response in patients that cannot be always explained by the expression levels of these targets. We hypothesize that the organization of the targeted proteins on the surface of the tumor cells plays a key role in antibody accessibility in the crowded membrane, and therefore in the effectiveness of these immunotherapies. CD38 is a glycoprotein highly expressed in MM cells, which has postulated it as a therapeutic target using clinical antibodies in MM patients. The most effective clinical antibody is Daratumumab, which presents a remarkable complement dependent cytotoxicity (CDC) effect. We are interested in studying CD38 organization on the surface of multiple myeloma (MM) cells, since we hypothesize that if CD38 is in a more clustered organization rather than randomly distributed, this will facilitate Daratumumab binding, as well as the IgG hexamer formation needed for CDC-mediated tumor cell killing. Similarly, we also aim to unravel the mechanisms determining CD38 membrane organization on MM. **Methods:** We study CD38 organization at the surface of Daratumumab resistant and sensitive MM cell line models combining advance confocal microscopy. Furthermore, to prove our hypothesis we also artificially modulate CD38 clustering using nanofilaments containing Daratumumab antibodies and optogenetics, which is a novel method to modulate protein clustering/distribution using light, which we expect will translate into an enhanced Daratumumab-mediated CDC killing. To characterize the mechanisms that determine CD38 organization, we are exploring the role of the actin network, as well as the role of membrane organizers such as Tetraspanins and Galectins. This is being studied by microscopy and immunoprecipitation followed by mass spectrometry. **Results:** Our confocal analysis has revealed that both CDC sensitive and resistant MM lines present a similar number of CD38 clusters, although these appear to be larger in our sensitive cell models. We have also seen that the actin network and galectins seem to play a role in CD38 organization. We have successfully immunoprecipitated CD38 and are waiting for the Mass Spectrometry results to dive into the binding partners of CD38. **Conclusions:** CD38 is organized in clusters, which appear to be bigger in the CDC sensitive cells, correlating with our hypothesis that a more clustered organization of CD38 leads to an enhanced CDC effect of Daratumumab. Ongoing experiments with the clustering modulators, both intracellularly and extracellularly, will confirm whether enhancing CD38 clustering also leads to an enhanced Daratumumab-mediated tumor cell killing. In parallel, the actin network and galectins appear to be playing a role in determining CD38 surface organization. Moreover, identifying CD38 binding partners at the plasma membrane of MM cells will shed light into the mechanisms governing its distribution and open novel avenues to modulate its clustering.

P-378

Longitudinal antibody and T-cell kinetics over four doses of COVID-19 vaccination and predictors of poor response in patients with multiple myeloma

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mice. Its survival benefit is only observed in immunocompetent but not in immunodeficient NSG mice, suggesting that Tra functions through an intact immune system. **Conclusions:** Our study provides a strong rational to develop Tra-based immunotherapies for treating RAS-driven hrMM and ultra hrMM.

P-377

CD38 targeting in multiple myeloma

Andrea Abel[1], Laia Querol Cano[1], Annemiek van Spriel[1], Roel Hammink[1], Martin ter Beest[1]

[1]Radboud Institute for Molecular Life Sciences (RIMLS)

Introduction: Despite recent advances in cancer immunotherapies targeting specific tumor proteins, there is a lack of response in patients that cannot be always explained by the expression levels of these targets. We hypothesize that the organization of the targeted proteins on the surface of the tumor cells plays a key role in antibody accessibility in the crowded membrane, and therefore in the effectiveness of these immunotherapies. CD38 is a glycoprotein highly expressed in MM cells, which has postulated it as a therapeutic target using clinical antibodies in MM patients. The most effective clinical antibody is Daratumumab, which presents a remarkable complement dependent cytotoxicity (CDC) effect. We are interested in studying CD38 organization on the surface of multiple myeloma (MM) cells, since we hypothesize that if CD38 is in a more clustered organization rather than randomly distributed, this will facilitate Daratumumab binding, as well as the IgG hexamer formation needed for CDC-mediated tumor cell killing. Similarly, we also aim to unravel the mechanisms determining CD38 membrane organization on MM. **Methods:** We study CD38 organization at the surface of Daratumumab resistant and sensitive MM cell line models combining advance confocal microscopy. Furthermore, to prove our hypothesis we also artificially modulate CD38 clustering using nanofilaments containing Daratumumab antibodies and optogenetics, which is a novel method to modulate protein clustering/distribution using light, which we expect will translate into an enhanced Daratumumab-mediated CDC killing. To characterize the mechanisms that determine CD38 organization, we are exploring the role of the actin network, as well as the role of membrane organizers such as Tetraspanins and Galectins. This is being studied by microscopy and immunoprecipitation followed by mass spectrometry. **Results:** Our confocal analysis has revealed that both CDC sensitive and resistant MM lines present a similar number of CD38 clusters, although these appear to be larger in our sensitive cell models. We have also seen that the actin network and galectins seem to play a role in CD38 organization. We have successfully immunoprecipitated CD38 and are waiting for the Mass Spectrometry results to dive into the binding partners of CD38. **Conclusions:** CD38 is organized in clusters, which appear to be bigger in the CDC sensitive cells, correlating with our hypothesis that a more clustered organization of CD38 leads to an enhanced CDC effect of Daratumumab. Ongoing experiments with the clustering modulators, both intracellularly and extracellularly, will confirm whether enhancing CD38 clustering also leads to an enhanced Daratumumab-mediated tumor cell killing. In parallel, the actin network and galectins appear to be playing a role in determining CD38 surface organization. Moreover, identifying CD38 binding partners at the plasma membrane of MM cells will shed light into the mechanisms governing its distribution and open novel avenues to modulate its clustering.

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P-379

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P-380

Immunological aging is associated with worse clinical outcome in elderly newly diagnosed multiple myeloma patients

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Results: In total, 141 MM patients (median age 66.6 years, 45% female) provided three longitudinal samples following doses 2-4, which were assayed for humoral (n=138) and T-cell (n=61) immune responses. Median Anti-S titres increased from post-2nd (1,065 IU/mL; 93% positive) to post-3rd (6,024 IU/mL; 96% positive) to post-4th (11,179 IU/mL; 98% positive) doses [p< 0.0001]. Longitudinal Anti-S responses were greater in those with a positive T-spot [p< 0.05] or previous natural COVID-19 infection [p< 0.001] and positively correlated with serum IgM [r=0.39-0.44, p< 0.0001]. In comparison, positive T-cell IGRA responses to S-antigen were observed in 62%, 56% and 70% of patients following doses 2-4, respectively. IGRA responses were stronger in patients who had received a mix of recombinant protein and mRNA-based vaccines (compared to mRNA-based alone) [p< 0.01] and positively correlated with lymphocyte count after four doses [r=0.35, p=0.0014]. Both poor myeloma disease status (as defined by International Myeloma Working Group response group) and concurrent anti-CD38/BCMA therapy predicted lower Anti-S and IGRA responses. **Conclusions:** In summary, our data support a robust humoral and cellular immune response to COVID-19 booster doses, including in those with an initial poor response. Our data establish the laboratory and clinical profile of poor vaccine responders, that could be targeted for more intensive COVID-19 risk management, and provide insights to interrogate the biological basis of variable immunity in MM.

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15) and HO143 (EudraCT: 2016-002600-90) trials, respectively. Older patients were further classified as intermediate fit or frail according to the IMWG frailty score. Comprehensive immune-profiling of T and NK cells was performed by flow cytometry on study-entry peripheral blood (PB) and bone marrow (BM) samples (n=462). Data were analyzed using FlowSOM. Additionally, a lasso penalized logistic regression model was trained using cross validation to identify older patients with younger versus older immune profiles based on T cell populations identified by FlowSOM. Survival differences of these profiles were evaluated in the HO143 trial using Kaplan Meier and cox regression analysis. **Results:** In both BM and PB, older patients displayed a distinct T cell profile compared with younger patients, while NK cell profiles were similar. Older patients showed increased frequencies of activated HLA-DR+CD4+, CD38+ CD8+ and CD25+ CD8+ T cells, regulatory CD4+ T cells (Tregs) and senescent (CD28-CD57+KLRG1+) CD8+ T cells. Additionally, we observed a higher proportion of effector memory CD8+ T cells and a lower proportion of naive and central memory CD8+ T cells in older patients. Explorative analysis of T cell populations identified by FlowSOM confirmed these findings and additionally revealed decreased naive γδ T cells and increased CD38+ Tregs in older patients. Subgroup analysis of intermediate fit and frail patients revealed higher PD1 expression on CD4+ T cells in frail than in intermediate fit patients, independent of age. Preliminary results of the logistic regression model identified 13.3% of older patients having a younger T cell profile. Notably, these patients had superior overall survival (HR 3.7; 95% CI 1.16-11.85, p = 0.027) and progression free survival (HR 2.0; 95% CI 1.09-3.84 p = 0.026) in the HO143 trial compared with their peers, which was independent of age, ISS stage and cytogenetic profile. **Conclusions:** Older MM patients had more differentiated, senescent, and activated T cells than younger patients. Importantly, we identified a subgroup of older patients having a younger T cell profile, which was associated with superior survival in the HO143 trial. These new insights may improve tailoring immunotherapies and risk stratification in older MM patients.

P-381

Mezigdomide (CC-92480) activates innate and adaptive immune populations in the bone marrow microenvironment of heavily pre-treated multiple myeloma patients

Lucia Chen[1], Michael Amatangelo[2], Oliver van Oekelen[1], Bhaskar Upadhyaya[1], Alessandro Lagana[1], Geoffrey Kelly[1], Seunghee Kim-Schulze[1], Adolfo Aleman[1], Tracy Chow[2], Antonina Kurtova[3], Anita Gandhi[3], Sarah Gooding[4], Sundar Jagannath[5], Anjan Thakurta[6], Erin Flynt[3], Udo Oppermann[7], Samir Parekh[1]

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Introduction: Mezigdomide (MEZI) is a novel cereblon E3 ligase modulator (CELMoD) that induces potent degradation of aiolos and ikaros. MEZI plus dexamethasone (MEZI+DEX) has demonstrated promising clinical efficacy in triple-class refractory multiple myeloma (MM) patients (pts) with ≥3 prior lines of therapy in the phase 1/2 study, CC-92480-MM-001. We report results from high-resolution mass-cytometry immune profiling of sequentially collected bone marrow (BM) samples from MM pts before and during MEZI+DEX treatment from part 1 and 2 of this study. **Methods:** A CyTOF panel of 39 markers was used for in-depth immune-phenotyping of paired longitudinal BM aspirates from MEZI+DEX-treated MM pts at baseline and mid cycle 2 or 3 of treatment. Approximately 3.6 million cells were analyzed from 38 pts dosed with 0.8-1mg of MEZI for 14 or more days of a 28-day cycle. Detailed analyses of B, T and NK cell populations were conducted using both manual hierarchical gating and a computational R workflow. **Results:** Significant changes within the BM tumour microenvironment (TME) were seen with MEZI+DEX treatment. Compared with baseline samples, on-treatment samples showed an increase in total NK (median 10.7% vs 16.5%, p=0.034) and NKT cells (median 7.6% vs 13.8%, p < 0.001). CD4 and CD8 effector memory (CCR7-CD45RA-) T cells increased on treatment (CD4 median 58.2% vs 73.9%, p < 0.001; and CD8 median 51.2% vs 71.1% p < 0.0001) with concurrent reductions in CD4 and CD8 central memory (CCR7+CD45RA-), naïve (CCR7+CD45RA+) and TEMRA (CD45RA+CCR7-) populations. Activated populations of T and NK cells also expanded on treatment. HLADR+ CD4 and CD8 T cells both increased more than three-fold (p< 0.0001), and significant increases in HLADR+ NK cells (median: 11.7% vs 17.9%, p=0.02) and ICOS+ CD4 T cells (median: 8.6% vs 14.1%, p< 0.001) were observed. Concurrently, T and NK cells showed a considerable reduction in the proportion of cells expressing the inhibitory markers KLRG1 (CD4 median 23.8% vs 15.8%, p=0.0016; CD8 median: 52.6% vs 41.0%, p=0.0013; NK median: 19.2% vs 14.9%, p=0.043) and TIGIT (CD8 median: 25.8% vs 8.2%, p< 0.0001; NK median: 18.1% vs 5.6%, p< 0.0001). Similar immune activation was observed regardless of number of prior lines of therapy and in pts refractory to pomalidomide or daratumumab. **Conclusions:** MEZI+DEX significantly activates NK and T cells in the BM TME of heavily pre-treated triple-class refractory MM pts, suggesting an important immunomodulatory mechanism of action. Marked reduction of inhibitory markers, such as KLRG1 and TIGIT, was observed in T cells and NK cells suggesting a potential role for MEZI+DEX in addressing immune cell exhaustion and promoting transition to a cytotoxic TME phenotype. While further studies are required to interrogate the role of these activated immune populations in the clearance of MM cells, this data supports the potential of MEZI+DEX to enhance the activity of other immune redirecting therapies for the treatment of MM.

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P-381

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P-382

Dysregulations of the immune tumor microenvironment in multiple myeloma

Dana Cholujova[1], Gabor Beke[2], Teru Hideshima[3], Lubos Klucar[2], Merav Leiba[4], Krzysztof Jamroziak[5], Paul Richardson[3], Efstathios Kastritis[6], David Dorfman[7], Kenneth Anderson[8], Jana Jakubikova[1]

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Introduction: The tumor microenvironment is considered essential to maintain tumor cell survival and growth, subclonal evolution, and stage of the disease. Interactions between tumor cells and immune cells form immunosuppressive tumor-supporting niche by regulating of immune cell responses either by reducing the antitumoral activity of immune cells, expanding of immune-suppressive cells or specific mechanisms of tumor-promoting cell polarization and activation. Therefore, revealing insights into the immune myeloma microenvironment will enhance our understanding of the pathogenesis of multiple myeloma (MM). **Methods:** Our pipeline has been designed for profiling of the complex immune landscape of the adaptive and innate immune bone marrow microenvironment during MM evolution and progression in BM samples from patients with MGUS, smoldering MM (SMM), and active MM by mass cytometry analysis (CyTOF). **Results:** Our data showed that both naïve and effector cytotoxic T cells, g/d T cells, immature and mature B cells were reduced in both premalignant and active myeloma stages. In addition, downregulation of immature T cells, naïve and effector memory T helper cells was showed in active MM, revealing profound adaptive immune-suppression in myeloma microenvironment. Profiling of the innate immune microenvironment, an increase in myeloblasts, non-canonical monocytes, erythroblasts, and platelets, and a decrease in pro-monocytes was observed in both premalignant and active MM conditions. Importantly, the transformation from MGUS to SMM was associated with alterations in central/effector memory T helper cells and/or effector cytotoxic T cells, as well as increases in monocytic and neutrophil subsets. Evaluation of myeloma B lymphopoiesis revealed a decrease in B cell progenies, immature and transitional B, and unswitched memory B cells, but an increase in switched memory B cells and plasmablasts along with PC subsets in SMM and active MM stages. In addition, modulation by immune checkpoints, including PD-1/PD-L1, TIGIT/PVR, CD137/ CD137-L, CTLA-4, BTLA and KIR expression, was indicated in innate and adaptive immune subsets of myeloma microenvironment. Corresponding analysis of immune subsets of each patient revealed stratification of MM patients with high frequencies of plasma cell subsets, plasmablasts, switched memory B cells, and myelocytes that were associated with poor clinical outcomes. **Conclusions:** In conclusion, exploring the immune tumor microenvironment revealed profound adaptive immune-suppression and extensive innate immune-infiltration in both premalignant and active MM stages. Therefore, our in-depth characterization of the immune ecosystem at various stages of MM demonstrates the utility of CyTOF technology for defining disease heterogeneity and prognosis in patients with MM. This study was supported by R01-50947 and P50-100707; 609427-SASPRO 0064/01/02; TRS-2015-00000170; 2019/14-BMCSAV-9; APVV-16-0484; APVV-20-0183; and APVV-19-0212.

P-383

A 16-gene signature reflecting tumor microenvironment predicts the risk of multiple myeloma patients treated by bortezomib-based therapies

Grazia Gargano[1], Susanna Anita Pappagallo[2], Angela Maria Quinto[2], Bernardo Rossini[2], Giuseppina Opinto[2], Paolo Mondelli[2], Maria Carmela Vegliante[2], Doriana Gramegna[3], Carolina Terragna[4], Vincenza Solli[5], Michele Cavo[4,6], Orazio Palumbo[7], Flavia Esposito[1], Nicoletta Del Buono[1], Attilio Guarini[2], Sabino Ciavarella[2]

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Introduction: Accessory stromal and immune cells are implicated in multiple myeloma (MM) pathogenesis, although the predictive role of peculiar tumor microenvironment (TME) cells toward specific treatments has been not fully clarified. Recent computational tools allow to infer quantitative and qualitative features of TME starting from bulk transcriptomic data, enabling associations of peculiar cellular components with patients' prognosis. The aim of this work was the development of a prognostic molecular model based on TME factors to improve risk stratification of MM patients. **Methods:** A total of 59 real-life pre-treatment BM aspirates underwent immunomagnetic separation of the CD138-negative cells to generate GEP by microarray (Clariom S). This training cohort included patients receiving induction therapy by bortezomib, cyclophosphamide and dexamethasone (VCD; n=55) or bortezomib, melphalan, prednisone (VMP; n = 4), and showing stringent complete response/complete response (responders; n=24) or stable disease/progression disease (non-responders; n=35).

P-382

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Introduction: The tumor microenvironment is considered essential to maintain tumor cell survival and growth, subclonal evolution, and stage of the disease. Interactions between tumor cells and immune cells form immunosuppressive tumor-supporting niche by regulating of immune cell responses either by reducing the antitumoral activity of immune cells, expanding of immune-suppressive cells or specific mechanisms of tumor-promoting cell polarization and activation. Therefore, revealing insights into the immune myeloma microenvironment will enhance our understanding of the pathogenesis of multiple myeloma (MM). **Methods:** Our pipeline has been designed for profiling of the complex immune landscape of the adaptive and innate immune bone marrow microenvironment during MM evolution and progression in BM samples from patients with MGUS, smoldering MM (SMM), and active MM by mass cytometry analysis (CyTOF). **Results:** Our data showed that both naïve and effector cytotoxic T cells, g/d T cells, immature and mature B cells were reduced in both premalignant and active myeloma stages. In addition, downregulation of immature T cells, naïve and effector memory T helper cells was showed in active MM, revealing profound adaptive immune-suppression in myeloma microenvironment. Profiling of the innate immune microenvironment, an increase in myeloblasts, non-canonical monocytes, erythroblasts, and platelets, and a decrease in pro-monocytes was observed in both premalignant and active MM conditions. Importantly, the transformation from MGUS to SMM was associated with alterations in central/effector memory T helper cells and/or effector cytotoxic T cells, as well as increases in monocytic and neutrophil subsets. Evaluation of myeloma B lymphopoiesis revealed a decrease in B cell progenies, immature and transitional B, and unswitched memory B cells, but an increase in switched memory B cells and plasmablasts along with PC subsets in SMM and active MM stages. In addition, modulation by immune checkpoints, including PD-1/PD-L1, TIGIT/PVR, CD137/ CD137-L, CTLA-4, BTLA and KIR expression, was indicated in innate and adaptive immune subsets of myeloma microenvironment. Corresponding analysis of immune subsets of each patient revealed stratification of MM patients with high frequencies of plasma cell subsets, plasmablasts, switched memory B cells, and myelocytes that were associated with poor clinical outcomes. **Conclusions:** In conclusion, exploring the immune tumor microenvironment revealed profound adaptive immune-suppression and extensive innate immune-infiltration in both premalignant and active MM stages. Therefore, our in-depth characterization of the immune ecosystem at various stages of MM demonstrates the utility of CyTOF technology for defining disease heterogeneity and prognosis in patients with MM. This study was supported by R01-50947 and P50-100707; 609427-SASPRO 0064/01/02; TRS-2015-00000170; 2019/14-BMCSAV-9; APVV-16-0484; APVV-20-0183; and APVV-19-0212.

P-383

A 16-gene signature reflecting tumor microenvironment predicts the risk of multiple myeloma patients treated by bortezomib-based therapies

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Molecular information, including cytogenetic alterations (i.e., t(4;14), t(14;16), t(14;20), amp(1q), and del(17p)) and clinical stage (R- ISS) were available for each case. We applied the CIBERSORTx to the CD138-deriving GEP to digitally purify specific stromal and immune cell types as well as their transcriptional profiles. Thus, we identified differentially expressed genes (DEGs) comparing GEP of each purified TME cytotype between the responders and non-responders subgroup, and applying a fine-tuned statistical filtering to obtain a final gene signature. This signature was finally used to build a PFS-based predictor by a penalized Cox regression. **Results:** Our approach led to the identification of 16 genes selected by a penalized Cox model, which also provided a prognostic expression threshold capable of stratifying cases into high- and low-risk groups. These 16 genes were related to monocytes/macrophages, CD8 T cells, dendritic, natural killer and stromal cells. According to the model, 43 patients (73%) were classified as at high risk and 16 (27%) at low risk. Interestingly, the high-risk group showed a considerably worse PFS when compared with the low-risk group (log-rank P < 0.0001). Moreover, our predictor was independent from the cytogenetics risk and R-ISS in multivariate analyses. **Conclusions:** In conclusion, we demonstrated that genes reflecting TME composition hold a remarkable prognostic value in MM and may help in improving patient risk stratification independently from cytogenetic features of tumor compartment and clinical stage. Although the model was built on bortezomib-based therapy response and is under independent validation, our methodological approach appears advantageous for i) the generation of new TME-based biological hypotheses; ii) the development of future molecular tools for more accurate risk prediction in MM; and iii) potential replication of our workflow with predictive purposes toward new immunotherapies.

P-384

Exploiting fiber-rich diet to perturb the microbiota-immune axis and thwart multiple myeloma progression

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Introduction: The gut microbiota may impact MM development and progression. We have previously demonstrated that Prevotella heparinolytica, a human commensal, expands Th17 cells that migrate to the bone marrow (BM) were they sustain myeloma plasma cells growth. Conversely, P. melaninogenica delays MM progression by limiting Th17 expansion. Through degradation of dietary fibers, Prevotellae generate immunomodulatory short-chain fatty acids (SCFAs) which reduce Th17 differentiation. Thus, we hypothesized that the administration of a high-fiber diet, by expanding SCFA-producing bacteria, restrains Th17 expansion and prevents MM evolution. **Methods:** C57BL/6J mice challenged with Vk*MYC-derived MM cells and transgenic Vk*MYC affected by asymptomatic MM (Early-MM) were orally fed with a high-fiber diet. Gut and BM T cell infiltration and effector functions, along with effects on disease progression and overall mouse survival were taken as indicative of high-fiber diet mediated effects. To assess the impact of dietary fibers on gut microbiota composition 16S ribosomal RNA sequencing was performed on stool samples. SCFAs were quantified by NMR. **Results:** The administration of high-fiber diet in mice challenged with MM cells (t-Vk*MYC) delayed disease appearance and prolonged mice survival. Early-MM VK*MYC mice are being enrolled in a trial investigating the capacity of fiber-rich diet to delay progression to symptomatic (Late)-MM. Because high-fiber diet expands SCFA-producing Prevotellae and mice treated with P. melaninogenica produced higher levels of SCFAs than P. heparinolytica, we treated t-Vk*MYC mice with butyrate. Treatment with butyrate reduced MM aggressiveness in MM mice reducing the Th17/T regulatory cell ratio. **Conclusions:** Modulation of the gut microbiota by probiotics and postbiotics may substantially modulate the immune response thus intercepting the trajectory of MM evolution.

P-385

Single cell RNA sequencing reveals activated translation machinery in memory T cells among exceptional responders to lenalidomide

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Introduction: Immunomodulatory agents remain the cornerstone of multiple myeloma (MM) treatment. We previously published the phase 2 trial of lenalidomide and dexamethasone (Rd) as initial therapy for MM. From this cohort, we identified a subset of long-term responders (LTRs) after Rd was discontinued. We hypothesized that improved immunosurveillance induced by the immunomodulatory actions of lenalidomide was responsible for these exceptional responses. To that end, we performed single cell transcriptomics to characterize their immune microenvironment. **Methods:** Between 2003 and 2011, 305 patients (pts) with newly diagnosed MM were treated with Rd induction. After exclusion of pts who were treated with stem cell transplantation or discontinued Rd for progression, there were 31 pts who discontinued Rd for reasons other than progression and were observed without treatment. These LTRs were defined as pts who were treated with Rd, with time to progression of 72 months or longer. Age matched controls were pts who received Rd induction but progressed within 72 months of Rd treatment. Single cell RNA sequencing was performed on CD138- sorted bone marrow (BM) at baseline and after 6 to 12 months of Rd. Gene set enrichment analyses using the reactome pathway were utilized to annotate differentially regulated biological processes using WebGestalt (http://www.webgestalt.org/). **Results:** 12 BM samples were available from 10 LTR pts and 12 control pts at baseline and after induction. BM cells were clustered based on gene expression profile and annotated to various cellular lineages using canonical marker genes. The median age at diagnosis among the LTRs was 61.5 years and controls was 53.8 years. The median duration of Rd treatment among LTRs was 72 months (range 5-125)

Molecular information, including cytogenetic alterations (i.e., t(4;14), t(14;16), t(14;20), amp(1q), and del(17p)) and clinical stage (R- ISS) were available for each case. We applied the CIBERSORTx to the CD138-deriving GEP to digitally purify specific stromal and immune cell types as well as their transcriptional profiles. Thus, we identified differentially expressed genes (DEGs) comparing GEP of each purified TME cytotype between the responders and non-responders subgroup, and applying a fine-tuned statistical filtering to obtain a final gene signature. This signature was finally used to build a PFS-based predictor by a penalized Cox regression. **Results:** Our approach led to the identification of 16 genes selected by a penalized Cox model, which also provided a prognostic expression threshold capable of stratifying cases into high- and low-risk groups. These 16 genes were related to monocytes/macrophages, CD8 T cells, dendritic, natural killer and stromal cells. According to the model, 43 patients (73%) were classified as at high risk and 16 (27%) at low risk. Interestingly, the high-risk group showed a considerably worse PFS when compared with the low-risk group (log-rank P < 0.0001). Moreover, our predictor was independent from the cytogenetics risk and R-ISS in multivariate analyses. **Conclusions:** In conclusion, we demonstrated that genes reflecting TME composition hold a remarkable prognostic value in MM and may help in improving patient risk stratification independently from cytogenetic features of tumor compartment and clinical stage. Although the model was built on bortezomib-based therapy response and is under independent validation, our methodological approach appears advantageous for i) the generation of new TME-based biological hypotheses; ii) the development of future molecular tools for more accurate risk prediction in MM; and iii) potential replication of our workflow with predictive purposes toward new immunotherapies.

P-384

Exploiting fiber-rich diet to perturb the microbiota-immune axis and thwart multiple myeloma progression

Laura Lucia Cogrossi[1], Anna Policastro[2], Matteo Grion[1], Sofia Sisti[1], Marta Chesi[3], Leif Bergsagel[3], Nicola Clementi[1], Bellone Matteo[2]

[1]San Raffaele Scientific Institute; [2]Vita-Salute San Raffaele University; [3]Mayo Clinic Arizona

Introduction: The gut microbiota may impact MM development and progression. We have previously demonstrated that Prevotella heparinolytica, a human commensal, expands Th17 cells that migrate to the bone marrow (BM) were they sustain myeloma plasma cells growth. Conversely, P. melaninogenica delays MM progression by limiting Th17 expansion. Through degradation of dietary fibers, Prevotellae generate immunomodulatory short-chain fatty acids (SCFAs) which reduce Th17 differentiation. Thus, we hypothesized that the administration of a high-fiber diet, by expanding SCFA-producing bacteria, restrains Th17 expansion and prevents MM evolution. **Methods:** C57BL/6J mice challenged with Vk*MYC-derived MM cells and transgenic Vk*MYC affected by asymptomatic MM (Early-MM) were orally fed with a high-fiber diet. Gut and BM T cell infiltration and effector functions, along with effects on disease progression and overall mouse survival were taken as indicative of high-fiber diet mediated effects. To assess the impact of dietary fibers on gut microbiota composition 16S ribosomal RNA sequencing was performed on stool samples. SCFAs were quantified by NMR. **Results:** The administration of high-fiber diet in mice challenged with MM cells (t-Vk*MYC) delayed disease appearance and prolonged mice survival. Early-MM VK*MYC mice are being enrolled in a trial investigating the capacity of fiber-rich diet to delay progression to symptomatic (Late)-MM. Because high-fiber diet expands SCFA-producing Prevotellae and mice treated with P. melaninogenica produced higher levels of SCFAs than P. heparinolytica, we treated t-Vk*MYC mice with butyrate. Treatment with butyrate reduced MM aggressiveness in MM mice reducing the Th17/T regulatory cell ratio. **Conclusions:** Modulation of the gut microbiota by probiotics and postbiotics may substantially modulate the immune response thus intercepting the trajectory of MM evolution.

P-385

Single cell RNA sequencing reveals activated translation machinery in memory T cells among exceptional responders to lenalidomide

Joselle Cook[1], Ying Li[1], Surendra Dasari[1], Linda Baughn[1], Diane Jelinek[2], Marta Chesi[2], Leif Bergsagel[2], Taxiarchis Kourelis[1]

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P-386

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P-387

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P-387

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gammopathy of undetermined significance (MGUS) and smoldering MM (SMM), with respective evolution rates of 1% and 10% per year. Understanding the factors that drive neoplastic transformation and managing high-risk patients are critical for improving clinical outcomes and implementing early therapeutic interventions. Because the genomic landscape often overlaps between premalignant conditions and active MM, the latest research has focused on the role of the BM immune microenvironment. This study aims to characterize BM immune changes during MGUS-MM progression and their association with outcome in MM patients. **Methods:** We used FlowCT, a semi-automated pipeline for flow cytometry data analysis, to compare the immune composition in the BM of 12 MGUS, 12 SMM, and 63 MM patients stained with two common 8-markers diagnostic tubes. Next, we performed Luminex assays for the simultaneous quantification of 48 cytokines and chemokines using plasma samples of BM and peripheral blood (HD=4, MGUS=12, SMM=12, and MM=12) to obtain a MM immune response profiling. **Results:** Progression to clinical MM was associated with a decrease in granulocytes (mean, 74.18% MGUS vs 73.86% SMM vs 65.59% MM; p< 0.05) and an increase in monocytes (mean, 4.97% MGUS vs 4.62% SMM vs 6.77% MM; p< 0.01), T lymphocytes (mean, 6.29% MGUS vs 7.56% SMM vs 11% MM; p< 0.01), and NK cells (mean, 0.88% MGUS vs 1.51% SMM vs 2.13% MM; p< 0.001). Effector CD38+CD81+CD28- NK/T lymphocytes were abundant in MM patients (mean, 2.50% MGUS vs 2.28% SMM vs 4.31% MM; p< 0.05) and CD27- vs CD27+ NK/T lymphocytes ratio augmented during disease progression (p< 0.05). Interestingly, we observed a concomitant reduction of GM-CSF, IFN-α2, IFN-γ, IL-1β, IL-2, IL-2Ra, IL-3, IL-10, IL-13, and MCP-1/CCL2 levels within the BM plasma along MM evolution which could contribute to the myeloid cell decline occurring in these patients. Moreover, PDGF-BB, IFN-α2, IL-16, and IL-8 decrease could be even observed in peripheral blood plasma along MM progression. From a clinical point of view, we evaluated the impact of previously disclosed BM changes on progression-free survival (PFS) of 50 patients with active MM and found that the abundance of granulocytes was associated with a longer PFS (HR: 0.15; p< 0.05). Furthermore, patients treated with daratumumab who had a high BM neutrophil/T lymphocyte ratio showed a substantially longer 1-year PFS (HR: 0.07; p< 0.01) than those who had a low ratio (86% vs 33%, respectively). **Conclusions:** Overall, our findings suggest that immune factors play a crucial role in disease development and response to therapy, emphasizing the importance of immune-based approaches for improving patient outcomes in MM.

P-388

An IL-1β driven neutrophil-stromal cell axis fosters a BAFF-rich tumor-supportive bone marrow environment in multiple myeloma patients

Madelon De Jong[1], Cathelijne Fokkema[1], Natalie Papazian[1], Sabrin Tahri[1], Mathijs Sanders[1], Francesca Gay[2], Philippe Moreau[3], Heiko Bruns[4], Mark van Duin[1], Annemiek Broijl[1], Pieter Sonneveld[1], Tom Cupedo[1]

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Introduction: The multiple myeloma (MM) bone marrow (BM) is characterized by IL-6 producing tumor-supportive inflammatory mesenchymal stromal cells (iMSC). iMSC are a source of neutrophil-modulation factors including IL6, C3 and chemokines for neutrophil-expressed CXCR1 and CXCR2. Since the BM permanently harbors large numbers of neutrophils, we hypothesized that stromal–neutrophil interactions might significantly impact the tumor-supportive BM environment in MM. **Methods:** To investigate BM neutrophils in MM, we generated a single-cell transcriptomic overview of the entire neutrophilic lineage from fresh BM aspirates of 6 newly diagnosed MM (NDMM) patients, 6 MM patients that had completed intensive first-line treatment and four age-matched controls. In addition, single-cell RNA libraries were generated from BM MSC of 5 MM patients after intensive treatment. Functional interrogation of neutrophils and stromal cells included ex-vivo co-cultures, flow cytometric analyses, and RNA sequencing. **Results:** Single-cell RNA-sequencing of the BM neutrophilic lineage in newly-diagnosed MM identified an increase in the percentage of mature neutrophils, and these cells were defined by inflammatory gene programs and genes associated with activation (DUSP1, GBP5), adhesion (ITGAX, ITGAL), and inflammation (OSM, CXCL8). Mature neutrophils in MM BM had an MM-supportive phenotype with increased transcription of the BCMA-ligand BAFF and the pro-inflammatory cytokine IL1B. In vitro co-cultures revealed that iMSC were sufficient to induce the MM neutrophil phenotype, including pro-inflammatory gene modules and production of BAFF and IL-1β. Neutrophil activation by iMSC was STAT3 dependent and could be abrogated by the STAT3-inhibitor Stattic. Reciprocally, iMSC-activated neutrophils gained the ability to induce MM-supportive iMSCs from non-activated stromal cells in an IL-1B-dependent manner. These data suggest that stromal cell-driven neutrophil activation could be involved in amplifying pro-tumor BM inflammation. To test whether this tumor-supportive inflammatory axis persists after first-line treatment, we performed single-cell RNA sequencing of neutrophils and MSC of patients that had completed induction- and consolidation therapy with triplet +/- anti-CD38 therapy, including high-dose melphalan and autologous stem cell transplant. iMSC were significantly reduced post-consolidation, but percentages remained elevated compared to controls. BM neutrophils, which were newly-formed post-transplant, had been re-activated and had re-acquired a pro-tumor phenotype. This was reflected in significantly elevated protein levels of BAFF and IL-1β in BM plasma of 52 patients after first-line treatment compared to non-cancer controls. **Conclusions:** We identified an MM-supportive BM environment driven by MSC-neutrophil interactions that persist after treatment. Our data warrant investigation into novel strategies targeting both stromal and immune activation to disrupt the tumor-supportive BM environment in MM.

gammopathy of undetermined significance (MGUS) and smoldering MM (SMM), with respective evolution rates of 1% and 10% per year. Understanding the factors that drive neoplastic transformation and managing high-risk patients are critical for improving clinical outcomes and implementing early therapeutic interventions. Because the genomic landscape often overlaps between premalignant conditions and active MM, the latest research has focused on the role of the BM immune microenvironment. This study aims to characterize BM immune changes during MGUS-MM progression and their association with outcome in MM patients. **Methods:** We used FlowCT, a semi-automated pipeline for flow cytometry data analysis, to compare the immune composition in the BM of 12 MGUS, 12 SMM, and 63 MM patients stained with two common 8-markers diagnostic tubes. Next, we performed Luminex assays for the simultaneous quantification of 48 cytokines and chemokines using plasma samples of BM and peripheral blood (HD=4, MGUS=12, SMM=12, and MM=12) to obtain a MM immune response profiling. **Results:** Progression to clinical MM was associated with a decrease in granulocytes (mean, 74.18% MGUS vs 73.86% SMM vs 65.59% MM; p< 0.05) and an increase in monocytes (mean, 4.97% MGUS vs 4.62% SMM vs 6.77% MM; p< 0.01), T lymphocytes (mean, 6.29% MGUS vs 7.56% SMM vs 11% MM; p< 0.01), and NK cells (mean, 0.88% MGUS vs 1.51% SMM vs 2.13% MM; p< 0.001). Effector CD38+CD81+CD28- NK/T lymphocytes were abundant in MM patients (mean, 2.50% MGUS vs 2.28% SMM vs 4.31% MM; p< 0.05) and CD27- vs CD27+ NK/T lymphocytes ratio augmented during disease progression (p< 0.05). Interestingly, we observed a concomitant reduction of GM-CSF, IFN-α2, IFN-γ, IL-1β, IL-2, IL-2Ra, IL-3, IL-10, IL-13, and MCP-1/CCL2 levels within the BM plasma along MM evolution which could contribute to the myeloid cell decline occurring in these patients. Moreover, PDGF-BB, IFN-α2, IL-16, and IL-8 decrease could be even observed in peripheral blood plasma along MM progression. From a clinical point of view, we evaluated the impact of previously disclosed BM changes on progression-free survival (PFS) of 50 patients with active MM and found that the abundance of granulocytes was associated with a longer PFS (HR: 0.15; p< 0.05). Furthermore, patients treated with daratumumab who had a high BM neutrophil/T lymphocyte ratio showed a substantially longer 1-year PFS (HR: 0.07; p< 0.01) than those who had a low ratio (86% vs 33%, respectively). **Conclusions:** Overall, our findings suggest that immune factors play a crucial role in disease development and response to therapy, emphasizing the importance of immune-based approaches for improving patient outcomes in MM.

P-388

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Introduction: The multiple myeloma (MM) bone marrow (BM) is characterized by IL-6 producing tumor-supportive inflammatory mesenchymal stromal cells (iMSC). iMSC are a source of neutrophil-modulation factors including IL6, C3 and chemokines for neutrophil-expressed CXCR1 and CXCR2. Since the BM permanently harbors large numbers of neutrophils, we hypothesized that stromal–neutrophil interactions might significantly impact the tumor-supportive BM environment in MM. **Methods:** To investigate BM neutrophils in MM, we generated a single-cell transcriptomic overview of the entire neutrophilic lineage from fresh BM aspirates of 6 newly diagnosed MM (NDMM) patients, 6 MM patients that had completed intensive first-line treatment and four age-matched controls. In addition, single-cell RNA libraries were generated from BM MSC of 5 MM patients after intensive treatment. Functional interrogation of neutrophils and stromal cells included ex-vivo co-cultures, flow cytometric analyses, and RNA sequencing. **Results:** Single-cell RNA-sequencing of the BM neutrophilic lineage in newly-diagnosed MM identified an increase in the percentage of mature neutrophils, and these cells were defined by inflammatory gene programs and genes associated with activation (DUSP1, GBP5), adhesion (ITGAX, ITGAL), and inflammation (OSM, CXCL8). Mature neutrophils in MM BM had an MM-supportive phenotype with increased transcription of the BCMA-ligand BAFF and the pro-inflammatory cytokine IL1B. In vitro co-cultures revealed that iMSC were sufficient to induce the MM neutrophil phenotype, including pro-inflammatory gene modules and production of BAFF and IL-1β. Neutrophil activation by iMSC was STAT3 dependent and could be abrogated by the STAT3-inhibitor Stattic. Reciprocally, iMSC-activated neutrophils gained the ability to induce MM-supportive iMSCs from non-activated stromal cells in an IL-1B-dependent manner. These data suggest that stromal cell-driven neutrophil activation could be involved in amplifying pro-tumor BM inflammation. To test whether this tumor-supportive inflammatory axis persists after first-line treatment, we performed single-cell RNA sequencing of neutrophils and MSC of patients that had completed induction- and consolidation therapy with triplet +/- anti-CD38 therapy, including high-dose melphalan and autologous stem cell transplant. iMSC were significantly reduced post-consolidation, but percentages remained elevated compared to controls. BM neutrophils, which were newly-formed post-transplant, had been re-activated and had re-acquired a pro-tumor phenotype. This was reflected in significantly elevated protein levels of BAFF and IL-1β in BM plasma of 52 patients after first-line treatment compared to non-cancer controls. **Conclusions:** We identified an MM-supportive BM environment driven by MSC-neutrophil interactions that persist after treatment. Our data warrant investigation into novel strategies targeting both stromal and immune activation to disrupt the tumor-supportive BM environment in MM.

P-389

Progression to myeloma reflects accelerating immunosenescence, loss of tumour MHC class I, and tumour growth-associated inflammation

Kane Foster[1], Elise Rees[1], Louise Ainley[2], Lydia Lee[2], Gwennan Ward[1], Daria Galas-Filipowicz[1], Anna Mikolajczak[1], Emma Lyon[1], Imran Uddin[1], Gordon Beattie[1], Mahima Turakhia[1], Yvette Hoade[1], Catherine Zhu[1], James Reading[1], Karthik Ramasamy[3], Javier Herrero[1], Benny Chain[4], Sergio Quezada[1], Kwee Yong[2]

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Introduction: Multiple Myeloma (MM) is associated with skewed immune cell activation and function. Univariate analyses show individual immune cells are altered in precursor states. However, a comprehensive model linking immune processes during progression and their interaction with tumour cells is lacking. **Methods:** We generated a large dataset of published and newly-generated bone marrow single-cell RNA sequencing (scRNAseq): >914,000 cells from patients with MM MM (n=46), the precursor conditions MGUS (n=19) and SMM (n=28) and non-cancer controls (n=58). scvi was used integration, and both regression and unsupervised approaches for differential abundance. Tumour cells were identified via their unique combination of immunoglobulin genes. **Results:** We characterise two immune profiles (immunotypes), composed of immune cells which co-associate in abundance. The first immunotype reflected aging-like differentiation including a loss of naive T cells, B cells, and haematopoietic progenitors; and an enrichment of differentiated T cells, NK cells and activated dendritic cells (DCs). This immunotype correlated with age in controls (R=-0.68, P< 0.001), reflecting healthy aging. This immunotype was enriched in MM patients independent of age (P=0.004), rising with advancing severity (MGUS to SMM to MM), such that patients had increasingly prematurely-aged immune composition. This immunotype correlated with tumour MHC class I (MHC-I) expression (R=0.43, P = 0.007), which fell between SMM to MM (HLA-C, P=0.029), meaning patients whose tumours expressed the lowest MHC-I were the most immunosenescent. Within this immunotype, a clonal effector memory CD8+ T cells expressing a genes enriched in non-viral clones (GZMB+ITGB1+) correlated with tumour MHC-I (R=0.33, P=0.002). The second immunotype was composed of inflammatory cell types, including Interferon Stimulated Gene (ISG)-expressing T and B cells, inflammatory CD4+ regulatory T cells and plasmacytoid DCs. This immunotype was enriched in osteoarthritic non-cancer controls alongside MM (but not MGUS or SMM) patients. This immunotype was most pronounced in highly-infiltrated marrows (aspirate CD138+ %) and those with the greatest proportion of proliferating tumour cells (% MKI67+ tumour), suggesting tumour growth-associated inflammatory niche remodelling. ISG+ effector T cells enriched in infiltrated marrows shared T cell receptors with cytotoxic terminal memory T cells accumulating within the aging-like immunotype, suggesting a link between these two immunotype processes. **Conclusions:** We unify the variation in bone marrow immune architecture in the progression to Myeloma into two key processes (immunotypes). Age-independent, tumour MHC-I-dependent immunosenescent-like differentiation could indicate an accumulation of historical anti-tumour responses leading up to progression. Osteoarthritic-like inflammatory cells enriched in MM reflecting local tumour burden and growth may possibly represent acute anti-tumour responses occurring in situ.

P-390

The differentiation and expansion of T cell clonotypes in the bone marrow following ASCT: insights from the Phase 2 CARDAMON study

Kane Foster[1], Daria Galas-Filipowicz[1], Evie Fitzsimons[1], William Wilson[2], Lydia Lee[1], Suzanne Byrne[1], Karthik Ramasamy[3], Rakesh Popat[4], Mike Chapman[5], Matthew Streetly[6], Ceri Bygrave[7], Reuben Benjamin[8], Ruth de Tute[9], Marquita Camilleri[10], Selina Chavda[11], Elizabeth Philips[12], Gavin Pang[2], Fu'ad Fananapazir[13], Krupali Parikh[2], Sumaiya Kamora[14], James Cavenagh[15], Roger Owen[16], Charlotte Tyson[14], Benny Chain[17], Kwee Yong[1]

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Introduction: The benefit of high-dose therapy and autologous stem cell transplantation (ASCT) comes largely from tumour reduction, enhancing depth of response. The degree to which ASCT amplifies host anti-tumour immunity is not fully understood. Immune reconstitution following ASCT manifest as the accumulation of differentiated T cell subsets, and studies in mice indicate this represents an expansion of tumour-specific CD8+ T cell clones. We compared T cell phenotypes and repertoires between patients receiving ASCT and those receiving chemotherapy only, to understand the specific role of ASCT in T cell responses. **Methods:** We utilised BM samples from patients in the Cardamon (ClinicalTrials.gov NCT02315716) Phase 2 study, where patients

P-389

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P-390

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received carfilzomib, cyclophosphamide and dexamethasone (KCd) induction followed by randomisation to ASCT or KCd consolidation (cons). For both arms, samples were acquired at baseline, and post-ASCT or post-cons. Viably frozen cells were thawed and used as input for flow cytometry, T cell receptor (TCR) sequencing (TCRseq), and 10x Genomics single-cell RNA and TCR sequencing (scRNA/TCR-seq). **Results:** Flow cytometry showed an enrichment of CD8+ terminal effector memory cells (CCR7-PD1-CD57+GZMB+) post-ASCT (n=10) compared to post-cons (n=10). On longitudinal bulk TCRseq, post-ASCT (n=14) displayed greater TCR clonality than post-cons (n=15), in part due to the expansion of pre-existing TCRs present at baseline (some expanding >10,000-fold). Within each patient, expanding TCRs possessed similar structural sequences suggesting shared antigen specificity, but were not enriched for clones annotated to HLA-matched virally-annotated TCRs. scRNA/TCR-seq of post-ASCT patients (n=4) connected the TCRs which expanded post-ASCT to a similar memory phenotype (CD8A+GZMB+CX3CR1+). Analysis of baseline (n=2) and longitudinal (n=1) ASCT patients showed the clones which subsequently expanded post-ASCT occupied this same memory phenotype at baseline, albeit at lower numbers. These clones exhibited a wider range of states post-ASCT, including early activated (GZMK+PDCD1+) and proliferating (MKI67+) clusters, but did not progress unidirectionally into a more terminally differentiated phenotype. This suggests ASCT elicits a phenotypic diversification rather than induction of terminal differentiation. Some clones which expanded post-ASCT were actively proliferating, suggesting an ongoing source of stimulation. Patients with the highest clonality and most proliferating KI67+CD8+ T cells by flow cytometry post-treatment were minimal residual disease (MRD) positive, suggesting ongoing anti-tumour responses. **Conclusions:** Our results provide of evidence of antigen-driven T cell expansion following ASCT that was not seen after chemotherapy consolidation. A small number of TCR clones present at baseline undergo phenotypic diversification and proliferate, expanding to occupy a large portion of the T cell compartment and may inform on or protect against residual tumour cells.

P-391

Checkpoint inhibitor PD-1H/VISTA mediates its effects on osteoclast cytoskeleton in myeloma bone disease via c-Src/Rac1 signaling

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Introduction: Multiple myeloma cells activate osteoclasts by producing osteoclastogenic factors. Our previous work demonstrated that matrix metalloproteinase 13 (MMP-13) is one of the critical osteoclastogenic factors highly secreted by MM cells (JCI 2016). Further studies indicated that checkpoint inhibitor PD-1H/VISTA functions as the MMP-13 receptor on osteoclasts and mediates the MMP-13-induced osteoclast activation. Interestingly, PD-1H pulldown mass spectrum assay suggests that PD-1H associates with cytoskeleton proteins. Further, we found PD-1H regulates the F-actin cytoskeleton reorganization which is critical for osteoclast bone resorption activity. Since Rho GTPases substrates Rac1/2 are the key regulators of the dynamic actin cytoskeleton rearrangements, we investigated its role in PD-1H mediated OCL formation/activation. **Methods:** Bone marrow mononuclear cells from WT or Pd-1h-/- mice were cultured in osteoclast differentiation medium without or with MMP-13. Activated Rac1 was detected in Rac1 pull-down complex from whole cell lysates by WB. Localization of c-Src, Rac1, PD-1H and F-actin ring in osteoclast were detected by confocal immunofluorescence (IF) microscope and activation of c-Src was detected by western blotting. The binding of c-Src with PD-1H and 1-215 mutant was checked by co-IP assay after co-expressed in HEK 293 cells. **Results:** Our results showed that MMP-13 activated Rac1 in WT, but not Pd-1h-/- osteoclasts. IF staining indicated that PD-1H and Rac1 co-localized, especially at the F-actin belt in WT osteoclasts. Consistent with the decreased Rac1 activation and F-actin belt formation observed in Pd-1h-/- osteoclasts, Rac1 failed to localize at F-actin-rich areas in Pd-1h knockout cells. Non-receptor tyrosine kinase c-Src associates with RANK and mediates RANKL-induced Rac1 activation and cytoskeleton reorganization. Confocal IF staining of the WT osteoclasts indicated that c-Src and PD-1H almost completely co-localized on the F-actin sealing belt and perinuclear area. Co-immunoprecipitation assays confirmed the direct binding of c-Src to the C-terminal intracellular domain of PD-1H as a PD-1H 1-215 mutant lacking its intracellular domain failed to bind c-Src. IF staining of c-Src, PD-1H and F-actin indicated that in contrast to WT osteoclasts, c-Src in Pd-1h-/- osteoclasts mainly accumulated in perinuclear areas, but not in the F-actin belt hereby not allowing appropriate cytoskeleton reorganization necessary for OCL formation. Finally, MMP-13 induced c-Src phosphorylation/activation in WT osteoclasts, which was impaired in Pd-1h-/- cells. **Conclusions:** This study reveals the novel role of MMP-13/PD-1H signaling in the regulation of osteoclasts cytoskeleton reorganization. MMP-13 binds to PD-1H and promotes c-Src/Rac1 signaling activation and subsequently promotes osteoclast bone resorption activities. This study hence revealed a novel role of the checkpoint inhibitor PD-1H/VISTA in osteoclast cytoskeleton regulation and subsequently multiple myeloma bone disease.

P-392

Daratumumab-induced in vivo immune modulation in relapsed and/refractory multiple myeloma patients treated with daratumumab-len-dex

Claudia Giannotta[1], Bachisio Ziccheddu[2], Mattia D'Agostino[3], Giuseppe Bertuglia[4], Elona Saraci[4], Stefania Oliva[4], Niccolo' Bolli[5], Ola Landgren[6], Benedetto Bruno[3], Mario Boccadoro[7], Francesco Maura[6], Massimo Massaia[1], Alessandra Larocca[8]

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received carfilzomib, cyclophosphamide and dexamethasone (KCd) induction followed by randomisation to ASCT or KCd consolidation (cons). For both arms, samples were acquired at baseline, and post-ASCT or post-cons. Viably frozen cells were thawed and used as input for flow cytometry, T cell receptor (TCR) sequencing (TCRseq), and 10x Genomics single-cell RNA and TCR sequencing (scRNA/TCR-seq). **Results:** Flow cytometry showed an enrichment of CD8+ terminal effector memory cells (CCR7-PD1-CD57+GZMB+) post-ASCT (n=10) compared to post-cons (n=10). On longitudinal bulk TCRseq, post-ASCT (n=14) displayed greater TCR clonality than post-cons (n=15), in part due to the expansion of pre-existing TCRs present at baseline (some expanding >10,000-fold). Within each patient, expanding TCRs possessed similar structural sequences suggesting shared antigen specificity, but were not enriched for clones annotated to HLA-matched virally-annotated TCRs. scRNA/TCR-seq of post-ASCT patients (n=4) connected the TCRs which expanded post-ASCT to a similar memory phenotype (CD8A+GZMB+CX3CR1+). Analysis of baseline (n=2) and longitudinal (n=1) ASCT patients showed the clones which subsequently expanded post-ASCT occupied this same memory phenotype at baseline, albeit at lower numbers. These clones exhibited a wider range of states post-ASCT, including early activated (GZMK+PDCD1+) and proliferating (MKI67+) clusters, but did not progress unidirectionally into a more terminally differentiated phenotype. This suggests ASCT elicits a phenotypic diversification rather than induction of terminal differentiation. Some clones which expanded post-ASCT were actively proliferating, suggesting an ongoing source of stimulation. Patients with the highest clonality and most proliferating KI67+CD8+ T cells by flow cytometry post-treatment were minimal residual disease (MRD) positive, suggesting ongoing anti-tumour responses. **Conclusions:** Our results provide of evidence of antigen-driven T cell expansion following ASCT that was not seen after chemotherapy consolidation. A small number of TCR clones present at baseline undergo phenotypic diversification and proliferate, expanding to occupy a large portion of the T cell compartment and may inform on or protect against residual tumour cells.

P-391

Checkpoint inhibitor PD-1H/VISTA mediates its effects on osteoclast cytoskeleton in myeloma bone disease via c-Src/Rac1 signaling

Jing Fu[1], Shirong Li[2], Huihui Ma[3], Guifen Liu[2], Markus Mapara[3], Suzanne Lentzsch[1]

[1]Columbia University Medical Center; [2]Columbia University Irving Medical Center; [3]Columbia Center for Translational Immunology

Introduction: Multiple myeloma cells activate osteoclasts by producing osteoclastogenic factors. Our previous work demonstrated that matrix metalloproteinase 13 (MMP-13) is one of the critical osteoclastogenic factors highly secreted by MM cells (JCI 2016). Further studies indicated that checkpoint inhibitor PD-1H/VISTA functions as the MMP-13 receptor on osteoclasts and mediates the MMP-13-induced osteoclast activation. Interestingly, PD-1H pulldown mass spectrum assay suggests that PD-1H associates with cytoskeleton proteins. Further, we found PD-1H regulates the F-actin cytoskeleton reorganization which is critical for osteoclast bone resorption activity. Since Rho GTPases substrates Rac1/2 are the key regulators of the dynamic actin cytoskeleton rearrangements, we investigated its role in PD-1H mediated OCL formation/activation. **Methods:** Bone marrow mononuclear cells from WT or Pd-1h-/- mice were cultured in osteoclast differentiation medium without or with MMP-13. Activated Rac1 was detected in Rac1 pull-down complex from whole cell lysates by WB. Localization of c-Src, Rac1, PD-1H and F-actin ring in osteoclast were detected by confocal immunofluorescence (IF) microscope and activation of c-Src was detected by western blotting. The binding of c-Src with PD-1H and 1-215 mutant was checked by co-IP assay after co-expressed in HEK 293 cells. **Results:** Our results showed that MMP-13 activated Rac1 in WT, but not Pd-1h-/- osteoclasts. IF staining indicated that PD-1H and Rac1 co-localized, especially at the F-actin belt in WT osteoclasts. Consistent with the decreased Rac1 activation and F-actin belt formation observed in Pd-1h-/- osteoclasts, Rac1 failed to localize at F-actin-rich areas in Pd-1h knockout cells. Non-receptor tyrosine kinase c-Src associates with RANK and mediates RANKL-induced Rac1 activation and cytoskeleton reorganization. Confocal IF staining of the WT osteoclasts indicated that c-Src and PD-1H almost completely co-localized on the F-actin sealing belt and perinuclear area. Co-immunoprecipitation assays confirmed the direct binding of c-Src to the C-terminal intracellular domain of PD-1H as a PD-1H 1-215 mutant lacking its intracellular domain failed to bind c-Src. IF staining of c-Src, PD-1H and F-actin indicated that in contrast to WT osteoclasts, c-Src in Pd-1h-/- osteoclasts mainly accumulated in perinuclear areas, but not in the F-actin belt hereby not allowing appropriate cytoskeleton reorganization necessary for OCL formation. Finally, MMP-13 induced c-Src phosphorylation/activation in WT osteoclasts, which was impaired in Pd-1h-/- cells. **Conclusions:** This study reveals the novel role of MMP-13/PD-1H signaling in the regulation of osteoclasts cytoskeleton reorganization. MMP-13 binds to PD-1H and promotes c-Src/Rac1 signaling activation and subsequently promotes osteoclast bone resorption activities. This study hence revealed a novel role of the checkpoint inhibitor PD-1H/VISTA in osteoclast cytoskeleton regulation and subsequently multiple myeloma bone disease.

P-392

Daratumumab-induced in vivo immune modulation in relapsed and/refractory multiple myeloma patients treated with daratumumab-len-dex

Claudia Giannotta[1], Bachisio Ziccheddu[2], Mattia D'Agostino[3], Giuseppe Bertuglia[4], Elona Saraci[4], Stefania Oliva[4], Niccolo' Bolli[5], Ola Landgren[6], Benedetto Bruno[3], Mario Boccadoro[7], Francesco Maura[6], Massimo Massaia[1], Alessandra Larocca[8]

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P-391

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P-392

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Introduction: Daratumumab (Dara) has become a mainstay in treatment-naïve and relapsed/refractory Multiple Myeloma patients (RRMM). While Dara is expected to bind myeloma cells, it also impacts the immune microenvironment by targeting CD38+ immune suppressor and effector cells. The clinical consequence of this redirected CD38-targeted activity is worth of investigation to understand the mechanisms of relapse and maximize the efficacy and duration of Dara treatment. **Methods:** We investigated the immune modulation induced by Dara in 32 RRMM enrolled in the NCT03848676 clinical study (Dara-Len-Dex) through extensive multiparametric flowcytometry phenotyping and quantification performed on bone marrow (BM) and peripheral blood (PB) mononuclear cells. For each patient BM and PB were profiled at baseline, with good concordance between the two compartments (linear regression slope=0.63, p< 0.001, r2=0.27). Longitudinal PB samples were collected every 3 months for a total of 170 samples profiled. **Results:** In all patients irrespective of the clinical response, we observed a long-lasting CD38 down-regulation in PB NK cells, T cells, Vγ9Vδ2 T cells, regulatory T cells (Tregs), and regulatory B cells (Bregs). On the contrary, PB Monocytes and Myeloid-derived suppressor cells (MDSC) showed CD38 variable and not persistent down-regulation pattern. In NK cells, CD38 decrease was associated with CD16 (FcγRIII) down-modulation and NK-cell subset re-distribution. Dara-Len-Dex also induced the persistent decrease of PB CD38+Tregs and CD38+Bregs and the increase of functionally exhausted T cells. A comparison between relapsed (R) (n=12) and non-relapsed (NR) (n=19) patients indicates that clinical outcomes were associated with specific baseline patterns of CD38 expression, BM Bregs abundance, PB T-cell and monocyte subpopulation redistribution, and expression of exhaustion T-cell markers. Low CD38 mean fluorescence intensity in myeloma cells and high CD38 expression in BM NK cells (p=0.03) were strongly associated with early progression (< 1 year). This pattern suggested that in R patients Dara was likely preferentially redirected towards NK cells rather than myeloma cells promoting more NK fratricide than antibody-dependent cellular cytotoxicity against myeloma cells. High CD38 expression in BM MDSC of R patients at baseline further reduce Dara-mediated myeloma cell targeting. T-cell and granulocytic-MDSC (Gn-MDSC) total counts were differently modulated by Dara-based treatment over time according to clinical outcomes. T cells increased from 9 months of therapy in NR but not in R patients (p=0.007). Likewise, Gn-MDSC were not affected in NR patients while increased in R patients from 9 months (p=0.009). **Conclusions:** Our data indicate that Dara-based treatment induces long-lasting changes in the immune populations involved in the disease control and unveil an association between CD38+ expression in selected immune cell subsets at baseline, Dara treatment, and response to treatment.

P-393

COVID-19 vaccine acceptance/hesitancy and influence on infection in patients with multiple myeloma: a national-wide multicenter survey in China

Huiwen He[1], Ziping Li[1], Shuangjiao Liu[2], Wenming Chen[3], Wanling Sun[4], Baolai Hua[5], Yongzhe Li[6], Junling Zhuang[2]

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Introduction: Patients with multiple myeloma (MM) are immunocompromised due to impaired humoral and cellular immunity in addition to immunosuppressive therapy. The situation and protective effects of severe coronavirus disease 2019 (COVID-19) vaccination in MM patients are not clarified. The study aimed to explore the reasons of COVID-19 vaccine hesitancy and its influence on severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection in MM patients during COVID-19 Omicron BA.4/5 subvariant outbreak in China. **Methods:** An anonymous online questionnaire designed by our team was distributed to MM patients national-wide from December 26, 2022, to April 20, 2023. Then content of questionnaire included the contents of disease status, vaccination and SARS-COV-2 infection. **Results:** A total of 508 valid questionnaires from 30 provinces were collected all over China. The vaccination rate of COVID-19 in MM patients was only 34.1% (n=173). The overall infection rate was 57.2%. Multivariate analysis showed that demographic characteristics were not factors affecting vaccination, while those accomplishing autologous stem cell transplantation (ASCT) presented a lower vaccination rate (20.2% vs. 48.4%, P< 0.001). In the survey of vaccine acceptance/hesitancy, voluntary choice (49%), concerns to COVID-19 infection (35.1%), and trust of vaccine efficacy (26.5%) were the three main reasons for receiving vaccines. Physicians' suggestion (52.0%), conflicts of MM treatment (37.8%) and concerns about MM progression (31.3%) were the top three reasons for vaccine hesitancy. Adverse events (AEs) after vaccination were mainly myalgia or joint pain, fatigue and erythema or swelling at the site of injection. No MM disease-related adverse effects were reported. Among 104 vaccinated MM patients with SARS-COV-2 infection, the median time since last vaccines to infections was 304 days (range 4-593). The infection rates between

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P-393

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the vaccinated population (n=173) versus non-vaccinated ones (n=335) were 60.1% vs. 55.8% respectively (P=0.35). In subgroup analyses, the infection rates in vaccinated patients were lower than those in unvaccinated ones including the elderly (49.3% vs. 55.2%), obese patients (BMI≥28) (50% vs. 63.3%), and R/RMM population (42.2% vs. 66.7%, P=0.005). The proportion of hospitalized patients due to SARS-COV-2 infection in vaccinated group was significantly lower than that in unvaccinated group (4.8% vs.12.3%, P=0.038). **Conclusions:** Vaccine hesitation is common in Chinese MM patients although inactivated COVID-19 vaccine only causes mild AEs. Lower infection rate in MM patients is probably due to strict self-quarantine. COVID-19 vaccination is not translated into less SARS-COV-2 infections, but does protect the elderly, obese or R/RMM patients from severe infections. Clinicians are suggested to encourage MM patients to receive COVID-19 vaccines for the sake of reducing severe infections and related mortality.

P-394

Proteomic analysis to discover bone marrow plasma biomarkers predicting outcome following autologous stem cell transplantation in multiple myeloma patients

Diane Jelinek[1], Caleb Stein[1], Charalampos Charalampous[2], Akhilesh Pandey[2], Taxiarchis Kourelis[2], Marta Chesi[1], Leif Bergsagel[1]

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Introduction: While the treatment of multiple myeloma (MM) has greatly improved, most patients eventually relapse. The time to relapse is variable with some patients relapsing within months and others remaining in remission for years. We hypothesize there are differences in the bone marrow (BM) microenvironment (ME) that underlie earlier progression; identification of factors associated with prolonged remission could be leveraged to benefit patients with early relapse. The BM ME is defined by specific cell types and proximity to MM cells and the rich array of plasma proteins, including those with regulatory activity impacting residual MM cell growth and survival. In this study, we analyzed BM plasma samples from MM patients with differing clinical outcome to identify plasma biomarkers that predict outcome at d100 post-autologous stem cell transplant (ASCT). **Methods:** Two different proteomic platforms were used. The SomaLogic platform is aptamer-based and measures 7000 proteins. For the SomaLogic studies, BM plasma samples were collected (2006-2019) from 104 MM patients ~d100 post-ASCT. Poor responders (PRs; n=38) were defined as relapsing 2yr if not put on MT and >4yr if placed on MT (n=66). The Olink Explore 3072 platform uses proximity extension assay technology coupled with NGS and measures 3000 proteins. For the Olink studies, BM plasma samples from an independent cohort of MM patients (40 PRs and 40 GRs) were collected at ~d100 post-ASCT (2017-2018), all of whom received MT post-ASCT. Initially, the top principal components of the most variable features were clustered via nearest neighbor routines to identify potential non-biological groupings in both sets of proteomic data. Subsequently, differential expression via limma was performed to identify the most significantly up-regulated and down-regulated features for PRs after controlling for the non-biological groupings. **Results:** Notably, an abundance of cytokines was observed in PRs at ~d100 using both platforms. In the SomaLogic data, key genes within the cytokine-cytokine receptor interactions pathway were identified among the top 50 up-regulated proteins including CXCL10, IL18, IL21R, CXCL14, and IL17RB. The Olink data also showed up-regulated proteins in the PRs were related to cytokines and included CXCL1, CXCL8, CXC11, and IRAK4. We also explored possible effects of residual plasma cells (PCs) present at ~d100 post-ASCT. After adjusting for the % of PCs present, we still observed CXCL1, CXCL8, and CXCL11 in the top 50 up-regulated proteins. **Conclusions:** Our data suggest that the BM plasma cytokine milieu in MM patients post-ASCT may indicate which patients are more likely to progress. Our data further suggest that the association between chemokines and poor prognosis is largely independent of tumor involvement and may largely reflect the BM ME instead.

P-395

The gut microbiota changes during multiple myeloma treatment

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Introduction: It is clinically experienced and also biologically documented that multiple myeloma (MM) is in itself a heterogeneous disorder as covers multiple different characterized clones. Currently, the treatment is not strictly individualized yet and includes still high-dose chemotherapy with melphalan in transplant-eligible patients. We focused on emerging data on gut microbiota which may be disturbed during chemotherapy and may have a role in the passage of inflammatory mediators through the intestinal barrier. We studied microbiota changes in MM patients and documented the data at diagnosis and after treatment. **Methods:** Stool samples were taken twice, before and after the 4th therapy course. The samples were sequenced using the next-generation sequencing (NGS) method after nucleic acid isolation. OTU (Operational taxonomic unit) tables were prepared using NCBI Blastn version 2.0.12 according to NCBI general 16S bacterial taxonomy reference dated 10.08.2021. The OTU tables were calculated and plotted using R Statistical Computer Language version 4.04 (readr, phyloseq, microbiome, vegan, descry, and ggplot2 packages) to calculate Alpha diversity. Statistical analyses were also performed using R Statistical Computer Language version 4.0.4 and Rstudio IDE 1.4 (tidyverse, readr, xlsx, and ggplot2 packages). The associated pathways were analyzed with the KEGG (Kyoto Encyclopedia of Genes and Genomes) database. **Results:** Fifteen newly diagnosed MM patients enrolled

the vaccinated population (n=173) versus non-vaccinated ones (n=335) were 60.1% vs. 55.8% respectively (P=0.35). In subgroup analyses, the infection rates in vaccinated patients were lower than those in unvaccinated ones including the elderly (49.3% vs. 55.2%), obese patients (BMI≥28) (50% vs. 63.3%), and R/RMM population (42.2% vs. 66.7%, P=0.005). The proportion of hospitalized patients due to SARS-COV-2 infection in vaccinated group was significantly lower than that in unvaccinated group (4.8% vs.12.3%, P=0.038). **Conclusions:** Vaccine hesitation is common in Chinese MM patients although inactivated COVID-19 vaccine only causes mild AEs. Lower infection rate in MM patients is probably due to strict self-quarantine. COVID-19 vaccination is not translated into less SARS-COV-2 infections, but does protect the elderly, obese or R/RMM patients from severe infections. Clinicians are suggested to encourage MM patients to receive COVID-19 vaccines for the sake of reducing severe infections and related mortality.

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[1]Mayo Clinic Arizona; [2]Mayo Clinic Rochester

Introduction: While the treatment of multiple myeloma (MM) has greatly improved, most patients eventually relapse. The time to relapse is variable with some patients relapsing within months and others remaining in remission for years. We hypothesize there are differences in the bone marrow (BM) microenvironment (ME) that underlie earlier progression; identification of factors associated with prolonged remission could be leveraged to benefit patients with early relapse. The BM ME is defined by specific cell types and proximity to MM cells and the rich array of plasma proteins, including those with regulatory activity impacting residual MM cell growth and survival. In this study, we analyzed BM plasma samples from MM patients with differing clinical outcome to identify plasma biomarkers that predict outcome at d100 post-autologous stem cell transplant (ASCT). **Methods:** Two different proteomic platforms were used. The SomaLogic platform is aptamer-based and measures 7000 proteins. For the SomaLogic studies, BM plasma samples were collected (2006-2019) from 104 MM patients ~d100 post-ASCT. Poor responders (PRs; n=38) were defined as relapsing 2yr if not put on MT and >4yr if placed on MT (n=66). The Olink Explore 3072 platform uses proximity extension assay technology coupled with NGS and measures 3000 proteins. For the Olink studies, BM plasma samples from an independent cohort of MM patients (40 PRs and 40 GRs) were collected at ~d100 post-ASCT (2017-2018), all of whom received MT post-ASCT. Initially, the top principal components of the most variable features were clustered via nearest neighbor routines to identify potential non-biological groupings in both sets of proteomic data. Subsequently, differential expression via limma was performed to identify the most significantly up-regulated and down-regulated features for PRs after controlling for the non-biological groupings. **Results:** Notably, an abundance of cytokines was observed in PRs at ~d100 using both platforms. In the SomaLogic data, key genes within the cytokine-cytokine receptor interactions pathway were identified among the top 50 up-regulated proteins including CXCL10, IL18, IL21R, CXCL14, and IL17RB. The Olink data also showed up-regulated proteins in the PRs were related to cytokines and included CXCL1, CXCL8, CXC11, and IRAK4. We also explored possible effects of residual plasma cells (PCs) present at ~d100 post-ASCT. After adjusting for the % of PCs present, we still observed CXCL1, CXCL8, and CXCL11 in the top 50 up-regulated proteins. **Conclusions:** Our data suggest that the BM plasma cytokine milieu in MM patients post-ASCT may indicate which patients are more likely to progress. Our data further suggest that the association between chemokines and poor prognosis is largely independent of tumor involvement and may largely reflect the BM ME instead.

P-395

The gut microbiota changes during multiple myeloma treatment

Sevgi Kalayoglu-Besisik[1], Fatma Savran Oguz[2], Zerrin Aktas[3], Oral Oncul[4], Ekin Ece Gurer[2], Tarik Onur Tiryaki[1], Ugur Sezerman[5]

[1]Istanbul University, Istanbul Faculty of Medicine/Department of Internal Medicine, Division of Hematology; [2]Istanbul University, Istanbul Faculty of Medicine/Medical Biology; [3]Istanbul Faculty of Medicine/Department of Clinical Microbiology; [4]Istanbul Faculty of Medicine/Department of Infectious Diseases and Clinical Microbiology; [5]Acibadem University, Faculty of Medicine/ Department of Biostatistics and Medical Informatics

Introduction: It is clinically experienced and also biologically documented that multiple myeloma (MM) is in itself a heterogeneous disorder as covers multiple different characterized clones. Currently, the treatment is not strictly individualized yet and includes still high-dose chemotherapy with melphalan in transplant-eligible patients. We focused on emerging data on gut microbiota which may be disturbed during chemotherapy and may have a role in the passage of inflammatory mediators through the intestinal barrier. We studied microbiota changes in MM patients and documented the data at diagnosis and after treatment. **Methods:** Stool samples were taken twice, before and after the 4th therapy course. The samples were sequenced using the next-generation sequencing (NGS) method after nucleic acid isolation. OTU (Operational taxonomic unit) tables were prepared using NCBI Blastn version 2.0.12 according to NCBI general 16S bacterial taxonomy reference dated 10.08.2021. The OTU tables were calculated and plotted using R Statistical Computer Language version 4.04 (readr, phyloseq, microbiome, vegan, descry, and ggplot2 packages) to calculate Alpha diversity. Statistical analyses were also performed using R Statistical Computer Language version 4.0.4 and Rstudio IDE 1.4 (tidyverse, readr, xlsx, and ggplot2 packages). The associated pathways were analyzed with the KEGG (Kyoto Encyclopedia of Genes and Genomes) database. **Results:** Fifteen newly diagnosed MM patients enrolled

the vaccinated population (n=173) versus non-vaccinated ones (n=335) were 60.1% vs. 55.8% respectively (P=0.35). In subgroup analyses, the infection rates in vaccinated patients were lower than those in unvaccinated ones including the elderly (49.3% vs. 55.2%), obese patients (BMI≥28) (50% vs. 63.3%), and R/RMM population (42.2% vs. 66.7%, P=0.005). The proportion of hospitalized patients due to SARS-COV-2 infection in vaccinated group was significantly lower than that in unvaccinated group (4.8% vs.12.3%, P=0.038). **Conclusions:** Vaccine hesitation is common in Chinese MM patients although inactivated COVID-19 vaccine only causes mild AEs. Lower infection rate in MM patients is probably due to strict self-quarantine. COVID-19 vaccination is not translated into less SARS-COV-2 infections, but does protect the elderly, obese or R/RMM patients from severe infections. Clinicians are suggested to encourage MM patients to receive COVID-19 vaccines for the sake of reducing severe infections and related mortality.

P-394

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P-396

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Introduction: Selinexor (SEL) is an oral first-in-class selective exportin 1 (XPO1) inhibitor. SEL in combination with dexamethasone (DEX) and bortezomib is FDA and EMA approved for treatment of patients with multiple myeloma (MM) who have received at least one prior line of therapy. In addition to activating tumor suppressor proteins, non-clinical studies have shown SEL down-regulates immune checkpoints, enhances immune cell surveillance and improves biologic immunotherapies. Herein we investigated the effects of selinexor on MM cell immune markers and the bone marrow (BM) microenvironment in samples from patients with relapsed/refractory MM (RRMM) treated with SEL combinations. **Methods:** Samples from patients enrolled in the STOMP trial, a multi-arm, open-label, Phase 1b/2 study evaluating SEL in combinations with different backbone therapies (NCT02343042), at our institute were included in this post-hoc analysis. Paired BM biopsy samples obtained at the time of initial diagnosis (n=12), immediately before SEL treatment (n=20), and at the end of the study (n=20) were assessed, as well as normal control BM samples (n=12). Samples were stained with CD138, CD3 and CD45 antibodies for morphologic identification then probed with the NanoString GeoMx Digital Spatial Profiling (DSP) Immuno-Oncology multiplex antibody panel for quantitative expression of 96 targets with spatial resolution. XPO1 expression was measured by dual color immunohistochemical (IHC). **Results:** From January 2017 to May 2022, a total of 47 RRMM patients enrolled in the STOMP trial at our institution. The median age was 66 years (ranging from 50 to 77 years) (males: 21 and females 26; African American patients: 17, Caucasian: 28, Hispanic: 2). Of the 47 patients, 10 were in Arm 1 (SEL+DEX+pomalidomide); 15 in Arm 5 (SEL+DEX+daratumumab); and 12 in Arm 6 (SEL+DEX+carfilzomab); with the remaining in other arms. Patients were treated with SEL-based regimens for a median of 270 days (ranging from 35 to 1709 days). Thirty-one patients (66%) achieved PR or better and 34% patients had ≥ VGPR. Thirty-eight patients (81%) discontinued treatment due to disease progression and five patients (11%) discontinued treatment due to toxicities. DSP and IHC are being performed on normal controls, diagnostic samples, and paired pre/post treatment samples from 4 patients in Arm 1, 10 in Arm 5 and 6 in Arm 6. Myeloma cell signaling pathway activations, BM microenvironment immune activity and XPO1 expression will be correlated with treatment response and drug resistance. Detailed and comprehensive results will be presented at the meeting. **Conclusions:** Our study provides insights in how SEL affects the endogenous immune system in the context of MM, with implications for sequencing SEL with immune directed therapies like CAR-T cell treatments. Moreover, our study will identify molecular mechanisms that contribute to drug resistance to SEL, with implications for combination therapies and predictive biomarkers.

P-397

Polyclonal immunoglobulin recovery in myeloma patients receiving maintenance after autologous hematopoietic stem cell transplantation with carfilzomib, lenalidomide and dexamethasone or lenalidomide

Tadeusz Kubicki[1], Dominik Dytfeld[2], Tomasz Wrobel[3], Krzysztof Jamroziak[4], Pawel Robak[5], Jaroslaw Czyz[6], Agata Tyczynska[7], Agnieszka Druzd-Sitek[8], Krzysztof Giannopoulos[9], Adam Nowicki[10], Anna Lojko-Dankowska[10], Magdalena Matuszak[10], Lidia Gil[10], Bartosz Pula[11], Justyna Rybka[3], Lidia Usnarska-Zubkiewicz[3], Olga Czabak[12], Andrew Stefka[1], Ken Jiang[1], Benjamin Derman[1], Andrzej Jakubowiak[1]

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the context of currently utilized extended post-ASCT maintenance therapy. Furthermore, the impact of more intensive regimens, beyond standard single-agent lenalidomide maintenance, on normal plasma cells has not been extensively studied. **Methods:** Using published results of the unplanned interim report (Dytfeld, Lancet Oncology 2023), we performed a longitudinal analysis of polyclonal immunoglobulin concentrations and unique B-cell sequences in patients enrolled in the phase 3 ATLAS trial that randomized 180 subjects to either carfilzomib, lenalidomide, dexamethasone (KRd) or lenalidomide (R) maintenance. In the KRd arm, patients with standard risk and minimal residual disease (MRD) negativity after 6 cycles de-escalated to R alone after cycle 8. **Results:** One year from the initiation of maintenance, complete recovery of uninvolved immunoglobulin was observed in 8/140 (5.7%) evaluable patients and partial recovery (at least one uninvolved immunoglobulin) in 86/140 (61.4%). At least partial recovery was observed in more patients on the R arm (58/66, 87.9%, p< 0.001) and in those who de-escalated from KRd to R (27/38, 71.1%, p< 0.001) compared to the KRd arm (9/36, 25.0%). The concentration of polyclonal immunoglobulin and the number of total unique B-cell sequences were significantly lower in patients who received continuous treatment with KRd throughout the analyzed period (cycles 6, 12, 18, 24, 30, 36). In patients who switched from KRd to R after cycle 8, the concentrations of uninvolved immunoglobulin and B-cell repertoire diversity increased over time after de-escalation, approaching values observed in the control R arm. At MRD assessment after C6, the concentration of uninvolved immunoglobulin was significantly lower among MRD-negative patients (p=0.03). There were no differences in PFS [HR = 1.07 (0.54-2.10), p=0.85] or OS [HR = 1.22 (0.34-4.37), p=0.76] between the patients with at least partial immunoglobulin recovery and the remaining population. The differences in PFS were not significant also when adjusted for the study arm. **Conclusions:** The findings from our study show that polyclonal immunoglobulin recovery one year after ASCT does not have prognostic significance for PFS after extended treatment with KRd versus R, indicating limited prognostic significance of polyclonal immunoglobulins recovery in the context of contemporary landscape of maintenance therapies.

P-398

Dynamic immune response in multiple myeloma patients infected with SARS-CoV-2 omicron BA.4/5 subvariant in China

Ziping Li[1], Huiwen He[1], Haolong Li[2], Shuangjiao Liu[3], Fujing Zhang[4], Yongzhe Li[5], Junling Zhuang[3]

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P-399

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the context of currently utilized extended post-ASCT maintenance therapy. Furthermore, the impact of more intensive regimens, beyond standard single-agent lenalidomide maintenance, on normal plasma cells has not been extensively studied. **Methods:** Using published results of the unplanned interim report (Dytfeld, Lancet Oncology 2023), we performed a longitudinal analysis of polyclonal immunoglobulin concentrations and unique B-cell sequences in patients enrolled in the phase 3 ATLAS trial that randomized 180 subjects to either carfilzomib, lenalidomide, dexamethasone (KRd) or lenalidomide (R) maintenance. In the KRd arm, patients with standard risk and minimal residual disease (MRD) negativity after 6 cycles de-escalated to R alone after cycle 8. **Results:** One year from the initiation of maintenance, complete recovery of uninvolved immunoglobulin was observed in 8/140 (5.7%) evaluable patients and partial recovery (at least one uninvolved immunoglobulin) in 86/140 (61.4%). At least partial recovery was observed in more patients on the R arm (58/66, 87.9%, p< 0.001) and in those who de-escalated from KRd to R (27/38, 71.1%, p< 0.001) compared to the KRd arm (9/36, 25.0%). The concentration of polyclonal immunoglobulin and the number of total unique B-cell sequences were significantly lower in patients who received continuous treatment with KRd throughout the analyzed period (cycles 6, 12, 18, 24, 30, 36). In patients who switched from KRd to R after cycle 8, the concentrations of uninvolved immunoglobulin and B-cell repertoire diversity increased over time after de-escalation, approaching values observed in the control R arm. At MRD assessment after C6, the concentration of uninvolved immunoglobulin was significantly lower among MRD-negative patients (p=0.03). There were no differences in PFS [HR = 1.07 (0.54-2.10), p=0.85] or OS [HR = 1.22 (0.34-4.37), p=0.76] between the patients with at least partial immunoglobulin recovery and the remaining population. The differences in PFS were not significant also when adjusted for the study arm. **Conclusions:** The findings from our study show that polyclonal immunoglobulin recovery one year after ASCT does not have prognostic significance for PFS after extended treatment with KRd versus R, indicating limited prognostic significance of polyclonal immunoglobulins recovery in the context of contemporary landscape of maintenance therapies.

P-398

Dynamic immune response in multiple myeloma patients infected with SARS-CoV-2 omicron BA.4/5 subvariant in China

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Introduction: Smoldering multiple myeloma is a heterogeneous disease in which patients with high-risk (HRSMM) stratification have high rates of progression to MM, making them suitable candidates for early intervention. Isatuximab, a selective anti-CD38 monoclonal antibody, is currently approved in two combination regimens for relapsed and/or refractory myeloma where, it improved progression free survival over standard of care. Here, we aimed to investigate the impact of single agent Isatuximab in the bone marrow immune microenvironment of HRSMM patients. **Methods:** Patients with HRSMM (based on immunoparesis and ≥95% immunophenotypically abnormal marrow plasma cells) treated in stage 1 of the ISAMAR study with isatuximab monotherapy (NCT02960555) with available formalin-fixed paraffin embedded tissue (FFPE) bone marrow biopsies were included in the study. A previously optimized and validated multiplex immunofluorescence (mIF) panel was developed to assess plasma cells (CD138), macrophages (CD68), immune checkpoints (PD-1, PD-L1), and subsets of T-cells (CD3, CD8, Foxp3, CD45RO). The slides were imaged using Vectra Polaris system (Akoya Biosciences, Marlborough, MA) and the whole tissue was selected for the analysis, and data was consolidated using Spotfire software. Differences in cell densities among different treatment time points: baseline, post-cycle 6 (pC6), post-cycle 18 (pC18), and end of treatment/post-cycle 30 (EOT) were evaluated with Kruskal-Wallis test using SAS Enterprise Guide 7.1. **Results:** Eighteen of 24 patients had available samples. Most patients were female (11/18, 61%), white (16/18, 88%) and had kappa light chain restriction (16/18, 88%). After a median follow-up of 40 months (range: 11-56 months), two patients had complete response, thirteen partial response and two had stable disease. Two patients died of other causes. Efficacy and toxicity were previously reported (Blood (2019) 134 (Supplement_1): 3116.). Sixty samples with a median area of 1.85 mm^2/case and a median number of 8947 cells/case were analyzed by mIF. When comparing different time points of treatment, cases pC6 and EOT had a had a significantly lower cell density of total CD138+ cells (p= 0.0002), though the residual plasma cells had significantly higher staining for CD138+/PD-L1+ (p< 0.0001). Also, there were higher levels of total CD3+ (p< 0.0001), CD3+/PD-1+ (p< 0.0001), CD3+/CD8+ (p< 0.0001), CD3+/Foxp3+/CD8- (p= 0.018), CD3+/CD45RO+ (p< 0.0001), CD3+/CD45RO+/CD8+ (p< 0.0001), CD3+/CD45RO+/CD8- (p=0.0002), and CD68+/PD-L1+ (p< 0.0001). Interestingly, among the patients with partial response only, except for CD3+/Foxp3+/CD8-, pC6 and EOT time points also showed the same statistically significant differences in the immune populations. **Conclusions:** Isatuximab promotes significant immune activation in the bone marrow of patients with HRSMM, characterized by upregulation of different subsets of T-cells, and PD-L1+ plasma cells and macrophages.

P-400

An immune atlas of the dysfunctional cellular and antibody response to COVID-19 vaccination in patients with multiple myeloma

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Introduction: Infection is the leading cause of death in patients with multiple myeloma (MM). However, the cell-specific extent of baseline immune dysfunction and of the weakened response to vaccination is poorly described. Thus, we aimed to identify the hallmarks of impaired immunity in MM using the COVID-19 mRNA vaccines as a case study. **Methods:** Twenty-eight MM patients and two control groups were studied: 53 patients with a B-cell lymphoproliferative disorder (B-CLPD) and 96 age-matched health care practitioners (HCP). A total of 1,099 peripheral blood and serum samples were collected at baseline, at days 7 and 14 after the first dose, at days 7 and 62 after the second dose, as well as before and after the booster. Immune profiling was performed using multidimensional and computational flow cytometry that systematically analyzed 56 immune cell-types per sample and time point. Serum levels of IgM, IgG and IgA against the receptor-binding domain (RBD) of the spike (S) glycoprotein, S glycoprotein, nucleocapsid (N) and main protease were quantified using a multiplex-microsphere-based flow cytometry assay. SARS-CoV-2-specific CD8 T cells were quantified using a dextramer panel of S, N, membrane, and ORF3 proteins. **Results:** When compared to HCP and B-CLPD, MM patients showed abnormal distribution at baseline and impaired expansion during vaccination of nearly all the 17 B-cell subsets analyzed in this study. Accordingly, anti-RBD IgM, IgA and IgG titers after the second dose were lower in patients with MM vs B-CLPD (P≤.002). When compared to HCP, both MM and B-CLPD patients showed significantly reduced anti-RBD and anti-S antibody levels over time. Significant deviations at baseline and longitudinally were also observed in classical monocytes, and 6 of 30 T-cell subsets. In contrast to HCP, the percentage of virus-specific CD8 T cells after the second dose did not increase in patients with

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MM and B-CLPD. Importantly, the booster increased anti-RBD IgG levels (20,184 to 186,629 IU/mL, P<.001) and virus-specific cells (0.08 to 0.14% among CD8 T cells, P=.02) in HCP, but not in MM and B-CLPD (P≥.14). Furthermore, the booster induced virus-specific CD8 T cell differentiation into an effector memory phenotype in HCP, whereas no antigen-dependent differentiation was observed in patients with MM and B-CLPD. Based on differences in immune-cell distribution using HCP as a reference, we calculated an immune dysregulation longitudinal cumulative score in each individual that included 48,496 parameters. Up to 34% MM and 17% B-CLPD patients showed notable immune dysregulation. Among them, 75% and 33%, respectively, had low seroconversion after the second dose. **Conclusions:** We provide an atlas of the immune dysfunction in MM patients and how it affects the efficacy of vaccination strategies such as for COVID-19. The schedule of vaccine doses may thus benefit from individualization according to patients' immune status, which could act as a surrogate of host, tumor and treatment-related immune dysfunction.

P-401

MiRNA-seq and clinical validation of miR-221/222 cluster in multiple myeloma

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P-402

Inhibition of proline production by stromal cells negatively impacts myeloma tumor growth by reducing cytokine and growth factor secretion

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MM and B-CLPD. Importantly, the booster increased anti-RBD IgG levels (20,184 to 186,629 IU/mL, P<.001) and virus-specific cells (0.08 to 0.14% among CD8 T cells, P=.02) in HCP, but not in MM and B-CLPD (P≥.14). Furthermore, the booster induced virus-specific CD8 T cell differentiation into an effector memory phenotype in HCP, whereas no antigen-dependent differentiation was observed in patients with MM and B-CLPD. Based on differences in immune-cell distribution using HCP as a reference, we calculated an immune dysregulation longitudinal cumulative score in each individual that included 48,496 parameters. Up to 34% MM and 17% B-CLPD patients showed notable immune dysregulation. Among them, 75% and 33%, respectively, had low seroconversion after the second dose. **Conclusions:** We provide an atlas of the immune dysfunction in MM patients and how it affects the efficacy of vaccination strategies such as for COVID-19. The schedule of vaccine doses may thus benefit from individualization according to patients' immune status, which could act as a surrogate of host, tumor and treatment-related immune dysfunction.

P-401

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P-403

Identification and quantification of novel circular RNAs (circRNAs) deriving from the apoptosis-related BCL2L12 gene in multiple myeloma cells, using targeted nanopore sequencing and nested qPCR

Maria Papatsirou[1], Nikolaos Machairas[1], Paraskevi Karousi[1], Ioannis Ntanasis-Stathopoulos[2], Aspasia Dimitriadou[1], Konstantina Xenou[1], Panagiotis Malandrakis[2], Christine-Ivy Liacos[1], Maria Gavriatopoulou[1], Efstathios Kastritis[2], Meletios Dimopoulos[1], Andreas Scorilas[1], Evangelos Terpos[2], Christos Kontos[1]

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P-404

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William Pilcher[1], Lijun Yao[2], Edgar Gonzalez Kozlova[3], Yered Pita-Juarez[4], Dimitra Karagkouni[5], Yuling Ma[4], Beena Thomas[1], Sarthak Satpathy[1], Swati Bhasin[1], Yizhe Song[2], Julia Wang[2], Travis Dawson[3], Darwin D'souza[3], Immune Network[6], Jessica Schulman[6],

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Introduction: A pivotal step to achieving better clinical responses is the early diagnosis of monoclonal disorders that can progress to multiple myeloma (MM), such as monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM). A class of RNA molecules with regulatory potential in MM are circular RNAs (circRNAs). However, our knowledge regarding circRNAs produced from apoptosis-related genes is limited. Prompted by this, we aimed to identify novel circRNAs of the BCL2L12 gene that are expressed in MM cells and develop a sensitive quantification protocol for circRNAs of interest in patients' samples. **Methods:** Total RNA was extracted from 3 cell lines (L-363, H929, and U266) and reverse-transcribed using random hexamers. Then, pairs of divergent primers were designed, and nested PCR protocols were implemented. Next, targeted 3rd-generation sequencing with nanopore technology was performed. Novel circRNA sequences were identified using in-house–built Perl-based algorithms. Bioinformatics analysis followed to predict the interactions of the novel BCL2L12 circRNAs, utilizing publicly available tools and databases, such as miRDB and dbDEMC. Then, circ-BCL2L12-36 and circ-BCL2L12-38 were chosen among the circRNAs that were common among all MM cell lines for further investigation. Total RNA was extracted from CD138+ plasma cells of 28 MGUS, 30 SMM, and 103 MM patients, and cDNA synthesis was performed. Subsequently, we developed in-house real-time qPCR assays, using specific divergent primers that span the circRNAs back-splice junction, to quantify these circRNAs in all samples. GAPDH was used as a reference gene for qPCR data normalization. **Results:** We identified 36 novel circRNAs deriving from the BCL2L12 gene, 4 of which are common among all MM cell lines. The structures of these novel circRNAs showed remarkable diversity, comprising currently annotated exons, as well as truncated exons and genomic regions that were not represented in BCL2L12 transcripts so far. Moreover, several BCL2L12 circRNAs are predicted to sponge miRNAs with a key role in MM, including miR-181 family members that have been associated with chemosensitivity, miR-195-5p which is correlated with thoracic lesions, and miR-455-3p that was decreased in MM patients with renal impairment. Furthermore, circ-BCL2L12-36 is expressed in 60% of patient samples, while circ-BCL2L12-38 is expressed in 84.5% of samples. **Conclusions:** In this study, 36 novel circRNAs of the BCL2L12 gene were annotated. These circRNAs are formed through various alternative back-splicing events of the known BCL2L12 exons. All novel circRNAs are predicted to bind miRNAs that are intricately implicated in MM. By sequestering these miRNAs, BCL2L12 circRNAs may affect patients' progression risk, response to therapy, and survival outcome. Finally, circ-BCL2L12-36 and circ-BCL2L12-38 were also successfully quantified and found to be expressed in the CD138+ cells of patients at different disease stages.

P-404

Single-cell profiling reveals inflammaging-associated dysregulations in rapidly progressing multiple myeloma patients

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Nick Pabustan[6], April Cook[6], Hearn Jay Cho[6], George Mulligan[6], Mark Hamilton[6], Taxiarchis Kourelis[7], Ioannis Vlachos[4], Sacha Gnjatic[3], Li Ding[2], Manoj Bhasin[1]

[1]Emory University; [2]Washington University in St. Louis; [3]Icahn School of Medicine at Mt. Sinai; [4]Beth Israel Deaconess Medical Center; [5]Harvard Medical School, Department of Pathology, Beth Israel Deaconess Medical Center, Broad Institute of MIT and Harvard; [6]MMRF; [7]Mayo Clinic

Introduction: Modern therapies for multiple myeloma (MM) rely on the immune system for their effectiveness and positive outcomes. Dysregulation in the immune compartment can promote disease progression and hamper the effectiveness of immune-based therapies. In this study for the characterization of bone marrow (BM) and its association with the kinetics of MM (Rapid Progression (RPs) = PFS4 years), we performed Single Cell Profiling on BM samples from the Multiple Myeloma Research Foundation CoMMpass cohort. **Methods:** Frozen CD138 negative fraction of BM samples from MM patients enrolled in the CoMMpass clinical trial (NCT01454297) underwent scRNA-seq at four different medical centers/Universities. ScRNA-seq data from 361 BM samples of 263 MM patients, collected at different time points (263 disease diagnosis (Dx), 59 relapses, 32 remissions, 7 other) were generated in phase I of the study. The scRNA-seq data were aligned and quality-controlled, doublet filtered, normalized, and batch-corrected before unsupervised and supervised analysis. The statistical analysis of annotated cellular clusters comparing RPs and NPs identified cell types, genes, and pathways associated with rapid progression. **Results:** ScRNA-seq on BM samples collected at Dx from 263 MM patients generated high-quality profiles of 886,329 cells. The unsupervised analysis yielded 106 clusters corresponding to myeloid, lymphoid, and erythroid lineages. The cellular proportion analysis comparing rapid progressors (n=67) and non-progressors (n=83) depicted significant differences (P1, P< 0.01), while NPs display significant enrichment of naïve markers (LTB, SELL, TCF7) associated with better outcomes. RP-enriched, GZMB+ cellular populations also lacked CD27 and CD28 expression, suggesting they are terminally and clonally expanded effector cells. **Conclusions:** Based on single-cell findings, the expansion of a senescent CD8+ effector population along with the reduction of the memory T cell population might be resulting in a lower effectiveness of immunotherapies in rapid progressors. This in-depth characterization of the BM microenvironment might assist in developing further therapies directed toward rapid progressors with inflammaging immune ecosystems.

P-405

Isotype matched immunoparesis could help in predicting progression to multiple myeloma in MGUS patients

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Introduction: Monoclonal Gammopathy of Undetermined Significance (MGUS) is a premalignant stage that eventually all multiple myeloma (MM) patients have suffered. According to the Mayo Clinic, risk factors to progression include M-protein size and isotype as well as free light chain (FLC) ratio. Classic immunoparesis is defined as the suppression of uninvolved immunoglobulins (Igs) and its role as MGUS to MM progression factor remains controversial. Nowadays, we can measure the uninvolved heavy/light chain pair of the same immunoglobulin (uHLC). However, little data have been reported regarding its role as a progression factor from MGUS to MM. The aim of this prospective, single center study was to assess the prognostic value of uHLC suppression (Isotype Matched Immunoparesis or IMI) in MGUS to MM progression. **Methods:** The study group was composed by 232 stored serum samples from 116 MGUS patients attending our hospital. Light chain only MGUS patients were not included in the analysis. We analyzed classic immunoglobulins and uHLC in the laboratory of our institution at diagnosis and in each routine visit. MGUS risk progression factors were assessed following Mayo Clinic guidelines. We considered classic immunoparesis (IP) at diagnosis when one or more uninvolved classic Ig were under lower limit of normality (LLN) and IMI when uHLC was under LLN. We defined the decrease of uHLC (duHLC) as the rate of change of uHLC concentration in the last follow-up or at progression compared to uHLC concentration at diagnosis. Recovery of uHLC was considered when suppressed uHLC at diagnosis reached at least LLN+10% in the last follow-up or at progression. **Results:** At diagnosis we found classic IP in 32% (37/116) of patients, whereas IMI was found on 43% (50/116) of them. Both classic IP and IMI were more common in IgA patients (40% and 83%, respectively) in comparison to IgG (30% and 41%) or IgM (33% and 21% respectively) patients. Interestingly, the presence of IMI was more frequent in patients with a higher risk of progression to MM, thus, IMI was only found in 31% of patients with no risk factors whereas the percentage increased as the number of risk factors did (1 risk factor 43% of patients and 2 risk factors 56%). Furthermore, MGUS patients who presented duHLC>50% had a higher risk of progression to MM (p=0.0067) with a median of progression of 8.35 years whereas in patients with a duHLC≤50% the median was not reached. Additionally, patients with duHLC>90% presented a median to progression of 5.5 years (p=0.047). Finally, MGUS patients that did not recover uHLC had a higher risk of progression to MM (p=0.029) with a hazard ratio of 3.821. **Conclusions:** Both uHLC decrease and recovery of uHLC have shown to be a risk factor in the progression from MGUS to MM in our patient cohort. Therefore, the measurement of uHLC in MGUS patients could be an additional tool to predict progression to MM.

Nick Pabustan[6], April Cook[6], Hearn Jay Cho[6], George Mulligan[6], Mark Hamilton[6], Taxiarchis Kourelis[7], Ioannis Vlachos[4], Sacha Gnjatic[3], Li Ding[2], Manoj Bhasin[1]

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P-405

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P-406

Development of a 3D bioreactor model using a perfusion bioreactor to study osteocyte progenitor cells and the Involvement of single ECM molecules in multiple myeloma bone disease

Wyonna Rindt[1], Louisa Belz[1], Franziska Sennefelder[1], Marietta Herrmann[2], Ana Rita Pereira[2], Martin Kuric[3], Melanie Krug[3], Kamal Mustafa[4], Shuntaro Yamada[4], Mohammed Ahmed Yassin[4], Regina Ebert[3], Franziska Jundt[1]

[1]Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany; [2]IZKF Group Tissue Regeneration in Musculoskeletal Diseases, University Hospital Würzburg, Würzburg Germany; [3]Department of Musculoskeletal Tissue Regeneration, Orthopedic Clinic König-Ludwig-Haus, University of Würzburg, Germany; [4]Centre of Translational Oral Research (TOR)-Tissue Engineering group, Department of Clinical Dentistry, University of Bergen, Norway

Introduction: Myeloma bone disease (MBD) is a hallmark of MM and affects 80% of MM patients. Current treatments do not fully regenerate osteolytic lesions, even in the absence of MM cells. We showed that tibial compressive loading prevents bone destruction, and reduces MM growth and dissemination in the MOPC315. BM mouse model. In this study, we established an in vitro 3D bioreactor model for MM to characterize the mechanobiological processes in osteocytes, the main mechanosensors controlling bone remodeling. **Methods:** Osteocytic IDG-SW3 cells were seeded onto three different scaffolds: decellularized and partially demineralized dBone derived from human femoral heads, synthetic ß-tricalcium phosphate (ß-TCP), and synthetic poly(L-lactide-co-trimethylene carbonate) (LTMC). To assess the colonization efficiency under static and dynamic conditions in the bioreactor, viability, and growth of IDG-SW3 cells were evaluated by MTT, PicoGreen assay, and LIVE/DEAD staining. Osteocytic differentiation was confirmed by alkaline phosphatase (ALP) staining and gene expression analysis of alkaline phosphatase (Alpl), sclerostin (Sost), and dentin matrix protein 1 (Dmp-1). Biophysical stimulation was exerted by compressing the scaffolds with a movable arm. Expression of the mechanoresponsive genes FBJ osteosarcoma oncogene (Fos) and cyclooxygenase-2 (Cox2) was analyzed to determine the mechanoresponse. **Results:** In all scaffolds, reproducible cell seeding capacity was detected with dBone scaffolds exhibiting donor variability. Homogeneous distribution and high density were achieved in dBone and LTMC scaffolds under static and dynamic conditions, whereas the cells colonized only on the top of the ß-TCP scaffolds and barely grew through after ten days. ß-TCP scaffolds demonstrated low mechanical loading capacity and disintegrated upon compression. We found that osteocytic differentiation was most efficiently induced under dynamic conditions, as evidenced by upregulation of the differentiation markers Alpl, Sost, Dmp-1, and by ALP staining. Fos and Cox2 were induced through mechanical loading of the LTMC scaffolds. **Conclusions:** The established bioreactor system is suitable to study molecular changes in osteocytes caused by MM and mechanical loading. Differences in pore size, porosity, and interconnectivity of these scaffolds affect the growth and cell migration of IDG-SW3 cells. Since the ß-TCP scaffolds did not show a homogenous distribution of the cells with also insufficient mechanical stability and the dBones exhibited inter- and intra-donor variability, the LTMC scaffolds provided the most reliable results. We will use the bioreactor in future studies to characterize the molecular mechanisms of mechanotransduction in osteocytes in the presence of MM cells and their supernatant to evaluate whether secreted factors of MM cells affect the differentiation and function of osteocytes.

P-407

3D organoid model: using primary cells to study therapeutic effects on patients' myeloma tumor niche

Cesar Rodriguez[1], Hanadi Rashad[2], Giovanni Insuasti[3], Graca Almeida-Porada[2]

[1]Icahn School of Medicine at Mount Sinai; [2]Wake Forest Institute of Regenerative Medicine; [3]Health Wake Forest Baptist

Introduction: Preclinical models have been the backbone for drug development and learning about cancer biology. The inability to properly recapitulate the tumor niche and the difficulty to use primary cells have been great detrimental factors when translating results from the bench to the bedside. We have previously reported results of an ex-vivo 3D organoid cell model with biomimetic microenvironment that allowed prolonged cell survival of primary myeloma cells for up to 14 days in co-cultures and chemosensitivity results. We now present the effects different drug conditions have on both the plasma cells as well as the immune compartment found in primary patient samples. **Methods:** After obtaining informed consent, we obtained bone marrow aspirate samples from patients with relapsed multiple myeloma. Using previously described technique, mononuclear cells were co-cultured cultured with stroma in a Matrigel scaffold. Each organoid containing 200,000 cells was plated on an individual well and nourished with enriched culture media. Batches of organoids from the same patient sample were exposed to three different chemotherapy agents (bortezomib 5 nM and 10nM, lenalidomide 50 µM and 100 µM, selinexor 10 µM and 30 µM) on day 5 of experiment and removed 72 hours later. Different timepoints prior to drug exposure (day 5), at the end of drug exposure (day 8), and six days later (day 14) were used to perform viability/proliferation assays with Alamar Blue and flow cytometry to assess different cellular compartments, specifically plasma cells and part of the immune repertoire (CD4, CD8, and NK cells). **Results:** Primary cells from bone marrow aspirates remained viable for the duration of the experiment (14 days). Alamar blue showed proliferation in the control group while significant differences were seen in viability based on agent and concentration (Image 1). When looking at flow cytometry data, we see different impact in T cell and NK cell found in the tumor niche (Image 2, 3, 4, 5, 6). **Conclusions:** While conventional preclinical models have been a cornerstone to drug development and advances in medicine, the current development of immunotherapies, including cellular therapy require a better physiological representation of the tumor niche. Organoid models

P-406

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P-407

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from primary patient samples provide an environment that allows evaluation of different study conditions and its impact not just on the patient's own myeloma cells, but their immune compartment as well. Additional studies to assess its application in T-cell redirecting therapy and other novel immunotherapies using this model is warranted to correlate with clinical outcomes.

P-408

Differential peripheral cytokine profile and tumor microenvironment in patients with or without a history of BCMA-directed therapy prior to elranatamab: analysis of MagnetisMM-3

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Introduction: MagnetisMM-3 (NCT04649359) is a phase 2 study of elranatamab in patients (pts) with relapsed/refractory multiple myeloma. Here, we compare the peripheral cytokine profile, its correlation with cytokine release syndrome (CRS) and tumor microenvironment (TME) in pts naïve to BCMA-directed therapy (Cohort A, n=123) vs. pts with prior exposure to BCMA-directed therapy (Cohort B, n=64) in MagnetisMM-3. **Methods:** Pts received subcutaneous elranatamab with 2-step-up doses of 12/32 mg followed by 76 mg QW. Serum samples were collected during cycle 1, and levels of 45 cytokines were analyzed by proximity extension assay and a longitudinal mixed effects model was applied to each cytokine separately. LM22 immune cell signatures were derived from gene expression analysis of bone marrow aspirate (BMA) collected at baseline. Clinical data cutoff was January 2023 with median follow up of 12.0 months. **Results:** There were no significant differences (≥2-fold; p< 0.05) in baseline levels of cytokines between BCMA-naïve and BCMA-exposed pts and no baseline cytokine correlated with the development of CRS in either group. In BCMA naïve patients, 7 cytokines (IL-6, IFN-g, IL-10, TNF-a, CCL-8, IL-27, IL-2) were differentially expressed (≥3-fold; unadjusted p< 0.05) during treatment in pts with CRS whereas in BCMA-exposed pts, only 6 cytokines (IL-10, IL-1b, IL-13, IL-18, TSL and IL-2) were differentially expressed in pts with CRS. Notably, the difference in cytokine expression in BCMA-exposed pts experiencing CRS was often smaller and/or peaked at different times than in BCMA-naïve pts, suggesting an altered cytokine response in pts with prior BCMA-directed therapy. Patients with prior exposure to a BCMA agent were treated either with an ADC (n=46) or a CAR-T agent (n=21). At baseline, there were no significant differences (≥2-fold; p< 0.05) in cytokine levels between the ADC vs. CAR-T subgroups. In patients that experienced CRS only two cytokines were differentially expressed (≥3-fold; p< 0.05) in pts experiencing CRS: higher IL-4 in the CAR-T subgroup (3.15-fold at C1D5; p=0.002) and higher IL-1b (3.2-fold at C1D2; p=0.011 and 3.4-fold at C1D15; p=0.001) in the ADC subgroup. Gene expression analysis of bulk BMA samples at baseline revealed a different immune cell signature with less abundant subsets of inferred T-cell populations in BCMA-exposed pts compared to BCMA naïve pts. The difference was driven by a lower abundance of T-cell population signatures in the CAR-T relative to the ADC subgroup, suggesting inherent differences in the baseline immune TME in these groups. Additionally, no significant association between CRS and baseline LM22 immune cell signatures in BCMA-naïve vs. BCMA-exposed pts was observed. **Conclusions:** Cytokine induction in pts experiencing CRS in prior-exposed BCMA patients was often different compared to BCMA naïve patients. Distinct immune cell signatures derived from gene expression analysis of the TME were observed in pts with prior BCMA-directed CAR-T therapy.

P-409

Elevated LAG-3 expression in plasma cells and lymphoid subpopulations at distinct stages of multiple myeloma disease progression

Hatice Satilmis[1], Niels Vandewalle[1], Emma Verheye[1], Rong Fan[1], Elke De Bruyne[1], Eline Menu[1], Nick Devoogdt[1], Karin Vanderkerken[2], Karine Breckpot[1], Kim De Veirman[2]

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from primary patient samples provide an environment that allows evaluation of different study conditions and its impact not just on the patient's own myeloma cells, but their immune compartment as well. Additional studies to assess its application in T-cell redirecting therapy and other novel immunotherapies using this model is warranted to correlate with clinical outcomes.

P-408

Differential peripheral cytokine profile and tumor microenvironment in patients with or without a history of BCMA-directed therapy prior to elranatamab: analysis of MagnetisMM-3

Paula Rodriguez-Otero[1], Mohamad Mohty[2], Nizar Bahlis[3], Michael Tomasson[4], Hang Quach[5], Sangeetha Sathiah[6], Douglas Robinson[7], Umberto Conte[7], Thomas O'Brien[7], Katja Weisel[8]

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Introduction: MagnetisMM-3 (NCT04649359) is a phase 2 study of elranatamab in patients (pts) with relapsed/refractory multiple myeloma. Here, we compare the peripheral cytokine profile, its correlation with cytokine release syndrome (CRS) and tumor microenvironment (TME) in pts naïve to BCMA-directed therapy (Cohort A, n=123) vs. pts with prior exposure to BCMA-directed therapy (Cohort B, n=64) in MagnetisMM-3. **Methods:** Pts received subcutaneous elranatamab with 2-step-up doses of 12/32 mg followed by 76 mg QW. Serum samples were collected during cycle 1, and levels of 45 cytokines were analyzed by proximity extension assay and a longitudinal mixed effects model was applied to each cytokine separately. LM22 immune cell signatures were derived from gene expression analysis of bone marrow aspirate (BMA) collected at baseline. Clinical data cutoff was January 2023 with median follow up of 12.0 months. **Results:** There were no significant differences (≥2-fold; p< 0.05) in baseline levels of cytokines between BCMA-naïve and BCMA-exposed pts and no baseline cytokine correlated with the development of CRS in either group. In BCMA naïve patients, 7 cytokines (IL-6, IFN-g, IL-10, TNF-a, CCL-8, IL-27, IL-2) were differentially expressed (≥3-fold; unadjusted p< 0.05) during treatment in pts with CRS whereas in BCMA-exposed pts, only 6 cytokines (IL-10, IL-1b, IL-13, IL-18, TSL and IL-2) were differentially expressed in pts with CRS. Notably, the difference in cytokine expression in BCMA-exposed pts experiencing CRS was often smaller and/or peaked at different times than in BCMA-naïve pts, suggesting an altered cytokine response in pts with prior BCMA-directed therapy. Patients with prior exposure to a BCMA agent were treated either with an ADC (n=46) or a CAR-T agent (n=21). At baseline, there were no significant differences (≥2-fold; p< 0.05) in cytokine levels between the ADC vs. CAR-T subgroups. In patients that experienced CRS only two cytokines were differentially expressed (≥3-fold; p< 0.05) in pts experiencing CRS: higher IL-4 in the CAR-T subgroup (3.15-fold at C1D5; p=0.002) and higher IL-1b (3.2-fold at C1D2; p=0.011 and 3.4-fold at C1D15; p=0.001) in the ADC subgroup. Gene expression analysis of bulk BMA samples at baseline revealed a different immune cell signature with less abundant subsets of inferred T-cell populations in BCMA-exposed pts compared to BCMA naïve pts. The difference was driven by a lower abundance of T-cell population signatures in the CAR-T relative to the ADC subgroup, suggesting inherent differences in the baseline immune TME in these groups. Additionally, no significant association between CRS and baseline LM22 immune cell signatures in BCMA-naïve vs. BCMA-exposed pts was observed. **Conclusions:** Cytokine induction in pts experiencing CRS in prior-exposed BCMA patients was often different compared to BCMA naïve patients. Distinct immune cell signatures derived from gene expression analysis of the TME were observed in pts with prior BCMA-directed CAR-T therapy.

P-409

Elevated LAG-3 expression in plasma cells and lymphoid subpopulations at distinct stages of multiple myeloma disease progression

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differences could be observed on SPECT/CT images of naïve and MM mice, ex vivo biodistribution analysis showed a significant uptake and increase of anti-LAG-3 nanobodies in the bone and spleen at 14 DPI (20-40% tumor load) and 21 DPI (60-80% tumor load) compared to naïve mice. Within the CD45+ population in the spleen, we observed an increase in neutrophils (CD11b+Ly6G+) and monocytes (CD11b+Ly6G) during MM disease progression. In the bone marrow (BM), we observed a significant increase in CD4+ T-cells and CD8+ T-cells at 14 DPI and 21 DPI within the CD45+ cell fraction. Flow cytometry analysis revealed a significant higher LAG-3 expression on MM cells upon disease progression. Within the lymphoid population, LAG-3 expression was increased in BM-derived CD8+ T-cells, while this remained unaffected in splenic T-cells. LAG-3 expression generally decreased in almost all myeloid subsets (e.g. macrophages, dendritic cells (DCs)), except splenic monocytes and plasmacytoid DCs, during MM disease progression. **Conclusions:** Ex vivo biodistribution data revealed increased LAG-3 expression and nanobody uptake in MM-infiltrating organs. Using flow cytometry, a high expression of LAG-3 was observed in MM cells and lymphoid cells, which significantly increased within BM-derived CD8+ T-cells at end-stage of disease. Altogether, these data illustrate increased expression of LAG-3 upon disease progression and fosters the evaluation of LAG-3 blocking therapies, particularly in the context of immunotherapeutic approaches in MM.

P-410

Abstract withdrawn

P-411

Large-scale single-cell dissection of immune dysregulation in patients with monoclonal gammopathies

Romanos Sklavenitis-Pistofidis[1], Ting Wu[2], Elizabeth Lightbody[1], Yoshinobu Konishi[1], Mahshid Rahmat[1], Michael Timonian[1], Junko Tsuji[2], Michelle Aranha[1], Danielle Firer[2], Nicholas Haradhvala[2], Daniel Heilpern-Mallory[1], Gad Getz[3], Irene Ghobrial[1]

[1]Dana-Farber Cancer Institute; [2]Broad Institute of MIT & Harvard; [2]Broad Institute of MIT & Harvard, Harvard Medical School, Massachusetts General Hospital Cancer Center

Introduction: Prior studies have suggested that immune dysregulation can already be observed in patients with Monoclonal Gammopathy of Undetermined Significance (MGUS); however, it is unclear (i) how it compares to the dysregulation observed in

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patients with Smoldering Multiple Myeloma (SMM), (ii) which populations may directly interact with the tumor, and (iii) which types of dysregulation may be true hallmarks of disease. **Methods:** Here, we present results from the largest single-cell RNA-sequencing cohort (n=398) of bone marrow (BM) CD138-negative (n=271) and peripheral blood mononuclear cell samples (n=127) from patients with monoclonal gammopathies [MGUS, n=51; SMM, n=226; asymptomatic Waldenstrom's Macroglobulinemia (AWM), n=28; Multiple Myeloma (MM), n=28; healthy donors (HD), n=61]. Libraries were prepared with the Chromium Single-cell 5' Gene Expression kit by 10X Genomics and sequenced at the Genomics Platform of the Broad Institute of MIT and Harvard (Cambridge, MA). **Results:** Overall, we profiled ~2.5M immune cells. Remarkably, despite their early stage, patients with MGUS presented extensive immune dysregulation compared to HD, suggesting that compositional changes may be established early on and that changes in gene expression and functionality may underlie progression. To identify subpopulations that are more likely to interact with tumor cells, we compared their abundance between matched BM CD138-positive and CD138-negative fractions in patients and HD. In patients, megakaryocytes were enriched in the CD138-positive fraction, an interaction previously shown to promote MM progression. Pro-B cells, pre-B cells, and memory B cells were enriched in the CD138-positive fraction of patients as well, suggesting that they could be involved in the clonal population or perhaps supporting its growth. Notably, granzyme K-expressing CD8+ T cells were significantly enriched in the CD138-positive fraction of patients, which is consistent with prior studies implicating this population in progression and response to therapy. To identify immune hallmarks of disease, we compared immune cell abundance and expression profiles between patients with SMM and patients with AWM, a different but related malignancy of the BM. We found that the significant increase in Th17 cells and Tregs we observed in patients with SMM is largely specific to myeloma, suggesting that these populations may be critical in sustaining MM cells. Furthermore, we observed myeloma-specific downregulation of the transcription factor CEBPD and its downstream targets, S100A8 and S100A9, in monocytes. **Conclusions:** In the largest to date single-cell RNA-sequencing study of immune cells from patients with monoclonal gammopathies, we have comprehensively mapped alterations in BM immune cell composition in patients with MGUS, identified subpopulations that are more likely to interact directly with tumor cells in the BM microenvironment, and described immune hallmarks of disease.

P-412

Loss of 3'U-tRFHisGTG in predicting poor survival and treatment outcome in multiple myeloma

Konstantinos Soureas[1], Maria-Alexandra Papadimitriou[1], Ioannis Ntanasis-Stathopoulos[2], Panagiotis Malandrakis[2], Aristea-Maria Papanota[1], Maria Gavriatopoulou[1], Efstathios Kastritis[2], Meletios Dimopoulos[1], Evangelos Terpos[2], Andreas Scorilas[1], Margaritis Avgeris[1]

[1]National and Kapodistrian University of Athens; [2]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Greece

Introduction: Despite the notable progress that has been achieved in the realm of multiple myeloma (MM) treatment and monitoring, the persistence of elevated relapse rates and therapy resistance remain a substantial hindrance to the effective management of the disease, highlighting the urgent need for the elucidation of molecular indicators supporting tailored patient's management. In this context, tRNA-derived fragments (tRFs), and specifically 3'U-tRFs, represent a novel class of small non-coding RNAs (ncRNAs), derived from pre-mature tRNAs, gathering attention due to their vital roles in regulating gene expression and their potential clinical utility in cancer prognosis and risk stratification. Overall, the aim of the present study was to investigate the involvement of 3'U-tRFHisGTG in MM. **Methods:** Bone marrow aspiration (BMA) samples were collected from 136 MM, 15 smoldering MM (sMM) and 15 monoclonal gammopathy of undetermined significance (MGUS) patients at diagnosis. Mononuclear cells were extracted from BM aspirates using Ficoll-Paque, and CD138+ plasma cells were separated through magnetic cell sorting, using immunomagnetic beads coated with anti-CD138 monoclonal antibodies. Based on target prediction and Gene Ontology (GO) enrichment, 3'U-tRFHisGTG was further evaluated for the first time in CD138+ plasma cells from the total study population. Following, total RNA extraction, polyadenylation at 3'-end, and reverse transcription using an oligo(dT) adapter primer, 3'U-tRFHisGTG levels were estimated through in-house qPCR. Finally, overall survival (OS) and progression-free survival (PFS) were evaluated, while internal validation was accomplished by bootstrap Cox proportional regression analysis. **Results:** In silico analysis unveiled the implication of 3'U-tRFHisGTG in cancer associated processes including, protein modification processes (protein acetylation), and autophagosome assembly. Our findings demonstrated the downregulated 3'U-tRFHisGTG levels in MM compared to its precursor stages sMM/MGUS (p=0.036), while focusing on MM patients, 3'U-tRFHisGTG loss depicted the association with bone disease (p=0.049). Furthermore, survival analysis revealed that loss of 3'U-tRFHisGTG was associated with significantly poor overall survival following treatment (p=0.018) and higher risk for short-term disease progression (p=0.036). Additionally, univariate Cox regression analysis strengthened both the inferior OS (HR: 2.375; p=0.022), and PFS (HR: 1.815; p=0.041) of MM patients with 3'U-tRFHisGTG loss. **Conclusions:** 3'U-tRFHisGTG loss in CD138+ cells of MM patients represent a novel molecular marker of unfavourable outcome, contributing to the improvement of personalized prognosis and patients' management.

P-413

Inflammatory markers characterize neutrophils and C1q+ TAMs in the day 100 bone marrow aspirate post ASCT of patients with early progression

Caleb Stein[1], Taxiarchis Kourelis[2], Charalampos Charalampous[2], Yuan Xiao Zhu[1],

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patients with Smoldering Multiple Myeloma (SMM), (ii) which populations may directly interact with the tumor, and (iii) which types of dysregulation may be true hallmarks of disease. **Methods:** Here, we present results from the largest single-cell RNA-sequencing cohort (n=398) of bone marrow (BM) CD138-negative (n=271) and peripheral blood mononuclear cell samples (n=127) from patients with monoclonal gammopathies [MGUS, n=51; SMM, n=226; asymptomatic Waldenstrom's Macroglobulinemia (AWM), n=28; Multiple Myeloma (MM), n=28; healthy donors (HD), n=61]. Libraries were prepared with the Chromium Single-cell 5' Gene Expression kit by 10X Genomics and sequenced at the Genomics Platform of the Broad Institute of MIT and Harvard (Cambridge, MA). **Results:** Overall, we profiled ~2.5M immune cells. Remarkably, despite their early stage, patients with MGUS presented extensive immune dysregulation compared to HD, suggesting that compositional changes may be established early on and that changes in gene expression and functionality may underlie progression. To identify subpopulations that are more likely to interact with tumor cells, we compared their abundance between matched BM CD138-positive and CD138-negative fractions in patients and HD. In patients, megakaryocytes were enriched in the CD138-positive fraction, an interaction previously shown to promote MM progression. Pro-B cells, pre-B cells, and memory B cells were enriched in the CD138-positive fraction of patients as well, suggesting that they could be involved in the clonal population or perhaps supporting its growth. Notably, granzyme K-expressing CD8+ T cells were significantly enriched in the CD138-positive fraction of patients, which is consistent with prior studies implicating this population in progression and response to therapy. To identify immune hallmarks of disease, we compared immune cell abundance and expression profiles between patients with SMM and patients with AWM, a different but related malignancy of the BM. We found that the significant increase in Th17 cells and Tregs we observed in patients with SMM is largely specific to myeloma, suggesting that these populations may be critical in sustaining MM cells. Furthermore, we observed myeloma-specific downregulation of the transcription factor CEBPD and its downstream targets, S100A8 and S100A9, in monocytes. **Conclusions:** In the largest to date single-cell RNA-sequencing study of immune cells from patients with monoclonal gammopathies, we have comprehensively mapped alterations in BM immune cell composition in patients with MGUS, identified subpopulations that are more likely to interact directly with tumor cells in the BM microenvironment, and described immune hallmarks of disease.

P-412

Loss of 3'U-tRFHisGTG in predicting poor survival and treatment outcome in multiple myeloma

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Introduction: Despite the notable progress that has been achieved in the realm of multiple myeloma (MM) treatment and monitoring, the persistence of elevated relapse rates and therapy resistance remain a substantial hindrance to the effective management of the disease, highlighting the urgent need for the elucidation of molecular indicators supporting tailored patient's management. In this context, tRNA-derived fragments (tRFs), and specifically 3'U-tRFs, represent a novel class of small non-coding RNAs (ncRNAs), derived from pre-mature tRNAs, gathering attention due to their vital roles in regulating gene expression and their potential clinical utility in cancer prognosis and risk stratification. Overall, the aim of the present study was to investigate the involvement of 3'U-tRFHisGTG in MM. **Methods:** Bone marrow aspiration (BMA) samples were collected from 136 MM, 15 smoldering MM (sMM) and 15 monoclonal gammopathy of undetermined significance (MGUS) patients at diagnosis. Mononuclear cells were extracted from BM aspirates using Ficoll-Paque, and CD138+ plasma cells were separated through magnetic cell sorting, using immunomagnetic beads coated with anti-CD138 monoclonal antibodies. Based on target prediction and Gene Ontology (GO) enrichment, 3'U-tRFHisGTG was further evaluated for the first time in CD138+ plasma cells from the total study population. Following, total RNA extraction, polyadenylation at 3'-end, and reverse transcription using an oligo(dT) adapter primer, 3'U-tRFHisGTG levels were estimated through in-house qPCR. Finally, overall survival (OS) and progression-free survival (PFS) were evaluated, while internal validation was accomplished by bootstrap Cox proportional regression analysis. **Results:** In silico analysis unveiled the implication of 3'U-tRFHisGTG in cancer associated processes including, protein modification processes (protein acetylation), and autophagosome assembly. Our findings demonstrated the downregulated 3'U-tRFHisGTG levels in MM compared to its precursor stages sMM/MGUS (p=0.036), while focusing on MM patients, 3'U-tRFHisGTG loss depicted the association with bone disease (p=0.049). Furthermore, survival analysis revealed that loss of 3'U-tRFHisGTG was associated with significantly poor overall survival following treatment (p=0.018) and higher risk for short-term disease progression (p=0.036). Additionally, univariate Cox regression analysis strengthened both the inferior OS (HR: 2.375; p=0.022), and PFS (HR: 1.815; p=0.041) of MM patients with 3'U-tRFHisGTG loss. **Conclusions:** 3'U-tRFHisGTG loss in CD138+ cells of MM patients represent a novel molecular marker of unfavourable outcome, contributing to the improvement of personalized prognosis and patients' management.

P-413

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Erin Meermeier[1], Diane Jelinek[1], Leif Bergsagel[1], Marta Chesi[1]
[1]Mayo Clinic in Arizona; [2]Mayo Clinic Rochester

Introduction: Autologous stem cell transplant (ASCT) remains standard of care for eligible patients with multiple myeloma (MM), but it is associated with variable outcomes that cannot be predicted by baseline risk factors. Here we investigate the composition and expression features of bone marrow aspirates collected from a cohort of patients treated with upfront ASCT and sufficiently long follow up at single cell resolution. **Methods:** To date, single cell RNA-Seq profiling (10X Genomics 5'v2 expression) has been performed on whole BM samples obtained 100 days following ASCT from 28 unique patients. Poor responders (PR; n=12) were defined as relapsing 2yr if not put on MT and >4yr if placed on MT (n=16). We compared these results with those obtained from whole BM or spleen samples collected from 67 Vk*MYC mice. Both sets of human and mice single cell data were processed with an additional reference-based clustering routine leveraging correlation with large, publicly available accession data from the ARCHS4 repository. **Results:** We have observed the expansion of tissue-specific C1q+ macrophages along with MM growth in untreated Vk*MYC BM (expressing C1qa/b/c and Fcgr4) and spleen (expressing C1qa/b/c, Apoe, and Selenop) suggesting that these C1q+ cells represent a tumor-associated macrophage (TAM) phenotype specific to MM. Similarly, in our post-ASCT human samples, we detected a small group of cells that overexpress C1QA/B/C, APOE, and SELENOP that are more highly represented in the PR. Globally, C1q+ TAMs in our Vk*MYC set are the highest expressers of Il18 suggesting a crucial pro-inflammatory function of these distinct cells. Neutrophils are highly involved in inflammatory response and demonstrate a gradient of maturation in Vk*MYC samples ranging from immature (expressing Camp and Ngp) to mature (expressing Il1b). Notably, some of the samples from GR were highly enriched for neutrophils that overexpressed markers of inhibition (PADI4, IRAK3, ANXA1) while those in the PR were up-regulated in pro-inflammatory markers such as FTH1. This result suggests that GR temper and control an inflammatory response directly post-ASCT while PR do not. **Conclusions:** This research suggests the involvement of an inflammatory microenvironment in disease progression post ASCT. In clinical practice, observing key modulations in the myeloid compartment following ASCT could serve as an early detection method for identifying patients likely to progress who could be candidates for clinical trials of anti-inflammatory therapy to delay MM progression.

P-414

Single-Cell profiling reveals aggressive tumor subcluster and compromised immune state in multiple myeloma

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[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China

Introduction: Despite advancements in managing multiple myeloma (MM) patients, a subset of individuals still undergoes rapid disease progression and early death (ED) within two years of diagnosis. To gain insights into the disease and identify treatment targets, we examined the molecular characteristics of malignant and non-malignant cells in the bone marrow of MM patients with ED. **Methods:** We used single-cell RNA (scRNA) sequencing to analyze bone marrow aspirates from four MM patients with ED, eight without ED (nED), and seven healthy donors. Additionally, we incorporated CHIP-seq data to investigate epigenetic modifications. We constructed a comprehensive differentiation trajectory from stem cells to plasma cells and identified mutation hotspots using whole-exome sequencing. Non-malignant cell variations within the myeloma microenvironment were explored using pan-cancer references. The scRNA findings were validated through in vitro and in vivo experiments. **Results:** We classified Ig light chain-restricted tumor cells into ten subclusters and found that subcluster 4 had a higher presence in ED patients. Other subclusters grouped with the classical MM cells phenotype (CD38+CD19-CD56+/-CD24-). Subcluster 4 displayed a plasmablast phenotype (CD38+CD19+CD56+CD24+) with increased proliferation and drug resistance. Chromosomal aberrations and mutation hotspots were more prevalent in this subcluster. The genes specific to subcluster 4 were enriched in H3K27ac-mediated epigenetic regulation. We constructed a gene score, with LILRB4 showing high specificity for subcluster 4, effectively identifying ED patients. Combining this gene score with clinical factors improved patient stratification. In vitro and in vivo experiments confirmed the enhanced properties of LILRB4+ cells. The evolution trajectory of CD8+ T cells was divided into cell fate 1 (exhausted) and cell fate 2 (activated). Exhausted T cells were more abundant in ED patients and showed metabolic inhibition, reduced cell cycle activity, and upregulated apoptosis pathways. Memory T cell differentiation was impaired in the ED group, with increased expression of immunosuppressive genes like PIM3. In vitro experiments demonstrated that inhibiting PIM promoted memory T cell differentiation. Cell-cell interaction analysis revealed a significant increase in MM cell-CD14+ monocyte interactions in the ED group, particularly through LILRB4-interacting molecules. Co-culture experiments revealed that LILRB4+ MM cells promoted the differentiation of CD14+ monocytes into myeloid-derived suppressor cells. **Conclusions:** Our study provides insights into aggressive tumor subclusters and compromised immune states in MM patients with ED. We identified a unique population of LILRB4+ tumor cells and developed a gene score to identify ED patients. We also confirmed T cell dysfunction and highlighted the role of LILRB4+ tumor cells in immune evasion. Targeting LILRB4 could be a promising therapeutic strategy for MM treatment.

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P-415

Profiling of patient bone marrow adipocytes in the myeloma microenvironment

Laura J. Trainor[1,2], Melissa D. Cantley[1,2], Cathal King[1,2], Natalya Plakhova[1], Mackenzie Skinner[1,2], Ryan Chai[3], Weng Hua Khoo[3], Peter Croucher[3], Kate Vandyke[1,2], Andrew Zannettino[1]

[1]University of Adelaide; [2]SAHMRI; [3]Garvan

Introduction: Bone marrow (BM) adipocytes (BMADs) make up 70% of the BM microenvironment and can promote multiple myeloma (MM) plasma cell proliferation and survival in vitro. The phenotypes of BMADs in MM and monoclonal gammopathy of undetermined significance (MGUS), and how BMADs support MM progression remain largely unknown. Here, we aimed to assess BMAD phenotype in differentiating and mature BMADs in BM samples from MGUS and MM patients and analyse their gene expression profile, to identify potential secreted factors which may play a role in supporting MMPC growth and survival. **Methods:** BMAD quantitation was conducted on CD138-stained trephines from age-matched controls (n=4), MGUS (n=9), and MM (n=14) patients via Osteomeasure and NDP.view2. Mesenchymal stromal cells (MSCs) isolated from control (n=7), MGUS (n=14), and MM (n=14) trephines were cultured in adipogenic media for 21 days, stained with Nile Red/DAPI and ImageJ used to quantitate BMAD number and lipid droplets/BMAD. For single cell RNA sequencing (scRNAseq) cells were enzymatically digested from 5 MM patient trephines (n=2 newly diagnosed, n=3 treated) and 1 control, viable GLYA- cells FACs sorted and scRNAseq conducted (10x Genomics Chromium V3.1). To identify novel microenvironmental factors that may interact with PCs, gene expression of secreted or cell surface ligands (ConnectomeDB2020) was assessed in sequenced cells, with cognate receptor expression in MM PCs confirmed in RNA sequencing data from 764 newly diagnosed MM patients (CoMMpass). Statistical analyses included Kruskal-Wallis, log-rank tests, and Pearson's correlation. **Results:** Histomorphometric analysis revealed MM patients with larger mean BMAD size (>2100um^2) had significantly poorer overall survival, compared with patients with smaller BMADs (median survival: 113.3 and 231.1 weeks; p=0.045, log-rank test). In vitro, there was two-fold reduction in BMAD number and 2.6-fold reduction in lipid droplets/BMAD in MM (p=0.0048), compared with MGUS. scRNAseq of 13683 BM cells, identified 81 mesenchymal lineage cells, characterised by CXCL12, FABP4, and SPP1 expression. 32% of the cluster were FABP4+ adipocyte-lineage cells, and uniquely expressed genes for 14 secreted or cell surface ligands, when compared with other MSC lineages. Furthermore, the receptor for 10/14 of these ligands were expressed by MMPCs in most of newly diagnosed MM patients, suggesting the potential for crosstalk between BMADs and MMPCs. **Conclusions:** Decreases in MM BMADs and lipid droplets demonstrated altered morphology and differentiation capacity in vitro, whilst histomorphometric analyses suggest association between BMAD phenotype and MM progression. For the first time, scRNAseq on MM trephines identified FABP4+ adipocyte-lineage cells express factors that directly interact with MMPCs. These findings help characterise BMADs as sources of MM-supportive factors, with further studies focussing on the identified factors and potential roles in MM progression.

P-416

Immunophenotypic profile defines cytogenetic stability and unveils distinct prognoses in patients with newly-diagnosed multiple myeloma (NDMM)

Wenqiang Yan[1], Lihui Shi[1], Jingyu Xu[1], Jian Cui[2], Yan Xu[1], Dehui Zou[1], Lugui Qiu[2], Gang An[2]

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Introduction: The prognostic significance of multiple immune antigens in patients with newly-diagnosed multiple myeloma (NDMM) has been well established. However, there is still a knowledge gap regarding the intrinsic relationship between immunophenotypes and cytogenetic stability, as well as the identification of specific immunophenotypes for precise risk stratification across different disease stages. **Methods:** To address these unresolved issues, we conducted a study involving 1389 NDMM patients enrolled in the National Longitudinal Cohort of Hematological Diseases in China (NCT04645199). **Results:** Our results revealed the correlation between antigen expression and cytogenetics is more prominent compared to cytopenia or organ dysfunction. Most immune antigens, except CD38, CD138, and CD81, exhibit significant associations with the incidence of at least one cytogenetic abnormality. In turn, CD38-low, CD138-low, CD27-neg, and CD28-pos expressions were associated with inferior survival outcomes (P< 0.05). Through multivariate analysis, we identified CD138-low/CD27-neg as a specific aggressive immunophenotypic profile with the highest predictive value for poor prognosis. This profile remained an independent prognostic factor on progression-free survival (HR, 1.51; P=0.003) and overall survival (HR, 1.80; P< 0.001) even in the context of cytogenetics. Importantly, CD138-low/CD27-neg profile at relapse was also associated with inferior survival after the first relapse (P< 0.001). The antigen expression profiles were not strictly similar from diagnosis to relapse, especially CD138-low/CD27-neg pattern notably increased following disease progression (19.1% to 29.1%; P=0.005). **Conclusions:** In summary, we systematically described the comprehensive immunophenotypic landscapes of NDMM patients in a large observational cohort. Diverse immune profiles are strongly associated with various cytogenetic abnormalities but weakly correlated with cytopenia or organ dysfunction. Importantly, specific immunophenotypes (CD138-low/CD27-neg) could independently predict a high risk of progression or death regardless of disease stages and aggressive statuses.

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P-417

SKY92 gene expression profiling and cytogenetics according to R2-ISS for multiple myeloma risk classification

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Introduction: SKY92 gene expression profiling (GEP) has been developed to identify high-risk (HR) multiple myeloma (MM). This study aimed to evaluate the combination of SKY92 and cytogenetics according to R2-ISS (del(17p), t(4;14), 1q CNA) for HR detection in newly diagnosed (ND) and relapsed/refractory (RR) MM. **Methods:** We performed a single-center prospective study. Cytogenetics were analyzed on purified CD138 positive cells by FISH. SKY92 risk status was determined with MMprofiler gene expression assay. Whole genome sequencing (WGS) was performed to elucidate the discrepancy between the both risk stratification systems SKY92 and FISH. **Results:** Overall, 258 patients were included (NDMM: n=109; RRMM: n=149). SKY92 classification was available for 216 (83.7%) patients. Samples of 26 (17.7%) patients, who showed significantly lower bone marrow infiltration than the remaining patients (median: 20% vs 50%, P=0.006), did not meet the SKY92 quality control criteria. HR SKY92 was significantly enriched in RRMM (57/121, 47.1%) compared to NDMM (17/95, 17.9%) (P< 0.001). In RRMM, HR SKY92 was significantly more frequent in patients with ≥4 prior lines of therapies (32/52, 61.5%) than those with < 4 therapy lines (25/65, 36.2%) (P=0.009). Moreover, HR SKY92 was more common in patients who received high-dose melphalan and autologous stem cell transplant (48/89, 53.9%) than the remaining patients (9/32, 28.1%) (P=0.01). RRMM with HR SKY92 showed significantly shorter progression free survival (PFS) (P< 0.001) and overall survival (OS) (P< 0.001) than standard-risk (SR). In NDMM, HR SKY92 also indicated a significantly inferior PFS (P< 0.001) in comparison to SR. We then combined SKY92 with FISH according to R2-ISS in 181 patients (NDMM: n=79; RRMM: n=102). We found a discrepancy between the both risk stratification systems, with 67 (37.0%) and 99 (54.7%) patients being defined as HR by SKY92 and FISH, respectively. Overall, 13 (16.4%) NDMM and 36 (35.3%) RRMM patients showed HR in both SKY92 and FISH ("double-HR"). Double-HR presented a negative prognostic factor for PFS in both NDMM (P< 0.001) and RRMM (P< 0.0001). Furthermore, "double-HR" patients showed the worst OS (P< 0.001) in RRMM. To elucidate the discrepancy between FISH and SKY92, we performed WGS in 16 patients who exhibited either only HR SKY92 (n=7) or only HR FISH (n=9). Interestingly, 1 patient with bi-allelic TP53 inactivation (del + mut) and 6 patients with 1q CNA were determined as SR by SKY92 but as HR by FISH. Moreover, 4 out of 7 patients with only HR SKY92 but SR FISH displayed 1q CNA, which was detected only by WGS, and del1p32 was found in 1 patients. Of note, we found CRBN mutation in 3 out of 7 patients with only HR SKY92 but SR FISH. The remaining 2 patients did not show any known HR genomic alterations. **Conclusions:** We provide the first prospective evidence that "double-HR" (SKY92 + FISH according to R2-ISS) indicates the highest-risk MM.

P-418

The metabolic profile of multiple myeloma

Jingyu Zhang[1], Gang An[2], Fangming Shi[1], Xingxing Jian[3], Xing Liu[1], Yanjuan He[4], Wei Jia[5], Lugui Qiu[1], Wen Zhou[6]

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Introduction: Our previous studies found that amino acids metabolism imbalance promotes multiple myeloma (MM) progression. We have revealed glycine was significantly increased in bone marrow (BM) microenvironment and blocking glycine utilization inhibits MM progression by disrupting glutathione balance. And excessive serine from the BM microenvironment impairs megakaryopoiesis and thrombopoiesis in MM. Moreover, with the kidney damage caused by the abnormal metabolism of amino acids, the excessive urea is accumulated and utilized by gut microbiota, and then results in nitrogen-recycling bacteria enrichment in MM. Our discoveries open new avenues for novel treatment strategies via intervention of amino acids intake in MM patients. However, the comprehensive metabolic profile and classification of MM is still lack. **Methods:** The BM and PB specimens were derived from health donors (nBM = 31; nPB = 31), newly diagnosed MM patients (nBM = 115; nPB = 115) and relapsed MM patients (nBM = 34; nPB = 34) with written consent from Xiangya Hospital, the Second Xiangya Hospital of CSU and the Blood Diseases Hospital of Chinese Academy of Medical Science & Peking Union Medical College. Plasma, sera and BM supernatants were extracted from these specimens and stored at −80 °C until analysis. Informed consent was obtained in accordance with the Declaration of Helsinki. **Results:** Identification of 6 metabolic subgroups in newly diagnosed MM based on PB metabolome. Based on the PB metabolome of MM patients, 6 metabolic subtypes were clustered (Type1, Type2, Type3, Type4, Type5, Type6), showing distinct metabolic profiles and clinical presentation. According to the metabolic characteristics, the subtypes were defined as amino acid & fatty acid (AA&FA) group, Carbohydrates (Carbs) group, Benzenoids (Ben) group, Carnitines & fatty acid (Carn & FA) group, Amino acid (AA) and short chain fatty acids (SCFA) group, respectively. Overall survival clinical characteristics differs in the 6 subgroups. To explore the difference

P-417

SKY92 gene expression profiling and cytogenetics according to R2-ISS for multiple myeloma risk classification

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Introduction: SKY92 gene expression profiling (GEP) has been developed to identify high-risk (HR) multiple myeloma (MM). This study aimed to evaluate the combination of SKY92 and cytogenetics according to R2-ISS (del(17p), t(4;14), 1q CNA) for HR detection in newly diagnosed (ND) and relapsed/refractory (RR) MM. **Methods:** We performed a single-center prospective study. Cytogenetics were analyzed on purified CD138 positive cells by FISH. SKY92 risk status was determined with MMprofiler gene expression assay. Whole genome sequencing (WGS) was performed to elucidate the discrepancy between the both risk stratification systems SKY92 and FISH. **Results:** Overall, 258 patients were included (NDMM: n=109; RRMM: n=149). SKY92 classification was available for 216 (83.7%) patients. Samples of 26 (17.7%) patients, who showed significantly lower bone marrow infiltration than the remaining patients (median: 20% vs 50%, P=0.006), did not meet the SKY92 quality control criteria. HR SKY92 was significantly enriched in RRMM (57/121, 47.1%) compared to NDMM (17/95, 17.9%) (P< 0.001). In RRMM, HR SKY92 was significantly more frequent in patients with ≥4 prior lines of therapies (32/52, 61.5%) than those with < 4 therapy lines (25/65, 36.2%) (P=0.009). Moreover, HR SKY92 was more common in patients who received high-dose melphalan and autologous stem cell transplant (48/89, 53.9%) than the remaining patients (9/32, 28.1%) (P=0.01). RRMM with HR SKY92 showed significantly shorter progression free survival (PFS) (P< 0.001) and overall survival (OS) (P< 0.001) than standard-risk (SR). In NDMM, HR SKY92 also indicated a significantly inferior PFS (P< 0.001) in comparison to SR. We then combined SKY92 with FISH according to R2-ISS in 181 patients (NDMM: n=79; RRMM: n=102). We found a discrepancy between the both risk stratification systems, with 67 (37.0%) and 99 (54.7%) patients being defined as HR by SKY92 and FISH, respectively. Overall, 13 (16.4%) NDMM and 36 (35.3%) RRMM patients showed HR in both SKY92 and FISH ("double-HR"). Double-HR presented a negative prognostic factor for PFS in both NDMM (P< 0.001) and RRMM (P< 0.0001). Furthermore, "double-HR" patients showed the worst OS (P< 0.001) in RRMM. To elucidate the discrepancy between FISH and SKY92, we performed WGS in 16 patients who exhibited either only HR SKY92 (n=7) or only HR FISH (n=9). Interestingly, 1 patient with bi-allelic TP53 inactivation (del + mut) and 6 patients with 1q CNA were determined as SR by SKY92 but as HR by FISH. Moreover, 4 out of 7 patients with only HR SKY92 but SR FISH displayed 1q CNA, which was detected only by WGS, and del1p32 was found in 1 patients. Of note, we found CRBN mutation in 3 out of 7 patients with only HR SKY92 but SR FISH. The remaining 2 patients did not show any known HR genomic alterations. **Conclusions:** We provide the first prospective evidence that "double-HR" (SKY92 + FISH according to R2-ISS) indicates the highest-risk MM.

P-418

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between the 6 subgroups, overall survival analysis reveals that MM patients in Carn & FA group and SCFA group presented better prognosis due to rich unsaturated fatty acids. Meanwhile, MM patients in Ben group and AA group presented poor prognosis. In addition, the plasma cell ratio in BM, secretion of immunoglobulin and β-microglobulin in serum were decreased in the Carn & FA group and SCFA group, meanwhile, the hemoglobin contents in serum were increased in the group. In contrast, MM patients in the AA group presented the malignant characteristics, which suggests amino acids rather than fatty acids correlates to malignant progression of MM. **Conclusions:** This study highlights, for the first time, the metabolic heterogeneity in MM patients and preliminary analysis on metabolic subtypes, which would play an active role in improving the current MM-stratification systems, and suggest that blocking amino acids may be an effective therapeutic intervention strategy.

P-419

Demographics, clinical features and treatment outcomes of waldenstrom macroglobulinemia from a tertiary care cancer centre in India

Bhausaheb Bagal[1], Lingaraj Nayak[1], Hasmukh Jain[1], Saswata Saha[2], Alok Shetty[1], Prashant Tembhare[3], Nikhil Patkar[2], Dhanlaxmi Shetty[2], Manju Sengar[1]

[1]Department of Medical Oncology, Tata Memorial Centre; [2]Tata Memorial Hospital; [3]Department of Hemato-pathology, ACTREC, Tata Memorial Centre

Introduction: Waldenstrom macroglobulinemia (WM) is a rare lymphoproliferative disorder that usually follows an indolent course. There is scarcity of data from Indian patients and available data suggest an early age of presentation, diagnosis with heavy disease burden. **Methods:** All consecutive patients diagnosed with WM between January 2013 and December 2022 were included in this analysis. The progression free survival (PFS) was calculated from date of treatment to disease progression or death and overall survival (OS) was defined as the duration from the diagnosis of WM to the date of death or last follow-up. **Results:** Seventy two patients were enrolled in this analysis and 57 patients were male (79 %) with a median age of 60 years (range 28-79 years). Most common presenting symptom was anaemia in 53 (74%), 4 had hemolytic anaemia, 13 out of 26 patients who had iron studies available showed concomitant iron deficiency anaemia and 4 of 44 patients tested had either vit B12 or folic acid deficiency. Symptoms of hyperviscosity were recorded in 21 (29%) patients out of which 5 patients underwent plasmapheresis. Symptom duration ranged from less than 1 month to 18 months with a median time of 4 months before diagnosis. The median haemoglobin at presentation was 7.3 gm/dl (range 3.9 -13.6) and median M band concentration was 3 gm/dl (range 0.1-10.5). Lymphadenopathy was recorded in 21 (27%) patients while splenomegaly was present in 23 (32%) patients. The International Prognostic Scoring System for WM (IPSSWM) at diagnosis was available for 57 patients with 29 (40%) in intermediate risk group and 27 (37.5%) in high risk group while only one patient in low risk group. Thirty seven patients had undergone MYD88 testing, out of which 31 (83%) patients were tested positive for MYD88 L265P mutation. Bendamustin-Rituximab was the most commonly used regimen followed by Bortezomib-Dexamethasome-Rituxima (BDR) in 33 (45%) and 22 (30%) respectively. Median lines of therapy received was one range (range 1-4) with second-line therapies administered to 15 (21%) patients while third or more lines were administered only in 4 (5%) patients. Over a median follow up period of 62 months, 28 patients have progressed with a median PFS of 5.4 months and 2 year and 5 years PFS of 80 and 62% respectively. Twenty patients have died with an estimated median OS of 12 years and 2 years and 5 year OS of 87 % and 70 % respectively. None of the variables tested including IPSS-WM scores, therapy received and MYD88 mutation status were significantly associated with PFS and OS. **Conclusions:** Despite the younger age of presentation most patients presented late with symptoms and intermediate or high risk IPSS-WM scores. Anaemia is the most common presentation with nutritional deficiencies/defective iron metabolism contributing in a significant number of patients. BR and BDR are two most commonly used regimens that result in comparable outcomes.

P-420

Unusual presentations of amyloidosis: a multicase analysis highlighting diverse clinical manifestations and diagnostic challenges

Ashwathy Balachandran Pillai[1], Melody Becnel[1]

[1]University of Texas MD Anderson Cancer Care Center

Introduction: Amyloidosis is a rare disorder characterized by extracellular deposition of abnormal protein fibrils in various organs. Light chain amyloidosis (AL) can be primary or secondary to lymphoproliferative disorders like multiple myeloma. We aim to provide detailed insights into the diverse clinical presentations and diagnostic challenges encountered in patients with AL. **Methods:** We conducted a retrospective analysis of four cases of AL, focusing on their unique clinical features, diagnostic evaluations, and treatment approaches. **Results:** 1: 54 yo F with recent COVID-19, presented with weakness, muscle stiffness, dyspnea, anemia& hypercalcemia. Imaging revealed lytic lesions, later diagnostics confirmed IgD kappa multiple myeloma. She developed dysphagia, dysphonia, cough, and dysphonia. Evaluation confirmed secondary AL with nerve, vocal cord, and muscle involvement. Treated with daratumumab, carfilzomib, lenalidomide & dexamethasone, followed ASCT using melphalan. Restaging assessments showed a significant reduction in osseous lesions and hematologic complete remission. Speech pathology evaluation and treatment of MM improved her symptoms noted above. 2: 48 yo F presented with intermittent vocal dysphonia felt to be due to vocal cord cyst. Excisional biopsy noted low-grade B-cell lymphoma with AL deposition. PET-CT revealed laryngeal uptake due to lymphoma. CT noted an enhancing ulcerated lesion on the right false cord. No evidence of systemic amyloid. No other treatment in the absence of any other lymphoid tissue involvement or symptoms. No evidence of recurrence or systemic AL. 3: 59 yo male presented with dysphonia following a respiratory infection that failed to improve despite steroids and H2 blockers. Laryngeal videostroboscopy noted an irregular and vascular lesion of vocal

between the 6 subgroups, overall survival analysis reveals that MM patients in Carn & FA group and SCFA group presented better prognosis due to rich unsaturated fatty acids. Meanwhile, MM patients in Ben group and AA group presented poor prognosis. In addition, the plasma cell ratio in BM, secretion of immunoglobulin and β-microglobulin in serum were decreased in the Carn & FA group and SCFA group, meanwhile, the hemoglobin contents in serum were increased in the group. In contrast, MM patients in the AA group presented the malignant characteristics, which suggests amino acids rather than fatty acids correlates to malignant progression of MM. **Conclusions:** This study highlights, for the first time, the metabolic heterogeneity in MM patients and preliminary analysis on metabolic subtypes, which would play an active role in improving the current MM-stratification systems, and suggest that blocking amino acids may be an effective therapeutic intervention strategy.

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fold submucosal, involving the posterior glottis and subglottis. He underwent direct micro laryngoscopy with CO2 laser excision of the lesions. Excisional biopsy confirmed AL. Workup negative for systemic involvement. He underwent focal radiation treatment. He is currently doing well with minimal change in voice quality and no evidence of recurrence. 4: A 59 yo F with chronic cough found to have a lesion on the posterior pharyngeal wall, which enlarged post-COVID infection. Initially felt to be benign and observed. However, the lesion later enlarged, and new nasopharyngeal and arytenoid lesions developed. Biopsy confirmed AL. She underwent transoral robotic surgery (TORS) resection of the lesions. No evidence of systemic AL or MM **Conclusions:** This multicase analysis highlights the diverse clinical presentations of AL as primary and secondary presentations. These cases underscore the diagnostic challenges faced in identifying amyloidosis and the importance of multidisciplinary collaboration in accurate diagnosis and appropriate management. Timely recognition and comprehensive evaluation are crucial for ruling out systemic involvement and ensuring optimal patient outcomes.

P-421

Reference interval of free light chain ratio for patients in chronic hemodialysis

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Introduction: In patients with chronic kidney disease (CKD), the concentration of serum free light chains (FLC) increases proportionally to the degree of reduction in glomerular filtration rate (GFR). The currently used reference range of the FLC ratio (FLCr) Kappa/Lambda (K/L) in patients with CKD is between 0.37 and 3.1. Nevertheless, the normal range of FLCr in patients in hemodialysis (HD) is unclear. Recently, Long et al reported new FLCr ranges according to CKD stage, based on estimated GFR. However, this study considered only a few patients on HD. **Methods:** This is an observational and analytical cohort study. Patients on HD from a single HD center were included. They had more than 3 months of permanence on conventional HD, 3 times a week, with a high-flux membrane (Helixone®). K and L FLC determinations were performed using the Freelite® assay according to the Laboratory's instructions (Binding Site, Birmingham, UK). We determined K and L values, and the K/L ratio. These results were correlated with age and residual kidney function (RKF), defined as residual diuresis ≥250mL/day. 95% reference intervals values were calculated according to the recommendations of The Clinical and Laboratory Standards Institute (CLSI EP28-A3c). Atypical data (outliers) were evaluated with Tukey's test, and not removed from the analysis. Normality was evaluated with the D'agostino Pearson test. For monoclonal gammopathy (MG) detection, we performed capillary sPEP and FLC to all patients. In patients with monoclonal spike, hypogammaglobulinemia or altered FLCr, immunosubtraction (Sebia) was also performed. Analysis was made with Software Medcalc v20.104 and SPSS. The protocol was approved by the local Institutional Review Board. **Results:** A total of 138 patients were studied, since 5 patients with MG incidentally detected were excluded (2 MM, 3 MGUS). K showed a non-parametric distribution, with a mean of 162.24 mg/L (64.46 - 281.76 mg/L). L also showed a non-parametric distribution, with a mean of 149.87mg/L (47.15 - 312.58 mg/L). The reference range of FLCr showed a parametric distribution of 0.54 to 1.75. Both K and L increases with age until the 9th decade when they tend to decrease. Twenty-four percent of the patients still presented RKF. The results in both groups (with vs without RKF, respectively) were for K 128.69 +/- 51.4 mg/L vs 174.48 +/- 52.19 mg/L (p< 0.01); For Lambda 111.30 +/- 60.11 mg/L vs 163.82 +/- 58.32mg/L (p< 0.01). Regarding the K/L ratio, in patients with RKF was 1.24 +/- 0.32, while in patients without RKF was 1.12 +/- 0.30 (p< 0.04). **Conclusions:** To our knowledge, this is the largest study that attempts to define the reference interval of FLCr in stable patients on chronic HD. The K/L ratio in this population was 0.54 - 1.75, closer to that of patients without CKD. We hypothesize that this is due to the clearance of middle molecules by the high-flux membranes. The ratio and FLC levels are influenced by the RKF.

P-422

Impact of early response and CXCR4 mutation status on progression-free survival with ibrutinib-based therapy in Waldenström macroglobulinemia: a post hoc analysis of the iNNOVATE trial

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[1]Dana-Farber Cancer Institute; [2]Massachusetts General Hospital; [3]Janssen Scientific Affairs, LLC; [4]Pharmacyclics LLC

Introduction: Ibrutinib is a Bruton tyrosine kinase inhibitor approved for adults with Waldenström macroglobulinemia (WM). In iNNOVATE (NCT02165397), a randomized, double-blind, phase 3 study, ibrutinib plus rituximab (I+R) was associated with greater progression-free survival (PFS) benefits compared with rituximab plus placebo (Buske C et al. J Clin Oncol. 2021). In patients with WM, achieving a partial response (PR) or better at 6 months with single-agent ibrutinib was prognostic of better PFS (Castillo JJ et al. Br J Haematol. 2021), and CXCR4 mutations were prognostic of inferior PFS (Castillo JJ et al. Blood Adv. 2022). This post hoc analysis of iNNOVATE assessed whether achievement of PR or very good PR (VGPR) by month 6 or 12 of I+R treatment was associated with a higher PFS rate. The role of CXCR4 mutation at baseline in predicting PFS with I+R was also assessed. **Methods:** We used landmark analysis to assess the probability of achieving PFS at ≤42 months in patients treated with I+R according to achievement of PR or VGPR at 6 (n=68) or 12 (n=64) months and according to CXCR4 mutation status at baseline (n=69). Hazard ratios were estimated using an unstratified Cox regression model with the response at 6 or 12 months or CXCR4 mutation status as covariates. P values were calculated using an unstratified log-rank test. **Results:** Patients who achieved PR or better at 6 months

fold submucosal, involving the posterior glottis and subglottis. He underwent direct micro laryngoscopy with CO2 laser excision of the lesions. Excisional biopsy confirmed AL. Workup negative for systemic involvement. He underwent focal radiation treatment. He is currently doing well with minimal change in voice quality and no evidence of recurrence. 4: A 59 yo F with chronic cough found to have a lesion on the posterior pharyngeal wall, which enlarged post-COVID infection. Initially felt to be benign and observed. However, the lesion later enlarged, and new nasopharyngeal and arytenoid lesions developed. Biopsy confirmed AL. She underwent transoral robotic surgery (TORS) resection of the lesions. No evidence of systemic AL or MM **Conclusions:** This multicase analysis highlights the diverse clinical presentations of AL as primary and secondary presentations. These cases underscore the diagnostic challenges faced in identifying amyloidosis and the importance of multidisciplinary collaboration in accurate diagnosis and appropriate management. Timely recognition and comprehensive evaluation are crucial for ruling out systemic involvement and ensuring optimal patient outcomes.

P-421

Reference interval of free light chain ratio for patients in chronic hemodialysis

Pablo Bustamante[1], Ricardo Valjalo[1], Alexis Bondi[1], Marco Alvarez[1], Ramón Perez[1], Viviana Balboa[1], Camila Peña[1]

[1]Hospital del Salvador, Santiago de Chile

Introduction: In patients with chronic kidney disease (CKD), the concentration of serum free light chains (FLC) increases proportionally to the degree of reduction in glomerular filtration rate (GFR). The currently used reference range of the FLC ratio (FLCr) Kappa/Lambda (K/L) in patients with CKD is between 0.37 and 3.1. Nevertheless, the normal range of FLCr in patients in hemodialysis (HD) is unclear. Recently, Long et al reported new FLCr ranges according to CKD stage, based on estimated GFR. However, this study considered only a few patients on HD. **Methods:** This is an observational and analytical cohort study. Patients on HD from a single HD center were included. They had more than 3 months of permanence on conventional HD, 3 times a week, with a high-flux membrane (Helixone®). K and L FLC determinations were performed using the Freelite® assay according to the Laboratory's instructions (Binding Site, Birmingham, UK). We determined K and L values, and the K/L ratio. These results were correlated with age and residual kidney function (RKF), defined as residual diuresis ≥250mL/day. 95% reference intervals values were calculated according to the recommendations of The Clinical and Laboratory Standards Institute (CLSI EP28-A3c). Atypical data (outliers) were evaluated with Tukey's test, and not removed from the analysis. Normality was evaluated with the D'agostino Pearson test. For monoclonal gammopathy (MG) detection, we performed capillary sPEP and FLC to all patients. In patients with monoclonal spike, hypogammaglobulinemia or altered FLCr, immunosubtraction (Sebia) was also performed. Analysis was made with Software Medcalc v20.104 and SPSS. The protocol was approved by the local Institutional Review Board. **Results:** A total of 138 patients were studied, since 5 patients with MG incidentally detected were excluded (2 MM, 3 MGUS). K showed a non-parametric distribution, with a mean of 162.24 mg/L (64.46 - 281.76 mg/L). L also showed a non-parametric distribution, with a mean of 149.87mg/L (47.15 - 312.58 mg/L). The reference range of FLCr showed a parametric distribution of 0.54 to 1.75. Both K and L increases with age until the 9th decade when they tend to decrease. Twenty-four percent of the patients still presented RKF. The results in both groups (with vs without RKF, respectively) were for K 128.69 +/- 51.4 mg/L vs 174.48 +/- 52.19 mg/L (p< 0.01); For Lambda 111.30 +/- 60.11 mg/L vs 163.82 +/- 58.32mg/L (p< 0.01). Regarding the K/L ratio, in patients with RKF was 1.24 +/- 0.32, while in patients without RKF was 1.12 +/- 0.30 (p< 0.04). **Conclusions:** To our knowledge, this is the largest study that attempts to define the reference interval of FLCr in stable patients on chronic HD. The K/L ratio in this population was 0.54 - 1.75, closer to that of patients without CKD. We hypothesize that this is due to the clearance of middle molecules by the high-flux membranes. The ratio and FLC levels are influenced by the RKF.

P-422

Impact of early response and CXCR4 mutation status on progression-free survival with ibrutinib-based therapy in Waldenström macroglobulinemia: a post hoc analysis of the iNNOVATE trial

Jorge Castillo[1], Shayna Sarosiek[1], Andrew Branagan[2], Alex Bokun[3], Hillary Peltier[4], Vincent Girardi[4], Michelle Pacia[4], Steven Treon[1]

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(n=39) had a higher PFS rate at 42 months than patients who did not (n=29) (78% [95% CI 60-88%] vs 68% [95% CI 48-82%]), but the difference over the entire study period was not significant (P=0.41). The difference was significant over the study period between patients who did (n=49) and did not achieve PR (n=15) at 12 months (P=0.027), with 42-month PFS rates of 80% (95% CI 63-90%) and 60% (95% CI 32-80%), respectively. For patients who achieved VGPR or better at 6 months (n=9) versus those who did not (n=59), the 42-month PFS rates were 86% (95% CI 33-98%) versus 72% (95% CI 58-82%), with overall P=0.19. The corresponding values for patients with (n=13) and without VGPR (n=51) at 12 months were 82% (95% CI 45-95%) and 74% (95% CI 57-85%); overall P=0.36. For patients with CXCR4 mutation at baseline (n=26) versus those without mutation (n=43), the PFS rates at 42 months were 63% (95% CI 40-79%) versus 85% (95% CI 70-93%), respectively (overall P=0.39). **Conclusions:** Patients treated with I+R maintained durable remission irrespective of CXCR4 mutational status or attainment of PR or VGPR at 6 or 12 months. A trend towards greater PFS benefits of I+R at 42 months was seen in patients who achieved PR or VGPR at months 6 or 12 and those without CXCR4 mutations. The findings are consistent with single-agent ibrutinib data (Castillo JJ et al. Br J Haematol. 2021), which showed a greater PFS rate in patients who achieved PR or better at 6 months and those who did not have CXCR4 mutations. The analysis is limited by a small sample size. The iNNOVATE study was funded by Pharmacyclics, LLC, an AbbVie company.

P-423

Partial response or better at 6 months is not a prognostic indicator of progression-free survival in Waldenström macroglobulinemia treated with zanubrutinib: a post hoc analysis of the ASPEN study

Jorge Castillo[1], Alessandra Tedeschi[2], Constantine Tam[3,4], Christian Buske[5], Roger Owen[6], Veronique Leblond[7], Stephen Opat[4], Andrew Branagan[8], Shayna Sarosiek[1], Gottfried von Keudell[9], Steven Treon[1], Heather Allewelt[10], Wai Chan[10], Jingjing Schneider[10], Meletios Dimopoulos[11]

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Introduction: Attaining partial response (PR) or better at 6 months was associated with superior progression-free survival (PFS) in patients (pts) with Waldenström macroglobulinemia (WM) treated with ibrutinib (IBR) monotherapy (Castillo et al. Br J Haematol. 2021); it could be a surrogate for PFS in prospective clinical trials evaluating Bruton tyrosine kinase inhibitors (BTKis) in pts with WM. This post hoc analysis of the ASPEN study aimed to evaluate the PFS prognostic value of attaining PR or better at 6 months in pts with WM treated with zanubrutinib (ZANU), a second-generation BTKi with more selectivity and sustained BTKi occupancy than IBR. The PFS prognostic value of very good partial response (VGPR) or better at 12 months was also evaluated. **Methods:** The methodology for the ASPEN study has been described previously (Tam et al. Blood. 2020). This post hoc analysis evaluated the attainment of PR or better at 6 months and VGPR at 12 months from therapy initiation. Responses were assessed based on criteria from the 11th International Workshop on Waldenstrom's macroglobulinemia (Treon et al. Semin Hematol. 2023). PFS was estimated starting at the 6-month mark in pts with response assessment at 6 months and the 12-month mark in pts with response assessment at 12 months. Since 2 analyses were done using the same dataset, P values <.025 were considered statistically significant. **Results:** In the IBR arm, response data at 6 months were available for 86 pts, of whom 57 (66%) attained PR or better. PR or better at 6 months was associated with favorable PFS in pts with WM treated with IBR (hazard ratio [HR], 0.47; 95% CI, 0.21-1.06; P=.0697). In the ZANU arm, response data at 6 months were available for 93 pts, of whom 67 (72%) attained PR or better. The PFS in pts with WM treated with ZANU was similar between those who did and did not attain PR or better at 6 months (HR, 1.53; 95% CI, 0.43-5.41; P=.5113). The 3-year landmark PFS event-free rates from the 6-month mark with ZANU (attained PR at 6 months, 81%; did not attain PR at 6 months, 87%) were consistently similar to those in IBR-treated pts with PR or better at 6 months (80%). In contrast, the event-free rate was lower (65%) in pts treated with IBR who did not attain PR or better at 6 months. In the IBR arm, response data at 12 months were available for 81 pts, of whom 11 (14%) attained VGPR or better. In the ZANU arm, response data at 12 months were available for 85 pts, of whom 22 (26%) attained VGPR or better. Pts treated with IBR (HR, 0.77; 95% CI, 0.18-3.32; P=.7225) or ZANU (HR, 0.86; 95% CI, 0.24-3.14; P=.8248) had similar PFS rates regardless of whether they attained VGPR or better at 12 months. **Conclusions:** Results of the ASPEN trial provide additional support for PR or better at 6 months as a positive prognostic factor for PFS in pts with WM treated with IBR. PFS in ZANU-treated pts, whether or not they attained PR or better at 6 months, was similar to PFS in IBR-treated pts with PR or better at 6 months.

P-424

Partial response or better at 6 months is not shown to be a prognostic indicator of progression-free survival in Waldenström macroglobulinemia treated with acalabrutinib: a post hoc analysis

Jorge Castillo[1], Shayna Sarosiek[1], Andrew Branagan[2], Gottfried von Keudell[3], Bob Shaw[4], Steven Treon[1]

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Introduction: Attaining partial response (PR) or better at 6 months was associated with superior progression-free survival (PFS) in patients (pts) with Waldenström macroglobulinemia (WM) treated with ibrutinib (IBR) monotherapy (Castillo et al. Br J Haematol. 2021); it could be a surrogate for PFS in prospective clinical trials evaluating Bruton tyrosine kinase inhibitors (BTKis) in pts with WM. This post hoc analysis of the ASPEN study aimed to evaluate the PFS prognostic value of attaining PR or better at 6 months in pts with WM treated with zanubrutinib (ZANU), a second-generation BTKi with more selectivity and sustained BTKi occupancy than IBR. The PFS prognostic value of very good partial response (VGPR) or better at 12 months was also evaluated. **Methods:** The methodology for the ASPEN study has been described previously (Tam et al. Blood. 2020). This post hoc analysis evaluated the attainment of PR or better at 6 months and VGPR at 12 months from therapy initiation. Responses were assessed based on criteria from the 11th International Workshop on Waldenstrom's macroglobulinemia (Treon et al. Semin Hematol. 2023). PFS was estimated starting at the 6-month mark in pts with response assessment at 6 months and the 12-month mark in pts with response assessment at 12 months. Since 2 analyses were done using the same dataset, P values <.025 were considered statistically significant. **Results:** In the IBR arm, response data at 6 months were available for 86 pts, of whom 57 (66%) attained PR or better. PR or better at 6 months was associated with favorable PFS in pts with WM treated with IBR (hazard ratio [HR], 0.47; 95% CI, 0.21-1.06; P=.0697). In the ZANU arm, response data at 6 months were available for 93 pts, of whom 67 (72%) attained PR or better. The PFS in pts with WM treated with ZANU was similar between those who did and did not attain PR or better at 6 months (HR, 1.53; 95% CI, 0.43-5.41; P=.5113). The 3-year landmark PFS event-free rates from the 6-month mark with ZANU (attained PR at 6 months, 81%; did not attain PR at 6 months, 87%) were consistently similar to those in IBR-treated pts with PR or better at 6 months (80%). In contrast, the event-free rate was lower (65%) in pts treated with IBR who did not attain PR or better at 6 months. In the IBR arm, response data at 12 months were available for 81 pts, of whom 11 (14%) attained VGPR or better. In the ZANU arm, response data at 12 months were available for 85 pts, of whom 22 (26%) attained VGPR or better. Pts treated with IBR (HR, 0.77; 95% CI, 0.18-3.32; P=.7225) or ZANU (HR, 0.86; 95% CI, 0.24-3.14; P=.8248) had similar PFS rates regardless of whether they attained VGPR or better at 12 months. **Conclusions:** Results of the ASPEN trial provide additional support for PR or better at 6 months as a positive prognostic factor for PFS in pts with WM treated with IBR. PFS in ZANU-treated pts, whether or not they attained PR or better at 6 months, was similar to PFS in IBR-treated pts with PR or better at 6 months.

P-424

Partial response or better at 6 months is not shown to be a prognostic indicator of progression-free survival in Waldenström macroglobulinemia treated with acalabrutinib: a post hoc analysis

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[1]Dana-Farber Cancer Institute; [2]Massachusetts General Hospital; [3]Beth Israel Deaconess Medical Center; [4]AstraZeneca

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J Haematol 2020); it could be a surrogate for PFS in prospective clinical trials evaluating Bruton tyrosine kinase inhibitors in WM. This post hoc analysis assessed the PFS prognostic value of attaining PR or better at 6 and 12 months in participants with WM treated with acalabrutinib, a second-generation BTK inhibitor. **Methods:** The methodology for the phase II study of acalabrutinib in WM has been described previously (Owen et al. Lancet Haematol 2020). This post hoc analysis evaluated the attainment of PR or better at 6 months and 12 months from therapy initiation. Responses were assessed based on criteria from the 11th International Workshop for WM (Treon et al. Semin Hematol 2023). PFS was estimated starting at the 6-month mark for participants with response assessment at 6 months and the 12-month mark for participants with response assessment at 12 months. Participants who died, progressed, or were not assessed at the landmarks were excluded from the analysis. Since two analyses were performed in the same data set, P-values < 0.025 were considered statistically significant. **Results:** At 6 months, response data were available from 94 participants, of whom 60 (64%) attained a PR or better on acalabrutinib. The median PFS was 61.9 months (95% CI 55.7-not reached) in the group that attained a PR or better versus not reached (95% CI 35.6 months-not reached) in the group that did not. The hazard ratio (HR) was 0.70 (95% CI 0.35-1.40; p=0.31; Figure, left). At 12 months, response data were available from 87 participants, 59 (68%) attained a PR or better. The median PFS was not reached (95% CI 50.1-not reached) in the group that attained a PR or better versus not reached (95% CI 30.1 months-not reached) in the group that did not. The hazard ratio (HR) was 0.61 (95% CI 0.29-1.30; p=0.20; Figure, right). **Conclusions:** This post hoc analysis supports attaining PR or better at 6 months as a numerically, though not a statistically, positive prognostic factor for PFS in patients with WM treated with acalabrutinib. This analysis, however, is underpowered, given the sample size and immature follow-up.

P-425

Cardiac AL amyloidosis experienced in the last decade from a single center

Simge Erdem[1], Metban Guzel Mastanzade[1], Pelin Karaca Ozer[2], Okan Cetin[3], Ali Cem Hacialioglu[3], Mehmet Aydogan[2], Gulcin Yegen[4], Sengul Beyaz[2], Sevgi Kalayoglu-Besisik[1]

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Keywords: AL amyloidosis, cardiac amyloidosis.

P-426

Thrombotic and bleeding complications in patients with AL amyloidosis

Despina Fotiou[1], Sotiria Spiliopoulou[1], Foteini Theodorakakou[1], Maria Gavriatopoulou[1], Magdalini Migkou[1], Nikolaos Kanellias[2], Evangelos Eleutherakis-Papaiakovou[1], Panagiotis Malandrakis[1], Vassiliki Spiliopoulou[1], Ioanna Dialoupi[1], Ioannis Ntanasis-Stathopoulos[1], Evangelos Terpos[1], Meletios Dimopoulos[1], Efstathios Kastritis[1]

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the causes of deregulated coagulation. **Methods:** We analyzed the records of 450 patients treated in a single center to identify clinically relevant episodes of venous (VTE), arterial embolic events (AEE) and bleeding events. **Results:** Median age was 65 years (39-95) and 54% were male. The median follow-up was 55.3 months (95% CI 49.3-63.0). In 26 (5.8%) patients at least one VTE was recorded; deep vein thrombosis in 2.3%, pulmonary embolism in 2.4%, other in 1.1%. Eighteen patients were on anti-clonal treatment at the time of the event; 11 were on IMiDs-agent based therapy. Among patients with VTE, 36% were on antiplatelets and 52% on antithrombotic prophylaxis. AEE was reported in 22 (5%) of patients; stroke 2.9%, acute myocardial infarction 1.6%, other in 0.5%. Median time from diagnosis to VTE was 9.5 months (0.1 – 107 months) and to AEE 14 months (0.62-114 months). Lower albumin levels (p=0.040), lower eGFR (p=0.010), extensive bone marrow infiltration (0.010), soft tissue involvement (p=0.029), IMiD-based therapy (p=0.001) and history of prior thrombosis (≤0.001) were associated with VTE. A prior VTE history remained the only prognostic variable in the multivariate model (HR 9.3, p=0.001, 95% CI 2.36-36.6). Coronary arterial disease (p=0.045), prior AEE (p=0.041), higher 24hour urine protein (p=0.008) and higher platelet count at diagnosis (p=0.020) were associated with AEE risk. Cardiac involvement and Mayo stage were not risk factors for thrombotic events. Significant bleeding events were reported in 41 patients (9%) and were the cause of death in 8 (mortality 19%); CNS in 1.3%, GI in 4.6%, other in 3.1%. Median time from diagnosis to bleeding events was 1.7 months (0.1 to 166 months). Bleeding risk was higher in patients on antiplatelets (15% vs 7.4%, p=0.05) but not on antithrombotic therapy. Higher serum creatinine (p=0.040) and higher baseline vWFAg (p=0.001, n=112) were linked to bleeding. Using competing risk analysis (death due to any cause as competing event), the cumulative probability of thrombosis and bleeding at 6 months was 4.1% and 4.6% vs 14.5% for death, at 1 year 6% and 5.6% vs 23% for death, at 2 years 7% and 6.8% vs 29% for death, and at 5 years 10.8%, 9.8% and 41% respectively. **Conclusions:** Hemostatic complications associated with AL amyloidosis are common. Increased thrombotic risk and hemorrhagic diathesis or both, increase morbidity and mortality and make optimal management highly complex. Most events occur early but a constant risk remains present throughout the disease course. To optimize anticoagulation clinical risk factors need to be coupled to clotting parameter abnormalities in future studies.

P-427

Smoldering multiple myeloma associated with a acquired von Willebrand syndrome, successfully treated by daratumumab, lenalidomide and dexamethasone

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Introduction: Acquired von Willebrand syndrome (AvWS) is a rare entity with approximately 700 cases described in the literature, probably underestimated due to a wide range of clinical features. The syndrome results from a quantitative or qualitative defect, with symptoms identical to the constitutional form of von Willebrand disease. Many etiologies are responsible for this condition, mainly lymphoproliferative and myeloproliferative syndromes, as well as cardiac diseases. Several mechanisms have been involved depending on the etiology. Monoclonal gammopathy is the leading cause of AvWS, the mechanism encountered in this case is the production of anti-von Willebrand factor antibodies, which may be specific and inactivate von Willebrand factor (VWF) or aspecific, resulting in rapid clearance of VWF. **Methods:** Here we report the case of a 84-year-old female, with no history of abnormal bleeding symptoms (spontaneous or provoked), regularly seen for recurrent digestive bleeds, requiring numerous blood transfusions (more than 25 transfusions in 4 years). A von Willebrand disease type 3 was confirmed with a von Willebrand factor antigen (vWF:Ag) at 3% (normal range, 50-120%), a activity of the cofactor of ristocetin (vWF:RCo) at 4% (normal range, 50-150%) and a coagulant activity of factor VIII (FVIII:C) at 4% (normal range, 50-150%). A complete work-up lead to the suspicion of an AvWS-SMM, with a monoclonal IgG kappa peak of 1.9g/L, and a bone marrow biopsy infiltrated by 15% plasma cells. **Results:** Treatment consists in either controlling spontaneous bleeding or preventing surgically induced bleeding on the one hand and treating the underlying pathology on the other. However, in patients with asymptomatic lymphoproliferative malignancies, this decision can be difficult to make because of the impact of these therapies on the patient's quality of life. First line options like DDAVP, IVIG treatment (in case of IgG peak) or VWF/FVIII concentrate should be proposed, but response are highly variable. Immunosuppressive agents such as rituximab, cyclophosphamide and azathioprine were ineffective in the majority of cases. When first line options are ineffective it is necessary to treat SMM. Treatment protocol is decided on a case-by-case basis, taking into account the benefit-risk ratio. Proteasome inhibitors and imide-based immunomodulatory drugs (IMiDs) can cause significant side effects, such as thrombocytopenia, and may require thromboprophylaxis that can complicate the management of such situations. Daratumumab is a human monoclonal antibody designed to specifically target the CD38 antigen expressed on plasma cells, approved for the treatment of multiple myeloma. **Conclusions:** After unsuccessful trials with DDAVP, IVIG, rituximab and the need for a chronic use of Wilate®, a combination of daratumumab, lenalidomide and dexamethasone was started with a favorable outcome after two cycles of treatment, with normalization of all coagulation parameters and by the absence of recurrent digestive bleeding.

the causes of deregulated coagulation. **Methods:** We analyzed the records of 450 patients treated in a single center to identify clinically relevant episodes of venous (VTE), arterial embolic events (AEE) and bleeding events. **Results:** Median age was 65 years (39-95) and 54% were male. The median follow-up was 55.3 months (95% CI 49.3-63.0). In 26 (5.8%) patients at least one VTE was recorded; deep vein thrombosis in 2.3%, pulmonary embolism in 2.4%, other in 1.1%. Eighteen patients were on anti-clonal treatment at the time of the event; 11 were on IMiDs-agent based therapy. Among patients with VTE, 36% were on antiplatelets and 52% on antithrombotic prophylaxis. AEE was reported in 22 (5%) of patients; stroke 2.9%, acute myocardial infarction 1.6%, other in 0.5%. Median time from diagnosis to VTE was 9.5 months (0.1 – 107 months) and to AEE 14 months (0.62-114 months). Lower albumin levels (p=0.040), lower eGFR (p=0.010), extensive bone marrow infiltration (0.010), soft tissue involvement (p=0.029), IMiD-based therapy (p=0.001) and history of prior thrombosis (≤0.001) were associated with VTE. A prior VTE history remained the only prognostic variable in the multivariate model (HR 9.3, p=0.001, 95% CI 2.36-36.6). Coronary arterial disease (p=0.045), prior AEE (p=0.041), higher 24hour urine protein (p=0.008) and higher platelet count at diagnosis (p=0.020) were associated with AEE risk. Cardiac involvement and Mayo stage were not risk factors for thrombotic events. Significant bleeding events were reported in 41 patients (9%) and were the cause of death in 8 (mortality 19%); CNS in 1.3%, GI in 4.6%, other in 3.1%. Median time from diagnosis to bleeding events was 1.7 months (0.1 to 166 months). Bleeding risk was higher in patients on antiplatelets (15% vs 7.4%, p=0.05) but not on antithrombotic therapy. Higher serum creatinine (p=0.040) and higher baseline vWFAg (p=0.001, n=112) were linked to bleeding. Using competing risk analysis (death due to any cause as competing event), the cumulative probability of thrombosis and bleeding at 6 months was 4.1% and 4.6% vs 14.5% for death, at 1 year 6% and 5.6% vs 23% for death, at 2 years 7% and 6.8% vs 29% for death, and at 5 years 10.8%, 9.8% and 41% respectively. **Conclusions:** Hemostatic complications associated with AL amyloidosis are common. Increased thrombotic risk and hemorrhagic diathesis or both, increase morbidity and mortality and make optimal management highly complex. Most events occur early but a constant risk remains present throughout the disease course. To optimize anticoagulation clinical risk factors need to be coupled to clotting parameter abnormalities in future studies.

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Michael Iarossi[1], Marie-Christiane Madeleine Vekemans[2], Nicolas Weynants[3], Cédric Hermans[1]

[1]Saint Luc Hospital; [2]Department of Internal Medicine, Université Catholique de Louvain (UCLouvain), Brussels, Belgium; [3]Hôpital d'Arlon

Introduction: Acquired von Willebrand syndrome (AvWS) is a rare entity with approximately 700 cases described in the literature, probably underestimated due to a wide range of clinical features. The syndrome results from a quantitative or qualitative defect, with symptoms identical to the constitutional form of von Willebrand disease. Many etiologies are responsible for this condition, mainly lymphoproliferative and myeloproliferative syndromes, as well as cardiac diseases. Several mechanisms have been involved depending on the etiology. Monoclonal gammopathy is the leading cause of AvWS, the mechanism encountered in this case is the production of anti-von Willebrand factor antibodies, which may be specific and inactivate von Willebrand factor (VWF) or aspecific, resulting in rapid clearance of VWF. **Methods:** Here we report the case of a 84-year-old female, with no history of abnormal bleeding symptoms (spontaneous or provoked), regularly seen for recurrent digestive bleeds, requiring numerous blood transfusions (more than 25 transfusions in 4 years). A von Willebrand disease type 3 was confirmed with a von Willebrand factor antigen (vWF:Ag) at 3% (normal range, 50-120%), a activity of the cofactor of ristocetin (vWF:RCo) at 4% (normal range, 50-150%) and a coagulant activity of factor VIII (FVIII:C) at 4% (normal range, 50-150%). A complete work-up lead to the suspicion of an AvWS-SMM, with a monoclonal IgG kappa peak of 1.9g/L, and a bone marrow biopsy infiltrated by 15% plasma cells. **Results:** Treatment consists in either controlling spontaneous bleeding or preventing surgically induced bleeding on the one hand and treating the underlying pathology on the other. However, in patients with asymptomatic lymphoproliferative malignancies, this decision can be difficult to make because of the impact of these therapies on the patient's quality of life. First line options like DDAVP, IVIG treatment (in case of IgG peak) or VWF/FVIII concentrate should be proposed, but response are highly variable. Immunosuppressive agents such as rituximab, cyclophosphamide and azathioprine were ineffective in the majority of cases. When first line options are ineffective it is necessary to treat SMM. Treatment protocol is decided on a case-by-case basis, taking into account the benefit-risk ratio. Proteasome inhibitors and imide-based immunomodulatory drugs (IMiDs) can cause significant side effects, such as thrombocytopenia, and may require thromboprophylaxis that can complicate the management of such situations. Daratumumab is a human monoclonal antibody designed to specifically target the CD38 antigen expressed on plasma cells, approved for the treatment of multiple myeloma. **Conclusions:** After unsuccessful trials with DDAVP, IVIG, rituximab and the need for a chronic use of Wilate®, a combination of daratumumab, lenalidomide and dexamethasone was started with a favorable outcome after two cycles of treatment, with normalization of all coagulation parameters and by the absence of recurrent digestive bleeding.

P-428

Clinicopathological profile and treatment outcomes in patients with monoclonal gammopathy of renal significance (MGRS): a single centre experience

Aditya Jandial[1], Ritambhra Nada[2], Uday Yanamandra[3], Charanpreet Singh[1], Arihant Jain[2], Deepesh Lad[1], Gaurav Prakash[2], Alka Khadwal[2], Raja Ramachandran[2], Ritu Aggarwal[2], Sreejesh Sreedharanunni[1], Reena Das[2], Pankaj Malhotra[1]

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Introduction: Monoclonal gammopathy of renal significance (MGRS) refers to a heterogeneous group of disorders where abnormal monoclonal protein produced by a plasma cell or B-cell clone results in renal dysfunction. These are rare disorders and do not meet diagnostic criteria for other hematologic malignancies. There is limited literature on MGRS from India. **Methods:** We performed a retrospective analysis of MGRS patients treated at PGIMER Chandigarh from January 2013 to December 2022. All patients required confirmation of MGRS on renal biopsy for inclusion in the study. Patients with cast nephropathy and renal AL Amyloidosis were excluded. Hematologic response was defined as complete response (CR) if normalization of FLC was achieved. Very good partial response (VGPR) and partial response (PR) required 90% or 50% monoclonal protein reduction, respectively. Renal response was defined as >30% reduction of 24 h proteinuria (in the absence of renal progression). **Results:** A total of 31 MGRS patients were analyzed. The median age at diagnosis was 48 years (range 29 – 65 years); 45.2% were females. The median duration of symptoms was 6 months (range 1 – 24 months). Most common presenting complaints were fatigue (82.8%), pedal edema (64.5%), and frothuria (32.2%). At presentation, 20 patients (64.5%) had eGFR 1 renal lesion on kidney biopsy. Most patients (n = 27; 87.1%) received bortezomib-based first-line therapy; 3 (9.6%) underwent autologous stem cell transplantation. Four patients (12.9%) underwent renal transplantation. The median follow-up duration was 8 months (range 4 - 96 months). The hematologic response was observed in 23/31 patients (74.1%); the median time to best hematologic response was 6 months (range 4-12 months). The renal response was observed in 16/31 patients (51.6%); the median time to best renal response was 12 months (range 6 – 24 months). Normal eGFR at baseline and achievement of CR/VGPR with therapy were independent predictors of renal response. Seven patients died during follow-up. The overall survival (OS) of the study cohort was 77.4%. **Conclusions:** These findings suggest that achieving deep hematologic responses with bortezomib-based therapy is crucial to obtaining renal responses in MGRS patients. Low eGFR at baseline is a risk factor for suboptimal renal response.

P-429

Real-world data of zanubrutinib treatment for patients with previously treated Waldenstrom Macroglobulinemia

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[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

Introduction: Waldenstrom macroglobulinemia (WM) is defined as lymphoplasmacytic lymphoma (LPL) associated with immunoglobulin M (IgM) monoclonal gammopathy, irrespective of the M protein size. The treatment of goal of WM is to control disease without compromising quality of life by treatment-related adverse events. Zanubrutinib, a second generation covalent BTK inhibitor, constitute the incumbent stand of care irrespective of line of therapy based on the recent success of ASPEN trial. Recognizing the lack of real-world data on zanubrutinib treatment for previously treated WM patients, we carried out this study. **Methods:** We conducted a retrospective cohort study of previously treated WM patients and identified 10 patients undergoing zanubrutinib treatment. All patients started on 160mg bid schedule The efficacy and safety of zanubrutinib treatment was investigated. The response was evaluated according to the 6th International Workshop on WM. Major response was defined as composite of complete response (CR) + very good partial response (VGPR) + partial response (PR). Overall response rate (ORR) was defined as minor response (MR) or better response. **Results:** The median age at WM diagnosis was 65, while the median age at zanubrutinib start was 70 years old. There were 7 males and 3 females. There were 2 patients with underlying arrhythmias and 1 with hypertension. The median time from diagnosis to zanubrutinib was 52 months (range 8-145), and 6 patients had 2 prior lines of therapy while 4 had 1 prior line of therapy. All but 2 were previously treated with chemoimmunotherapy, and there were 4 patients previous exposure to bortezomib. The median time from last line of therapy to zanubrutinib was 4 months (range 0-72 months). The reason for starting zanubrutinib were neuropathy (2), anemia (1), kidney-related (3), extramedullary manifestation (1), Bing Neel Syndrome (1), and physician's decision (2). During the median follow-up of 17 months, 5 (50%) achieved VGPR, 4 (40%) achieved PR and 1 (10%) achieved MR. ORR was 100% and major response 100% without CR. There was 1 patient with prior exposure to ibrutinib: this patient achieved PR after 6 months of treatment. The median time to initial response was 39 days, median time to best response 9 months, and median duration of response 15 months. One patient underwent dose reduction (to 80mg bid) due to dyspnea. There was 1 case of grade 1 thrombocytopenia. Otherwise, zanubrutinib was well tolerated. **Conclusions:** Real-world data are consistent with previously published data from trials with zanubrutinib in WM.

P-428

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P-430

Incidence of primary plasma cell leukemia with the new diagnostic criteria

Virginia Jano[1], Irene Padilla[1], Marta Castellanos[1], Belen Ballina[1], María del Carmen Gilabert[1], Javier Sánchez-Real[1], Agata Almela[1], Abdolah Ahmadi[1], Jose Antonio Rodríguez[1], Fernando Escalante[1]

[1]University Hospital of Leon

Introduction: Plasma cell leukemia (PCL) is the most aggressive form of plasma cell neoplasms, accounting for 1% of this group. Traditionally, PCL has been defined by a peripheral blood plasma cell count >2x10^9/L or a peripheral blood smear plasma cell count >20% of total nucleated cells. However, the latest recommendations suggest that the required percentage for diagnosis should be reduced to 5%. This is because patients with Multiple Myeloma (MM) with circulating plasma cells levels starting from this threshold have a poor prognosis, similar to patients traditionally diagnosed with PCL. **Methods:** Objective: The objective of this study is to describe the epidemiological and clinical characteristics and analyze the treatment response in patients diagnosed with primary plasma cell leukemia (pPCL). Materials and methods: This is a descriptive, retrospective study in which a search was conducted for patients meeting the new criteria for pPCL in our center between January 2021 and May 2023. **Results:** The studied patients were in an age range from 45 to 87 years, with 85.7% of cases being women. All cases with available cytogenetic studies at the time of analysis showed adverse cytogenetic abnormalities. The average peripheral blood plasma cell count was 19.6%, with a count higher than 5% in all cases and only 42.9% exceeding 20%. Regarding treatment, individualized regimens were decided based on age and comorbidities. Thus, 71.4% of patients were considered suitable for intensive treatment with different regimens reflected in Table 2. Of these, 40% achieved complete response (CR) and another 40% achieved very good partial response (VGPR), without subsequent disease progression. The response in one patient cannot be evaluated because she had recently started treatment. Symptomatic/palliative treatment was decided for two cases: one of them achieved a partial response (PR) which he maintained for a year, but finally the disease progressed and the patient died. The other patient started treatment while these data were being analyzed. **Conclusions:** Currently, the incidence of pPCL with the new diagnostic criteria is unknown, but in our case series, the cumulative incidence is 2 cases per 100,000 inhabitants in two years and five months, much higher than those reported in other series (4 cases per 10 million inhabitants). This could reflect that the disease has been underdiagnosed for years, and the modification of diagnostic criteria will allow early identification of these patients. This, combined with the therapeutic arsenal available, could have significant results in the overall survival of these patients. The treatment of these patients is a challenge, with no defined guideline regardless of whether they are eligible or non-eligible for autologous stem cell transplantation (HSCT) In them, the best available treatment should be initiated as soon as possible.

P-431

Clinical characteristics, prognostic factors and treatment outcomes in patients diagnosed with primary plasma cell leukemia based on the revised criteria (KMM2204)

Sung-Hoon Jung[1], Je-Jung Lee[2], Hee Jeong Cho[2], Dae Sik Kim[3], Jongheon Jung[4], Ji Hyun Lee[5], Kihyun Kim[6], Ja Min Byun[7], Dok Hyun Yoon[8], Yoon Seok Choi[9], Jae-Cheol Jo[10], Ho-Young Yhim[11], Myung-Won Lee[12], Sung-Nam Lim[13], Jae Hoon Lee[14], Sung-Soo Park[15], Chang-Ki Min[16]

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Introduction: Recently, the diagnostic criteria for plasma cell leukemia (PCL) were revised to lower the cut-off value of 5% circulating plasma cells (CPCs) in peripheral blood smear. **Methods:** This retrospective study evaluated the clinical characteristics, prognostic factors and treatment outcomes in patients diagnosed with primary PCL based on the revised criteria. **Results:** At diagnosis, 127 patients diagnosed with primary PCL; 70 had CPCs ≥ 20%, and 57 had CPCs 5-19%. The study found no significant difference in progression free survival (PFS) and overall survival (OS) between the two groups (CPCs≥ 20% and 5-19%), but patients with CPCs≥20% had significantly higher white blood cell counts, lactate dehydrogenase levels and extramedually plasmacytoma compared to those with CPCs 5-19%. Multivariate analysis identified poor performance status, thrombocytopenia and del17p as significant predictor of OS. In this study, 33 patients underwent 18F-FDG PET/CT prior to initial treatments, and 11 showed more than 3 focal lesions. However, there was no difference of survival outcomes according to the PET/CT postivity. In addition, patients who achieved a complete response (CR) after induction therapy showed significantly improved PFS and OS than other patients. When evaluating response rates according to the induction therapies such as daratumumab-based quadruplets, bortezomib and thalidomide or bortezomib and lenalidomide combinations, bortezomib-based combinations, and IMiDs based combinations, CR rate was the highest in daratumumab-based quadruplets than other induction therapy. **Conclusions:** In conclusion, while there were some clinical

P-430

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P-431

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and laboratory differences bwteeen patients with CPCs 5-19% and ≥ 20%, there was no difference in survival outcomes. Achieving CR after induction therapy was crucial for improving survival outcomes, and daratumumab-based quadruplets may be reasonable choice as an induction therapy for primary PCL.

P-432

Nasopharyngeal plasmacytoma with tumefactive amyloidosis ("amyloidoma") presenting with unilateral hearing loss

Elif Sakci[1], Metban Guzel Mastanzade[1], Beyza Sen[1], Zakir Sakci[2], Ipek Yonal Hindilerden[1], Sevgi Kalayoglu-Besisik[1]

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Introduction: Amyloid light chain deposition may be localized primarily in the aerodigestive system. A rare presentation type is a discrete mass the formation of termed amyloidoma, which may be associated with monoclonal plasma cells in the interstitium of amyloid tissue. Amyloidoma may be localized as primary solitary amyloidoma and has in general an excellent prognosis with surgical management but may result in morbidity due to mass effect. The detection of light chain amyloid may be the first sign of an underlying lymphoproliferative disorder (LPD). It is imperative, therefore, to evaluate in detail to pursue a systemic disease. **Methods:** Our case presentation was as nasopharyngeal plasmacytoma with amyloidoma imitating localized solitary involvement but had systemic plasma cell dyscrasia. **Results:** A 30-year-old male presented with hearing loss and ear pain. Otoscopy suggested unilateral serous otitis media. A course of antimicrobial treatment was ineffective and magnetic resonance imaging was performed which showed mucosal thickening. Histologic examination of laryngoscopic biopsy sample showed amorphous eosinophilic material stained positive with Congo red and IgD kappa-type monoclonal plasma cell infiltration in the interstitium. A PET-CT did not show an LPD-pointing lesion except for an inflammatory change in bilateral rosenmuller fossa with minimal FDG uptake. He had a low level of M protein at 0.3 gr/dl with an abnormal free light chain ratio as being of 9. The paraprotein was IgD kappa type and bone marrow proved to be a clonal plasma cell dyscrasia with an increase of less than 10%. A debulking surgery was performed followed by curative radiotherapy. Despite all of these serum paraprotein levels showed a progressive increase and systemic remission induction was decided. A combined treatment modality as VTD-PACE was used for stem cell mobilization and six courses of VRD was given as anti-plasma cell therapy which succeeded paraprotein decrease. Consolidation was with a high dose of melphalan rescued by autologous stem cell transplantation (ASCT). The patient achieved complete remission. **Conclusions:** AAmyloidoma, is a benign, but rare form of amyloidosis, and surgical resection may result in a favorable prognosis. According to the involved organ or location, amyloidoma may not be completely resectable and radiotherapy may support mass reduction. In our case, however, amyloidoma was associated with plasmacytoma and systemic plasma cell dyscrasia as bone marrow involvement. The effective resolution was achieved after surgery with radiotherapy followed by anti-plasma cell therapy as remission induction and consolidation with ASCT.

P-433

Targeting free light chain secretion via botulinum neurotoxin is a novel therapeutic strategy in AL amyloidosis by inducing a terminal unfolded protein response

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Introduction: AL amyloidosis (AL) is an incurable plasma cell (PC) disorder with only one FDA-approved therapy. Deposition of immunoglobulin free light chain (FLC) fibrils in target organs is the sole pathogenic mechanism in AL. However, therapeutic strategies directly targeting FLC secretion are not available. SNARE proteins, the specific target of botulinum neurotoxin (BoNT), mediate docking and fusion of secretory vesicles. We hypothesized that targeting specific sets of SNAREs via BoNT will block FLC exocytosis, causing retention of FLC-loaded vesicles and triggering a terminal unfolded protein response (UPR) and apoptosis in AL cells. We postulate that SNAREs are potential novel targets in AL and other plasma cell disorders. **Methods:** We stably expressed 7 distinct, inducible BoNT serotypes (BoNT/A-F) in FLC-secreting AL (ALMC1 and ALMC2) and multiple myeloma (MM, KMS11) cell lines via tetracycline-inducible (Tet-On) bicistronic lentiviral vectors with a P2A-GFP which allowed us to use GFP as a biomarker of BoNT expression. We established monoclones of successfully transduced cells for each BoNT. We performed flow cytometry to assess kinetics of GFP induction and assess for apoptosis via AnnexinV/DAPI staining. Western blot (WB) was used to assess cleavage of SNAREs upon expression of each BoNT serotype. We used WB and ELISA to assess FLC secretion per cell upon BoNT expression. We used TurboID proximity labeling followed by mass spectrometry to identify cytotoxic BoNT interacting partners. We used RNP-based CRISPR-Cas9 gene editing to knock out (KO) putative BoNT targets. **Results:** By querying the IFM170 gene expression database of newly diagnosed MM patients, we identified VAMP2, VAMP3, and SNAP23 as the top expressed SNAREs. Their high expression was retained in a large AL and MM cell line panel. Expression of all BoNT serotypes, except BoNT B, led to rapid apoptosis of AL and MM cells, with BoNT F standing out for extent and rapidity of cytotoxicity. Dual cleavage of SNAP23 and VAMP3 correlated with cytotoxicity of BoNT in AL and MM cell lines. Mechanistically, we showed that cytotoxic BoNTs, but not non-toxic BoNT B, led to decreased FLC secretion and increased FLC retention and triggered the PERK pathway of the UPR with

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Introduction: Amyloid light chain deposition may be localized primarily in the aerodigestive system. A rare presentation type is a discrete mass the formation of termed amyloidoma, which may be associated with monoclonal plasma cells in the interstitium of amyloid tissue. Amyloidoma may be localized as primary solitary amyloidoma and has in general an excellent prognosis with surgical management but may result in morbidity due to mass effect. The detection of light chain amyloid may be the first sign of an underlying lymphoproliferative disorder (LPD). It is imperative, therefore, to evaluate in detail to pursue a systemic disease. **Methods:** Our case presentation was as nasopharyngeal plasmacytoma with amyloidoma imitating localized solitary involvement but had systemic plasma cell dyscrasia. **Results:** A 30-year-old male presented with hearing loss and ear pain. Otoscopy suggested unilateral serous otitis media. A course of antimicrobial treatment was ineffective and magnetic resonance imaging was performed which showed mucosal thickening. Histologic examination of laryngoscopic biopsy sample showed amorphous eosinophilic material stained positive with Congo red and IgD kappa-type monoclonal plasma cell infiltration in the interstitium. A PET-CT did not show an LPD-pointing lesion except for an inflammatory change in bilateral rosenmuller fossa with minimal FDG uptake. He had a low level of M protein at 0.3 gr/dl with an abnormal free light chain ratio as being of 9. The paraprotein was IgD kappa type and bone marrow proved to be a clonal plasma cell dyscrasia with an increase of less than 10%. A debulking surgery was performed followed by curative radiotherapy. Despite all of these serum paraprotein levels showed a progressive increase and systemic remission induction was decided. A combined treatment modality as VTD-PACE was used for stem cell mobilization and six courses of VRD was given as anti-plasma cell therapy which succeeded paraprotein decrease. Consolidation was with a high dose of melphalan rescued by autologous stem cell transplantation (ASCT). The patient achieved complete remission. **Conclusions:** AAmyloidoma, is a benign, but rare form of amyloidosis, and surgical resection may result in a favorable prognosis. According to the involved organ or location, amyloidoma may not be completely resectable and radiotherapy may support mass reduction. In our case, however, amyloidoma was associated with plasmacytoma and systemic plasma cell dyscrasia as bone marrow involvement. The effective resolution was achieved after surgery with radiotherapy followed by anti-plasma cell therapy as remission induction and consolidation with ASCT.

P-433

Targeting free light chain secretion via botulinum neurotoxin is a novel therapeutic strategy in AL amyloidosis by inducing a terminal unfolded protein response

Emre Karayol[1], Maria Moscvin[1], Tianzeng Chen[1], Peter Czarnecki[2], Annamaria Gulla[3], Kenneth Anderson[4], Giada Bianchi[1]

[1]Brigham and Women's Hospital; [2]Beth Israel Deaconess Medical Center; [3]Candiolo Cancer Institute; [4]LeBow Institute for Myeloma Therapeutics and Jerome Lipper Center for Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

Introduction: AL amyloidosis (AL) is an incurable plasma cell (PC) disorder with only one FDA-approved therapy. Deposition of immunoglobulin free light chain (FLC) fibrils in target organs is the sole pathogenic mechanism in AL. However, therapeutic strategies directly targeting FLC secretion are not available. SNARE proteins, the specific target of botulinum neurotoxin (BoNT), mediate docking and fusion of secretory vesicles. We hypothesized that targeting specific sets of SNAREs via BoNT will block FLC exocytosis, causing retention of FLC-loaded vesicles and triggering a terminal unfolded protein response (UPR) and apoptosis in AL cells. We postulate that SNAREs are potential novel targets in AL and other plasma cell disorders. **Methods:** We stably expressed 7 distinct, inducible BoNT serotypes (BoNT/A-F) in FLC-secreting AL (ALMC1 and ALMC2) and multiple myeloma (MM, KMS11) cell lines via tetracycline-inducible (Tet-On) bicistronic lentiviral vectors with a P2A-GFP which allowed us to use GFP as a biomarker of BoNT expression. We established monoclones of successfully transduced cells for each BoNT. We performed flow cytometry to assess kinetics of GFP induction and assess for apoptosis via AnnexinV/DAPI staining. Western blot (WB) was used to assess cleavage of SNAREs upon expression of each BoNT serotype. We used WB and ELISA to assess FLC secretion per cell upon BoNT expression. We used TurboID proximity labeling followed by mass spectrometry to identify cytotoxic BoNT interacting partners. We used RNP-based CRISPR-Cas9 gene editing to knock out (KO) putative BoNT targets. **Results:** By querying the IFM170 gene expression database of newly diagnosed MM patients, we identified VAMP2, VAMP3, and SNAP23 as the top expressed SNAREs. Their high expression was retained in a large AL and MM cell line panel. Expression of all BoNT serotypes, except BoNT B, led to rapid apoptosis of AL and MM cells, with BoNT F standing out for extent and rapidity of cytotoxicity. Dual cleavage of SNAP23 and VAMP3 correlated with cytotoxicity of BoNT in AL and MM cell lines. Mechanistically, we showed that cytotoxic BoNTs, but not non-toxic BoNT B, led to decreased FLC secretion and increased FLC retention and triggered the PERK pathway of the UPR with

and laboratory differences bwteeen patients with CPCs 5-19% and ≥ 20%, there was no difference in survival outcomes. Achieving CR after induction therapy was crucial for improving survival outcomes, and daratumumab-based quadruplets may be reasonable choice as an induction therapy for primary PCL.

P-432

Nasopharyngeal plasmacytoma with tumefactive amyloidosis ("amyloidoma") presenting with unilateral hearing loss

Elif Sakci[1], Metban Guzel Mastanzade[1], Beyza Sen[1], Zakir Sakci[2], Ipek Yonal Hindilerden[1], Sevgi Kalayoglu-Besisik[1]

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increased expression of CHOP and GADD34 preceding onset of apoptosis. We identified SNAP23 as an interacting partner of cytotoxic BoNT F, but not non-toxic BoNT B. KO experiment showed SNAP23 KO to be partially toxic for AL and MM cell lines but did not recapitulate the effects of cytotoxic BoNTs entirely, suggesting "synthetic lethality" with concurrent targeting of yet unidentified SNAREs. **Conclusions:** Our data provide proof of concept that blocking FLC secretion in AL and MM cells is feasible and results in rapid cell apoptosis by triggering a terminal UPR, thus representing a promising, novel therapeutic approach. Using BoNT as a biological tool, we identified SNAP23 as a critical component of FLC exocytosis, paving the way for the design of novel therapeutics.

P-434

A patient with CD20-positive small cell variant plasma cell myeloma misdiagnosed as lymphoplasmacytic lymphoma

Miyoung Kim[1], Daehyun Chu[1], Young-Uk Cho[1], Sang-Hyun Hwang[1], Seongsoo Jang[1], Eul-Ju Seo[1], Han-Seung Park[1]

[1]Asan Medical Center, University of Ulsan College of Medicine

Introduction: We report a patient with CD20-positive light chain-type small cell variant plasma cell myeloma who was misdiagnosed with lymphoplasmacytic lymphoma and did not respond to anti-CD20 immunotherapy. **Methods:** Not applicable **Results:** An 80-year-old Korean man with pancytopenia visited our institution in August 2020. He had undergone a hemithyroidectomy for follicular thyroid carcinoma 6 years prior. His complete blood count showed hemoglobin (Hb), 88 g/L; white blood cells (WBCs), 3.4×10^9/L; and platelets, 106×10^9/L. Small mature-looking lymphocytes comprised 50,0% of all leukocytes; rouleaux formation was absent. In the bone marrow (BM) aspirate, 15.0% of total nucleated cells were mature lymphocytes, and 25.8% were plasma cells. On immunohistochemistry (IHC) of the BM biopsy sample, both the lymphocytes and plasma cells were positive for CD20, CD138, and kappa; partially positive for CD117; and negative for lambda. His serum calcium, creatinine, protein, and albumin levels were 8.2 mg/dL, 0.91 mg/dL, 6.9 g/dL, and 3.9 g/dL, respectively. Serum protein electrophoresis (PEP) and immunofixation electrophoresis (IFE) showed an M-peak of 0.2 g/dL (free kappa type). Urine PEP and IFE showed a monoclonal band of 47.5% (free kappa type). The serum free kappa/lambda light chain ratio was 1121.59:1. The karyotype was 42,XY,del(1)(q12),add(7)(p21),del(8)(q12q23),-9,add(10)(p13),+add(11)(p11.2),-13,-14,der(14)t(1;14)(p22;q32),add(16)(q11.2),add(17)(p11.2),add(17)(q25),-20,-20,add(22)(q13)[10]/46,XY[40]. The patient was diagnosed with lymphoplasmacytic lymphoma based on cell morphology and CD20-positivity and was treated with five cycles of a bendamustine-rituximab regimen for 17 months. Three subsequent BM analyses showed findings similar to the original, suggesting disease persistence. His pancytopenia was sustained with Hb, 69 g/L; WBC, 2.2×10^9/L; and platelets, 100×10^9/L. Plasmacytoid cells comprised 18,0% of all leukocytes with no rouleaux formation observed; they also comprised 77.0% of the BM aspirate, resembling small or plasmacytoid lymphocytes. The BM cellularity was 90%, mostly with plasmacytoid cells that were positive for CD138, kappa, CD20, and CD117; partially positive for CD56, CD79a, and cyclin D1; and negative for CD3, lambda, and PAX5. Flow cytometric immunophenotyping showed a large CD45-negative population that was positive for CD138, CD38, CD20, and CD56 but negative for CD19 and surface light chain. Based on these findings, the diagnosis was revised to plasma cell myeloma, small cell variant. The patient refused further treatment owing to his poor general condition. **Conclusions:** Small cell-variant plasma cell myeloma could be misdiagnosed as other mature B-cell neoplasms owing to its small lymphocyte-like morphology, frequent CD20-positivity, and frequent light chain type that lacks a rouleaux formation. Flow cytometric immunophenotyping and IHC for CD45 and CD138 may assist in the differential diagnosis.

P-435

Acquired angioedema, a rare manifestation of MGCS

Quentin Leman[1], Hélène Georgery[1], Gaspard Jadot[1], Michael Iarossi[1], Marie-Astrid Van Dievoet[1], Delphine Pranger[2], Cédric Hermans[3], Marie-Christiane Vekemans[1]

[1]Cliniques Universitaires Saint-Luc, UCL; [2]Grand Hôpital de Charleroi; [3]Saint Luc Hospital

Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a common condition that results from a small and/or quiescent secreting B-cell clone, completely asymptomatic, that requires only regular monitoring. Sometimes, although quiescent and not requiring any treatment per se, the clone is associated with potentially severe organ damage due to the toxicity of the monoclonal immunoglobulin. This situation refers to the concept of monoclonal gammopathy of clinical significance (MGCS). It is increasingly observed but still poorly recognized and frequently undertreated, although it often requires rapid specific intervention to preserve involved organ function. Here, we report a case of MGCS relying on manifestations of an acquired angioedema related to a monoclonal protein. **Methods:** A 48-year-old male patient presented in February 2020 with a first attack of angioedema that manifested by a swelling of the hands, feet and lips, and abdominal pain, that resolved within 24 hours. Lab test documented a low C1 inhibitor level (below 16%) with low C1 inhibitor activity (19%), and very low C4 and C1q levels, leading to the diagnosis of acquired angioedema. The patient had no personal nor familial history of angioedema. Additional work-up encompassed serum and urine protein electrophoresis, free light chain assay, lymphocyte typing by flow cytometry, bone marrow aspiration and PET-CT but was not conclusive. Treatment successively included Tranexamic Acid, plasma exchanges, 4 infusions of Rituximab, Mycophenolate Mofetil without any improvement, persistent angioedema attacks occurring every 3 to 4 weeks. **Results:** The patient was then referred to our center in September 2021. With subcutaneous injections of lanadelumab, an IgG1 Kappa monoclonal antibody directed against Kallikrein received on a compassionate use basis, he was freed from all symptoms till the program was stopped and attacks reoccurred.

increased expression of CHOP and GADD34 preceding onset of apoptosis. We identified SNAP23 as an interacting partner of cytotoxic BoNT F, but not non-toxic BoNT B. KO experiment showed SNAP23 KO to be partially toxic for AL and MM cell lines but did not recapitulate the effects of cytotoxic BoNTs entirely, suggesting "synthetic lethality" with concurrent targeting of yet unidentified SNAREs. **Conclusions:** Our data provide proof of concept that blocking FLC secretion in AL and MM cells is feasible and results in rapid cell apoptosis by triggering a terminal UPR, thus representing a promising, novel therapeutic approach. Using BoNT as a biological tool, we identified SNAP23 as a critical component of FLC exocytosis, paving the way for the design of novel therapeutics.

P-434

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Introduction: We report a patient with CD20-positive light chain-type small cell variant plasma cell myeloma who was misdiagnosed with lymphoplasmacytic lymphoma and did not respond to anti-CD20 immunotherapy. **Methods:** Not applicable **Results:** An 80-year-old Korean man with pancytopenia visited our institution in August 2020. He had undergone a hemithyroidectomy for follicular thyroid carcinoma 6 years prior. His complete blood count showed hemoglobin (Hb), 88 g/L; white blood cells (WBCs), 3.4×10^9/L; and platelets, 106×10^9/L. Small mature-looking lymphocytes comprised 50,0% of all leukocytes; rouleaux formation was absent. In the bone marrow (BM) aspirate, 15.0% of total nucleated cells were mature lymphocytes, and 25.8% were plasma cells. On immunohistochemistry (IHC) of the BM biopsy sample, both the lymphocytes and plasma cells were positive for CD20, CD138, and kappa; partially positive for CD117; and negative for lambda. His serum calcium, creatinine, protein, and albumin levels were 8.2 mg/dL, 0.91 mg/dL, 6.9 g/dL, and 3.9 g/dL, respectively. Serum protein electrophoresis (PEP) and immunofixation electrophoresis (IFE) showed an M-peak of 0.2 g/dL (free kappa type). Urine PEP and IFE showed a monoclonal band of 47.5% (free kappa type). The serum free kappa/lambda light chain ratio was 1121.59:1. The karyotype was 42,XY,del(1)(q12),add(7)(p21),del(8)(q12q23),-9,add(10)(p13),+add(11)(p11.2),-13,-14,der(14)t(1;14)(p22;q32),add(16)(q11.2),add(17)(p11.2),add(17)(q25),-20,-20,add(22)(q13)[10]/46,XY[40]. The patient was diagnosed with lymphoplasmacytic lymphoma based on cell morphology and CD20-positivity and was treated with five cycles of a bendamustine-rituximab regimen for 17 months. Three subsequent BM analyses showed findings similar to the original, suggesting disease persistence. His pancytopenia was sustained with Hb, 69 g/L; WBC, 2.2×10^9/L; and platelets, 100×10^9/L. Plasmacytoid cells comprised 18,0% of all leukocytes with no rouleaux formation observed; they also comprised 77.0% of the BM aspirate, resembling small or plasmacytoid lymphocytes. The BM cellularity was 90%, mostly with plasmacytoid cells that were positive for CD138, kappa, CD20, and CD117; partially positive for CD56, CD79a, and cyclin D1; and negative for CD3, lambda, and PAX5. Flow cytometric immunophenotyping showed a large CD45-negative population that was positive for CD138, CD38, CD20, and CD56 but negative for CD19 and surface light chain. Based on these findings, the diagnosis was revised to plasma cell myeloma, small cell variant. The patient refused further treatment owing to his poor general condition. **Conclusions:** Small cell-variant plasma cell myeloma could be misdiagnosed as other mature B-cell neoplasms owing to its small lymphocyte-like morphology, frequent CD20-positivity, and frequent light chain type that lacks a rouleaux formation. Flow cytometric immunophenotyping and IHC for CD45 and CD138 may assist in the differential diagnosis.

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P-435

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Additional work-up identified then an IgA Lambda monoclonal peak (1.9 g/L), with a discrete marrow infiltration, a situation considered as a MGCS. Treatment with SQ Daratumumab was proposed with the initial disappearance of any angioedema attack after the first 2 months of therapy, but relapses thereafter, persisting after 6 cycles of SQ Daratumumab. The patient was further rechallenged with lanadelumab with success. **Conclusions:** We report a case of acquired angioedema, a rare form of MGCS, that exemplifies the difficulty to understand the relationship between a monoclonal component and the clinical manifestations of the disease, since a therapy targeting directly the clone was not efficacious in this setting. This case also highlights the spectrum of various disorders associated with MGUS.

P-436

Clonal hematopoiesis of indeterminate potential (CHIP) in patients with amyloid light chain (AL) amyloidosis

Paolo Lopedote[1], Alfredo Marchetti[2], Benjamin Evans[3], Shannon Miller[4], Tianzeng Chen[5], Maria Moscvin[6], Niccolo' Bolli[7], Giada Bianchi[8]

[1]St Elizabeth's Medical Center; [2]Universita' degli studi di Milano; [3]Brigham and Women's Hospital; [4]Dana Farber Cancer Center; [5]Medical College of Wisconsin; [6]Stanford Health Care; [7]Division of Hematology & Stem Cell Transplantation, University of Milano, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [8]Brigham and Women/s Hospital/Harvard Medical School/Dana Farber Cancer Institute

Introduction: The hallmark of AL Amyloidosis is the production, aggregation, and deposition of immunoglobulin free light chains in target organs. Cardiac events are the major cause of mortality in AL amyloidosis. Clonal hematopoiesis of unknown potential (CHIP) is associated with increased cardiovascular risk in the general population and decreased overall survival in multiple myeloma patients receiving autologous stem cell transplant. Large studies looking at incidence and outcome of patients with concurrent CHIP and AL amyloidosis are missing. We performed a single center, retrospective analysis to evaluate the prevalence of CHIP in AL amyloidosis and associated disease characteristics and outcomes, including major organ dysfunction progression free survival (MOD-PFS). **Methods:** Demographics and clinical characteristics of patients diagnosed with AL amyloidosis at DFCI from January 2018 to April 2023 who received a bone marrow aspirate/biopsy with a rapid heme panel (RHP) were collected. Variables of interest included age, ethnicity, Mayo stage, Palladini renal stage, involved organs, FISH abnormalities, left ventricular ejection fraction, and anginal symptoms. MOD-PFS was defined based on Kastritis et al. Variant alle fraction (VAF) to define CHIP was set at 2%. Two samples independent t-test, Wilcoxon rank sum test, Fisher exact test were used for comparison between groups. We used the Cox proportional hazard regression model to estimate the association between CHIP status and MOD-PFS. All analyses were carried out with the STATA statistical package. This study was approved by the institutional review board. **Results:** Seventy-six patients were identified meeting criteria. Of these, 16 (21%) were found to meet diagnostic criteria for CHIP. DNMT3A was the most frequently involved gene (7/16, 44%), followed by GNB1, TET2, ATM (each 2/16, 12.5%), and SF3B1, ZRSR2, EZH2, BRCC3, PPM1D, ASXL1 (6%). Among the variables of interest, patients with CHIP had a higher prevalence of t(11;14) (11/13, 85%, versus 15/41, 37%, p=0.004) and a lower Palladini renal stage (p=0.001). Median follow-up time for the entire cohort was 25 months (range 1 – 175 months). In a univariate analysis model, CHIP presence was not associated with an increased hazard for lower MOD-PFS (hazard ratio 0.998, 95% CI 0.38 – 2.64), although a limited number of events was recorded given short duration of follow up. **Conclusions:** This is the first, large series describing the prevalence and clinical implications of CHIP in patients with AL amyloidosis. In our study, CHIP was associated with presence of t(11;14), the most frequent cytogenetics in AL amyloidosis and a negative prognostic factor. A lower Palladini renal risk score was noted in patients with CHIP. Because of the limited number of events, no multi-variate Cox regression analysis was performed. Future studies will help confirm our findings and clarify the impact of CHIP in AL amyloidosis patients' outcome.

P-437

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Additional work-up identified then an IgA Lambda monoclonal peak (1.9 g/L), with a discrete marrow infiltration, a situation considered as a MGCS. Treatment with SQ Daratumumab was proposed with the initial disappearance of any angioedema attack after the first 2 months of therapy, but relapses thereafter, persisting after 6 cycles of SQ Daratumumab. The patient was further rechallenged with lanadelumab with success. **Conclusions:** We report a case of acquired angioedema, a rare form of MGCS, that exemplifies the difficulty to understand the relationship between a monoclonal component and the clinical manifestations of the disease, since a therapy targeting directly the clone was not efficacious in this setting. This case also highlights the spectrum of various disorders associated with MGUS.

P-436

Clonal hematopoiesis of indeterminate potential (CHIP) in patients with amyloid light chain (AL) amyloidosis

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Concomitant positivity was present in 8 cases. Of the 64 patients with negative MSGB, 53 were not diagnosed with Amyloidosis AL, resulting in a specificity of 99.5% (95% CI: 93.28% to 99.9%). 4 patients with negative MSGB but positive BMB received diagnosis of Amyloidosis AL. 7 patients were diagnosed with Amyloidosis AL despite both negative MSGB and BMB. Of the 53 patients without Amyloidosis AL, 25 received diagnosis of Smouldering Myeloma, 14 of Multiple Myeloma, 4 of Waldenstrom Macroglobulinemia and 10 of MGUS. **Conclusions:** To our knowledge, this is one of the largest studies comparing salivary gland and bone marrow biopsies as diagnostic tools in Amyloidosis AL. Our findings demonstrate that minor salivary gland biopsy is a valuable and reliable option with a sensitivity non inferior to other alternatives and, in our case, higher than bone marrow biopsy, thus providing valuable diagnostic information when positive. Comparing our results with data from studies evaluating different bioptic methods for Amyloidosis AL, MSGB holds promise as an initial diagnostic approach, potentially sparing patients from the risks associated with more invasive procedures. Further studies with larger sample sizes and prospective designs are warranted to validate our results and establish standardized protocols for minor salivary gland biopsy as frontrunner in the diagnosis of Amyloidosis AL.

P-438

Castleman disease: histopathologic reclassification, clinical characteristics and endpoints in a reference center in Mexico

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Introduction: Castleman's Disease (CD) circumscribes several clinicopathologic disorders at the intersection of hematology, oncology, rheumatology and virology, with convergence in histopathologic and clinical features. Information about CD in Latin America is scarce. **Methods:** Patients with CD diagnosis from January 2006 to July 2022 were included. A retrospective review of the clinical charts and examination of the biopsies by a trained hematopathologist was performed. The immunohistochemical panel was extended to exclude differentials and PCR to confirm infection by HHV8 and classification of the cases. **Results:** Twenty-seven patients were included; 37% were unicentric Castleman disease (UCD) and 63% multicentric Castleman disease (MCD); median age at diagnosis was 37 and 41 years respectively; 80% of women in UCD and 76% of men in MCD (p=0.018). In UCD the most frequent nodal areas affected were cervical in 40% and mesenteric in 40%. Media nodal size was 7.1 cm; the 80% hyaline vascular (HV) variety and 20% mixed variant (MV). Successful surgical removal was performed in all cases and none of the patients have relapsed. The distribution of MCD was 59% idiopathic MCD (iMCD), 35% associated to POEMS syndrome and 6% to HHV8. Fifty-nine percent experienced B symptoms, 70% presented fluid retention and 35% experienced skin involvement. Hepatomegaly was present in 88% and splenomegaly in 53%, mean 18.3 cm and 14.6 cm respectively. The treatment received by 16 patients with MCD was only chemotherapy in 37%, rituximab as monotherapy in 19%, rituximab in combination with corticosteroids 19% and 25% in combination with CHOP-like chemotherapy. Response to treatment was evaluable in 13 patients: 38% achieved a complete response, 38% a partial response, 15% stable disease and one patient progressive disease. The revision of the cases derived in the reclassification of 13 %. Cases were more frequently reclassified in MCD. At 66 months follow-up, median overall survival, and progression free survival have not been reached. Patients with MCD associated to POEMS Syndrome relapsed more frequently 83% vs 17% (p=0.005). Uni and multivariate analysis revealed that the association to POEMS Syndrome increased relapse risk OR 50 (IC 95% 2.559 - 976), p=0.010 and OR 31.64 (IC 95% 1.48-676), p=0.027, respectively. Median PFS in this group was 53 months vs non reached in patients with iMCD or associated to HHV8 (p=0.031). **Conclusions:** This is the first series of CD cases in the Latin population that includes a complete description of the clinical and histopathological characteristics and reclassification according to current diagnostic criteria. Opposed to data reported in the literature, the MV corresponded to 20% of UCD and showed a predominance of cervical nodal involvement. Different from data published, in our cohort we found less mediastinal involvement in UCD (10% vs 16-40%). In MCD associated to POEMS Syndrome, the PFS was inferior, the poor outcome of this association had not been previously described.

P-439

Identifying early suboptimal haematological response in patients with AL amyloidosis treated with bortezomib-based chemotherapy

Peter Mollee[1], Anthea Gibbons[1], Niri Ranjit Anderson[1], Dariusz Korczyk[1], Simon Gibbs[2], Hasib Sidiqi[3]

[1]Princess Alexandra Hospital; [2]Eastern Health Monash University Clinical School; [3]Fiona Stanley Hospital, WA, Australia

Introduction: The achievement of rapid, deep haematological response is critical in the treatment of AL amyloidosis. The timing and depth of FLC reduction that defines suboptimal response and the need to switch to second-line therapy is uncertain. We aimed to determine the impact of haematological response after 2 months of bortezomib-based therapy on subsequent best haematological and organ responses and survival. **Methods:** Subjects had a histological diagnosis of AL amyloidosis, symptomatic organ involvement and initial treatment with a bortezomib-based regimen. The impact of haematological response after 2 months of treatment on subsequent best haematological and renal response was assessed using Fisher's exact test. The impact on OS was assessed by landmark analysis using log-rank or Cox regression analysis. **Results:** 150 patients with AL amyloidosis were identified: Median age was 66 yrs and 35% were male. 75% of cases were lambda restricted, the median dFLC was 160mg/L, 75% had ≥ 10% bone marrow plasmacytosis and 9% had symptomatic myeloma. Cardiac stage was: 1 (13%), 2 (55%), 3A

Concomitant positivity was present in 8 cases. Of the 64 patients with negative MSGB, 53 were not diagnosed with Amyloidosis AL, resulting in a specificity of 99.5% (95% CI: 93.28% to 99.9%). 4 patients with negative MSGB but positive BMB received diagnosis of Amyloidosis AL. 7 patients were diagnosed with Amyloidosis AL despite both negative MSGB and BMB. Of the 53 patients without Amyloidosis AL, 25 received diagnosis of Smouldering Myeloma, 14 of Multiple Myeloma, 4 of Waldenstrom Macroglobulinemia and 10 of MGUS. **Conclusions:** To our knowledge, this is one of the largest studies comparing salivary gland and bone marrow biopsies as diagnostic tools in Amyloidosis AL. Our findings demonstrate that minor salivary gland biopsy is a valuable and reliable option with a sensitivity non inferior to other alternatives and, in our case, higher than bone marrow biopsy, thus providing valuable diagnostic information when positive. Comparing our results with data from studies evaluating different bioptic methods for Amyloidosis AL, MSGB holds promise as an initial diagnostic approach, potentially sparing patients from the risks associated with more invasive procedures. Further studies with larger sample sizes and prospective designs are warranted to validate our results and establish standardized protocols for minor salivary gland biopsy as frontrunner in the diagnosis of Amyloidosis AL.

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Introduction: Castleman's Disease (CD) circumscribes several clinicopathologic disorders at the intersection of hematology, oncology, rheumatology and virology, with convergence in histopathologic and clinical features. Information about CD in Latin America is scarce. **Methods:** Patients with CD diagnosis from January 2006 to July 2022 were included. A retrospective review of the clinical charts and examination of the biopsies by a trained hematopathologist was performed. The immunohistochemical panel was extended to exclude differentials and PCR to confirm infection by HHV8 and classification of the cases. **Results:** Twenty-seven patients were included; 37% were unicentric Castleman disease (UCD) and 63% multicentric Castleman disease (MCD); median age at diagnosis was 37 and 41 years respectively; 80% of women in UCD and 76% of men in MCD (p=0.018). In UCD the most frequent nodal areas affected were cervical in 40% and mesenteric in 40%. Media nodal size was 7.1 cm; the 80% hyaline vascular (HV) variety and 20% mixed variant (MV). Successful surgical removal was performed in all cases and none of the patients have relapsed. The distribution of MCD was 59% idiopathic MCD (iMCD), 35% associated to POEMS syndrome and 6% to HHV8. Fifty-nine percent experienced B symptoms, 70% presented fluid retention and 35% experienced skin involvement. Hepatomegaly was present in 88% and splenomegaly in 53%, mean 18.3 cm and 14.6 cm respectively. The treatment received by 16 patients with MCD was only chemotherapy in 37%, rituximab as monotherapy in 19%, rituximab in combination with corticosteroids 19% and 25% in combination with CHOP-like chemotherapy. Response to treatment was evaluable in 13 patients: 38% achieved a complete response, 38% a partial response, 15% stable disease and one patient progressive disease. The revision of the cases derived in the reclassification of 13 %. Cases were more frequently reclassified in MCD. At 66 months follow-up, median overall survival, and progression free survival have not been reached. Patients with MCD associated to POEMS Syndrome relapsed more frequently 83% vs 17% (p=0.005). Uni and multivariate analysis revealed that the association to POEMS Syndrome increased relapse risk OR 50 (IC 95% 2.559 - 976), p=0.010 and OR 31.64 (IC 95% 1.48-676), p=0.027, respectively. Median PFS in this group was 53 months vs non reached in patients with iMCD or associated to HHV8 (p=0.031). **Conclusions:** This is the first series of CD cases in the Latin population that includes a complete description of the clinical and histopathological characteristics and reclassification according to current diagnostic criteria. Opposed to data reported in the literature, the MV corresponded to 20% of UCD and showed a predominance of cervical nodal involvement. Different from data published, in our cohort we found less mediastinal involvement in UCD (10% vs 16-40%). In MCD associated to POEMS Syndrome, the PFS was inferior, the poor outcome of this association had not been previously described.

P-439

Identifying early suboptimal haematological response in patients with AL amyloidosis treated with bortezomib-based chemotherapy

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Introduction: The achievement of rapid, deep haematological response is critical in the treatment of AL amyloidosis. The timing and depth of FLC reduction that defines suboptimal response and the need to switch to second-line therapy is uncertain. We aimed to determine the impact of haematological response after 2 months of bortezomib-based therapy on subsequent best haematological and organ responses and survival. **Methods:** Subjects had a histological diagnosis of AL amyloidosis, symptomatic organ involvement and initial treatment with a bortezomib-based regimen. The impact of haematological response after 2 months of treatment on subsequent best haematological and renal response was assessed using Fisher's exact test. The impact on OS was assessed by landmark analysis using log-rank or Cox regression analysis. **Results:** 150 patients with AL amyloidosis were identified: Median age was 66 yrs and 35% were male. 75% of cases were lambda restricted, the median dFLC was 160mg/L, 75% had ≥ 10% bone marrow plasmacytosis and 9% had symptomatic myeloma. Cardiac stage was: 1 (13%), 2 (55%), 3A

(17%) and 3B (15%). 71% had renal involvement with a median eGFR of 69mls/min and median proteinuria of 2.4g/d, with 9% dialysis dependent at presentation. Bortezomib regimens were: VCD (72%), VCD+daratumumab (13%), MDV (7%), VD (6%) and VRD (3%), with a median of 6 cycles delivered. Median OS was 6.2 years which was adversely associated with more advanced cardiac disease: stage 1 (not reached), stage 2 (90 months), stage 3A (52 months) and stage 3B (9 months)(p=0.0001). Haematological response after 2 months of bortezomib-based induction was: CR (17%), VGPR (40%), PR (17%) and less than PR (16%). 10% of patients died prior to 2 month response assessment. Failure to achieve PR by 2 months was associated with a low chance of achieving deep responses, with only 5% going on to achieve VGPR or better (p< 0.001). Similarly, failure to achieve PR by 2 months predicted a low likelihood of improving organ function with less chance of cardiac (6% vs 47%, p=0.001) and renal (20% vs 41%, p=0.044) responses. In a landmark analysis, failure to achieve PR after 2 months predicted worse OS (median 48 vs 93 months, p=0.041), a finding confirmed in multivariate analysis including cardiac stage. This effect was particularly evident for patients with cardiac stage 3A and 3B disease, where the early achievement of PR was associated with a median OS of 70 months vs 7 months if PR was not achieved. Failure to achieve VGPR by 2 months was not associated with therapeutic futility, with 65% of patients going on to achieve VGPR or better as their best response. **Conclusions:** Failure to achieve haematological PR after 2 months of bortezomib-based therapy is associated low likelihood of subsequently achieving deep haematological response and organ responses and predicts poor survival, especially for cardiac stage 3A and 3B disease. Such patients should be switched to alternate salvage therapy.

P-440

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Introduction: The R2-ISS risk stratification system revises the R-ISS scoring system to improve risk stratification in newly diagnosed multiple myeloma (NDMM). The R2-ISS scoring system was derived in a clinical trial population composed mainly of European patients and hence by default the treatments those patients received were different to current standards of care in different parts of the world. Further, the applicability of this scoring in a real-world population from Asia remains unknown. The aim of this study was to explore the validity of the R2-ISS scoring system in a real-world Asian population we applied the R2-ISS scoring to a cohort of Asian patients recruited into the Asia-Pacific (APAC) Myeloma and Related Diseases Registry (MRDR). Registry patients from 4 participating Asian countries/regions across multiple sites from Korea, Singapore, Malaysia and Taiwan were included. **Methods:** R2-ISS scoring was retrospectively applied to a NDMM cohort from the APAC MRDR diagnosed between 1st January 2018 and 22nd October 2022. The Kaplan-Meier method was used to plot curves for progression-free survival (PFS) and overall survival (OS). Different risk groups were compared using the log-rank test. **Results:** Of the 946 patients in the APAC MRDR from the 4 countries, complete staging data (ISS, LDH and FISH) was available for 642 patients. The median follow-up for the entire cohort was 12.3 months. Top 5 treatment regimens used for the whole cohort were VCD / VTD / RD / VMP and VRD. R2-ISS delineated the patients into 4 groups (Categories 1-4) with median PFS of NR, 29, 25 and 15 months respectively. PFS difference was significant between R2-ISS I vs III and R2-ISS I vs IV but not between R2-ISS I vs II. Similarly, OS was significantly longer for R2-ISS I vs IV group patients only. OS was not significantly different for R2-ISS I vs II whilst I vs III showed a trend towards significance. Of the 372 patients originally belonging to the R-ISS2 category, 2, 114, 240 and 16 patients were re-classified as R2-ISS 1,2,3,4 groups respectively (mPFS 7, 29, 25 and 13 months). Apart from the 2 patients with R2-ISS score 1, the PFS of the rest of R2-ISS score patients delineated suggesting the validity of this scoring system in this group of patients. When R2ISS groups 1&2 and 3&4 were pooled together PFS was NR Vs 21.2 months. OS is not mature at the present time. **Conclusions:** In this analysis, the R2-ISS system was able to stratify our cohort of Asian NDMM patients into four risk groups according to PFS. OS data is immature and longer follow-up is required. However, the clear distinction between groups I versus II was not seen in this real-world study likely due to the very low numbers in group 1. The R2-ISS effectively differentiates the R-ISS stage II category, addressing a disadvantage of the R-ISS system.

P-441

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Yashwanth Sudhini[1], Binod Dhakal[2], Jochen Reiser[1], Mehmet Altintas[1], Eunsil Hahm[1], Vasil Peev[1], Parameswaran Venugopal[1], Agne Paner[1]

[1]Rush University Medical Center; [2]Medical College of Wisconsin, Milwaukee, WI, USA

Introduction: Soluble Urokinase Plasminogen Activator Receptor (SuPAR) is an inflammatory mediator of kidney injury in various clinical settings. SuPar levels have been found to be higher in patients with multiple myeloma (MM) when compared to healthy controls, and have been correlated with worse kidney function in MM pts. However, data is limited to its role in mediating kidney injury and

(17%) and 3B (15%). 71% had renal involvement with a median eGFR of 69mls/min and median proteinuria of 2.4g/d, with 9% dialysis dependent at presentation. Bortezomib regimens were: VCD (72%), VCD+daratumumab (13%), MDV (7%), VD (6%) and VRD (3%), with a median of 6 cycles delivered. Median OS was 6.2 years which was adversely associated with more advanced cardiac disease: stage 1 (not reached), stage 2 (90 months), stage 3A (52 months) and stage 3B (9 months)(p=0.0001). Haematological response after 2 months of bortezomib-based induction was: CR (17%), VGPR (40%), PR (17%) and less than PR (16%). 10% of patients died prior to 2 month response assessment. Failure to achieve PR by 2 months was associated with a low chance of achieving deep responses, with only 5% going on to achieve VGPR or better (p< 0.001). Similarly, failure to achieve PR by 2 months predicted a low likelihood of improving organ function with less chance of cardiac (6% vs 47%, p=0.001) and renal (20% vs 41%, p=0.044) responses. In a landmark analysis, failure to achieve PR after 2 months predicted worse OS (median 48 vs 93 months, p=0.041), a finding confirmed in multivariate analysis including cardiac stage. This effect was particularly evident for patients with cardiac stage 3A and 3B disease, where the early achievement of PR was associated with a median OS of 70 months vs 7 months if PR was not achieved. Failure to achieve VGPR by 2 months was not associated with therapeutic futility, with 65% of patients going on to achieve VGPR or better as their best response. **Conclusions:** Failure to achieve haematological PR after 2 months of bortezomib-based therapy is associated low likelihood of subsequently achieving deep haematological response and organ responses and predicts poor survival, especially for cardiac stage 3A and 3B disease. Such patients should be switched to alternate salvage therapy.

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P-441

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P-441

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ultimately renal recovery. In this pilot study we compared baseline suPAR values between patients with MM requiring treatment and those with smoldering state or MGUS. We also determined whether suPAR levels correlate with the level of renal impairment, response to myeloma treatment and kidney recovery. **Methods:** SuPAR levels were measured in patients at the time of diagnosis, including seven patients with smoldering myeloma or MGUS and 11 patients with newly diagnosed MM requiring treatment. Among patients undergoing treatment for MM suPAR levels were repeated after induction therapy and after autologous stem cell transplant (ASCT). Renal function and MM response to treatment were assessed at the same time points. **Results:** Patients with smoldering myeloma and MGUS had lower average suPAR level 3.35 ng/ml (SD +/- 1.78) than patients with MM requiring treatment 4.5 ng/ml (SD +/- 1.97) at baseline, but it was not statistically significant (p 0.22). Average suPAR level was higher in patients with glomerular filtration rate (GFR) of less than 40 ml/min/1.73 m^2 compared to the rest of study subjects 3.85 (SD +/- 1.8) vs 4.74 (SD +/- 2.44), but also not statistically significant (0.49). Four patients in the study underwent treatment for MM and had serial measurements of SuPAR levels. All patients achieved VGPR or better to the induction regimen. Two of the three patients with available data had a decline in suPAR level after induction regimen and kidney function remained stable. One patient had stable suPAR level around 3 ng/ml and showed improvement of kidney function. **Conclusions:** This pilot study shows that suPAR levels are elevated both in patients with multiple myeloma requiring treatment and patients with MGUS and smoldering multiple myeloma. We found no difference in suPAR levels in patients with MM and GFR of less than 40 ml/min/1.73 m^2 vs more than 40 ml/min/1.73 m^2. A suPAR level around 3 ng/ml before or after treatment appears to be beneficial for stable or improving kidney function. This finding supports further study of suPAR as a prognostic factor in multiple myeloma. SuPAR effect on myeloma prognosis and GFR in patients with renal impairment, will be evaluated in a large phase 2 trial Bortezomib, Isatuximab, Cyclophosphamide and Dexamethasone Induction in Transplant-Eligible Multiple Myeloma Patients (NCT04240054).

P-442

Imaging cardiac amyloidosis using 18F-florbetaben positron electron topography (PET) in systemic light chain (AL) amyloidosis

Nirija Ranjit Anderson[1], Joshua Tobin[1], Phillip Law[1], Peter Mollee[1]

[1]Princess Alexandra Hospital, Queensland Health

Introduction: 18F-florbetaben is a novel radiotracer that has previously demonstrated capability in delineating between cardiac amyloidosis and other causes of cardiac hypertrophy. We aim to assess the utility of 18F-florbetaben PET for cardiac imaging in patients with systemic AL to define cardiac involvement at baseline and following treatment. **Methods:** Newly diagnosed or relapsed patients with systemic AL amyloidosis and cardiac involvement, as determined by 2D speckled transthoracic echocardiogram and cardiac biomarkers, between June 2018 and December 2020 were approached to undertake a PET scan using 18F-florbetaben. Mean and maximal left ventricular (LV) myocardial standardised uptake values (SUV) were recorded and used to graph time activity curves (TAC). Percentage myocardial 18F-florbetaben retention was calculated from the TAC and compared with the following variables: LV global longitudinal strain (GLS) and intraventricular septal wall thickness (IVs); serum brain natriuretic peptide (BNP) and cardiac troponin I (cTnI), using Pearson Correlation for statistical analysis. Pearson's chi-squared test was used for correlation between cardiac staging (using Mayo 2004 staging for AL amyloidosis) and SUV. The Kaplan-Meir method was used to calculate overall survival. **Results:** 12 patients with systemic AL amyloidosis and suspected cardiac involvement (11 newly diagnosed, 1 relapsed) underwent a 18F-florbetaben PET scan prior to commencement of systemic therapy; 42% were female with a mean age of 63 years at diagnosis. There were 5 deaths (42%), all related to progressive AL amyloidosis. Two-year survival was 58.3%, with a mean overall survival of 7.3 years (95% CI 4.08 – 10.52). Statistical significance was not reached but there was a trend towards correlation between percentage myocardial 18F-florbetaben retention and LV GLS (r=0.5, p=0.08). There was no correlation demonstrated between IVs, BNP or cTnI in this study. There was also a trend towards higher SUVmean with stage 3 cardiac amyloidosis, which holds prognostic relevance clinically as these patients have a significantly lower overall survival. Of note, a previously defined cut-off in a pilot study using a percentage myocardial 18F-florbetaben retention of less than 40% to exclude cardiac amyloidosis did prompt review of 2 patients' cases in this cohort and findings supported either an alternative cause of heart failure or low likelihood of cardiac involvement with AL amyloidosis (IgM type, with normal cardiac biomarkers and borderline echocardiogram findings). **Conclusions:** The utility of 18F-florbetaben PET in AL amyloidosis is complementary to currently available assessment tools and may add value in patients with potentially multifactorial causes of cardiac dysfunction, those with unclear cardiac involvement as part of their initial work up, and to identify patients with more severe cardiac amyloid burden. Analysis of serial imaging at end of treatment to assess role in monitoring of disease burden and organ response will follow.

P-443

Localised light chain (AL) amyloidosis: presentation, treatment and outcomes; an observational study

Nirija Ranjit Anderson[1], Emad Abro[1], Dariusz Korczyk[1], Peter Mollee[1]

[1]Princess Alexandra Hospital, Queensland Health

Introduction: Localised immunoglobulin light chain associated amyloid deposition is a rare disease. Tissue biopsy does not discriminate between localised and systemic forms of amyloidosis, thus clinical assessment of pattern of presentation, organ involvement and the presence or absence of a monoclonal component is required to discern between the two. Treatment recommendations are vastly different dependent on this diagnosis. We report the clinical characteristics, treatment modalities and outcomes in

ultimately renal recovery. In this pilot study we compared baseline suPAR values between patients with MM requiring treatment and those with smoldering state or MGUS. We also determined whether suPAR levels correlate with the level of renal impairment, response to myeloma treatment and kidney recovery. **Methods:** SuPAR levels were measured in patients at the time of diagnosis, including seven patients with smoldering myeloma or MGUS and 11 patients with newly diagnosed MM requiring treatment. Among patients undergoing treatment for MM suPAR levels were repeated after induction therapy and after autologous stem cell transplant (ASCT). Renal function and MM response to treatment were assessed at the same time points. **Results:** Patients with smoldering myeloma and MGUS had lower average suPAR level 3.35 ng/ml (SD +/- 1.78) than patients with MM requiring treatment 4.5 ng/ml (SD +/- 1.97) at baseline, but it was not statistically significant (p 0.22). Average suPAR level was higher in patients with glomerular filtration rate (GFR) of less than 40 ml/min/1.73 m^2 compared to the rest of study subjects 3.85 (SD +/- 1.8) vs 4.74 (SD +/- 2.44), but also not statistically significant (0.49). Four patients in the study underwent treatment for MM and had serial measurements of SuPAR levels. All patients achieved VGPR or better to the induction regimen. Two of the three patients with available data had a decline in suPAR level after induction regimen and kidney function remained stable. One patient had stable suPAR level around 3 ng/ml and showed improvement of kidney function. **Conclusions:** This pilot study shows that suPAR levels are elevated both in patients with multiple myeloma requiring treatment and patients with MGUS and smoldering multiple myeloma. We found no difference in suPAR levels in patients with MM and GFR of less than 40 ml/min/1.73 m^2 vs more than 40 ml/min/1.73 m^2. A suPAR level around 3 ng/ml before or after treatment appears to be beneficial for stable or improving kidney function. This finding supports further study of suPAR as a prognostic factor in multiple myeloma. SuPAR effect on myeloma prognosis and GFR in patients with renal impairment, will be evaluated in a large phase 2 trial Bortezomib, Isatuximab, Cyclophosphamide and Dexamethasone Induction in Transplant-Eligible Multiple Myeloma Patients (NCT04240054).

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Introduction: 18F-florbetaben is a novel radiotracer that has previously demonstrated capability in delineating between cardiac amyloidosis and other causes of cardiac hypertrophy. We aim to assess the utility of 18F-florbetaben PET for cardiac imaging in patients with systemic AL to define cardiac involvement at baseline and following treatment. **Methods:** Newly diagnosed or relapsed patients with systemic AL amyloidosis and cardiac involvement, as determined by 2D speckled transthoracic echocardiogram and cardiac biomarkers, between June 2018 and December 2020 were approached to undertake a PET scan using 18F-florbetaben. Mean and maximal left ventricular (LV) myocardial standardised uptake values (SUV) were recorded and used to graph time activity curves (TAC). Percentage myocardial 18F-florbetaben retention was calculated from the TAC and compared with the following variables: LV global longitudinal strain (GLS) and intraventricular septal wall thickness (IVs); serum brain natriuretic peptide (BNP) and cardiac troponin I (cTnI), using Pearson Correlation for statistical analysis. Pearson's chi-squared test was used for correlation between cardiac staging (using Mayo 2004 staging for AL amyloidosis) and SUV. The Kaplan-Meir method was used to calculate overall survival. **Results:** 12 patients with systemic AL amyloidosis and suspected cardiac involvement (11 newly diagnosed, 1 relapsed) underwent a 18F-florbetaben PET scan prior to commencement of systemic therapy; 42% were female with a mean age of 63 years at diagnosis. There were 5 deaths (42%), all related to progressive AL amyloidosis. Two-year survival was 58.3%, with a mean overall survival of 7.3 years (95% CI 4.08 – 10.52). Statistical significance was not reached but there was a trend towards correlation between percentage myocardial 18F-florbetaben retention and LV GLS (r=0.5, p=0.08). There was no correlation demonstrated between IVs, BNP or cTnI in this study. There was also a trend towards higher SUVmean with stage 3 cardiac amyloidosis, which holds prognostic relevance clinically as these patients have a significantly lower overall survival. Of note, a previously defined cut-off in a pilot study using a percentage myocardial 18F-florbetaben retention of less than 40% to exclude cardiac amyloidosis did prompt review of 2 patients' cases in this cohort and findings supported either an alternative cause of heart failure or low likelihood of cardiac involvement with AL amyloidosis (IgM type, with normal cardiac biomarkers and borderline echocardiogram findings). **Conclusions:** The utility of 18F-florbetaben PET in AL amyloidosis is complementary to currently available assessment tools and may add value in patients with potentially multifactorial causes of cardiac dysfunction, those with unclear cardiac involvement as part of their initial work up, and to identify patients with more severe cardiac amyloid burden. Analysis of serial imaging at end of treatment to assess role in monitoring of disease burden and organ response will follow.

P-443

Localised light chain (AL) amyloidosis: presentation, treatment and outcomes; an observational study

Nirija Ranjit Anderson[1], Emad Abro[1], Dariusz Korczyk[1], Peter Mollee[1]

[1]Princess Alexandra Hospital, Queensland Health

Introduction: Localised immunoglobulin light chain associated amyloid deposition is a rare disease. Tissue biopsy does not discriminate between localised and systemic forms of amyloidosis, thus clinical assessment of pattern of presentation, organ involvement and the presence or absence of a monoclonal component is required to discern between the two. Treatment recommendations are vastly different dependent on this diagnosis. We report the clinical characteristics, treatment modalities and outcomes in

ultimately renal recovery. In this pilot study we compared baseline suPAR values between patients with MM requiring treatment and those with smoldering state or MGUS. We also determined whether suPAR levels correlate with the level of renal impairment, response to myeloma treatment and kidney recovery. **Methods:** SuPAR levels were measured in patients at the time of diagnosis, including seven patients with smoldering myeloma or MGUS and 11 patients with newly diagnosed MM requiring treatment. Among patients undergoing treatment for MM suPAR levels were repeated after induction therapy and after autologous stem cell transplant (ASCT). Renal function and MM response to treatment were assessed at the same time points. **Results:** Patients with smoldering myeloma and MGUS had lower average suPAR level 3.35 ng/ml (SD +/- 1.78) than patients with MM requiring treatment 4.5 ng/ml (SD +/- 1.97) at baseline, but it was not statistically significant (p 0.22). Average suPAR level was higher in patients with glomerular filtration rate (GFR) of less than 40 ml/min/1.73 m^2 compared to the rest of study subjects 3.85 (SD +/- 1.8) vs 4.74 (SD +/- 2.44), but also not statistically significant (0.49). Four patients in the study underwent treatment for MM and had serial measurements of SuPAR levels. All patients achieved VGPR or better to the induction regimen. Two of the three patients with available data had a decline in suPAR level after induction regimen and kidney function remained stable. One patient had stable suPAR level around 3 ng/ml and showed improvement of kidney function. **Conclusions:** This pilot study shows that suPAR levels are elevated both in patients with multiple myeloma requiring treatment and patients with MGUS and smoldering multiple myeloma. We found no difference in suPAR levels in patients with MM and GFR of less than 40 ml/min/1.73 m^2 vs more than 40 ml/min/1.73 m^2. A suPAR level around 3 ng/ml before or after treatment appears to be beneficial for stable or improving kidney function. This finding supports further study of suPAR as a prognostic factor in multiple myeloma. SuPAR effect on myeloma prognosis and GFR in patients with renal impairment, will be evaluated in a large phase 2 trial Bortezomib, Isatuximab, Cyclophosphamide and Dexamethasone Induction in Transplant-Eligible Multiple Myeloma Patients (NCT04240054).

P-442

Imaging cardiac amyloidosis using 18F-florbetaben positron electron topography (PET) in systemic light chain (AL) amyloidosis

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patients with localised AL amyloidosis reviewed at a quaternary amyloidosis referral centre. **Methods:** Database and medical records for all patients referred between January 2010 to May 2023 with a confirmed diagnosis of localised AL amyloidosis were reviewed. Demographic data, sites of organ involvement, treatment received, and recurrence or progression were assessed for each patient. Overall survival was estimated by the Kaplan-Meier method. **Results:** 121 patients with localised AL amyloidosis were reviewed with the mean age of diagnosis being 58.4 years; 48% were female. The most common sites of presentation were pulmonary 20%, genitourinary and gastrointestinal tract with 18% each, followed by cutaneous/soft tissue 17%. Other commonly involved sites include the larynx and eye 10% each. Rarer sites were nodal 3%, central nervous system 2%, and nasopharynx 2%. 67% were treated with observation alone following their original biopsy. 21% had surgical management for symptomatic mass effect; the greatest proportion of these consisting of laryngeal or urinary tract involvement, with 28% and 24% respectively. 4% underwent radiotherapy for either an underlying lymphoproliferative disorder or for a site not amenable to surgery. 3% received systemic therapy (chemotherapy/immunotherapy), all were for localised nodal amyloid associated with lymphoma. 3% received other treatment options, such as autologous stem cell transplantation (for localised amyloid deposition associated with a plasmacytoma), topical therapy, or antiviral eradication therapy. The remaining 4% had incomplete records to enable assessment of treatment. Localised disease recurrence occurred in 14% of cases, with the most common site of recurrence being laryngeal at 30%. There was no progression to systemic AL amyloidosis in any patient. 10% of patients died during the review period, all from causes other than AL amyloidosis. The estimated 5-year overall survival was 91% (95% CI 83–96%) compared to 64% (95% CI 54-73%) for systemic AL amyloidosis. **Conclusions:** Localised AL amyloidosis is a distinctively different entity which needs to be distinguished from systemic amyloidosis, especially between AL and ATTR types. It has comparatively different presenting organ involvement patterns and a favourable natural history profile without active intervention in most cases. Localised site recurrences occur and can be managed through minimally invasive surgical approaches if symptomatic.

P-444

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Introduction: Correct diagnosis of amyloidosis subtype is a critical step to direct patient management, inform prognosis and guide targeted genetic testing. Laser capture microdissection and tandem mass spectrometry (LMD-MS) analysis of formalin-fixed paraffin-embedded (FFPE) biopsy samples is emerging as the new gold-standard diagnostic technique in amyloid subtyping, with likely superiority to conventional immunohistochemistry (IHC) based approaches. **Methods:** To assess this, a novel LMD-MS assay was developed. In brief, 10-micron sections were cut from FFPE biopsies, deparaffinised and stained with Congo red. Laser microdissection was performed of Congo red positive deposits. Proteins from dissected tissue were digested to peptides and analysed with high-performance liquid chromatography (HPLC) coupled with a ThermoFisher scientific Q Exactive plus mass spectrometer and peptide matches assessed against the Swiss-Prot/Uniprot human protein database with the addition of the Kabat library. 121 patient samples were assessed using both LMD-MS and an IHC panel consisting of 4 commercial antibodies: kappa, lambda, transthyretin and serum amyloid A. Each IHC was assessed independently by two experienced pathologists and graded quantitatively. LMD-MS was reported using institutional bioinformatic reporting algorithms. **Results:** Biopsy sites were most frequently renal (25.6%), cardiac (17%) and gastrointestinal tract (25.6%). IHC assessment was considered non-diagnostic in 44% of samples. 121 samples were assessed for LMD-MS and 110 were samples were suitable for analysis with the assay. An amyloid subtype was confidently identified in 96% of samples analysed, with only 4 samples not identifying an amyloid forming protein. Concordance was assessed between LMD-MS and IHC. 3 cases of IHC typed light chain amyloidosis were reclassified as non-AL amyloid types and 3 cases of IHC typed AA amyloidosis were reclassified as AL-amyloidosis, both with potentially significant therapeutic implications. **Conclusions:** Proteomic assessment of amyloid biopsy with laser capture microdissection and mass spectrometry is superior to immunohistochemical analysis using commercial antibodies for amyloidosis subtyping.

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the clinical diagnostic laboratory, optimisation and validation of this assay was required. **Methods:** LMD-MS was performed on 78 patient samples and results evaluated assessing key MS measurements and the identification of amyloid signature and amyloid forming proteins. A bioinformatic reporting algorithm was developed and applied to a validation set of 226 samples. 121 samples were assessed by both IHC and LMD-MS for comparative assessment. 11 samples were assayed by this LMD-MS assay with results compared to those obtained at international laboratories. **Results:** Critical MS datapoints contributing to confident amyloid forming protein identification were protein mean intensity, number of spectral matches and relative abundance. The addition of the Kabat protein library to the Swiss-Prot/Uniprot database did not interfere with identification of the amyloid proteins and showed superior diagnostic yield. Technical changes including buffer formulation and MS analyser technology variation had no impact on amyloid forming protein identification. A bioinformatic reporting algorithm was created which confidently identified an amyloid subtype in 96.1% of patient samples. LMD-MS was shown to be superior to IHC in subtyping of amyloid proteins with a non-diagnostic rate of only 3.6% The local LMD-MS assay showed 100% concordance with international laboratory analysis. **Conclusions:** A novel LMD-MS assay has been developed and validated and shows superiority to the previous IHC based standard of care assessment and, while bioinformatic algorithm differs, gives identical information to LMD-MS from international centres.

P-446

Waldenström Macroglobulinaemia lymphoma patients have impaired platelet haemostatic function

Dipti Talaulikar[1,2], Simone Brysland[2], Elizabeth Gardiner[2]

[1]Canberra Health Services; [2]Australian National University

Introduction: Waldenström Macroglobulinaemia (WM) is a B-cell lymphoma with clinical features including thrombocytopenia, IgM-mediated hyperviscosity, bleeding and bruising. Treatment of WM patients with Bruton's tyrosine kinase inhibitors (BTKis) may exacerbate bleeding risk. Abnormal haemostasis may result from platelet dysfunction and altered coagulation, however the extent of dysregulation of these processes in WM patients is unknown. We therefore aimed to evaluate haemostatic and platelet dysfunction in WM patients. **Methods:** Platelet receptor levels in samples from 19 clinically annotated WM patients or healthy donors (HDs) were measured by flow cytometry. Thrombin generation in plasma ± platelets was measured by fluorescence resonance energy transfer assay. Whole blood clotting potential was evaluated by rotational thromboelastometry (ROTEM). Levels of plasma soluble GPVI (sGPVI) and serum thrombopoietin (TPO) were measured by enzyme-linked immunosorbent assays. **Results:** WM platelets had reduced levels of GPIbα (p=0.0153), GPVI (p=0.0347) and reticulation (p=0.0005), and increased overall sialylation (p=0.0079) and tetraspanin CD9 levels (p< 0.0001). WM plasma displayed significantly reduced thrombin generation potential (p=0.0408) and WM platelets contributed less to thrombus initiation (p=0.0208) and rate (p< 0.0001) by ROTEM, but displayed normal responses to agonists, except in the presence of BTKis. Plasma sGPVI were within normal ranges and TPO levels were increased (p< 0.0001). **Conclusions:** The impaired haemostatic potential in WM samples was independent of BTKi therapy. Reduced platelet GPIbα and GPVI may arise from altered megakaryocyte maturation and thrombopoiesis, associated with bone marrow malignancy. Monitoring platelet and coagulation properties may help stratify WM patients for bleeding risk.

P-447

Daratumumab based Induction for plasma cell leukaemia & early ASCT: experience from a tertiary care hospital in North India

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Introduction: Plasma cell leukaemia (PCL) is the most aggressive form of plasma cell dyscrasia. Usually It requires VDT-PACE like aggressive Induction chemotherapy. When patient is not fit for VDT –PACE, Daratumumab based Induction therapy is an option. **Methods:** We are presenting a case of plasma cell leukaemia treated with Daratumumab based induction Chemotherapy, followed by early autologous transplant **Results:** A 48 year old female referred to hematology department from Nephrology ICU, she was admitted to the nephrology ICU with Complaint of oliguria & CCF. She underwent 2 cycles of haemodialysis. On work up the cause of AKI was found to be plasma cell leukaemia. She was having IgG Lambda M band (Qty- 5.8g/dl), Sr Kappa -31, Sr Lambda- 11,000 & Kappa/lambda ratio of 0.002. Her Myeloma FISH panel was showing t (11; 14) & gain 1q. She was started on DARA-VCD induction, in view of fungal pneumonia at presentation. After 4 cycles of DARA-VCD chemotherapy, she was in VGPR, with M band of 0.2g/dl & Sr Lambda of 7. On pre-transplant workup she was MRD positive, PET negative, with eGFR of 29 ml/min/ 1.73m^2, PFT was showing mild restriction. She underwent G-CSF+ Plerixafor mobilization, with CD4 cell count of 3.9x 10^6 cells/Kg. Mel 140 conditioning was used for conditioning, due to her low eGFR. Febrile neutropenia, & Mucositis (Grade 3-4) was major issues during transplant otherwise she tolerated well. She engrafted for neutrophils on ay 12 & for platelets on day 15. There were no major complications till Day +100; Day +100 Marrow was MRD Negative. She was given 2 cycles of DARA-VCD consolidation & then switched to Dara/Bortezomib based maintenance therapy. She is absolutely fine, currently on Day +180. **Conclusions:** Daratumumab based Induction therapy is an important treatment alternative for VDT –PACE chemotherapy for PCL.A randomised control trial should be conducted in more number of patients.

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Introduction: Waldenström Macroglobulinaemia (WM) is a B-cell lymphoma with clinical features including thrombocytopenia, IgM-mediated hyperviscosity, bleeding and bruising. Treatment of WM patients with Bruton's tyrosine kinase inhibitors (BTKis) may exacerbate bleeding risk. Abnormal haemostasis may result from platelet dysfunction and altered coagulation, however the extent of dysregulation of these processes in WM patients is unknown. We therefore aimed to evaluate haemostatic and platelet dysfunction in WM patients. **Methods:** Platelet receptor levels in samples from 19 clinically annotated WM patients or healthy donors (HDs) were measured by flow cytometry. Thrombin generation in plasma ± platelets was measured by fluorescence resonance energy transfer assay. Whole blood clotting potential was evaluated by rotational thromboelastometry (ROTEM). Levels of plasma soluble GPVI (sGPVI) and serum thrombopoietin (TPO) were measured by enzyme-linked immunosorbent assays. **Results:** WM platelets had reduced levels of GPIbα (p=0.0153), GPVI (p=0.0347) and reticulation (p=0.0005), and increased overall sialylation (p=0.0079) and tetraspanin CD9 levels (p< 0.0001). WM plasma displayed significantly reduced thrombin generation potential (p=0.0408) and WM platelets contributed less to thrombus initiation (p=0.0208) and rate (p< 0.0001) by ROTEM, but displayed normal responses to agonists, except in the presence of BTKis. Plasma sGPVI were within normal ranges and TPO levels were increased (p< 0.0001). **Conclusions:** The impaired haemostatic potential in WM samples was independent of BTKi therapy. Reduced platelet GPIbα and GPVI may arise from altered megakaryocyte maturation and thrombopoiesis, associated with bone marrow malignancy. Monitoring platelet and coagulation properties may help stratify WM patients for bleeding risk.

P-447

Daratumumab based Induction for plasma cell leukaemia & early ASCT: experience from a tertiary care hospital in North India

Sanjeev Yadav[1], Faheema Hasan[1], Dinesh Chandra[1], Manish Kumar Singh[1], Khaiqur Rahman[1], Ruchi Gupta[1], Rajesh Kashyap[1]

[1]Sanjay Gandhi Postgraduate Institute of Medical Sciences

Introduction: Plasma cell leukaemia (PCL) is the most aggressive form of plasma cell dyscrasia. Usually It requires VDT-PACE like aggressive Induction chemotherapy. When patient is not fit for VDT –PACE, Daratumumab based Induction therapy is an option. **Methods:** We are presenting a case of plasma cell leukaemia treated with Daratumumab based induction Chemotherapy, followed by early autologous transplant **Results:** A 48 year old female referred to hematology department from Nephrology ICU, she was admitted to the nephrology ICU with Complaint of oliguria & CCF. She underwent 2 cycles of haemodialysis. On work up the cause of AKI was found to be plasma cell leukaemia. She was having IgG Lambda M band (Qty- 5.8g/dl), Sr Kappa -31, Sr Lambda- 11,000 & Kappa/lambda ratio of 0.002. Her Myeloma FISH panel was showing t (11; 14) & gain 1q. She was started on DARA-VCD induction, in view of fungal pneumonia at presentation. After 4 cycles of DARA-VCD chemotherapy, she was in VGPR, with M band of 0.2g/dl & Sr Lambda of 7. On pre-transplant workup she was MRD positive, PET negative, with eGFR of 29 ml/min/ 1.73m^2, PFT was showing mild restriction. She underwent G-CSF+ Plerixafor mobilization, with CD4 cell count of 3.9x 10^6 cells/Kg. Mel 140 conditioning was used for conditioning, due to her low eGFR. Febrile neutropenia, & Mucositis (Grade 3-4) was major issues during transplant otherwise she tolerated well. She engrafted for neutrophils on ay 12 & for platelets on day 15. There were no major complications till Day +100; Day +100 Marrow was MRD Negative. She was given 2 cycles of DARA-VCD consolidation & then switched to Dara/Bortezomib based maintenance therapy. She is absolutely fine, currently on Day +180. **Conclusions:** Daratumumab based Induction therapy is an important treatment alternative for VDT –PACE chemotherapy for PCL.A randomised control trial should be conducted in more number of patients.

the clinical diagnostic laboratory, optimisation and validation of this assay was required. **Methods:** LMD-MS was performed on 78 patient samples and results evaluated assessing key MS measurements and the identification of amyloid signature and amyloid forming proteins. A bioinformatic reporting algorithm was developed and applied to a validation set of 226 samples. 121 samples were assessed by both IHC and LMD-MS for comparative assessment. 11 samples were assayed by this LMD-MS assay with results compared to those obtained at international laboratories. **Results:** Critical MS datapoints contributing to confident amyloid forming protein identification were protein mean intensity, number of spectral matches and relative abundance. The addition of the Kabat protein library to the Swiss-Prot/Uniprot database did not interfere with identification of the amyloid proteins and showed superior diagnostic yield. Technical changes including buffer formulation and MS analyser technology variation had no impact on amyloid forming protein identification. A bioinformatic reporting algorithm was created which confidently identified an amyloid subtype in 96.1% of patient samples. LMD-MS was shown to be superior to IHC in subtyping of amyloid proteins with a non-diagnostic rate of only 3.6% The local LMD-MS assay showed 100% concordance with international laboratory analysis. **Conclusions:** A novel LMD-MS assay has been developed and validated and shows superiority to the previous IHC based standard of care assessment and, while bioinformatic algorithm differs, gives identical information to LMD-MS from international centres.

P-446

Waldenström Macroglobulinaemia lymphoma patients have impaired platelet haemostatic function

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P-448

Impact of molecular cytogenetic abnormalities on the risk of disease progression in solitary bone plasmacytomas

Udit Yadav[1], Shaji Kumar[1], Angela Dispenzieri[1], Francis Buadi[1], David Dingli[1], Martha Lacy[1], Rafael Fonseca[2], Leif Bergsagel[2], Ricardo Parrondo[3], Suzanne Hayman[1], Prashant Kapoor[1], Nelson Leung[1], Joselle Cook[1], Moritz Binder[1], Abhishek Seth[1], Eli Muchtar[1], Rahma Warsame[1], Taxiarchis Kourelis[1], Sikander Ailawadhi[3], Vivek Roy[3], Ronald Go[1], Robert Kyle[1], Vincent Rajkumar[1], Wilson Gonsalves[1]

[1]Mayo Clinic, Rochester; [2]Mayo Clinic, Phoenix; [3]Mayo Clinic, Jacksonville

Introduction: The standard treatment for solitary bone plasmacytoma (SBP) with or without minimal marrow involvement is definitive radiation therapy followed by observation. However, most patients with SBP progress to MM. Whether the presence of high-risk (HR) cytogenetic abnormalities by FISH detected in the clonal plasma cells obtained either directly from the SBP tissue or the corresponding bone marrow aspirate performed at the time of diagnosis is associated with a shorter time to progression (TTP) to MM has not been studied to date. **Methods:** We evaluated all patients diagnosed with SBP with or without minimal marrow involvement seen at the Mayo Clinic from January 2012 to July 2022. The presence of del(17p), t(14;16), t(4;14), or +1q (gain or amplification) by FISH in clonal plasma cells was defined as HR. All patients were required to have had a biopsy-proven plasmacytoma arising from a bone, advanced cross-sectional imaging (positron emission tomography (PET)/computed tomography (CT), whole body-CT Skeletal Survey, or whole-body magnetic resonance imaging (WB-MRI)) demonstrating the absence of any additional lytic or FDG avid bone lesions or plasmacytomas, a posterior iliac crest bone marrow biopsy and aspirate containing fewer than 10% clonal plasma cells and no clinical evidence of CRAB symptoms (anemia, elevated creatinine and hypercalcemia) which would fulfill the diagnosis for MM as per the International Myeloma Working Group (IMWG) criteria. We excluded patients with concurrent light chain amyloidosis, POEMS syndrome, 10% or more plasma cells on bone marrow biopsy, and patients who fulfilled the criteria for smoldering or active MM. **Results:** A total of 114 patients were included in this cohort, and FISH was available for 55 patients (48.2%), of which 22 were classified as HR (40%). In patients with FISH results available, more patients with HR FISH (N = 20, 91%) progressed to MM compared to patients without HR FISH (N=16,48%) (p=0.0012) after a median follow-up of 54 months. The median TTP to MM for patients with HR FISH was 8 months (95%CI 6.3-26) compared to 42 months (95%CI 25-NR) in patients without HR FISH (p < 0.001). In patients with HR FISH, 59% progressed within 12 months of diagnosis compared to 15% of patients without HR FISH (p < 0.001) and 73% of patients with HR FISH progressed within 24 months of diagnosis compared to 27% of patients without HR FISH (p< 0.001). In a multivariate analysis, only the presence of HR FISH was a significant predictor for shorter TTP to MM, independent of the presence of minimal marrow involvement and an abnormal serum free light chain (sFLC) ratio at diagnosis. **Conclusions:** Patients with SBP and HR FISH have a significantly higher risk and shorter TTP to MM compared to patients with SBP and without HR FISH. There is an unmet need to investigate novel therapeutic strategies to prevent the rather rapid disease progression to MM in this patient population.

P-449

Role of education and empowerment in multiple myeloma patients

Jennifer Ahlstrom[1], Marilú Nájera Flores[1], Scott Campbell[2], Tara Roy[2], Patricia Alejandra Flores Pérez[1], Jorge Arturo Hurtado Martínez[1], Nathan Sweeney[1], Rachel Kremen[3], Jay Hydren[1]

[1]HealthTree Foundation; [2]Takeda Pharmaceuticals International Co.; [3]Lumanity

Introduction: Multiple myeloma (MM) significantly affects patients' (pts) lives, partly due to its complexity and variety of treatments. Health education has been reported to improve outcomes and self-management in cancer pts, suggesting that a growing abundance of resources to educate and empower could offset the burdens of MM. This study aimed to evaluate the impact of MM diagnosis on pts' lives and study the differences in education and empowerment between pts with Newly Diagnosed MM (NDMM) vs. Relapsed and Refractory MM (RRMM). **Methods:** HealthTree® Cure Hub for Multiple Myeloma is an online portal for pts with plasma cell dyscrasias to help navigate their disease. Using this platform, we conducted a 25-question survey covering patient education, empowerment, and the impact of MM diagnosis. We compared responses between NDMM and RRMM pts. The survey was determined to be of minimal risk and exempted by the WCG Institutional Review Board. **Results:** Of 250 survey participants, 54% were NDMM. The majority were females (53%), college-educated (75%), with an age of 67±8 yrs. At diagnosis, both groups reported obtaining diagnosis-related data mainly from their healthcare team (92%). However, NDMM pts report a higher use of social media for this purpose (26%) than RRMM (19%), and NDMM reported less usage of medical journals (22%) than RRMM (39%). Additionally, in both groups, there was a dramatic increase in the use of online patient advocacy groups to get disease-related information, from 52% (at diagnosis) to 82% (current). Moreover, 79% of pts in both groups reported having a strong or higher desire to learn more about future treatment options. Both felt empowered by their relationship with at least one member of their healthcare team (87%), aiding in information gathering and decision-making. Furthermore, both indicated that care partners play a role in emotional support (79%) and decision-making (59%). Frequent impacts of MM on both patient groups involve exercise (60%) and hobbies (54%). Mental health (53%) and financial impact (55%) significantly increased by 15%-20% in RRMM compared to NDMM (38% and 35%, respectively). The financial burden is moderate to significant for NDMM pts at 67%, and even more so for RRMM pts at 77%. This financial strain reflects why over

P-448

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P-449

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44% of pts in both categories resort to using their personal savings to cover healthcare costs. **Conclusions:** This survey highlighted the critical roles of healthcare teams and online patient advocacy groups in educating and empowering NDMM and RRMM pts, becoming increasingly important resources over time. MM mainly impacts exercise, the ability to do their favorite things, mental health, and finances, particularly in RRMM pts. Financial strain may have led to using personal savings for medical expenses. These findings underscore the importance of education, empowerment, and comprehensive support in addressing the physical and financial aspects of MM patient care.

P-450

Comparison of a battery powered device (OnControl) versus manual Jamshidi needle for bone marrow biopsy in adult patients with plasma cell disorders: a prospective randomized control trial (RCT)

Joel Andrews[1], Nisha Joseph[1], Jessica Neely[1], Angela Hatcher[1], Cecilia Rosand[1], Alex Palmer[1], Maggie Harrington[1], Danielle Roberts[1], Caleb Raine[1], Rosie Pruitt[1], Vikas Gupta[1], Craig Hofmeister[1], Madhav Dhodapkar[1], Lawrence Boise[1], Charise Gleason[1], Jonathan Kaufman[1], Sagar Lonial[1], Ajay Nooka[1]

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Introduction: Bone marrow aspiration and biopsies (BMA&B) provide diagnostic and prognostic information in patients with plasma cell disorders. The use of Jamshidi needle for manual BMA&B has been the established method of choice. Powered biopsy devices (OnControl) are gaining popularity due to shorter procedural time and operator convenience, but are limited by increased incidence of crush artifact and inadequate sampling. We performed a prospective randomized control trial (RCT) to assess the quality of BMA&B and the patient and provider convenience. **Methods:** Adult patients with plasma cell disorders undergoing BMA&B were consented by nine operators who are familiar with both techniques. A total of 100 patients underwent randomization to receive BMA&B by OnControl drill vs manual Jamshidi needle. A questionnaire was used to assess the intensity of pain and the impact of BMA&B on general activity, work, and sleep at baseline and on days 1, 3 and 7. Sedation information, time for completion of procedure, and demographic data were collected. The BM core biopsy length (in mm), crush artifact, and adequacy of the BMA&B were assessed by a pathologist blinded for randomization. The provider convenience with both techniques were collected from the operators prior to the availability of results. **Results:** There were no significant demographic differences between the 2 groups (OnControl vs Jamshidi, respectively). The median age was 65.5 (37-79) vs 63 (35-81) years. Overall, 50% of patients were male, and 35% were black. 91% had a prior BMA&B within the last 2 years (65.9% had 2-4 prior BMA&B and 83.5% had a prior OnControl drill experience). 31% had chronic pain. 38% had lytic lesions, 6% had osteoporosis, 5% had osteopenia and 31% were on active bisphosphonates. 22% had compression fractures and 11% had a prior h/o kyphoplasty. 26% (11% vs 15%, p=0.247) had inadequate sampling - unsuccessful core biopsy (1% vs 4%, p=0.181), aspiration artifact (3% vs 2%, p=0.530), cortical bone only (3% vs 3%, p=0.631) and hemodiluted specimen (5% vs 6%, p=0.575) but were not statistically different between 2 groups. The core length was significantly longer for the OnControl [14 (5-30) vs 9.5 (3-23) mm, p=0.003]. The time for procedure was significantly shorter for OnControl [7 (3-24) vs 10.5 (4-30) minutes, p=0.06]. There were no differences observed between the 2 groups in terms of pain post procedure, or the impact of pain. Operator assessment unanimously favored the use of OnControl device. On a scale of 1-10 (1 being the least inconvenient and 10 the most convenient), median operator convenience for OnControl vs Jamshidi was 10 (range, 9-10) vs 3 (range, 2-7), p< 0.001. **Conclusions:** The OnControl system was associated with less procedural time and a better core biopsy without increased incidence of crush artifact. The robust size of the core biopsy may negate the need for repeat procedures. The operators favored the use of OnControl device over a manually exhausting Jamshidi needle for BMA&B.

P-451

Association between dexamethasone exposure and visually significant cataracts in myeloma

Rahul Banerjee[1], Jorge Arturo Hurtado Martinez[2], Patricia Alejandra Flores Pérez[2], Nolan Porras[2], Jay Hydren[2], Jennifer Ahlstrom[2], Andrew Cowan[3]

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Introduction: Ocular comorbidities such as cataracts, which may lead to blurry vision and QOL impairments, are more common in relapsed multiple myeloma (MM) than in new diagnoses (Ailawadhi 2022). Pre-belantamab ophthalmological analyses from DREAMM-2 [3+ prior lines of therapy (LoT), over half aged ≥65] showed that 60% of pts with relapsed/refractory MM had cataracts at baseline (Popat 2022). In contrast, only 34% of US adults aged ≥65 have cataracts (Wittenborn 2023). We hypothesized that dexamethasone (dex) dose intensity and duration would predict both cataract occurrence as well as visual significance (pt-reported interference with QOL). **Methods:** This was a secondary analysis of pt-reported treatment data collected from users of the HealthTree Cure Hub for Multiple Myeloma database. Pts who recalled developing cataracts with any LoT were asked to rate their cataract-related symptoms on a 1-5 Likert scale. Dex exposure was assessed by calculating the total duration and dosage across all LoTs until cataracts were first reported; cycles were assumed to be 28 days long regardless of regimen. Time-to-cataract survival analyses were conducted to assess the risk of cataracts. Ordinal logistic regression and correlation analyses were performed to evaluate the association between dex exposure and cataract severity. **Results:** Of n=231 pts with MM who recalled developing cataracts, median age at cataract onset was 65 years (range 31-85) with median 23 prior dex cycles (IQR: 3.5-33.3). Of these pts, 36% developed cataracts within 6 cycles of dex and 48% within 12 cycles of dex. Cataract severity (on a 1-5

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Introduction: Ocular comorbidities such as cataracts, which may lead to blurry vision and QOL impairments, are more common in relapsed multiple myeloma (MM) than in new diagnoses (Ailawadhi 2022). Pre-belantamab ophthalmological analyses from DREAMM-2 [3+ prior lines of therapy (LoT), over half aged ≥65] showed that 60% of pts with relapsed/refractory MM had cataracts at baseline (Popat 2022). In contrast, only 34% of US adults aged ≥65 have cataracts (Wittenborn 2023). We hypothesized that dexamethasone (dex) dose intensity and duration would predict both cataract occurrence as well as visual significance (pt-reported interference with QOL). **Methods:** This was a secondary analysis of pt-reported treatment data collected from users of the HealthTree Cure Hub for Multiple Myeloma database. Pts who recalled developing cataracts with any LoT were asked to rate their cataract-related symptoms on a 1-5 Likert scale. Dex exposure was assessed by calculating the total duration and dosage across all LoTs until cataracts were first reported; cycles were assumed to be 28 days long regardless of regimen. Time-to-cataract survival analyses were conducted to assess the risk of cataracts. Ordinal logistic regression and correlation analyses were performed to evaluate the association between dex exposure and cataract severity. **Results:** Of n=231 pts with MM who recalled developing cataracts, median age at cataract onset was 65 years (range 31-85) with median 23 prior dex cycles (IQR: 3.5-33.3). Of these pts, 36% developed cataracts within 6 cycles of dex and 48% within 12 cycles of dex. Cataract severity (on a 1-5

44% of pts in both categories resort to using their personal savings to cover healthcare costs. **Conclusions:** This survey highlighted the critical roles of healthcare teams and online patient advocacy groups in educating and empowering NDMM and RRMM pts, becoming increasingly important resources over time. MM mainly impacts exercise, the ability to do their favorite things, mental health, and finances, particularly in RRMM pts. Financial strain may have led to using personal savings for medical expenses. These findings underscore the importance of education, empowerment, and comprehensive support in addressing the physical and financial aspects of MM patient care.

P-450

Comparison of a battery powered device (OnControl) versus manual Jamshidi needle for bone marrow biopsy in adult patients with plasma cell disorders: a prospective randomized control trial (RCT)

Joel Andrews[1], Nisha Joseph[1], Jessica Neely[1], Angela Hatcher[1], Cecilia Rosand[1], Alex Palmer[1], Maggie Harrington[1], Danielle Roberts[1], Caleb Raine[1], Rosie Pruitt[1], Vikas Gupta[1], Craig Hofmeister[1], Madhav Dhodapkar[1], Lawrence Boise[1], Charise Gleason[1], Jonathan Kaufman[1], Sagar Lonial[1], Ajay Nooka[1]

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Introduction: Bone marrow aspiration and biopsies (BMA&B) provide diagnostic and prognostic information in patients with plasma cell disorders. The use of Jamshidi needle for manual BMA&B has been the established method of choice. Powered biopsy devices (OnControl) are gaining popularity due to shorter procedural time and operator convenience, but are limited by increased incidence of crush artifact and inadequate sampling. We performed a prospective randomized control trial (RCT) to assess the quality of BMA&B and the patient and provider convenience. **Methods:** Adult patients with plasma cell disorders undergoing BMA&B were consented by nine operators who are familiar with both techniques. A total of 100 patients underwent randomization to receive BMA&B by OnControl drill vs manual Jamshidi needle. A questionnaire was used to assess the intensity of pain and the impact of BMA&B on general activity, work, and sleep at baseline and on days 1, 3 and 7. Sedation information, time for completion of procedure, and demographic data were collected. The BM core biopsy length (in mm), crush artifact, and adequacy of the BMA&B were assessed by a pathologist blinded for randomization. The provider convenience with both techniques were collected from the operators prior to the availability of results. **Results:** There were no significant demographic differences between the 2 groups (OnControl vs Jamshidi, respectively). The median age was 65.5 (37-79) vs 63 (35-81) years. Overall, 50% of patients were male, and 35% were black. 91% had a prior BMA&B within the last 2 years (65.9% had 2-4 prior BMA&B and 83.5% had a prior OnControl drill experience). 31% had chronic pain. 38% had lytic lesions, 6% had osteoporosis, 5% had osteopenia and 31% were on active bisphosphonates. 22% had compression fractures and 11% had a prior h/o kyphoplasty. 26% (11% vs 15%, p=0.247) had inadequate sampling - unsuccessful core biopsy (1% vs 4%, p=0.181), aspiration artifact (3% vs 2%, p=0.530), cortical bone only (3% vs 3%, p=0.631) and hemodiluted specimen (5% vs 6%, p=0.575) but were not statistically different between 2 groups. The core length was significantly longer for the OnControl [14 (5-30) vs 9.5 (3-23) mm, p=0.003]. The time for procedure was significantly shorter for OnControl [7 (3-24) vs 10.5 (4-30) minutes, p=0.06]. There were no differences observed between the 2 groups in terms of pain post procedure, or the impact of pain. Operator assessment unanimously favored the use of OnControl device. On a scale of 1-10 (1 being the least inconvenient and 10 the most convenient), median operator convenience for OnControl vs Jamshidi was 10 (range, 9-10) vs 3 (range, 2-7), p< 0.001. **Conclusions:** The OnControl system was associated with less procedural time and a better core biopsy without increased incidence of crush artifact. The robust size of the core biopsy may negate the need for repeat procedures. The operators favored the use of OnControl device over a manually exhausting Jamshidi needle for BMA&B.

P-451

Association between dexamethasone exposure and visually significant cataracts in myeloma

Rahul Banerjee[1], Jorge Arturo Hurtado Martinez[2], Patricia Alejandra Flores Pérez[2], Nolan Porras[2], Jay Hydren[2], Jennifer Ahlstrom[2], Andrew Cowan[3]

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Likert scale) was rated as hardly noticeable by 23%, uncomfortable by 29%, disruptive by 36%, severely disruptive by 11%, and requiring treatment discontinuation by 1%. Ordinal regression analyses of 97/231 pts with detailed dex dosing data available (from concurrent chart review) showed a significant association between total dex exposure and cataract severity (coefficient estimate [ce] 0.255, p< 0.05), which was confirmed by correlation analysis (r=0.143). However, age at cataract onset (ce 0.004, p=0.81) and dex dose per cycle (ce -0.004, p=0.19) did not show a significant relationship with cataract severity. **Conclusions:** Of pts with MM who develop cataracts, almost half rate their cataracts as disruptive or severely disruptive to QOL. Over 30% of pts who report cataracts recall developing this toxicity within 6 months of exposure to dex-containing regimens, a concerning finding given that pts may remain on dex for years with regimens like Dara-Kd or Isa-Kd in the relapsed setting. While limited by recall bias and lack of a control group who did not develop cataracts, strengths of our analysis include its direct focus on the pt experience. Given the unclear contribution of dex to most MM regimens apart from preventing infusion reactions during the 1st cycle, discontinuation of chronic dex after the first few cycles should be considered in all pts with MM and not just for frail or late-line pts.

P-452

Financial toxicity and time toxicity among patients with multiple myeloma

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P-453

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Introduction: Autologous stem cell transplantation (ASCT) for multiple myeloma (MM) is associated with quality of life (QOL) impairments that may lead to long-term psychosocial issues or premature workforce retirement. Our pilot study previously demonstrated the feasibility of digital life coaching (DLC), whereby certified coaches work with patients via phone/text to provide wellness-related support during the peri-ASCT period. We now report the results of a randomized Phase II trial of DLC (clinicaltrials.gov ID NCT04589286) in this population. **Methods:** English-speaking patients with MM who owned cellphones were randomized to wellness handouts (control) versus an additional 16-week coaching subscription (DLC) beginning at Day -10. Endpoints included benzodiazepine or zolpidem-drug (B/Z) medication use, physical/mental QOL (PROMIS Global Health), distress (Distress Thermometer), insomnia (PROMIS Sleep Disturbances 4A), and

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Likert scales regarding study interventions. Linear mixed-effect modeling (LMM) was used to compare patient-reported endpoints. **Results:** Due to uneven rates of post-enrollment ASCT deferrals, 50 patients (coaching n = 21, control n = 29) were evaluable. Baseline characteristics, B/Z use, mental QOL, and insomnia were similar between arms apart from age (medians 68 in the DLC arm vs 61 in the control arm, p< 0.01). Physical QOL was improved with coaching (mean LMM difference +4.9, 95% CI +2.0 to +7.9); 86% versus 67% of patients achieved a meaningful physical QOL improvement at study conclusion compared to engraftment (≥5 points). Distress was borderline improved as well (mean LMM difference -0.7 points, 95% CI -1.6 to +0.1); for example, 10% (DLC) versus 28% (control) reported elevated distress (≥4) at the final assessment. Net Promoter Scores (with positive scores indicating high perceived value by patients) were -16% for handouts and +6% for DLC. **Conclusions:** Although limited by underpowering and global reductions in B/Z use compared to our historical data, our study demonstrated that DLC during ASCT was associated with improved physical QOL and a clear trend toward lower levels of distress. Future investigations of DLC in other oncologic settings, including relapsed MM, are under way.

P-454

Patients views on the relevance of quality of life (QoL) questionnaires commonly applied to evaluate the QoL of patients with AL amyloidosis

Sotirios Bristogiannis[1], Jahanzaib Khwaja[2], Darren Foard[3], Sarah Worthington[2], Yadanar Lwin[4], Joshua Bomsztyk[2], Sosana Delimpasi[1], Ayesha Shameem Mahmood[3], Brendan Wisniowski[3], Ashutosh Wechelaker[3], Charalampia Kyriakou[2]

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Introduction: Systemic AL Amyloidosis remains an incurable disease despite the treatment advances that have considerably prolonged patients' survival. Optimizing patients' QoL impacted by both the disease and the treatment is a fundamental objective. Several non disease- specific QoL Questionnaires (QLQs), either generic or applied for similar diseases, are used in clinical and research practice. The aim of this study was to evaluate the relevance of the content of these QLQs to the actual QoL issues of patients with AL amyloidosis. **Methods:** Patients followed at the National Amyloidosis Centre (UK), were asked to complete the online survey assessing the relevance of 257 questions from the internationally commonly used QLQs (SF-36; PROMIS-GH; PROMIS-29 Profile; EORTC QLQ-C30; EQ-5D; EORTC-QLQ-MY20; MDASI-MM; FACT-BMT; FACIT-COST; FACT-GOG NTx; FACT-G; HPRSS; WPAI; KCCQ-12; DT; SWLS; STAI-Y; CSI; CESD; NPRS; MIH-13; CARG-GA) to their QoL. Patient demographics, disease and treatment characteristics were collected. The relevance of each question of the QLQs were graded using the 5-point Likert scale: not relevant, slightly relevant, relevant, fairly relevant, and very relevant. Analyses were performed for (I) 'not relevant' versus 'very relevant' questions and further (II) the 'non relevant' + 'slightly relevant' versus 'fairly relevant' +'very relevant'. Relevance was defined as agreement ≥ 50% between respondents. **Results:** 153 patients of various ages, ethnicities, time from diagnosis and on different treatment regimens completed the survey. Only 8 questions were graded as very relevant for the entire cohort that referred to two issues: tolerance to strenuous physical activity and family support. Sub-analysis of the responses, revealed 55 further relevant questions in stage II that referred to 7 additional QoL aspects: (i) Physical Limitation to Moderate Activity secondary to fatigue and/or fluid retention; Limitations of the (ii) Working capacity (iii)Family role (iii) Social Role and (iv) Leisure activities; (v) Sleep quality;(vi) Sensory/ Autonomic neuropathy; (vii) Family/ Emotional support. Nonetheless, work and family role restrictions were considered by more than half of the patients as not at all relevant in DT. Similarly, patients' views were divided in stage II of the analysis for 76 questions with some referring to the above seven issues in different wording but quite a few referring to pain, cognition, gastrointestinal manifestations and sexual life. **Conclusions:** This survey confirms the lack of an existing reliable QLQ to reflect the AL Amyloidosis patients' real daily QoL issues. The survey has identified some very relevant disease-specific issues that should be considered in the development of the core module. Further analysis is required for determining issues relevant to certain disease subgroups and proper question wording.

P-455

Survey of multiple myeloma (MM) patients and healthcare professionals (HCPs) on the relevance of existing health quality-of-life (QoL) questionnaires (QoLQ) to real-world QoL issues of MM patients

Sotirios Bristogiannis[1], Catherine SY. Lecat[2], Dipal Mehta[2], Jahanzaib Khwaja[2], Yadanar Lwin[3], Emma Dowling[2], Nuno Correia[2], Kate Xu[2], Annabel McMillan[2], Neil Rabin[2], Jonathan Sive[2], Rakesh Popat[2], Xenofon Papanikolaou[2], Lydia Lee[2], Kwee Yong[2], Sosana Delimpasi[1], Charalampia Kyriakou[2]

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Introduction: Treatment advances have improved the survival of MM patients. Optimizing QoL has become a priority and there is a need for a representative updated QoL Questionnaire (QoLQ) since the validity of the existing ones is debated. The aim of this study was to evaluate the relevance of these QLQs and identify the real-life QoL issues of MM patients. **Methods:** MM patients and Healthcare professionals (HCPs) at University College London Hospital (UK) were asked to complete online surveys assessing the relevance of 172 questions from QoLQs that are commonly used for MM patients internationally (EORTC QLQ-C30, EORTC QLQ-MY20, EORTC QLQ-CIPN20, EQ-5D-3L, FACT-G, FACT-N; FACT-MM, FACIT-F, FACT-BMT) to patients' QoL.

Likert scales regarding study interventions. Linear mixed-effect modeling (LMM) was used to compare patient-reported endpoints. **Results:** Due to uneven rates of post-enrollment ASCT deferrals, 50 patients (coaching n = 21, control n = 29) were evaluable. Baseline characteristics, B/Z use, mental QOL, and insomnia were similar between arms apart from age (medians 68 in the DLC arm vs 61 in the control arm, p< 0.01). Physical QOL was improved with coaching (mean LMM difference +4.9, 95% CI +2.0 to +7.9); 86% versus 67% of patients achieved a meaningful physical QOL improvement at study conclusion compared to engraftment (≥5 points). Distress was borderline improved as well (mean LMM difference -0.7 points, 95% CI -1.6 to +0.1); for example, 10% (DLC) versus 28% (control) reported elevated distress (≥4) at the final assessment. Net Promoter Scores (with positive scores indicating high perceived value by patients) were -16% for handouts and +6% for DLC. **Conclusions:** Although limited by underpowering and global reductions in B/Z use compared to our historical data, our study demonstrated that DLC during ASCT was associated with improved physical QOL and a clear trend toward lower levels of distress. Future investigations of DLC in other oncologic settings, including relapsed MM, are under way.

P-454

Patients views on the relevance of quality of life (QoL) questionnaires commonly applied to evaluate the QoL of patients with AL amyloidosis

Sotirios Bristogiannis[1], Jahanzaib Khwaja[2], Darren Foard[3], Sarah Worthington[2], Yadanar Lwin[4], Joshua Bomsztyk[2], Sosana Delimpasi[1], Ayesha Shameem Mahmood[3], Brendan Wisniowski[3], Ashutosh Wechelaker[3], Charalampia Kyriakou[2]

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Introduction: Systemic AL Amyloidosis remains an incurable disease despite the treatment advances that have considerably prolonged patients' survival. Optimizing patients' QoL impacted by both the disease and the treatment is a fundamental objective. Several non disease- specific QoL Questionnaires (QLQs), either generic or applied for similar diseases, are used in clinical and research practice. The aim of this study was to evaluate the relevance of the content of these QLQs to the actual QoL issues of patients with AL amyloidosis. **Methods:** Patients followed at the National Amyloidosis Centre (UK), were asked to complete the online survey assessing the relevance of 257 questions from the internationally commonly used QLQs (SF-36; PROMIS-GH; PROMIS-29 Profile; EORTC QLQ-C30; EQ-5D; EORTC-QLQ-MY20; MDASI-MM; FACT-BMT; FACIT-COST; FACT-GOG NTx; FACT-G; HPRSS; WPAI; KCCQ-12; DT; SWLS; STAI-Y; CSI; CESD; NPRS; MIH-13; CARG-GA) to their QoL. Patient demographics, disease and treatment characteristics were collected. The relevance of each question of the QLQs were graded using the 5-point Likert scale: not relevant, slightly relevant, relevant, fairly relevant, and very relevant. Analyses were performed for (I) 'not relevant' versus 'very relevant' questions and further (II) the 'non relevant' + 'slightly relevant' versus 'fairly relevant' +'very relevant'. Relevance was defined as agreement ≥ 50% between respondents. **Results:** 153 patients of various ages, ethnicities, time from diagnosis and on different treatment regimens completed the survey. Only 8 questions were graded as very relevant for the entire cohort that referred to two issues: tolerance to strenuous physical activity and family support. Sub-analysis of the responses, revealed 55 further relevant questions in stage II that referred to 7 additional QoL aspects: (i) Physical Limitation to Moderate Activity secondary to fatigue and/or fluid retention; Limitations of the (ii) Working capacity (iii)Family role (iii) Social Role and (iv) Leisure activities; (v) Sleep quality;(vi) Sensory/ Autonomic neuropathy; (vii) Family/ Emotional support. Nonetheless, work and family role restrictions were considered by more than half of the patients as not at all relevant in DT. Similarly, patients' views were divided in stage II of the analysis for 76 questions with some referring to the above seven issues in different wording but quite a few referring to pain, cognition, gastrointestinal manifestations and sexual life. **Conclusions:** This survey confirms the lack of an existing reliable QLQ to reflect the AL Amyloidosis patients' real daily QoL issues. The survey has identified some very relevant disease-specific issues that should be considered in the development of the core module. Further analysis is required for determining issues relevant to certain disease subgroups and proper question wording.

P-455

Survey of multiple myeloma (MM) patients and healthcare professionals (HCPs) on the relevance of existing health quality-of-life (QoL) questionnaires (QoLQ) to real-world QoL issues of MM patients

Sotirios Bristogiannis[1], Catherine SY. Lecat[2], Dipal Mehta[2], Jahanzaib Khwaja[2], Yadanar Lwin[3], Emma Dowling[2], Nuno Correia[2], Kate Xu[2], Annabel McMillan[2], Neil Rabin[2], Jonathan Sive[2], Rakesh Popat[2], Xenofon Papanikolaou[2], Lydia Lee[2], Kwee Yong[2], Sosana Delimpasi[1], Charalampia Kyriakou[2]

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P-455

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Introduction: Treatment advances have improved the survival of MM patients. Optimizing QoL has become a priority and there is a need for a representative updated QoL Questionnaire (QoLQ) since the validity of the existing ones is debated. The aim of this study was to evaluate the relevance of these QLQs and identify the real-life QoL issues of MM patients. **Methods:** MM patients and Healthcare professionals (HCPs) at University College London Hospital (UK) were asked to complete online surveys assessing the relevance of 172 questions from QoLQs that are commonly used for MM patients internationally (EORTC QLQ-C30, EORTC QLQ-MY20, EORTC QLQ-CIPN20, EQ-5D-3L, FACT-G, FACT-N; FACT-MM, FACIT-F, FACT-BMT) to patients' QoL.

Demographics, disease and treatment characteristics were collected for each survey. The relevance of each question of the QoLQs was graded using the 5-point Likert scale: not relevant, slightly relevant, relevant, fairly relevant, and very relevant. HCPs' and patients' responses were analysed separately. MM patients' results were further stratified based on age, the presence of renal and bone disease. **Results:** 224 patients (M: 129, F: 89) of various ethnicities, disease duration and treatment history completed the survey. The 20 most 'relevant' questions for patients were related to functional well-being (cognition, working capacity, physical ability, leisure activities and sleep quality), emotional support from their environment (family, friends and HCPs) and disease sequelae (vulnerability to infections, appetite, pain). The majority of the most irrelevant questions referred to disease and treatment specific symptoms/signs (e.g. peripheral neuropathy, nausea). Of note, few patients regretted having a bone marrow transplant. Sub-group analysis by age identified minor differences: patients ≤70 years old reported additionally anxiety for their future and physical limitations due to the disease and its complications (neuropathy) whereas patients>70 years reported fatigue and did not consider mobility issues as relevant to MM. For renal and bone disease subgroups, limitations to strenuous activities and pain were significantly relevant. The bone disease group had higher anxiety for disease progression. For the 42 surveyed HCPs, the median weighted average per question was higher (3.12, range: 1.76-3.82) than that of patients (1.23, range: 0.54-2.94). HCPs graded fatigue, physical limitations, impact on usual roles (e.g. family, work), pain and neuropathy as more relevant compared to patient. Contrary to patients, effects of treatment (e.g. hair loss) were considered significant by HCPs. **Conclusions:** This survey highlighted significant differences between HCPs' and patients' views of QoL issues. It identified the significant areas that we would advocate to be included in a new disease QoLQ.

P-456

Survey on real world quality of life (QoL) issues relevant to distinct AL amyloidosis patient subgroups

Sotirios Bristogiannis[1], Jahanzaib Khwaja[2], Darren Foard[3], Sarah Worthington[2], Joshua Bomsztyk[3], Yadanar Lwin[4], Ayesha Shameem Mahmood[3], Sosana Delimpasi[5], Ashutosh Wechelaker[3], Charalampia Kyriakou[2]

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Introduction: Amyloidosis is a systemic disease, associated with multiorgan involvement with considerable disease and treatment-related morbidity. Therapeutic advances have improved survival and QoL is becoming a significant treatment decision-making factor. There is no validated specific QoL Questionnaire (QOLQ) for AL Amyloidosis. The aim of this survey was to identify the most relevant QoL issues to patients from the existing reported QoLQ. **Methods:** Patients with AL Amyloidosis, followed at the UK National Amyloidosis Centre, were invited to complete an online survey assessing the relevance of the total of 257 questions from the internationally commonly used QLQs to their QoL (SF-36; PROMIS-GH; PROMIS-29 Profile; EORTC QLQ-C30; EQ-5D; EORTC-QLQ-MY20; MDASI-MM; FACT-BMT; FACIT-COST; FACT-GOG NTx; FACT-G; HPRSS; WPAI; KCCQ-12; DT; SWLS; STAI-Y; CSI; CESD; NPRS; MIH-13; CARG-GA). Patient demographics, disease and treatment characteristics were collected. The relevance of each question of the QLQs were graded using the 5-point Likert scale (not relevant, slightly relevant, relevant, fairly relevant, very relevant). Relevance was defined as agreement ≥ 50% between respondents on the grading scale. The entire cohort identified Physical Limitation to Intense Activity and Family Support as the only common very relevant QoL issues. Sub-group analysis was based on age, disease duration (≤ 1y, 1-2 y, ≥2 to 4 y, ≥4 y), the presence of cardiac, renal and nerve involvement. **Results:** 153 patients (M: 88, F: 55) of various ethnicities and on different treatment regimens completed the survey. Both patient groups ≤ 70 yr. and reported significant physical decline,For the elderly, fatigue was also common, while for the younger sleep quality, family and emotional support were relevant, too Irrespective of their age, patients with neuropathy experienced pain and paresthesia, sought family and emotional support and were limited in the kind of work. Of these, those >70 yr, reported, limited social and leisure activities and suffered from heart failure. Patients diagnosed ≥2 yr reported, in contrast to those 70 y.o. suffered from peripheral edema and dry mouth. **Conclusions:** AL Amyloidosis manifests in a diverse and evolving manner. This patient survey identified the difference in relevance of some of the existing used QOL issues in the different patient subgroups. This stresses the need for the development of relevant QLQ that should capture the QOL issues of distinct patients subgroups to reliably guide treatment decision-making.

P-457

Waldenstrom's Macroglobulinaemia (WM) patients' online survey -currently available QoLQs not representative of real-world health quality-of-life (QoL) issues of WM patients

Sotirios Bristogiannis[1], Jahanzaib Khwaja[2], Ibrahim Tohidi-Esfahani[3], Nicole Japzon[2], David Young[4], Yadanar Lwin[5], Sosana Delimpasi[1], Shirley D'Sa[2], Judith Trotman[3], Charalampia Kyriakou[2]

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Introduction: Waldenstrom's Macroglobulinaemia (WM) is an indolent lymphoproliferative disease with prolonged survival but recognised diverse range of disabling symptoms related to bone marrow burden and disease's immune manifestations. Literature

Demographics, disease and treatment characteristics were collected for each survey. The relevance of each question of the QoLQs was graded using the 5-point Likert scale: not relevant, slightly relevant, relevant, fairly relevant, and very relevant. HCPs' and patients' responses were analysed separately. MM patients' results were further stratified based on age, the presence of renal and bone disease. **Results:** 224 patients (M: 129, F: 89) of various ethnicities, disease duration and treatment history completed the survey. The 20 most 'relevant' questions for patients were related to functional well-being (cognition, working capacity, physical ability, leisure activities and sleep quality), emotional support from their environment (family, friends and HCPs) and disease sequelae (vulnerability to infections, appetite, pain). The majority of the most irrelevant questions referred to disease and treatment specific symptoms/signs (e.g. peripheral neuropathy, nausea). Of note, few patients regretted having a bone marrow transplant. Sub-group analysis by age identified minor differences: patients ≤70 years old reported additionally anxiety for their future and physical limitations due to the disease and its complications (neuropathy) whereas patients>70 years reported fatigue and did not consider mobility issues as relevant to MM. For renal and bone disease subgroups, limitations to strenuous activities and pain were significantly relevant. The bone disease group had higher anxiety for disease progression. For the 42 surveyed HCPs, the median weighted average per question was higher (3.12, range: 1.76-3.82) than that of patients (1.23, range: 0.54-2.94). HCPs graded fatigue, physical limitations, impact on usual roles (e.g. family, work), pain and neuropathy as more relevant compared to patient. Contrary to patients, effects of treatment (e.g. hair loss) were considered significant by HCPs. **Conclusions:** This survey highlighted significant differences between HCPs' and patients' views of QoL issues. It identified the significant areas that we would advocate to be included in a new disease QoLQ.

P-456

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P-457

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P-457

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suggests that its QoL impact is imperfectly mirrored by the available QoL Questionnaires (QoLQ) and this was meant to be evaluated further in this study. **Methods:** Patients with WM followed up at the University College London Hospital (UK) or enrolled in the WMozzies' Registry (Australia), were asked to complete an online survey assessing the relevance to their QoL of a total of 412 questions from commonly used QoLQs internationally (EORTC QLQ-C30; EQ-5D-5L; FACT-G; FACIT-F; FACT-An; FACT-GOG/NTx; FACT-Lym; SF-36; HADS; DASS-21; QLACS; IES; FSS; IPA). Patient demographics, disease and treatment characteristics were collected. Patients graded the relevance of each question using the 5-point Likert scale: not relevant, slightly relevant, relevant, fairly relevant, and very relevant. Analysis was performed initially for (I) 'not relevant' versus 'very relevant' responses and further for (II) 'non relevant' + 'slightly relevant' versus 'fairly relevant' + 'very relevant'. Relevance was defined as agreement ≥50% between respondents on the grading scale. Percentage difference ≤10% between different grades was defined as non-significant. **Results:** 92 patients (M: 45, F: 47) of various ethnicities, disease duration and on different treatment regimens completed the survey. Only 1 question was very relevant for the entire cohort, which referred to family support. Of the remaining 398 questions: 59 were graded as not relevant, for 88 the views on their significance were divided and the rest were fairly relevant. In stage II of the analysis, 33 further relevant questions were identified that referred to fatigue, limitations of physical, social, leisure activities and occupation as well as to sleep quality, pain, emotional burden and family well-being. These were derived from several of the QoLQ, but primarily the FACT-G core module. Asymptomatic WM patients reported limits to their ability for moderate activities, their life enjoyment and anxiety for the future, so they seek emotional support from their environment. WM patients with peripheral neuropathy are often restricted to even light activities, often reported breathing difficulty and have neuropathic symptoms that cannot be reflected by existing QoLQs. Similarly, WM patients with cold agglutinin disease report limitations to even light exertion. Lastly, WM patients with B-symptoms report sleeping problems, considerable fatigue and concerns about their future that urges them to seek emotional support. **Conclusions:** This real-world patient survey showed that there is a lack of a representative QoLQ for WM. A new, disease specific QoLQ is needed that should take into account the QoL issues acknowledged in this survey by patients with various presentations of the disease.

P-458

The impact of continuous therapy on the quality of life in Romanian patients with multiple myeloma

Daniel Coriu[1], Sorina Nicoleta Badelita[1], Ruxandra Irimia[1], Sinziana Barbu[1], Loredana Cirlan[1], Larisa Zidaru[1], Andreea Jercan[1]

[1]*Fundeni Clinical Institute*

Introduction: The treatment paradigm of Multiple Myeloma (MM) has shifted in the past years, as continuous therapy is becoming the standard of care in both newly diagnosed as well as relapsed patients. Although it is undisputable that this approach has added a great benefit on the progression-free as well as overall survival, it is still unclear how the quality of life is impacted in these patients. **Methods:** The study includes 155 adult MM patients from Fundeni Clinical Institute in Romania, receiving continuous therapy containing Daratumumab, Proteasone Inhibitors, Immunomodulators or bi-specific antibodies. We developed a quantitative questionnaire to interrogate the effect of the therapy on their personal and professional life, their regard towards the therapy and to identify the side effects that have the strongest impact on their Quality of Life. **Results:** 80.6% of the patients reported that the treatment they are receiving negatively impacts their quality of life. More than half of the patients considered that the most detrimental aspects of the therapy are the financial burden, the impact on the professional life, and the inability of making plans for the future. 45.1% of the patients report that the therapy is negatively impacting their family life and over one third states that it has a deleterious effect on their relationship with their partner. One third of the patients also stated that the frequent visits to the hospital are causing them a medium-high level of anxiety. In terms of the side effects experienced, two-thirds of the patients consider that tiredness is the main factor causing a decrease in their quality of life, closely followed by the gastro-intestinal disturbances in half of the patients. Despite this, none of the patients considered dropping the therapy and more than half of the patients consider that the frequent visits to the hospital offer them a psychological comfort. In addition, 77.4% of the patients declare that they are afraid to stop the therapy if given the choice, the main concerns being the fear for an early relapse. **Conclusions:** Although continuous therapy is associated with a high financial burden and a negative impact on both the professional and personal life, the frequent visits to the hospital appear to be reassuring. Moreover, the patients would not opt for treatment discontinuation and feel safer when monitored frequently.

P-459

A randomized, controlled phase 2 trial of uproleselan, an e-selectin inhibitor, vs placebo to reduce GI toxicity in patients with multiple myeloma undergoing autologous hematopoietic cell transplant

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have shown upro+chemotherapy reduced GI toxicity in mice by blocking secondary migration of inflammatory macrophages to GI epithelium. Subsequent clinical trials evaluating upro+chemotherapy in AML showed reduced GI toxicities vs historical controls. **Methods:** This was a Phase 2, single-center, randomized, double-blind, placebo-controlled trial of patients undergoing melphalan-conditioned (200mg/m^2) ASCT for MM, randomized 1:1 to prophylactic upro+standard of care (SoC) vs placebo+SoC. The primary objective was to demonstrate superiority of upro+SoC to reduce mean diarrhea severity (CTCAE v5.0) during days 1-14 post-ASCT. Secondary endpoints included patient reported outcomes (PRO) of GI-related quality of life (QoL) (NCI PRO-CTCAE v1.0), Bristol Stool Scale (BSS), alternative GI toxicities and metrics of healthcare resource utilization. Exploratory sensitivity analyses of the primary endpoint evaluated diarrhea severity on days 1-10, 1-7 and 3-10 post-ASCT. Significance level of p< 0.2 was predefined for all endpoints. **Results:** Fifty adults with MM enrolled from 5/2021-10/2022. Demographics were similar across arms. Over days 1-14 post-ASCT, a lower mean diarrhea severity score (1.07 vs 1.19, 95% CI -0.28; 0.04, p=0.34) and lower incidence of >Grade 2 diarrhea (odds ratio [OR] 0.61, 95% CI 0.35; 1.07, p=0.26) were observed favoring upro+SoC, but neither met significance level of pGrade 2 diarrhea over those times were all significantly lower favoring upro+SoC (p=0.11, p=0.02 and p=0.14). Time to neutrophil engraftment and response rates were similar. **Conclusions:** In this randomized, controlled trial, upro+SoC prior to melphalan-conditioned ASCT in MM did not meet its primary endpoint but met key secondary endpoints of reduced >Grade 2 diarrhea, reduced severe diarrhea by BSS and improved patient reported QoL, vs placebo+SoC. Further studies are needed to verify these observations.

P-460

Evaluation of a precision-based exercise program for patients with multiple myeloma

Ulrike Dapunt[1], Pauline Ehret[1], Jean-Luc Paratte[2], Rea Kühl[2], Joachim Wiskemann[2], Carsten Müller-Tidow[3], Dirk Jäger[4], Marc Raab[5], Hartmut Goldschmidt[1]

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Introduction: Multiple Myeloma is often associated with severe loss of bone substance which might endanger stability of the skeletal system. Even though the benefits of regular physical exercise in cancer patients have been demonstrated in depth and patients frequently express interest in structured exercise programs, uncertainties regarding bone stability are of great concern to both patients and oncologic healthcare providers. Because of the heterogeneity of bone involvement, exercise programs should be tailored to individual clinical conditions and require an interdisciplinary assessment. **Methods:** Data of multiple myeloma patients (n=100) who received a precision-based exercise program (PEP) according to an orthopaedic evaluation of bone stability and individual physical fitness were analysed retrospectively. Bone stability was assessed by current whole-body CT-scan according to established scoring systems (Spinal Instability Neoplastic Score (SINS), Mirels' score). All patients with stable and unstable osteolyses received a PEP which included body awareness, stretching, coordination and muscle strength training at different levels. Subsequently, PEP was continued home-based supported by an exercise therapy mobile app or under 1:1 supervision led by a local physical therapist. Patients (n=91) were contacted for a follow-up interview. **Results:** Median age was 61.5 years (range: 27-83, IQR: 13) and the majority of patients (53%) asked for consultation on physical exercise during maintenance therapy. Whole body CT-scans showed multiple (>7) osteolytic lesions in most patients and in 60 % at least one osteolysis of the spine was considered potentially unstable or unstable according to SINS. 90% of patients already pursued some aerobic exercise and 24% resistance training. Following consultation on bone stability and a PEP-introductory session, the number of patients performing resistance training could be significantly increased (55% ≥2 sessions/week, 24% 1 session/week or intermittent, 21% no training). Musculoskeletal pain was reported frequently (31% mild, 36% moderate, 8% severe). At the follow-up interview, 75% of patients who performed PEP stated that painful symptoms could be effectively alleviated by exercise. Moreover, only patients that exercised regularly were able to discontinue pain medication. No injuries were reported in association with PEP. **Conclusions:** We were able to demonstrate that individualized resistance training is feasible and safe, even for patients with unstable bone lesions (SINS >12). By means of a precision-based exercise program, patients' self-efficacy in managing musculoskeletal pain was enhanced and pain medication could be reduced.

P-461

An overview of challenges experienced in multiple myeloma: perspectives of hematologist-oncologists and specialist nurses

Faith Davies[1], Hayley Beer[2], Beth Faiman[3], Joseph Mikhael[4], J Blake Bartlett[5], Georgia Attfield[6], Tallulah Price[6], Maya Gilbert[6]

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Introduction: Multiple myeloma (MM) is a highly heterogeneous and incurable disease. Progress has been made to improve patient outcomes over recent years, but there is a need to better understand the challenges experienced by patients, to both improve the patient and carer experience, and support healthcare professionals (HCPs)

have shown upro+chemotherapy reduced GI toxicity in mice by blocking secondary migration of inflammatory macrophages to GI epithelium. Subsequent clinical trials evaluating upro+chemotherapy in AML showed reduced GI toxicities vs historical controls. **Methods:** This was a Phase 2, single-center, randomized, double-blind, placebo-controlled trial of patients undergoing melphalan-conditioned (200mg/m^2) ASCT for MM, randomized 1:1 to prophylactic upro+standard of care (SoC) vs placebo+SoC. The primary objective was to demonstrate superiority of upro+SoC to reduce mean diarrhea severity (CTCAE v5.0) during days 1-14 post-ASCT. Secondary endpoints included patient reported outcomes (PRO) of GI-related quality of life (QoL) (NCI PRO-CTCAE v1.0), Bristol Stool Scale (BSS), alternative GI toxicities and metrics of healthcare resource utilization. Exploratory sensitivity analyses of the primary endpoint evaluated diarrhea severity on days 1-10, 1-7 and 3-10 post-ASCT. Significance level of p< 0.2 was predefined for all endpoints. **Results:** Fifty adults with MM enrolled from 5/2021-10/2022. Demographics were similar across arms. Over days 1-14 post-ASCT, a lower mean diarrhea severity score (1.07 vs 1.19, 95% CI -0.28; 0.04, p=0.34) and lower incidence of >Grade 2 diarrhea (odds ratio [OR] 0.61, 95% CI 0.35; 1.07, p=0.26) were observed favoring upro+SoC, but neither met significance level of pGrade 2 diarrhea over those times were all significantly lower favoring upro+SoC (p=0.11, p=0.02 and p=0.14). Time to neutrophil engraftment and response rates were similar. **Conclusions:** In this randomized, controlled trial, upro+SoC prior to melphalan-conditioned ASCT in MM did not meet its primary endpoint but met key secondary endpoints of reduced >Grade 2 diarrhea, reduced severe diarrhea by BSS and improved patient reported QoL, vs placebo+SoC. Further studies are needed to verify these observations.

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Introduction: Multiple Myeloma is often associated with severe loss of bone substance which might endanger stability of the skeletal system. Even though the benefits of regular physical exercise in cancer patients have been demonstrated in depth and patients frequently express interest in structured exercise programs, uncertainties regarding bone stability are of great concern to both patients and oncologic healthcare providers. Because of the heterogeneity of bone involvement, exercise programs should be tailored to individual clinical conditions and require an interdisciplinary assessment. **Methods:** Data of multiple myeloma patients (n=100) who received a precision-based exercise program (PEP) according to an orthopaedic evaluation of bone stability and individual physical fitness were analysed retrospectively. Bone stability was assessed by current whole-body CT-scan according to established scoring systems (Spinal Instability Neoplastic Score (SINS), Mirels' score). All patients with stable and unstable osteolyses received a PEP which included body awareness, stretching, coordination and muscle strength training at different levels. Subsequently, PEP was continued home-based supported by an exercise therapy mobile app or under 1:1 supervision led by a local physical therapist. Patients (n=91) were contacted for a follow-up interview. **Results:** Median age was 61.5 years (range: 27-83, IQR: 13) and the majority of patients (53%) asked for consultation on physical exercise during maintenance therapy. Whole body CT-scans showed multiple (>7) osteolytic lesions in most patients and in 60 % at least one osteolysis of the spine was considered potentially unstable or unstable according to SINS. 90% of patients already pursued some aerobic exercise and 24% resistance training. Following consultation on bone stability and a PEP-introductory session, the number of patients performing resistance training could be significantly increased (55% ≥2 sessions/week, 24% 1 session/week or intermittent, 21% no training). Musculoskeletal pain was reported frequently (31% mild, 36% moderate, 8% severe). At the follow-up interview, 75% of patients who performed PEP stated that painful symptoms could be effectively alleviated by exercise. Moreover, only patients that exercised regularly were able to discontinue pain medication. No injuries were reported in association with PEP. **Conclusions:** We were able to demonstrate that individualized resistance training is feasible and safe, even for patients with unstable bone lesions (SINS >12). By means of a precision-based exercise program, patients' self-efficacy in managing musculoskeletal pain was enhanced and pain medication could be reduced.

P-461

An overview of challenges experienced in multiple myeloma: perspectives of hematologist-oncologists and specialist nurses

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Introduction: Multiple myeloma (MM) is a highly heterogeneous and incurable disease. Progress has been made to improve patient outcomes over recent years, but there is a need to better understand the challenges experienced by patients, to both improve the patient and carer experience, and support healthcare professionals (HCPs)

to optimize care. As a first step, this research aims to identify challenges experienced in MM from an HCP perspective. **Methods:** 1-hour in-depth, virtual, double-blind interviews were conducted between 09/13/22-11/09/22, with 18 hematologist-oncologists (hem-oncs) 44% of whom work in academic centers, and 4 specialist nurses, from 8 countries: US, UK, Spain, France, Germany, Italy, Japan, and Brazil. The interview questions covered 3 themes: the evolution and future of MM, the healthcare ecosystem, and perceived patient perspectives on current care. Key words were used to identify concepts discussed and quantify the qualitative data. Each interviewee discussed multiple concepts under each of the themes. **Results:** Of 18 hem-oncs interviewed, 56% (n=10) stated that treatment decisions were a major challenge in MM care, a challenge identified globally. 28% (n=5) of hem-oncs cited cost concerns and limited treatment availability as further exacerbating the challenge of treatment decision making, particularly within self-pay markets such as the US and Brazil. 44% (n=8) stated that staying up to date with research, including novel therapies, is of utmost importance to move the MM field closer to cure. 72% (n=13) of hem-oncs stated that availability, cost, and the logistics of MM treatment remain a key practical challenge in the effective delivery of MM care. Further to this, only 17% (n=3) of hem-oncs stated that managing quality-of-life (QoL) in MM patients was challenging for them. In contrast, when hem-oncs were asked about what they perceive to be the biggest challenges for patients, 50% (n=9) stated QoL, side effect management, and psychological wellbeing as most concerning. A sample of specialist nurses (n=4) were used to gain insight into areas of concern raised by MM patients during consultations. Cost and availability of treatment, logistical challenges of care, long waiting lists, and limited resources, including a lack of nurse time, were highlighted as overarching challenges, especially from EU countries. Other themes included delayed diagnosis, the need for multidisciplinary team input and improved access to supportive care. **Conclusions:** Many challenges have been identified in the management of MM, highlighting existing unmet needs in MM care for both patients and HCPs. There is a need to corroborate the findings of this research with MM patients to better understand challenges and gaps in care from a patient perspective. Further research combined with multi-stakeholder efforts are needed to address these challenges and support the holistic needs of patients and HCPs. One such ongoing initiative is the MM Call-to-Action.

P-462

Free light chain ratio over 100 and risk of hemodialysis in multiple myeloma

David Garrido[1], Cecibel Vasquez[1], Lucia Pérez Baliero[1], Eloísa Riva[2]

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Introduction: Acute kidney injury (AKI) is a major complication of multiple myeloma (MM), primarily attributed to the accumulation of immunoglobulin light chains (LC) in the distal nephron. **Objective:** The FLC ratio (FLCr, involved/non-involved) over 100 is a novel criterion for diagnosing active MM. Considering the effects of FLC on renal health, we aimed to analyze the risk of hemodialysis at MM diagnosis associated with an FLCr≥100. **Methods:** This observational, analytical, and retrospective study was conducted at the Hospital de Clínicas "Dr. Manuel Quintela" in Montevideo, Uruguay. We included adult (18 years) patients with newly diagnosed MM who did not have prior chronic kidney disease requiring dialysis. Patients with incomplete information regarding the evaluation of FLC and those with non-secretory MM were excluded. The standard methodology for sFLC evaluation was Freelite (The Binding Site). We calculated FLCr by dividing compromised FLC by non-compromised FLC. Dialysis risk was estimated using odds ratios, and medians were compared using non-parametric methods. We used SPSS and R for statistical analysis. **Results:** We included 74 patients, median age was 63 years (IQR 19.5), 55.4% were male. Regarding MM subtype, 62.2% had IgG, 20.3% had IgA, 16.2% had LC, and 1.3% had IgM. Risk stratification was represented as follows: ISS-1 (24.3%), ISS-2 (39.2%), ISS-3 (36.5%); RISS-1 (20%), RISS-2 (65%), and RISS-3 (15%). Median serum creatinine, hemoglobin, and serum calcium levels were 1.1 mg/dl (IQR 1.6), 9.2 g/dl (IQR 3.53), and 9.6 mg/dl (IQR 1.9), respectively. An FLCr ≥ 100 was observed in 23% of cases, with median values for FLCr, kappa chain, lambda chain, involved chain, and non-involved chain of 35.1 (IQR 91.9), 46.9 (IQR 475.5), 25.5 (IQR 325.8), 384 (IQR 1410.9), and 10.4 (IQR 18.1), respectively. Bortezomib-based regimens (BBR) were used in 59.5% of cases, and high-dose melphalan followed by autologous stem cell transplantation was used in 29.2% as consolidative therapy. The frequency of hemodialysis requirement at MM diagnosis was 14.9%, with 9.5% requiring chronic hemodialysis. The median serum creatinine for patients with FLCr≥100 was 1.6 (IQR 6.8), while for those with FLCr< 100 it was 1.0 (IQR 1.0) (p< 0.01). Additionally, the odds ratio for requiring hemodialysis at MM diagnosis in patients with FLCr≥100 was 9.3 (95% CI 2.8 to 37.7, p< 0.01). In a multivariate analysis including hemoglobin level, serum calcium, ISS, RISS, and age, FLCr≥100 was the only variable with a significant effect on the risk of hemodialysis OR 10.6 (95% CI 1.5 to 69.0, p=0.02). **Conclusions:** An FLCr≥100 is a strong risk factor for kidney injury and renal replacement requirement. However, given the limitations of the study design and sample size, our results need to be corroborated by further investigations.

P-463

Patient characteristics and burden in lenalidomide refractory multiple myeloma patients in Europe: a real-world survey

Francesca Gay[1], João Mendes[2], Emily Luke[3], Caspian Kluth[3], Phoebe Salmon[3], Abigail Bailey[3], Amanda Ribbands[3], Joaquín Martínez-López[4]

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Introduction: Lenalidomide (LEN) is the standard of care for Multiple Myeloma (MM) patients (pts), often given until progression. Progressive disease negatively impacts quality of life

to optimize care. As a first step, this research aims to identify challenges experienced in MM from an HCP perspective. **Methods:** 1-hour in-depth, virtual, double-blind interviews were conducted between 09/13/22-11/09/22, with 18 hematologist-oncologists (hem-oncs) 44% of whom work in academic centers, and 4 specialist nurses, from 8 countries: US, UK, Spain, France, Germany, Italy, Japan, and Brazil. The interview questions covered 3 themes: the evolution and future of MM, the healthcare ecosystem, and perceived patient perspectives on current care. Key words were used to identify concepts discussed and quantify the qualitative data. Each interviewee discussed multiple concepts under each of the themes. **Results:** Of 18 hem-oncs interviewed, 56% (n=10) stated that treatment decisions were a major challenge in MM care, a challenge identified globally. 28% (n=5) of hem-oncs cited cost concerns and limited treatment availability as further exacerbating the challenge of treatment decision making, particularly within self-pay markets such as the US and Brazil. 44% (n=8) stated that staying up to date with research, including novel therapies, is of utmost importance to move the MM field closer to cure. 72% (n=13) of hem-oncs stated that availability, cost, and the logistics of MM treatment remain a key practical challenge in the effective delivery of MM care. Further to this, only 17% (n=3) of hem-oncs stated that managing quality-of-life (QoL) in MM patients was challenging for them. In contrast, when hem-oncs were asked about what they perceive to be the biggest challenges for patients, 50% (n=9) stated QoL, side effect management, and psychological wellbeing as most concerning. A sample of specialist nurses (n=4) were used to gain insight into areas of concern raised by MM patients during consultations. Cost and availability of treatment, logistical challenges of care, long waiting lists, and limited resources, including a lack of nurse time, were highlighted as overarching challenges, especially from EU countries. Other themes included delayed diagnosis, the need for multidisciplinary team input and improved access to supportive care. **Conclusions:** Many challenges have been identified in the management of MM, highlighting existing unmet needs in MM care for both patients and HCPs. There is a need to corroborate the findings of this research with MM patients to better understand challenges and gaps in care from a patient perspective. Further research combined with multi-stakeholder efforts are needed to address these challenges and support the holistic needs of patients and HCPs. One such ongoing initiative is the MM Call-to-Action.

P-462

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David Garrido[1], Cecibel Vasquez[1], Lucia Pérez Baliero[1], Eloísa Riva[2]

[1]Hospital de Clínicas; [2]Hospital Británico, Montevideo, Uruguay

Introduction: Acute kidney injury (AKI) is a major complication of multiple myeloma (MM), primarily attributed to the accumulation of immunoglobulin light chains (LC) in the distal nephron. **Objective:** The FLC ratio (FLCr, involved/non-involved) over 100 is a novel criterion for diagnosing active MM. Considering the effects of FLC on renal health, we aimed to analyze the risk of hemodialysis at MM diagnosis associated with an FLCr≥100. **Methods:** This observational, analytical, and retrospective study was conducted at the Hospital de Clínicas "Dr. Manuel Quintela" in Montevideo, Uruguay. We included adult (18 years) patients with newly diagnosed MM who did not have prior chronic kidney disease requiring dialysis. Patients with incomplete information regarding the evaluation of FLC and those with non-secretory MM were excluded. The standard methodology for sFLC evaluation was Freelite (The Binding Site). We calculated FLCr by dividing compromised FLC by non-compromised FLC. Dialysis risk was estimated using odds ratios, and medians were compared using non-parametric methods. We used SPSS and R for statistical analysis. **Results:** We included 74 patients, median age was 63 years (IQR 19.5), 55.4% were male. Regarding MM subtype, 62.2% had IgG, 20.3% had IgA, 16.2% had LC, and 1.3% had IgM. Risk stratification was represented as follows: ISS-1 (24.3%), ISS-2 (39.2%), ISS-3 (36.5%); RISS-1 (20%), RISS-2 (65%), and RISS-3 (15%). Median serum creatinine, hemoglobin, and serum calcium levels were 1.1 mg/dl (IQR 1.6), 9.2 g/dl (IQR 3.53), and 9.6 mg/dl (IQR 1.9), respectively. An FLCr ≥ 100 was observed in 23% of cases, with median values for FLCr, kappa chain, lambda chain, involved chain, and non-involved chain of 35.1 (IQR 91.9), 46.9 (IQR 475.5), 25.5 (IQR 325.8), 384 (IQR 1410.9), and 10.4 (IQR 18.1), respectively. Bortezomib-based regimens (BBR) were used in 59.5% of cases, and high-dose melphalan followed by autologous stem cell transplantation was used in 29.2% as consolidative therapy. The frequency of hemodialysis requirement at MM diagnosis was 14.9%, with 9.5% requiring chronic hemodialysis. The median serum creatinine for patients with FLCr≥100 was 1.6 (IQR 6.8), while for those with FLCr< 100 it was 1.0 (IQR 1.0) (p< 0.01). Additionally, the odds ratio for requiring hemodialysis at MM diagnosis in patients with FLCr≥100 was 9.3 (95% CI 2.8 to 37.7, p< 0.01). In a multivariate analysis including hemoglobin level, serum calcium, ISS, RISS, and age, FLCr≥100 was the only variable with a significant effect on the risk of hemodialysis OR 10.6 (95% CI 1.5 to 69.0, p=0.02). **Conclusions:** An FLCr≥100 is a strong risk factor for kidney injury and renal replacement requirement. However, given the limitations of the study design and sample size, our results need to be corroborated by further investigations.

P-463

Patient characteristics and burden in lenalidomide refractory multiple myeloma patients in Europe: a real-world survey

Francesca Gay[1], João Mendes[2], Emily Luke[3], Caspian Kluth[3], Phoebe Salmon[3], Abigail Bailey[3], Amanda Ribbands[3], Joaquín Martínez-López[4]

[1]Division of Hematology 1, Clinical trial unit AOU città della salute e della scienza, University of Torino; [2]Janssen-Cilag, Porto Salvo, Portugal; [3]Adelphi Real World, Bollington, UK; [4]Hematología Hospital 12 de Octubre, Madrid, Spain

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to optimize care. As a first step, this research aims to identify challenges experienced in MM from an HCP perspective. **Methods:** 1-hour in-depth, virtual, double-blind interviews were conducted between 09/13/22-11/09/22, with 18 hematologist-oncologists (hem-oncs) 44% of whom work in academic centers, and 4 specialist nurses, from 8 countries: US, UK, Spain, France, Germany, Italy, Japan, and Brazil. The interview questions covered 3 themes: the evolution and future of MM, the healthcare ecosystem, and perceived patient perspectives on current care. Key words were used to identify concepts discussed and quantify the qualitative data. Each interviewee discussed multiple concepts under each of the themes. **Results:** Of 18 hem-oncs interviewed, 56% (n=10) stated that treatment decisions were a major challenge in MM care, a challenge identified globally. 28% (n=5) of hem-oncs cited cost concerns and limited treatment availability as further exacerbating the challenge of treatment decision making, particularly within self-pay markets such as the US and Brazil. 44% (n=8) stated that staying up to date with research, including novel therapies, is of utmost importance to move the MM field closer to cure. 72% (n=13) of hem-oncs stated that availability, cost, and the logistics of MM treatment remain a key practical challenge in the effective delivery of MM care. Further to this, only 17% (n=3) of hem-oncs stated that managing quality-of-life (QoL) in MM patients was challenging for them. In contrast, when hem-oncs were asked about what they perceive to be the biggest challenges for patients, 50% (n=9) stated QoL, side effect management, and psychological wellbeing as most concerning. A sample of specialist nurses (n=4) were used to gain insight into areas of concern raised by MM patients during consultations. Cost and availability of treatment, logistical challenges of care, long waiting lists, and limited resources, including a lack of nurse time, were highlighted as overarching challenges, especially from EU countries. Other themes included delayed diagnosis, the need for multidisciplinary team input and improved access to supportive care. **Conclusions:** Many challenges have been identified in the management of MM, highlighting existing unmet needs in MM care for both patients and HCPs. There is a need to corroborate the findings of this research with MM patients to better understand challenges and gaps in care from a patient perspective. Further research combined with multi-stakeholder efforts are needed to address these challenges and support the holistic needs of patients and HCPs. One such ongoing initiative is the MM Call-to-Action.

P-462

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David Garrido[1], Cecibel Vasquez[1], Lucia Pérez Baliero[1], Eloísa Riva[2]

[1]Hospital de Clínicas; [2]Hospital Británico, Montevideo, Uruguay

Introduction: Acute kidney injury (AKI) is a major complication of multiple myeloma (MM), primarily attributed to the accumulation of immunoglobulin light chains (LC) in the distal nephron. **Objective:** The FLC ratio (FLCr, involved/non-involved) over 100 is a novel criterion for diagnosing active MM. Considering the effects of FLC on renal health, we aimed to analyze the risk of hemodialysis at MM diagnosis associated with an FLCr≥100. **Methods:** This observational, analytical, and retrospective study was conducted at the Hospital de Clínicas "Dr. Manuel Quintela" in Montevideo, Uruguay. We included adult (18 years) patients with newly diagnosed MM who did not have prior chronic kidney disease requiring dialysis. Patients with incomplete information regarding the evaluation of FLC and those with non-secretory MM were excluded. The standard methodology for sFLC evaluation was Freelite (The Binding Site). We calculated FLCr by dividing compromised FLC by non-compromised FLC. Dialysis risk was estimated using odds ratios, and medians were compared using non-parametric methods. We used SPSS and R for statistical analysis. **Results:** We included 74 patients, median age was 63 years (IQR 19.5), 55.4% were male. Regarding MM subtype, 62.2% had IgG, 20.3% had IgA, 16.2% had LC, and 1.3% had IgM. Risk stratification was represented as follows: ISS-1 (24.3%), ISS-2 (39.2%), ISS-3 (36.5%); RISS-1 (20%), RISS-2 (65%), and RISS-3 (15%). Median serum creatinine, hemoglobin, and serum calcium levels were 1.1 mg/dl (IQR 1.6), 9.2 g/dl (IQR 3.53), and 9.6 mg/dl (IQR 1.9), respectively. An FLCr ≥ 100 was observed in 23% of cases, with median values for FLCr, kappa chain, lambda chain, involved chain, and non-involved chain of 35.1 (IQR 91.9), 46.9 (IQR 475.5), 25.5 (IQR 325.8), 384 (IQR 1410.9), and 10.4 (IQR 18.1), respectively. Bortezomib-based regimens (BBR) were used in 59.5% of cases, and high-dose melphalan followed by autologous stem cell transplantation was used in 29.2% as consolidative therapy. The frequency of hemodialysis requirement at MM diagnosis was 14.9%, with 9.5% requiring chronic hemodialysis. The median serum creatinine for patients with FLCr≥100 was 1.6 (IQR 6.8), while for those with FLCr< 100 it was 1.0 (IQR 1.0) (p< 0.01). Additionally, the odds ratio for requiring hemodialysis at MM diagnosis in patients with FLCr≥100 was 9.3 (95% CI 2.8 to 37.7, p< 0.01). In a multivariate analysis including hemoglobin level, serum calcium, ISS, RISS, and age, FLCr≥100 was the only variable with a significant effect on the risk of hemodialysis OR 10.6 (95% CI 1.5 to 69.0, p=0.02). **Conclusions:** An FLCr≥100 is a strong risk factor for kidney injury and renal replacement requirement. However, given the limitations of the study design and sample size, our results need to be corroborated by further investigations.

P-463

Patient characteristics and burden in lenalidomide refractory multiple myeloma patients in Europe: a real-world survey

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Introduction: Lenalidomide (LEN) is the standard of care for Multiple Myeloma (MM) patients (pts), often given until progression. Progressive disease negatively impacts quality of life

(QoL), however real-world evidence in LEN refractory (Ref) pts is lacking. **Methods:** Data were drawn from the Adelphi MM Disease Specific Programme™, a cross-sectional survey with retrospective data completed by haematologists/haem-oncologists in Europe (France, Germany, Italy, Spain, and United Kingdom) from May-Nov 2021. Physicians completed patient record forms for their next 8 pts with a MM diagnosis, actively receiving treatment, and aligned to the following quota: 2x each of: first-line (1L) or second-line (2L), third-line (3L), fourth-line and beyond (4L+), and tri-exposed (exposed to a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 targeted drug). Eligible pts voluntarily completed a questionnaire which included the EuroQol Visual Analogue Scale (EQ-VAS) [range: 0-1; 1 = best health] and European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaires (EORTC-QLQ-C30 and EORT-QLQ-MY20) [range: 0-100; 100 = best functioning / worst symptomology]. Bivariate comparisons were made between LEN and non-LEN Ref pts at time of data collection. LEN Ref is defined by the International Myeloma Working Group as progressive disease during LEN treatment or within 60 days of discontinuation. **Results:** 173 physicians provided data for 1,163 MM pts; 528 (45%) were LEN Ref, which had a higher mean [SD] age (71.9 [8.73] vs 70.4 [8.91] years; p=0.0058), were more likely to receive caregiver support (44% vs 36%, p=0.0082), experience bone lesions (70% vs 62%, p=0.0026) and more comorbidities vs non-LEN Ref pts (84% vs 78%, p=0.0248). Meaningful differences in employment status (p=0.0158) and Katz Activities of Daily Living (ADL) scores (p=0.008) were also observed, as 79% and 74% of LEN Ref and non-LEN Ref pts were retired, and 5% and 10% were in full/part-time work (respectively). 75% of LEN Ref pts and 82% of non-LEN Ref scored 5-6 (full independence) in the Katz ADL. Of pts that completed the questionnaire (n=248), 106 were LEN-Ref (46%) and had lower mean [SD] EQ-VAS scores (56.9 [17.86] vs 61.6 [16.83]; p=0.0326), reported more bone fractures (13% vs 2%, p=0.0017) and worse mean [SD] EORTC fatigue scores (49.6 [20.12] vs 43.5 [22.09], p=0.0280). The mean [SD] EORTC functioning score domains were 59.7 [23.40] vs 62.4 [22.25] (p=0.3501) for physical, 53.4 [26.01] vs 55.8 [27.67] (p=0.4928) for role, 69.8 [23.42] vs 72.9 [24.29] (p=0.3109) for cognitive, and 60.0 [25.5] vs 64.44 [27.45] (p=0.2028) for social, across LEN and non-LEN Ref pts respectively. **Conclusions:** This data shows that LEN Ref pts experience more bone lesions and frequent fractures, have less independence and report numerically inferior QoL compared to non-LEN Ref pts. There is an unmet need for new and innovative treatments that can reduce burden and improve QoL in LEN Ref pts.

P-464

Treatment decision-making in patients diagnosed with multiple myeloma

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Introduction: Shared decision-making is an important component in patient-centered healthcare, particularly for patients with multiple myeloma (MM) seeking individualized treatment options. In this study, we assessed how patients and caregivers make decisions related to stem-cell transplantation (SCT) and identified unmet needs in this process. **Methods:** Adult patients diagnosed with MM who received SCT within the past 5 years or their caregivers were recruited to participate in virtual structured 2-hour focus group discussions through involvement in a Patient Engagement Research Council focused on experiences with SCT. Discussions focused on information sources, patient understanding of SCT, conversations with doctors and families, and how these factors contributed to decision-making. **Results:** Discussions included 17 participants (14 patients, 3 caregivers). Approximately half of all participants (n=9, 53%) were < 60 years old, and 70% were female (n=12). Participants came from diverse racial/ethnic backgrounds (White, n=5; Black, n=6; other ethnic groups, n=6) and varied in educational experience (postgraduate, n=4; college graduate or some college, n=11; high school, n=2). Almost all participants learned about SCT from their oncologist or hematologist early in treatment planning, when SCT was presented as the expected treatment course. Although around half of the participants recalled initially having limited knowledge of SCT, many sought information from outside organizations (eg, foundations/societies, patient support groups); some received resources from their doctor. Key factors considered before deciding to proceed with SCT included long-term health impacts, side effects, and logistical or financial concerns. Participants spoke with their doctors about the SCT treatment process and potential risks and outcomes; family members were consulted regarding caregiving or logistical support needs. Decisions related to SCT were often made quickly; 2 patients made the decision on the day of diagnosis or within a few weeks. Approximately two-thirds of participants reported that they never considered, or were never offered, other treatment options. Participants recalled feeling nervous before their decision, followed by feelings of relief or hopefulness after deciding to undergo SCT. Four participants desired more information about the SCT process, particularly the recovery period, and 2 participants recalled feeling overwhelmed during decision-making. However, participants overall felt that they were adequately informed about SCT, and none regretted their decision to undergo SCT. **Conclusions:** Patients deciding to undergo SCT for MM drew on multiple information sources during the decision-making process but relied heavily on doctors' recommendations. Shared decision-making between patients, families, and providers—including education and discussion of alternative options and recovery—is important for patients facing a complex treatment process.

P-465

Global disparities in multiple myeloma: examining adverse events and drug toxicity trends

Majid Jaberi-Douraki[1], Xuan Xu[1], Remya Ampadi Ramachandran[1], Beth Faiman[2], Faiz Anwer[2], Christy Samaras[2], Jim Riviere[1], Nuwan Indika Millagaha Gedara[1],

(QoL), however real-world evidence in LEN refractory (Ref) pts is lacking. **Methods:** Data were drawn from the Adelphi MM Disease Specific Programme™, a cross-sectional survey with retrospective data completed by haematologists/haem-oncologists in Europe (France, Germany, Italy, Spain, and United Kingdom) from May-Nov 2021. Physicians completed patient record forms for their next 8 pts with a MM diagnosis, actively receiving treatment, and aligned to the following quota: 2x each of: first-line (1L) or second-line (2L), third-line (3L), fourth-line and beyond (4L+), and tri-exposed (exposed to a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 targeted drug). Eligible pts voluntarily completed a questionnaire which included the EuroQol Visual Analogue Scale (EQ-VAS) [range: 0-1; 1 = best health] and European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaires (EORTC-QLQ-C30 and EORT-QLQ-MY20) [range: 0-100; 100 = best functioning / worst symptomology]. Bivariate comparisons were made between LEN and non-LEN Ref pts at time of data collection. LEN Ref is defined by the International Myeloma Working Group as progressive disease during LEN treatment or within 60 days of discontinuation. **Results:** 173 physicians provided data for 1,163 MM pts; 528 (45%) were LEN Ref, which had a higher mean [SD] age (71.9 [8.73] vs 70.4 [8.91] years; p=0.0058), were more likely to receive caregiver support (44% vs 36%, p=0.0082), experience bone lesions (70% vs 62%, p=0.0026) and more comorbidities vs non-LEN Ref pts (84% vs 78%, p=0.0248). Meaningful differences in employment status (p=0.0158) and Katz Activities of Daily Living (ADL) scores (p=0.008) were also observed, as 79% and 74% of LEN Ref and non-LEN Ref pts were retired, and 5% and 10% were in full/part-time work (respectively). 75% of LEN Ref pts and 82% of non-LEN Ref scored 5-6 (full independence) in the Katz ADL. Of pts that completed the questionnaire (n=248), 106 were LEN-Ref (46%) and had lower mean [SD] EQ-VAS scores (56.9 [17.86] vs 61.6 [16.83]; p=0.0326), reported more bone fractures (13% vs 2%, p=0.0017) and worse mean [SD] EORTC fatigue scores (49.6 [20.12] vs 43.5 [22.09], p=0.0280). The mean [SD] EORTC functioning score domains were 59.7 [23.40] vs 62.4 [22.25] (p=0.3501) for physical, 53.4 [26.01] vs 55.8 [27.67] (p=0.4928) for role, 69.8 [23.42] vs 72.9 [24.29] (p=0.3109) for cognitive, and 60.0 [25.5] vs 64.44 [27.45] (p=0.2028) for social, across LEN and non-LEN Ref pts respectively. **Conclusions:** This data shows that LEN Ref pts experience more bone lesions and frequent fractures, have less independence and report numerically inferior QoL compared to non-LEN Ref pts. There is an unmet need for new and innovative treatments that can reduce burden and improve QoL in LEN Ref pts.

P-464

Treatment decision-making in patients diagnosed with multiple myeloma

Doris Hansen[1], Todd Bixby[2], Karen Fixler[2], Lisa Shea[2], Christine Brittle[3], Kimberly Brunisholz[2], Yi-Hsuan Liu[2], Stephen Huo[2]

[1]Moffiitt Cancer Center; [2]Janssen Pharmaceuticals; [3]CorEvitas

Introduction: Shared decision-making is an important component in patient-centered healthcare, particularly for patients with multiple myeloma (MM) seeking individualized treatment options. In this study, we assessed how patients and caregivers make decisions related to stem-cell transplantation (SCT) and identified unmet needs in this process. **Methods:** Adult patients diagnosed with MM who received SCT within the past 5 years or their caregivers were recruited to participate in virtual structured 2-hour focus group discussions through involvement in a Patient Engagement Research Council focused on experiences with SCT. Discussions focused on information sources, patient understanding of SCT, conversations with doctors and families, and how these factors contributed to decision-making. **Results:** Discussions included 17 participants (14 patients, 3 caregivers). Approximately half of all participants (n=9, 53%) were < 60 years old, and 70% were female (n=12). Participants came from diverse racial/ethnic backgrounds (White, n=5; Black, n=6; other ethnic groups, n=6) and varied in educational experience (postgraduate, n=4; college graduate or some college, n=11; high school, n=2). Almost all participants learned about SCT from their oncologist or hematologist early in treatment planning, when SCT was presented as the expected treatment course. Although around half of the participants recalled initially having limited knowledge of SCT, many sought information from outside organizations (eg, foundations/societies, patient support groups); some received resources from their doctor. Key factors considered before deciding to proceed with SCT included long-term health impacts, side effects, and logistical or financial concerns. Participants spoke with their doctors about the SCT treatment process and potential risks and outcomes; family members were consulted regarding caregiving or logistical support needs. Decisions related to SCT were often made quickly; 2 patients made the decision on the day of diagnosis or within a few weeks. Approximately two-thirds of participants reported that they never considered, or were never offered, other treatment options. Participants recalled feeling nervous before their decision, followed by feelings of relief or hopefulness after deciding to undergo SCT. Four participants desired more information about the SCT process, particularly the recovery period, and 2 participants recalled feeling overwhelmed during decision-making. However, participants overall felt that they were adequately informed about SCT, and none regretted their decision to undergo SCT. **Conclusions:** Patients deciding to undergo SCT for MM drew on multiple information sources during the decision-making process but relied heavily on doctors' recommendations. Shared decision-making between patients, families, and providers—including education and discussion of alternative options and recovery—is important for patients facing a complex treatment process.

P-465

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P-464

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P-465

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[1]Kansas State University; [2]Cleveland Clinic Taussig Cancer Institute; [3]University of Iowa Hospitals & Clinics; [4]University of Kansas Medical Center; [5]Indiana University; [6]Case Comprehensive Cancer Center; [7]Saint Luke's Cancer Institute

Introduction: Multiple myeloma (MM) is a complex hematologic malignancy with significant disparities in outcomes and treatment-related toxicities across different regions globally. This study aims to examine global disparities in adverse events and drug toxicity trends in MM and assess the impact of advances in MM regimens on mortality and hospitalization rates. **Methods:** A retrospective analysis was conducted using a large dataset from the Food and Drug Administration (FDA) Adverse Event Reporting System, a database maintained by the FDA that collects and analyzes information on adverse events. The dataset comprises 401,576 MM patients from North America (NA), Europe (EU), Asia (AS), Africa (AF), Oceania (OC), and Latin America & the Caribbean (LA), representing 129 countries and 27 phenotypic systems/organs categories. The dataset was curated to include patients' data from 2005 onwards. **Results:** The findings indicated a notable decrease in mortality and hospitalization rates since 2012, particularly in NA, which can be attributed to advancements in MM regimens. However, higher mortality rates were observed among patients from AF and AS followed by EU compared to NA and OC. The results highlight the existence of significant disparities in MM outcomes and AMDR toxicities on a global scale. We also found evidence of an increase in secondary neoplasm in regions including AS (M&F) and AF (M), and Oceania (M&F). Our results also showed that the availability of specific AMDRs used in each region played a significant role in the differences in toxicities as shown in Table 1. For instance, R, P, and Rd were among the top AMDRs in NA, and R, Rd, and NRd are the top AMDRs in EU, while V, R, and P were prescribed more frequently in OC. **Conclusions:** The variations observed in mortality rates among different regions underscore the need for targeted interventions to address these disparities. By understanding the regional differences in drug toxicity trends, healthcare professionals can develop personalized treatment strategies to optimize patient outcomes. Further research is warranted to delve deeper into the underlying factors contributing to these disparities, including genetic, socioeconomic, and healthcare system-related factors.

Table 1 Toxicities

AF	%	AS	%	EU	%	LA	%	NA	%	OC	%
R	14.4	R	17.1	R	9.5	R	25.8	R	61.5	V	38.1
V	9.1	Rd	11	Rd	8.3	V	13.6	P	15.7	R	14.6
VTd	8.6	NRd	6.2	NRd	7.9	D	9.6	Rd	2.7	P	7.1
T	8.6	V	6.1	Pd	6.2	K	9.4	T	2.7	T	4.4
VCd	7.4	P	5.1	V	4.9	VDd	3.9	VRd	1.5	K	3.9
D	6.6	Pd	4.3	B	4.5	Vd	3.4	V	1.3	VCd	3.7
N	5.3	Vd	4.3	Vd	3.7	DRd	2.6	N	1.1	VKRT	2.4
VRd	4.1	N	3.7	VRd	2.9	VD	2.3	K	1.1	Rd	2
Rd	3.3	DRd	3.3	DRd	2.7	N	2.1	VR	0.9	Pd	1.8
K	2.5	VRd	3	VTd	2.4	NRd	1.8	NR	0.8	B	1.4

Proteasome inhibitors: bortezomib (V), carfilzomib (K), and ixazomib (N); Immunomodulating Agents: thalidomide (T), lenalidomide (R), and pomalidomide (P); Alkylating Agents: melphalan (E) and cyclophosphamide (C); Corticosteroids: dexamethasone (d); Monoclonal Antibodies: daratumumab (D); and Bisphosphonates (B).

P-466

Peripheral and severe autonomic neuropathy characterized by dizziness, orthostatic hypotension and weight loss caused by bortezomib

Anand Jillella[1], Irnia Shishkina[1], Gita Giddens[1], Courtney Corley[1], Kimberly Green[1], Joy Brown[1], Rachel Ashley[1], Sarah Jimenez[1], Locke Bryan[1], Ayushi Chauhan[1], Amany Keruakous[1], Molly Denlinger[1], Mohammed Anwarul Huq. Mian[1], Danielle Bradshaw[1], Vamsi Kota[1]

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Introduction: Bortezomib (B), used to treat Multiple Myeloma (MM) causes peripheral neuropathy (PN) in an estimated 75% of patients. There are reports of dizziness, muscle weakness and other neurologic problems caused by B. Among patients that received B based induction, in addition to PN, in a small subset we observed profound weight loss, dizziness and orthostatic hypotension (OH). These symptoms frequently impair patients' performance status requiring interruption of therapy. There are few publications on autonomic neuropathy (AN) caused by B but we believe it is under recognized and under diagnosed. We report a series of patients that presented with significant weight loss and OH suggestive of AN, to bring awareness to this problem. **Methods:** From July 2017 to July 2022, patients with MM requiring transplant; complaining of weight loss and dizziness were identified. Medical records were reviewed and a pattern of symptoms and clinical course were identified. Statistics are descriptive and this retrospective study was approved by our Institutional review board. **Results:** Fourteen patients were noted to have symptoms suggestive of AN. 12 received VRD and 2 received (Daratumumab) D-VRD induction. B was given subcutaneously and twice weekly. The median age was 61 years (range 51-76). Nine were African American and 5 White; 5 female, 4 had diabetes but no prior neuropathy. The interval between initiation of therapy and AN symptoms was a median of 124 days (range 50-219) and the median B dose was 20.8 mg/M2 (range 11.7-40.33 mg/M2). All 14 patients had weight loss. The median weight loss and percentage weight loss (compared to baseline weight) were 19.5 Kgs (range 7-39.14 Kgs) and 21% (range 7-41) respectively. Further treatment was held due to decline in performance status in all patients. Eight patients received appetite stimulants; 2 megestrol and 6 dronabinol.

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P-466

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OH was seen in all patients; 3 received fludrocortisone and one received midodrine. 12 patients also had PN requiring neuropathic pain medications and narcotic analgesics. Transplant was delayed by 6 months (range 2-11) to enable recovery and the end-point was weight gain, and resolution of OH. 12 patients received transplant; Post-transplant 1 patient had persistent diarrhea and 1 had persistent dizziness. One patient developed severe mucositis, dysphagia, poor appetite and required hyper alimentation, nasogastric feeding and a feeding gastrostomy tube. With a follow up of 30.2 (range 8.47-53.6) months, the median survival is 30.82 months. **Conclusions:** Severe AN characterized by weight loss, dizziness, OH in association with painful neuropathy is an under recognized complication of B. Transplantation without resolution of symptoms could possibly worsen the morbidity and delay post-transplant recovery. To the best of our knowledge, we are the first group to report a series of patients with this symptom complex and strongly feel it should be studied further in a larger cohort of patients.

P-467

Dietary risk factors for monoclonal gammopathy of undetermined significance in a racially diverse national health and nutrition examination survey (NHANES) case-control study

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) has a prevalence of 3% over age 50 with a 1% annual risk of progression to multiple myeloma. Although one cohort study in Caucasians from Iceland reported that diets low in whole wheat bread and fruits were associated with MGUS (Thordardottir et al. 2018), research on diet and MGUS in a more diverse population is scarce. Given that diet can vary greatly between ethnic/racial groups, we conducted a population-based study of diet and MGUS in a racially diverse population. **Methods:** Using the National Health and Nutrition Examination Survey (NHANES), we conducted a case-control study in 373 individuals with MGUS and 1,406 controls frequency matched on age, body mass index, NHANES cycle, sex, and race. The study sample was diverse, with 27.2% Non-Hispanic Black and 16.0% Mexican American. Diet was characterized by one 24-hour dietary recall, with gram intake of individual foods and beverages aggregated into groups. MGUS status was determined by blood screening. Individuals with MGUS were risk stratified based on Mayo Clinic criteria into low (n=158) and intermediate/high risk (n=180). Unconditional multivariable logistic regressions were used to model associations between intake of several food groups and MGUS and risk stratified MGUS, with odds ratios (OR) and 95% confidence intervals (CI) reported for the highest relative to the lowest quantile of intake. **Results:** Daily intake of several food and beverage groups were significantly associated with MGUS, low-risk MGUS (LRM) or intermediate/high-risk MGUS (IHRM). Inverse associations were observed for fruits and vegetables: OR=0.69 (95% CI 0.52-0.93) (MGUS); fruits: OR=0.62 (95% CI 0.38-0.99) (LRM); vegetables: OR=0.75 (95% CI 0.56-0.99) (MGUS); tomatoes: OR=0.72 (95% CI 0.51-1.00) (MGUS); cruciferous vegetables: OR=0.44 (95% CI 0.26-0.74) (MGUS); OR=0.22 (95% CI 0.09-0.57) (IHRM) and whole-grain bread, oats, rice: OR=0.52 (95% CI 0.28-0.95) (LRM). Direct associations were observed for sugar-sweetened beverages: OR=1.34 (95% CI 1.00-1.78) (MGUS); OR=1.68 (95% CI 1.13-2.49) (LRM); sugar-sweetened soft drinks: OR=1.41 (95% CI 1.01-1.96) (MGUS); artificially sweetened soft drinks: OR=1.55 (95% CI 1.04-2.33) (MGUS); OR=2.13 (95% CI 1.28-3.56) (LRM); and cola, combined sugar- and artificially sweetened: OR=1.59 (95% CI 1.14-2.22) (MGUS); OR=1.77 (95% CI 1.13-2.78) (LRM). There were more significant findings for LRM than IHRM, suggesting potential contributing etiologic differences. **Conclusions:** Our study shows that low intake of whole grains, fruits, and vegetables and high intake of sweetened beverages are associated with MGUS. The identification of dietary risk factors for MGUS in a diverse population is of direct public health relevance. These findings also provide rationale for exploration of mechanistic links between diet and plasma cell disorders, such as the ongoing studies NCT04920084, NCT05640843, and NCT05312255.

P-468

Risk of secondary primary malignancies after multiple myeloma in the novel therapy era: a nationwide case-control cohort study

Heejoo Ko[1], Suein Choi[2], Seunghoon Han[2], Chang-Ki Min[3], Ja Min Byun[4], Sung-Soo Park[1]

[1]Department of Hematology, Seoul St. Mary's Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Department of Pharmacology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Seoul St. Mary's Hospital, Seoul, South Korea; [4]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea

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P-467

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[1]Roswell Park Comprehensive Cancer Center; [2]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami; [3]Memorial Sloan Kettering Cancer Center, New York City NY, USA; [4]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City NY, USA

Introduction: Monoclonal gammopathy of undetermined significance (MGUS) has a prevalence of 3% over age 50 with a 1% annual risk of progression to multiple myeloma. Although one cohort study in Caucasians from Iceland reported that diets low in whole wheat bread and fruits were associated with MGUS (Thordardottir et al. 2018), research on diet and MGUS in a more diverse population is scarce. Given that diet can vary greatly between ethnic/racial groups, we conducted a population-based study of diet and MGUS in a racially diverse population. **Methods:** Using the National Health and Nutrition Examination Survey (NHANES), we conducted a case-control study in 373 individuals with MGUS and 1,406 controls frequency matched on age, body mass index, NHANES cycle, sex, and race. The study sample was diverse, with 27.2% Non-Hispanic Black and 16.0% Mexican American. Diet was characterized by one 24-hour dietary recall, with gram intake of individual foods and beverages aggregated into groups. MGUS status was determined by blood screening. Individuals with MGUS were risk stratified based on Mayo Clinic criteria into low (n=158) and intermediate/high risk (n=180). Unconditional multivariable logistic regressions were used to model associations between intake of several food groups and MGUS and risk stratified MGUS, with odds ratios (OR) and 95% confidence intervals (CI) reported for the highest relative to the lowest quantile of intake. **Results:** Daily intake of several food and beverage groups were significantly associated with MGUS, low-risk MGUS (LRM) or intermediate/high-risk MGUS (IHRM). Inverse associations were observed for fruits and vegetables: OR=0.69 (95% CI 0.52-0.93) (MGUS); fruits: OR=0.62 (95% CI 0.38-0.99) (LRM); vegetables: OR=0.75 (95% CI 0.56-0.99) (MGUS); tomatoes: OR=0.72 (95% CI 0.51-1.00) (MGUS); cruciferous vegetables: OR=0.44 (95% CI 0.26-0.74) (MGUS); OR=0.22 (95% CI 0.09-0.57) (IHRM) and whole-grain bread, oats, rice: OR=0.52 (95% CI 0.28-0.95) (LRM). Direct associations were observed for sugar-sweetened beverages: OR=1.34 (95% CI 1.00-1.78) (MGUS); OR=1.68 (95% CI 1.13-2.49) (LRM); sugar-sweetened soft drinks: OR=1.41 (95% CI 1.01-1.96) (MGUS); artificially sweetened soft drinks: OR=1.55 (95% CI 1.04-2.33) (MGUS); OR=2.13 (95% CI 1.28-3.56) (LRM); and cola, combined sugar- and artificially sweetened: OR=1.59 (95% CI 1.14-2.22) (MGUS); OR=1.77 (95% CI 1.13-2.78) (LRM). There were more significant findings for LRM than IHRM, suggesting potential contributing etiologic differences. **Conclusions:** Our study shows that low intake of whole grains, fruits, and vegetables and high intake of sweetened beverages are associated with MGUS. The identification of dietary risk factors for MGUS in a diverse population is of direct public health relevance. These findings also provide rationale for exploration of mechanistic links between diet and plasma cell disorders, such as the ongoing studies NCT04920084, NCT05640843, and NCT05312255.

P-468

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29,351 individuals without MM were matched as controls using 1:4 propensity score matching based on age, sex, and comorbidities. Cumulative incidence of secondary malignancy was compared using the Gray test, treating death as a competing risk. Incidences of secondary malignancy and subtypes were compared, and hazard ratios (HR) were computed using the Fine-Gray subdistribution hazard model. Subgroup analysis based on transplant eligibility was conducted to explore the impact of high dose chemotherapy for autologous stem cell transplantation on the secondary malignancy occurrence. **Results:** Median follow-up was 45.6 months for cases and 51.3 months for controls. The 10-year cumulative incidence rate of any secondary malignancy was significantly higher in cases than controls (10.52% vs. 8.68%, p< 0.001, HR 1.58, 95% confidence interval [CI] 1.38-1.80). The risk of hematologic malignancy was significantly higher in cases than controls (HR 8.03, 95% CI 5.40-11.92; 10-year incidence 2.34% vs. 0.36%, p< 0.001). Notably, the incidence of therapy-related myeloid neoplasms (t-MN) was significantly higher in cases (HR 12.06, 95% CI 6.84-21). There were no significant differences in the 10-year cumulative incidence of non-hematologic malignancy (6.17% vs. 8.29%, p=0.122, HR 0.9) or its subtypes. In the subgroup analysis, any secondary malignancy had significantly increased in the transplant-eligible MM patients compared to transplant-ineligible patients (p< 0.001). **Conclusions:** The incidence of secondary solid malignancies did not differ markedly between MM cases and controls. However, the risk of hematologic malignancy and t-MN in MM patients was significantly higher compared to the general population. Transplant-eligible MM patients had a higher risk of developing any malignancies, suggesting that stem cell transplantation might be an important factor associated with the development of secondary malignancies in patients with MM.

P-469

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P-470

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Matthew Lei[1], Erica Tavares[1], Uvette Lou[1], E. Bridget Kim[1], Jack Malespini[1], Noopur Raje[1], Andrew Yee[1]

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P-470

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Bivariate analyses were performed. The Kaplan Meier method was used to estimate time to CR. **Results:** A total of 27 patients were included. 37% (n=10) of patients had newly diagnosed MM. 19% (n=5) of patients received a dose of 60 mg, the majority of whom had significant renal dysfunction; all other patients received a dose of 120 mg. Most patients received HC treatment as an inpatient (67% inpatient vs. 33% outpatient). A minority of patients had received IVBs in the past 90 days (15%; n=4). The median CSC was 12.2 mg/dL (interquartile range [IQR], 11.5-14.0). Baseline median serum creatinine (SCr) and creatinine clearance (CrCl) was 2.2 mg/dL (IQR, 1.2-3.0) and 30.7 mL/min (IQR, 20.8-42.2), respectively. Incidence of AKI at baseline was 63% (n=17). The CR rate by day 10 was 81%. The median time to CR was 3 days (95% CI, 2.7-3.2). Three patients did not achieve CR. HC relapse occurred in 4 (15%) patients. All grade hypocalcemia was 56% (n=15) while grade ≥2 hypocalcemia was 37%; one patient experienced grade 3 hypocalcemia. No patients in the denosumab group received an additional dose of denosumab within 14 days of initial dose. **Conclusions:** We describe our experience with denosumab for the management of HC in patients with MM. The median time to CR was 3 days in our MM only population that was not bisphosphonate refractory. A high incidence of grade 2 hypocalcemia was noted. Conclusions on renal safety are limited by the small sample size. Denosumab represents an acceptable alternative to intravenous bisphosphonates for the management of HC in MM patients with further investigation necessary in those with renal dysfunction.

P-471

The MMRF cure cloud research study: a real-world longitudinal investigation of patient treatments and outcomes, including patient reported outcome (PRO) surveys

Eva Lepisto[1], Mark Fiala[2], April Cook[1], Jessica Schulman[1], Anne Quinn Young[1], Erin Mensching[1], Jennifer Rogers[1], Ibrahim Akorede[1], Elizabeth Kane[1], Mary DeRome[1], George Mulligan[1], Hearn Jay Cho[1]

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Introduction: Despite lack of clear curative regimens for multiple myeloma (MM) patients, survival has increased over the past 2 decades. Patients are managed on therapy for years, often progressing through complex treatment regimens. Unfortunately, some patients (e.g. Black Americans, those with high-risk disease) have consistently worse outcomes, and it remains unclear how to optimize therapy for every patient. The MMRF is enrolling a longitudinal research study called CureCloud to engage a US cohort of MM patients along their treatment journey in efforts to understand their treatments, outcomes, personal experiences, and molecular features of the disease. There are no specific therapy or demographic requirements for entry. Patients enroll with their clinical care team or via a direct-to-patient portal, and blood is collected in participants' homes. The study integrates molecular and real-world evidence data, including electronic health records (EHR) and PROs collected at six-month intervals, and is expected to enroll and follow 5000 patients for at least five years. Here we report the first learnings on RWE towards better understanding the impact of therapy on MM patients' short- and long-term quality of life. **Methods:** This was an analysis of the baseline PRO data. The FACIT-COmprehensive Score for financial Toxicity (COST) and the Cancer Therapy Satisfaction Questionnaire (CTSQ) were administered to consented patients with at least 6 months follow-up in 2022 using an emailed web-based link sent to patients between October and December 2022. Patients not completing surveys within the first week received a second email link to the surveys. For completed surveys, a composite score for the COST data was calculated with possible scores ranging from 0-44; higher scores indicate better financial well-being. The CTSQ subscales were calculated with scores ranging from 0-100; higher scores indicate higher satisfaction. **Results:** 976 (96%) of the 1020 consented patients received the PROs. 192 (19%) patients completed the CTSQ and 190 (19%) the COST. Analyses were limited to 175 with active MM (91%) at time of completion. The average score for the CTSQ's expectation of therapy (ET) was 56.5 [SD 18.7], satisfaction with therapy (SWT) was 67.9 [SD 10.8], and feelings about side effects (FSE) 72.5 [SD 16.6]. In bivariate analysis newly diagnosed patients showed increased expectations of therapy. The average COST score was 27.9 [SD 9.3], and no significant differences were observed across demographic characteristics. For both PROs, the relationship with patients' race couldn't be studied due to low representation. **Conclusions:** This longitudinal study continues to enroll active MM patients (newly diagnosed and relapsed), both at clinical sites and through a unique direct to patient format https://mmrfcurecloud.org/ with an emphasis on ensuring inclusivity and racial diversity. The current data reveal initial patient experiences over their MM journey.

P-472

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Bivariate analyses were performed. The Kaplan Meier method was used to estimate time to CR. **Results:** A total of 27 patients were included. 37% (n=10) of patients had newly diagnosed MM. 19% (n=5) of patients received a dose of 60 mg, the majority of whom had significant renal dysfunction; all other patients received a dose of 120 mg. Most patients received HC treatment as an inpatient (67% inpatient vs. 33% outpatient). A minority of patients had received IVBs in the past 90 days (15%; n=4). The median CSC was 12.2 mg/dL (interquartile range [IQR], 11.5-14.0). Baseline median serum creatinine (SCr) and creatinine clearance (CrCl) was 2.2 mg/dL (IQR, 1.2-3.0) and 30.7 mL/min (IQR, 20.8-42.2), respectively. Incidence of AKI at baseline was 63% (n=17). The CR rate by day 10 was 81%. The median time to CR was 3 days (95% CI, 2.7-3.2). Three patients did not achieve CR. HC relapse occurred in 4 (15%) patients. All grade hypocalcemia was 56% (n=15) while grade ≥2 hypocalcemia was 37%; one patient experienced grade 3 hypocalcemia. No patients in the denosumab group received an additional dose of denosumab within 14 days of initial dose. **Conclusions:** We describe our experience with denosumab for the management of HC in patients with MM. The median time to CR was 3 days in our MM only population that was not bisphosphonate refractory. A high incidence of grade 2 hypocalcemia was noted. Conclusions on renal safety are limited by the small sample size. Denosumab represents an acceptable alternative to intravenous bisphosphonates for the management of HC in MM patients with further investigation necessary in those with renal dysfunction.

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autologous stem cell transplantation between December 2010 and December 2022 were recruited to determine the usefulness of latent TB infection screening tests. **Results:** Most of the enrolled patients were male (58.7%) with a median age of 54 years old (range, 40 ~ 69 years old). Remission induction therapy was as follows; 40 (58.8%) of bortezomib-based regimens, such as VD or VTD, 12 (17.6%) of lenalidomide-based regimens, such as RVD, and 16 (23.5%) of thalidomide-based regimens, such as TD or TCD. Fifty-three (78%) patients achieved partial response after remission induction and the maximal response before ASCT was as follows; 24 (35.3%) patients of CR, 28 (41.2%) of VGPR, 14 (20.5%) of PR, and 2 (2.9%) of SD, respectively. For conditioning regimen, 54 (79.4%) patients received high-dose melphalan and 14 patients received busulfan-based conditioning. The QuantiFERON screening test was performed within one month before ASCT. Sixty-eight (85%) patients out of a total of 80 patients performed QuantiFERON test screening: 10 (14.7%) were positive, 6 (8.8%) indeterminate, and 52 (76.5%) were negative. There was no difference in test-positive rates between men and women. However, the positive rate was statistically significantly higher in elderly patients more than 60 years (p=0.014). Only 20% of the patients whose test was QuantiFERON test positive took isoniazid prophylaxis, and none of them progressed to active TB over a median follow-up period of 38 months. Active TB recurrence did not occur even in 80% of QuantiFERON test-positive who did not take isoniazid, also. All patients who took isoniazid prophylaxis discontinued it prematurely because of drug side effects. **Conclusions:** In conclusion, 14.7% of our ASCT population had latent TB infection and only 20% of them received isoniazid prophylaxis. Regardless of the use of isoniazid prophylaxis, there was no case of active TB progression in a cohort of 68 multiple myeloma patients who underwent ASCT from 2010 to 2022.

P-473

Real-world evidence of statins and oral antidiabetics for multiple myeloma

Nieves Lopez-Muñoz[1], Gema Hernández-Ibarburu[2], Jose Maria Sanchez[1], Rafael Alonso[1], Clara Cuellar[1], Maria Calbacho[1], M Teresa Cedena[1], Ana Jimenez-Ubieto[1], Rosa Ayala[1], Laura Meloni[3], David Perez-Rey[2], Joaquín Martínez-López[4]

[1]Hematología Hospital 12 de Octubre, Madrid, Spain; [2]Biomedical Informatics Group, Universidad Politécnica de Madrid; [3]TriNetX, LLC, Cambridge, MA USA

Introduction: Statins are drugs frequently used in patients with hypercholesterolaemia, and metformin is frequently used in patients with diabetes mellitus. The first one act by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which functions in the same metabolic pathway as bisphosphonates. Some studies have suggested that statins may increase survival in patients with multiple myeloma, in addition to decreasing bone events. On the other hand, studies suggest that metformin stops the cell cycle of multiple myeloma cells, impairing mitochondrial function. The objective of this study is analyzing the impact of statins and oral antidiabetics treatment in a large cohort of patients with multiple myeloma. For the proposed analysis, we used data from TriNetx, a global federated health research platform that includes patients from Europe and US. **Methods:** Patients had symptomatic multiple myeloma (ICD-10-CM code C90.0) diagnosed between 2007 and 2022. First of all, comparator cohorts included 16,852 MM patients from US and EMEA Collaborative Networks, 7529 were treated with statins. After propensity scoring matching by age, sex, and date of diagnosis we selected 5038 patients in each cohorts. In both groups, patients received the statin as a treatment for hypercholesterolemia. In relation to oral antidiabetics treatment, comparator cohorts included 13,972 MM patients from US and EMEA Collaborative Networks, 7094 were treated with oral antidiabetics. After propensity scoring matching by age, sex, and date of diagnosis we selected 6495 patients in each cohorts. Kaplan−Meier analysis was used to estimate survival probabilities, and between-group differences were tested using the log-rank test and hazard ratio. **Results:** Patients treated with statins had a longer overall survival (OS) than those who did not: HR 0.789 (0.740, 0.841; 95%) p< 0.001. (Figure 1). The median OS was 96.11 months vs. 74.25 months, respectively. Also, patients treated with oral antidiabetics had a longer overall survival (OS), the median OS was 110.66 months vs. 86.16 months, respectively (p< 0.001) (Figure 2). **Conclusions:** This large-scale study based on real-world data confirms the statins and oral antidiabetics significantly prolongs survival in MM.

P-474

The effect of elranatamab on patient-reported outcomes in patients with relapsed/refractory multiple myeloma naïve and exposed to BCMA-directed therapies: results from the MagnetisMM-3 study

Mohamad Mohty[1], Nizar Bahlis[2], Ajay Nooka[3], Marco DiBonaventura[4], Jinma Ren[4], Umberto Conte[4], Andrea Viqueira[5]

[1]Sorbonne University, Saint-Antoine Hospital, AP-HP INSERM UMRs 938, Paris, France; [2]Arnie Charbonneau Cancer Institute, University of Calgary; [3]Winship Cancer Institute, Emory University School of Medicine; [4]Pfizer Inc; [5]Pfizer SLU, Madrid, Spain

Introduction: Elranatamab is a humanized bispecific antibody that targets both B-cell maturation antigen (BCMA)-expressing multiple myeloma (MM) cells and CD3-expressing T cells. MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study to evaluate the safety and efficacy of elranatamab monotherapy in patients (pts) with relapsed/refractory MM (RRMM). Patient-reported outcomes (PROs) from this study are presented. **Methods:** MagnetisMM-3 enrolled two cohorts of pts (Cohort A: BCMA-naïve; Cohort B: BCMA-exposed) who were refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody. Pts received subcutaneous elranatamab 76 mg QW on a 28-day cycle with a 2-step-up priming dose regimen (12 mg and 32 mg) administered during the first week. PROs included the EORTC QLQ-C30, the EORTC MY20, and the EQ-5D generic quality of life (QoL) questionnaire. PROs were

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autologous stem cell transplantation between December 2010 and December 2022 were recruited to determine the usefulness of latent TB infection screening tests. **Results:** Most of the enrolled patients were male (58.7%) with a median age of 54 years old (range, 40 ~ 69 years old). Remission induction therapy was as follows; 40 (58.8%) of bortezomib-based regimens, such as VD or VTD, 12 (17.6%) of lenalidomide-based regimens, such as RVD, and 16 (23.5%) of thalidomide-based regimens, such as TD or TCD. Fifty-three (78%) patients achieved partial response after remission induction and the maximal response before ASCT was as follows; 24 (35.3%) patients of CR, 28 (41.2%) of VGPR, 14 (20.5%) of PR, and 2 (2.9%) of SD, respectively. For conditioning regimen, 54 (79.4%) patients received high-dose melphalan and 14 patients received busulfan-based conditioning. The QuantiFERON screening test was performed within one month before ASCT. Sixty-eight (85%) patients out of a total of 80 patients performed QuantiFERON test screening: 10 (14.7%) were positive, 6 (8.8%) indeterminate, and 52 (76.5%) were negative. There was no difference in test-positive rates between men and women. However, the positive rate was statistically significantly higher in elderly patients more than 60 years (p=0.014). Only 20% of the patients whose test was QuantiFERON test positive took isoniazid prophylaxis, and none of them progressed to active TB over a median follow-up period of 38 months. Active TB recurrence did not occur even in 80% of QuantiFERON test-positive who did not take isoniazid, also. All patients who took isoniazid prophylaxis discontinued it prematurely because of drug side effects. **Conclusions:** In conclusion, 14.7% of our ASCT population had latent TB infection and only 20% of them received isoniazid prophylaxis. Regardless of the use of isoniazid prophylaxis, there was no case of active TB progression in a cohort of 68 multiple myeloma patients who underwent ASCT from 2010 to 2022.

P-473

Real-world evidence of statins and oral antidiabetics for multiple myeloma

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Introduction: Statins are drugs frequently used in patients with hypercholesterolaemia, and metformin is frequently used in patients with diabetes mellitus. The first one act by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which functions in the same metabolic pathway as bisphosphonates. Some studies have suggested that statins may increase survival in patients with multiple myeloma, in addition to decreasing bone events. On the other hand, studies suggest that metformin stops the cell cycle of multiple myeloma cells, impairing mitochondrial function. The objective of this study is analyzing the impact of statins and oral antidiabetics treatment in a large cohort of patients with multiple myeloma. For the proposed analysis, we used data from TriNetx, a global federated health research platform that includes patients from Europe and US. **Methods:** Patients had symptomatic multiple myeloma (ICD-10-CM code C90.0) diagnosed between 2007 and 2022. First of all, comparator cohorts included 16,852 MM patients from US and EMEA Collaborative Networks, 7529 were treated with statins. After propensity scoring matching by age, sex, and date of diagnosis we selected 5038 patients in each cohorts. In both groups, patients received the statin as a treatment for hypercholesterolemia. In relation to oral antidiabetics treatment, comparator cohorts included 13,972 MM patients from US and EMEA Collaborative Networks, 7094 were treated with oral antidiabetics. After propensity scoring matching by age, sex, and date of diagnosis we selected 6495 patients in each cohorts. Kaplan−Meier analysis was used to estimate survival probabilities, and between-group differences were tested using the log-rank test and hazard ratio. **Results:** Patients treated with statins had a longer overall survival (OS) than those who did not: HR 0.789 (0.740, 0.841; 95%) p< 0.001. (Figure 1). The median OS was 96.11 months vs. 74.25 months, respectively. Also, patients treated with oral antidiabetics had a longer overall survival (OS), the median OS was 110.66 months vs. 86.16 months, respectively (p< 0.001) (Figure 2). **Conclusions:** This large-scale study based on real-world data confirms the statins and oral antidiabetics significantly prolongs survival in MM.

P-474

The effect of elranatamab on patient-reported outcomes in patients with relapsed/refractory multiple myeloma naïve and exposed to BCMA-directed therapies: results from the MagnetisMM-3 study

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Introduction: Elranatamab is a humanized bispecific antibody that targets both B-cell maturation antigen (BCMA)-expressing multiple myeloma (MM) cells and CD3-expressing T cells. MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study to evaluate the safety and efficacy of elranatamab monotherapy in patients (pts) with relapsed/refractory MM (RRMM). Patient-reported outcomes (PROs) from this study are presented. **Methods:** MagnetisMM-3 enrolled two cohorts of pts (Cohort A: BCMA-naïve; Cohort B: BCMA-exposed) who were refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody. Pts received subcutaneous elranatamab 76 mg QW on a 28-day cycle with a 2-step-up priming dose regimen (12 mg and 32 mg) administered during the first week. PROs included the EORTC QLQ-C30, the EORTC MY20, and the EQ-5D generic quality of life (QoL) questionnaire. PROs were

assessed on day (D) 1 and 15 of the first 3 cycles and D1 of each subsequent cycle (C) through C12, the last cycle included in this analysis. The data cut-off was January 12, 2023 (approximately 12 months after the last pt's initial dose). **Results:** 123 and 64 pts were enrolled and treated with elranatamab in Cohort A and B, respectively. Median age was 68.0 and 67.0 years, 55.3% and 46.9% were male, 58.5% and 68.8% were White. At baseline, 25.2% and 20.3% had high risk cytogenetics, 15.4% and 23.4% had R-ISS III, and 31.7% and 57.8% had extramedullary disease. The median number of prior treatment lines was 5.0 (range: 2-22) and 7.5 (3-19). Among pts in Cohort A, a transient worsening in the global health score (QLQ-C30) and side effects domain (MY20) relative to baseline was observed through C2D15 (least square mean [LSM] change=-5.9 [95%CI: -10.7, -1.1] and 4.3 [1.4, 7.2], respectively); both domains reverted to baseline levels by C3D1 and generally showed (non-significant) improvement from baseline starting at C7D1/C8D1. Significant reductions in pain (QLQ-C30) and disease symptoms (MY20) were observed starting at C4D1 (-6.7 [-13.0, -0.4]) and C5D1 (-6.9 [-10.6, -3.1], respectively) and were maintained. Overall QoL (EQ-5D) significantly improved by C11D1 (0.06 [0.02, 0.09]) and was maintained. Cohort B results were largely similar, though, due to small sample sizes, significant differences were less frequent. Only a modest (non-significant) worsening in the global health score was observed with the nadir at C1D15 (-2.0 [-8.0, 4.0]) followed by a (non-significant) improvement relative to baseline by C2D15 (5.2 [-2.6, 13.0]) which was maintained. A reduction (significant at select time points) of pain and disease symptoms was largely observed starting at C2D1 (-5.1 [-13.0, 2.8] and -9.9 [-17.4, -2.4]) and maintained. **Conclusions:** Despite occasional early transient decreases, the results suggest that subcutaneous 76 mg QW elranatamab can improve the symptom and overall QOL of pts with RRMM, regardless of prior BCMA-targeted treatment.

P-475

Are we downplaying toxicity with our choice of words? A systematic review of randomized myeloma trials

Mimi Najjar[1], John McCarron[2], Edward Cliff[3], Katherine Berger[4], David Steensma[5], Samer Al Hadidi[6], Rajshekhar Chakraborty[7], Aaron Goodman[8], Douglas Sborov[9], Ghulam Rehman Mohyuddin[9]

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Introduction: Advances in multiple myeloma (MM) treatment have led to improved survival, but most patients still require long-term therapy. Treatment can result in burdensome toxicities and profoundly affect patients' quality of life. In seeking to emphasize the efficacy of tested treatments, reports of clinical trials may use subjective, vague, or otherwise minimizing terms to downplay adverse events (AEs). To evaluate how AE patterns are reported, we conducted a systematic review of MM randomized controlled trials (RCTs) from 2015-2023. We sought to estimate the prevalence of the use of minimizing terms in MM RCTs and to identify and explore the characteristics of studies that use these terms. **Methods:** We searched MEDLINE/PubMed, Embase, and the Cochrane Registry of Controlled Trials to measure the prevalence of minimizing terms in MM RCTs. Our inclusion criteria were all published MM RCTs from 2015-2023. The Chi square test was used to calculate differences in proportions. "Minimizing terms" were defined as subjective terms used to describe the safety profile of the intervention. Terms searched included "convenient", "manageable", "acceptable', "expected", "well-tolerated", "tolerable", "favorable" and "safe". **Results:** A total of 65 RCTs were included. Among these trials, 86% employed minimizing terms when describing treatment toxicities. The most frequently used terms were "well-tolerated" or "tolerable" in 45% of studies, "manageable" in 28% and "acceptable" in 25% of studies. The rates of grade 3/4 adverse events in the examined RCTs ranged from 23.1%-94% with a median of 74.7%. Minimizing terms were used in 88% of study reports with more grade 3/4 AEs than the median (i.e., >74.7% high grade AE rates), compared to a similar frequency (85%, X2 (1, N = 65) = .082, p = .774 (>.05)) in studies with fewer grade 3/4 AEs than the median. The rates of grade 5 adverse events ranged from 0%-19% with a median of 3%; minimizing terms were used in 100% of studies with more grade 5 AEs (deaths) than the median (3%), which was similar (82.1%, X2 (1, N = 65) = 3.606, p = .058 (>.05)) in studies with fewer than median grade 5 AEs. This suggests that the use of minimizing terms was not associated with the actual incidence of grade 3/4 toxicities or of treatment-related deaths.Industry-sponsored studies were more likely to use minimizing terms: 37/39 industry-sponsored studies (95%) vs 19/26 non-industry/cooperative group studies (73%) used minimizing terms, X2 (1, N = 65) = 6.2, p = .013. A minority of studies (25 of 65, 39%) reported patient reported outcomes (PROs). Studies that reported PROs used minimizing terms less often (18 out of 25, 72%) compared to those that did not report PROs (38 out of 40, 95%), X2 (1, N = 65) = 6.8, p = .009. **Conclusions:** Trial investigators and sponsors regularly use minimizing terms to describe toxicity in MM trials, especially in industry-sponsored studies, and this descriptive terminology does not reflect the actual rates of AEs or deaths in these studies.

P-476

More efficient delivery of high-cost standard-of-care therapies in relapsed multiple myeloma using real-time feedback of patient-reported outcome measures: the MY-PROMPT-2 trial

Elizabeth Moore[1], Simon Harrison[2], Phoebe Joy Ho[3], Adam Irving[1], Tracy King[3], Georgia McCaughan[4], Zoe McQuilten[1], Peter Mollee[5], Susanna Park[6], Dennis Petrie[1], John Reynolds[3], Claudia Rutherford[3], Tina van Tonder[1], Cameron Wellard[1], Erica Wood[1], Andrew Spencer[7]

[1]Monash University; [2]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Sir Peter MacCallum Department of Oncology,

assessed on day (D) 1 and 15 of the first 3 cycles and D1 of each subsequent cycle (C) through C12, the last cycle included in this analysis. The data cut-off was January 12, 2023 (approximately 12 months after the last pt's initial dose). **Results:** 123 and 64 pts were enrolled and treated with elranatamab in Cohort A and B, respectively. Median age was 68.0 and 67.0 years, 55.3% and 46.9% were male, 58.5% and 68.8% were White. At baseline, 25.2% and 20.3% had high risk cytogenetics, 15.4% and 23.4% had R-ISS III, and 31.7% and 57.8% had extramedullary disease. The median number of prior treatment lines was 5.0 (range: 2-22) and 7.5 (3-19). Among pts in Cohort A, a transient worsening in the global health score (QLQ-C30) and side effects domain (MY20) relative to baseline was observed through C2D15 (least square mean [LSM] change=-5.9 [95%CI: -10.7, -1.1] and 4.3 [1.4, 7.2], respectively); both domains reverted to baseline levels by C3D1 and generally showed (non-significant) improvement from baseline starting at C7D1/C8D1. Significant reductions in pain (QLQ-C30) and disease symptoms (MY20) were observed starting at C4D1 (-6.7 [-13.0, -0.4]) and C5D1 (-6.9 [-10.6, -3.1], respectively) and were maintained. Overall QoL (EQ-5D) significantly improved by C11D1 (0.06 [0.02, 0.09]) and was maintained. Cohort B results were largely similar, though, due to small sample sizes, significant differences were less frequent. Only a modest (non-significant) worsening in the global health score was observed with the nadir at C1D15 (-2.0 [-8.0, 4.0]) followed by a (non-significant) improvement relative to baseline by C2D15 (5.2 [-2.6, 13.0]) which was maintained. A reduction (significant at select time points) of pain and disease symptoms was largely observed starting at C2D1 (-5.1 [-13.0, 2.8] and -9.9 [-17.4, -2.4]) and maintained. **Conclusions:** Despite occasional early transient decreases, the results suggest that subcutaneous 76 mg QW elranatamab can improve the symptom and overall QOL of pts with RRMM, regardless of prior BCMA-targeted treatment.

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University of Melbourne, Melbourne, VIC, Australia; [3]Royal Prince Alfred Hospital, The University of Sydney; [4]St Vincents Hospital; [5]Princess Alexandra Hospital; [6]School of Medical Sciences, University of Sydney; [7]Alfred Health-Monash University, Melbourne, VIC, Australia

Introduction: Many patients on the ANZ Myeloma and Related Diseases Registry (MRDR) stop standard-of-care (SoC) therapy prematurely. This impaired duration on therapy (DoT) reduces the potential survival benefit of the therapy. We hypothesise that if clinicians were made aware of emerging symptoms, DoT could be optimised with timely supportive care, which would enhance treatment effectiveness. MY-PROMPT-2 builds on our pilot MY-PROMPT randomized controlled trial (RCT) that confirmed the feasibility and acceptability of real-time patient reported outcome measure (PROM) feedback to clinicians. In patients with relapsed MM (RMM), receiving SoC lenalidomide (R), carfilzomib (K) or daratumumab (D)-based therapies, we aim to determine whether routine real-time PROMs feedback to clinicians at patient visits improves event-free survival (EFS: time from randomization to an event [permanent discontinuation of treatment, progression or death]) compared to patients on SoC alone. **Methods:** This parallel, non-blinded, multicenter Bayesian RCT, uses 1:1 allocation, stratified by 3 SoC regimens (R, K, or D-based) and age with provision to recruit 200 adults. **Intervention:** PROM results summary fed back to clinicians at monthly visits for 12 months. PROMs used: 1. MyPOS: MM-specific, 30 items - symptoms/ mood/ healthcare support. 2. Additional regimen-specific questions (≤5) for common side effects of K, and D-based regimens. **ePROM system:** REDCap-based for easy implementation in routine care. PROMs are emailed to intervention patients 1 week before visits. Completion in clinic is also available. A PROM summary is emailed to the clinician, patient, and site staff. PROMs to compare health-related quality of life (EORTC QLQ-C30) and treatment satisfaction (TSQM-9) between groups are collected 3-monthly in both arms for 12 months. Novel statistical trial design: Once ≥60 events have been observed between the 2 arms, EFS monitoring comparing the intervention versus control arm, starts. Using pre-established criteria, if monitoring shows: 1. the intervention arm is inferior to controls, the trial will be stopped; 2. the intervention arm is superior to controls, the Trial Management Committee can declare: 1. Proof of concept (i.e. publish) - if statistical thresholds are met or 2. Recommend further expansion of trial (subject to funding). An economic evaluation will explore the cost-effectiveness of the new model of care. **Results:** Recruitment has commenced and will be active at up to 15 sites. **Conclusions:** This is the first registry-based multicenter trial in patients with RMM to test the benefit of real-time PROM reporting. The widely used ePROM platform facilitates translation into practice and the pragmatic trial design suits rare diseases allowing a smaller sample size to guide decisions to adopt real-time PROM reporting. Findings could be translatable to other cancers, chronic diseases and disease registries.

P-477

Pre-exposure prophylaxis for COVID-19 with tixagevimab/cilgavimab (evusheld) in patients with multiple myeloma in the omicron SARS-COV-2 era

Ioannis Ntanasis-Stathopoulos[1], Maria Gavriatopoulou[1], Evangelos Eleutherakis-Papaiakovou[1], Panagiotis Malandrakis[1], Vassiliki Spiliopoulou[1], Rodanthi-Eleni Syrigou[1], Foteini Theodorakakou[1], Despina Fotiou[1], Magdalini Migkou[1], Maria Roussou[1], Efstathios Kastritis[1], Meletios Dimopoulos[1], Evangelos Terpos[1]

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Introduction: In patients with multiple myeloma (MM), SARS-CoV-2 infection has been associated with severe clinical course and high mortality rates, due to the concomitant disease- and treatment-related immunosuppression. Furthermore, immune response to COVID-19 vaccination is attenuated. Therefore, patients with MM are eligible to receive pre-exposure prophylaxis with tixagevimab/cilgavimab (Evusheld). **Methods:** Consecutive patients with MM were prospectively enrolled in the study. All patients had measurement of neutralizing antibodies (NAbs) against SARS-CoV-2 using an FDA approved methodology (enzyme-linked immunosorbent assay, cPass SARS-CoV-2 NAbs Detection Kit; GenScript, Piscataway, NJ, USA) before the administration of tixagevimab/cilgavimab and at one month thereafter. Evusheld was administered at 150mg as two intramuscular injections. **Results:** Fifty-five patients with MM were included in this analysis and were followed for a median of 5 months (range 3-6 months) after receiving tixagevimab/cilgavimab. The median age was 63 years (range 36-84), whereas 27 (49%) were females. The majority of the patients had performance status (PS) 0 (n=27, 49%), 22 patients (40%) has PS 1 and 6 patients (11%) had PS 2. Thirty patients (55%) were ISS 1, 17 (30%) were ISS 2 and 8 (15%) were ISS 3. Most patients (n=37, 67%) were at their first line of treatment, 16 (19%) were receiving their second line of treatment, one patient was at the third and one at the fifth line of treatment. Thirty-one patients (56%) had previously received autologous stem cell transplant. At the time of tixagevimab/cilgavimab administration, 19 patients (34%) were receiving combinations including anti-BCMA agents, 24 patients (44%) were receiving combination including anti-CD38 drugs and 12 (22%) were on other treatments. Four patients had a prior history of COVID-19. Regarding vaccination status for COVID-19, 42 patients (76%) had received 4 vaccine doses and 13 patients (24%) had received 3 vaccine shots. All patients were vaccinated with mRNA-based vaccines. The median NAb level before the administration of tixagevimab/cilgavimab was 87% (range 0-98%), whereas it increased to 97% (range 0-98%) at one month thereafter. Overall, 5 patients (9%) were diagnosed with COVID-19 at a median of 1 month (range 1-2) after receiving tixagevimab/cilgavimab. All of these patients received nirmatrelvir/ritonavir (Paxlovid) for 5 days as outpatients along with supportive care as per standard clinical practice and recovered completely. There were no COVID-19-related hospitalization or deaths. Tixagevimab/

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Introduction: Many patients on the ANZ Myeloma and Related Diseases Registry (MRDR) stop standard-of-care (SoC) therapy prematurely. This impaired duration on therapy (DoT) reduces the potential survival benefit of the therapy. We hypothesise that if clinicians were made aware of emerging symptoms, DoT could be optimised with timely supportive care, which would enhance treatment effectiveness. MY-PROMPT-2 builds on our pilot MY-PROMPT randomized controlled trial (RCT) that confirmed the feasibility and acceptability of real-time patient reported outcome measure (PROM) feedback to clinicians. In patients with relapsed MM (RMM), receiving SoC lenalidomide (R), carfilzomib (K) or daratumumab (D)-based therapies, we aim to determine whether routine real-time PROMs feedback to clinicians at patient visits improves event-free survival (EFS: time from randomization to an event [permanent discontinuation of treatment, progression or death]) compared to patients on SoC alone. **Methods:** This parallel, non-blinded, multicenter Bayesian RCT, uses 1:1 allocation, stratified by 3 SoC regimens (R, K, or D-based) and age with provision to recruit 200 adults. **Intervention:** PROM results summary fed back to clinicians at monthly visits for 12 months. PROMs used: 1. MyPOS: MM-specific, 30 items - symptoms/ mood/ healthcare support. 2. Additional regimen-specific questions (≤5) for common side effects of K, and D-based regimens. **ePROM system:** REDCap-based for easy implementation in routine care. PROMs are emailed to intervention patients 1 week before visits. Completion in clinic is also available. A PROM summary is emailed to the clinician, patient, and site staff. PROMs to compare health-related quality of life (EORTC QLQ-C30) and treatment satisfaction (TSQM-9) between groups are collected 3-monthly in both arms for 12 months. Novel statistical trial design: Once ≥60 events have been observed between the 2 arms, EFS monitoring comparing the intervention versus control arm, starts. Using pre-established criteria, if monitoring shows: 1. the intervention arm is inferior to controls, the trial will be stopped; 2. the intervention arm is superior to controls, the Trial Management Committee can declare: 1. Proof of concept (i.e. publish) - if statistical thresholds are met or 2. Recommend further expansion of trial (subject to funding). An economic evaluation will explore the cost-effectiveness of the new model of care. **Results:** Recruitment has commenced and will be active at up to 15 sites. **Conclusions:** This is the first registry-based multicenter trial in patients with RMM to test the benefit of real-time PROM reporting. The widely used ePROM platform facilitates translation into practice and the pragmatic trial design suits rare diseases allowing a smaller sample size to guide decisions to adopt real-time PROM reporting. Findings could be translatable to other cancers, chronic diseases and disease registries.

P-477

Pre-exposure prophylaxis for COVID-19 with tixagevimab/cilgavimab (evusheld) in patients with multiple myeloma in the omicron SARS-COV-2 era

Ioannis Ntanasis-Stathopoulos[1], Maria Gavriatopoulou[1], Evangelos Eleutherakis-Papaiakovou[1], Panagiotis Malandrakis[1], Vassiliki Spiliopoulou[1], Rodanthi-Eleni Syrigou[1], Foteini Theodorakakou[1], Despina Fotiou[1], Magdalini Migkou[1], Maria Roussou[1], Efstathios Kastritis[1], Meletios Dimopoulos[1], Evangelos Terpos[1]

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cilgavimab was well tolerated; no infusion-related reactions or major adverse events were reported. Fifteen patients (27%) experienced pain at the injection site that resolved after a few days. **Conclusions:** Tixagevimab/cilgavimab (Evusheld) seems beneficial in patients with MM who had a low incidence of COVID-19 infections during the Omicron wave. No new safety concerns emerged.

P-478

Humanistic, clinical, and economic burden in patients with relapsed or refractory multiple myeloma on second line or higher therapy: a systematic literature review

Kody Pierce[1], Kaustav Chatterjee[1], Yao Wang[2], Amyn Malik[2], Erin Cook[2], Yan Song[2], Allison Quintana[2], Tulika Mohan[2], Cesar Rodriguez[3], Paula Rodríguez-Otero[4]

[1]AbbVie; [2]Analysis Group, Inc; [3]Icahn School of Medicine at Mount Sinai; [4]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain

Introduction: Novel therapies in relapsed/refractory multiple myeloma (RRMM) are demonstrating promising efficacy, however the complexity of their administration in real-world settings could further impact the humanistic aspect of management; thus, making an emphasis on QOL and patient reported outcomes (PRO) key in future clinical trials. The objective of the study was to understand real-world evidence on the humanistic, clinical, and economic burden of RRMM. **Methods:** A systematic literature review (SLR) was conducted to identify real-world studies of patients with RRMM from 2018 to September 1, 2022, with outcomes of interest. Studies were identified via the MEDLINE and EMBASE databases, and selected conference proceedings. All studies were required to have at least 100 patients. Titles/abstracts and full text articles were reviewed by 2 reviewers in parallel. Data were extracted from relevant articles and were descriptively summarized. **Results:** Of the 1,170 studies identified, 51 were included in the review. The majority of the studies (n=38) reported clinical outcomes, 12 reported economic outcomes and 3 reported humanistic outcomes. Overall survival (OS) was included in most studies reporting clinical outcomes (34, 89.5%) with progression free survival (PFS) included in (27,71.1%) studies. The median OS of patients with 4L+ RRMM ranged from 8.2 to 21.1 months while the median PFS ranged from 2.0 to 8.9 months. The mean all-cause cost per patient per month ranged from $2,952-$15,726 for inpatient and $5,025-$15,807 for outpatient. Of studies identified on humanistic burden most focused on burden from the patient perspective including PROs and health related quality of life (HRQoL). However, some studies reported on humanistic burden from a macro or caregiver perspective including absenteeism and caregiver QoL. For patients with 4L+, thinking about illness, worried about health, and worried about dying PRO domains only worsened from baseline (N=87, LS mean change from BL was –7.5, –9.7, and –14.4 respectively). Another study reported on the diminished QoL for caregivers using the CareGiver Oncology QOL questionnaire (74.5 for newly diagnosed multiple myeloma [NDMM], 73.2 for 2-3L, and 71.7 for 4L+; scored 0-100 with 100 representing normal/better QoL). **Conclusions:** The median OS for patients with 4L+ RRMM was less than 2 years, indicating that the 4L+ population continues to have a large unmet need for therapy options. Patient and caregiver burden in MM is significant and there is an urgent need for effective therapies that can reduce patient and caregiver burden and improve efficacy while maintaining quality of life.

P-479

Disparities in clinical trial enrolment and survival outcomes by socio-economic class in multiple myeloma

Amrutha Sridhar[1], Selina Chavda[2], Hannah Hsu[1], Hanna Renshaw[1], Fatjon Dekaj[1], Samir Asher[3], Catriona Mactier[4], Shumi Tattersfield[1], Neil Rabin[3], Kwee Yong[2], Ashutosh Wechalekar[4], Ayesha Shameem Mahmood[5], Lydia Lee[3], Annabel McMillan[3], Xenofon Papanikolaou[3], Jonathan Sive[3], Charalampia Kyriakou[3], Rakesh Popat[1]

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Introduction: Disparities in patients enrolled into clinical trials compared to real world populations have been reported with underrepresentation of different racial groups. However socio-economic class may also serve as a cause of inequity, particularly as social deprivation has been associated with overall survival (OS). Adequate sociodemographic representation is required for equitable access and for clinical trials to be informative of the population they serve. The aims of the study were to identify the distribution of patients enrolled into Multiple Myeloma (MM) clinical trials according to social deprivation and understand interactions with race, prognostic markers, and OS. **Methods:** This was a retrospective analysis of MM patients treated in the UK between 2014-2023 from electronic medical records. Social deprivation was assessed using the English Indices of Multiple Deprivation (IMD) ranking, derived from income, employment, health, education, housing barriers, services, crime, and living environment. Comparator data was obtained from the National Cancer Registration and Analysis Service for England (NCRAS, 2006-2015). OS was estimated using Kaplan Meier Curves and correlative analysis by Cox regression models with GraphPad prism V9. **Results:** 580 consecutive patients were grouped by 3 cohorts: standard of care (SOC, n=212), clinical trials (n=355): early phase trials (EPT, Phase I/II, n=103) late phase trials (LPT, Phase II & III, n=252). Median age was 66 years (35-90), M:F ratio was 1.3:1 and had a median of 3 prior lines (0-14). 406 (70%) were White, 80 (13.8%) Black, 40 (6.9%) Asian, 38 (6.6%) Mixed/Other and 16 (2.8%) unknown. There were significantly less patients enrolled into clinical trials (both EPT and LPT) from deprived areas compared to the expected social demographic of MM patients in England (7% (trials) vs 14% (England) for IMD 5, p=< 0.001).

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P-479

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P-479

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47.6% (n=169) of enrolled patients were referrals from other centres and were from less deprived areas in England (8% trials vs 14% England for IMD 5, p=0.02). Patients in LPT from more deprived areas had an inferior OS than those from more affluent areas (268 months vs 135 months, p= 0.03). Non-white patients in trials were from more deprived areas than white patients (25% IMD 1-2, 43% IMD 4-5 vs 58% IND 1-2m 29% IND 4-5, p=0.018). Patients ≥ 75 with worse social deprivation indices had an inferior OS to those from more affluent areas (median 120m vs 268m p=0.01). **Conclusions:** Patients enrolled into clinical trials were from less socially deprived areas than expected from the distribution of MM in England with referrals favouring higher socio-economic class. As lower socio-economic class impacts overall survival independently of racial group, it is vital that clinical trials enrol from a diverse but balanced socio-economic population. Enrolment should be monitored according to socioeconomic deprivation to ensure there is adequate representation of the geographical population served.

P-480

Outcome of pneumocystis jirovecii pneumonia in patients with multiple myeloma

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Introduction: Patients with multiple myeloma (MM) are at high risk for infections, including opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP). We conducted a retrospective analysis of patients with MM developing PJP over a six-year period at the University Hospital of Würzburg. **Methods:** Between January 2016 and December 2021, positive results for P. jirovecii in respiratory specimens were retrospectively retrieved through our microbiology database as a quality improvement project in cooperation between the in-house antimicrobial stewardship team (AMS) and the department of hematology. Cases were screened for patients with MM and diagnoses of probable and proven PJP were assessed according to EORTC invasive fungal disease definitions. Patient characteristics, diagnostic findings, disease course, outcome and use of PJP prophylaxis were analyzed in PJP patients. **Results:** From 2016 to 2021, 201 respiratory specimens were tested positive for P. jirovecii. Of these cases, 13 patients with a diagnosis of MM fulfilled the definition of probable PJP. We observed two peaks of PJP incidence, one in patients after autologous or allogeneic transplantation during first line treatment (n = 5), the other in heavily pretreated patients with six or more prior lines of therapy (n = 6). There was high morbidity with nine (69%) patients admitted to the ICU with seven of those (78%) requiring mechanical ventilation, and high mortality (62%, n = 8) within four weeks after PJP diagnosis or due to PJP-related complications, partly complicated by CMV or HSV reactivation (n = 3). Of note, only two of the 13 (15%) patients had received PJP prophylaxis. The main reason for halting prophylaxis with trimethoprim-sulfomethoxazole was grade IV neutropenia. **Conclusions:** PJP can occur in every treatment phase of MM, but mainly affects patients after stem cell transplantation and heavily pretreated patients. Morbidity and mortality in MM patients are significant and even higher than reported for patients with hematologic malignancy in general. Indication for PJP prophylaxis is still incompletely defined, even in HIV-negative patients, but should be assessed individually in patients with risk factors, and halting PJP prophylaxis due to leukopenia needs to be reconsidered. According to current guidelines, prophylaxis use would have been clearly recommended in no more than three (23%) of the 13 patients.

P-481

The effect of touch on pain, anxiety and the patient experience during bone marrow biopsies

Anna Schaal[1], Natahsa Dhawan[1], Jacob Pushee[1], Kathleen Broglio[1]

[1]Dartmouth Health

Introduction: Patients with Multiple Myeloma receive a number of bone marrow biopsies over their disease trajectory. Many patients report severe pain and anxiety during bone marrow biopsies (BMBx), but there is no formal consensus on the best approach to managing these symptoms during the procedure. This study aimed to evaluate the effect of simple foot touch on pain and anxiety during BMBx, and describe the patients' experience during the procedure. **Methods:** A single-center randomized control trial using permuted block randomization was conducted at a rural academic cancer center. Nursing assistants without specialized massage training performed simple foot touch on patients in the intervention arm, while the BMBx was performed by advanced practice registered nurses. Patients rated pain and anxiety levels before and after BMBx using the Visual Analog Scale (VAS) and Spielberger State-Trait Anxiety Inventory (STAI) scales, respectively. All participants completed a post-intervention survey about their experience. **Results:** 46 patients were enrolled in the study; 21 in the intervention arm (median age 64.1 years) and 25 in the control arm (median age 64.4 years). There was no difference in the use of anxiolytics (p=0.51) or opioids (p=0.48) during the procedure between the two arms. There were no statistically significant differences on the VAS (p=0.37) or STAI (p=0.40) between the intervention and control arms. Participants in the intervention arm reported more positive feedback and fewer suggestions for improving the patient experience compared to the control arm. **Conclusions:** This is the first study to use an interdisciplinary team approach to evaluate the impact of touch on pain, anxiety, and the patient experience during BMBx. While the intervention did not impact pain or anxiety scores, it may be a feasible, minimal-risk, and no-cost intervention to improve patients' overall experience during BMBx.

47.6% (n=169) of enrolled patients were referrals from other centres and were from less deprived areas in England (8% trials vs 14% England for IMD 5, p=0.02). Patients in LPT from more deprived areas had an inferior OS than those from more affluent areas (268 months vs 135 months, p= 0.03). Non-white patients in trials were from more deprived areas than white patients (25% IMD 1-2, 43% IMD 4-5 vs 58% IND 1-2m 29% IND 4-5, p=0.018). Patients ≥ 75 with worse social deprivation indices had an inferior OS to those from more affluent areas (median 120m vs 268m p=0.01). **Conclusions:** Patients enrolled into clinical trials were from less socially deprived areas than expected from the distribution of MM in England with referrals favouring higher socio-economic class. As lower socio-economic class impacts overall survival independently of racial group, it is vital that clinical trials enrol from a diverse but balanced socio-economic population. Enrolment should be monitored according to socioeconomic deprivation to ensure there is adequate representation of the geographical population served.

P-480

Outcome of pneumocystis jirovecii pneumonia in patients with multiple myeloma

Christine Riedhammer[1], Johannes Duell[1], Christian Kestler[1], Sofie Kadel[1], Johanna Franz[1], Philipp Weis[1], Florian Eisele[1], Xiang Zhou[1], Maximilian Steinhardt[1], Lukas Scheller[1], Julia Mersi[1], Johannes Waldschmidt[1], Hermann Einsele[1], Martin Kortüm[1], Doris Turnwald[1], Güzin Surat[1], Leo Rasche[1]

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Introduction: Patients with multiple myeloma (MM) are at high risk for infections, including opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP). We conducted a retrospective analysis of patients with MM developing PJP over a six-year period at the University Hospital of Würzburg. **Methods:** Between January 2016 and December 2021, positive results for P. jirovecii in respiratory specimens were retrospectively retrieved through our microbiology database as a quality improvement project in cooperation between the in-house antimicrobial stewardship team (AMS) and the department of hematology. Cases were screened for patients with MM and diagnoses of probable and proven PJP were assessed according to EORTC invasive fungal disease definitions. Patient characteristics, diagnostic findings, disease course, outcome and use of PJP prophylaxis were analyzed in PJP patients. **Results:** From 2016 to 2021, 201 respiratory specimens were tested positive for P. jirovecii. Of these cases, 13 patients with a diagnosis of MM fulfilled the definition of probable PJP. We observed two peaks of PJP incidence, one in patients after autologous or allogeneic transplantation during first line treatment (n = 5), the other in heavily pretreated patients with six or more prior lines of therapy (n = 6). There was high morbidity with nine (69%) patients admitted to the ICU with seven of those (78%) requiring mechanical ventilation, and high mortality (62%, n = 8) within four weeks after PJP diagnosis or due to PJP-related complications, partly complicated by CMV or HSV reactivation (n = 3). Of note, only two of the 13 (15%) patients had received PJP prophylaxis. The main reason for halting prophylaxis with trimethoprim-sulfomethoxazole was grade IV neutropenia. **Conclusions:** PJP can occur in every treatment phase of MM, but mainly affects patients after stem cell transplantation and heavily pretreated patients. Morbidity and mortality in MM patients are significant and even higher than reported for patients with hematologic malignancy in general. Indication for PJP prophylaxis is still incompletely defined, even in HIV-negative patients, but should be assessed individually in patients with risk factors, and halting PJP prophylaxis due to leukopenia needs to be reconsidered. According to current guidelines, prophylaxis use would have been clearly recommended in no more than three (23%) of the 13 patients.

P-481

The effect of touch on pain, anxiety and the patient experience during bone marrow biopsies

Anna Schaal[1], Natahsa Dhawan[1], Jacob Pushee[1], Kathleen Broglio[1]

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P-481

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P-482

Dietary habits correlate with myeloma pathogenesis and treatment outcome in multiple myeloma

Lilli Sester[1,2], Anna Katharina Gambihler[1,3], Michael Kilian[4,5], Mirco Friedrich[1,6], Jan Frenking[1,2], Juliana de Castilhos[7], Lukas John[1,2], Elias Mai[1,8], Michael Platten[4,5], Carsten Müller-Tidow[1,9], Niels Weinhold[1,2], Hartmut Goldschmidt[10], Christoph Stein-Thoeringer[7], Marc Raab[1]

[1]Department of Hematology, Oncology and Rheumatology, Heidelberg University Hospital, Heidelberg, Germany; [2]Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [4]Clinical Cooperation Unit Neuroimmunology and Brain Tumor Immunology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [5]Department of Neurology, MCTN, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [6]Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA; [7]Internal Medicine I, University Clinic Tuebingen, Tuebingen, Germany; [8]GMMG Study Group at University Hospital Heidelberg, Heidelberg, Germany; [9]National Center for Tumor Diseases (NCT), Heidelberg, Germany; [10]Internal Medicine V, GMMG Study Group at University Hospital Heidelberg, Heidelberg, Germany

Introduction: Dietary interventions in multiple myeloma (MM) have recently gained interest due to the interplay between the gut microbiome and tumor biology. However, the extent to which specific nutrients can modify myeloma pathogenesis through interactions with the microbiome and immune system remains to be elucidated. This study investigated the association between dietary patterns of patients with MM and their disease characteristics and treatment outcomes. **Methods:** 62 newly diagnosed MM (NDMM) patients were included in this study between July 2021 and April 2023. NDMM patients reported their dietary habits using a standardized Food Frequency Questionnaire (FFQ). The FFQ data were then analyzed using DGExpert2.0 software. All patients received Dara-VTD induction therapy. Response after four cycles was assessed according to IMWG response criteria. The impact of dietary habits on myeloma pathogenesis was validated using an immunocompetent preclinical model of MM in BALB/c mice. Mice harboring MOPC-315 myeloma grafts were administered both a control diet and a diet supplemented with oleic acid (n=10/group), aiming to replicate the nutritional characteristics observed in NDMM patients. **Results:** When examining the intake of specific fatty acids, the consumption of long-chain unsaturated fatty acids showed a significant correlation with decreased tumor burden in patients classified with International Staging System (ISS) Score I compared to those with ISS Score II and III (Oleic acid: $p< 0.001$, Linoleic acid: $p=0.005$). In contrast, higher carbohydrate intake, driven by sucrose consumption, was linked to elevated ISS scores (ISS I vs. II/III, Carbohydrates: $p=0.007$, Sucrose: $p< 0.001$). In line, a dietary pattern rich in plant-based unsaturated fatty acids and low in sucrose was associated with lower levels of plasma cell infiltration in the bone marrow and reduced paraprotein production. When comparing the dietary intakes of different responder groups, patients who reported lower sucrose consumption and higher intake of unsaturated fatty acids exhibited a higher likelihood of achieving a complete response (CR) (Sucrose: $p< 0.001$ and Oleic acid: $p< 0.001$ for CR vs. non-CR). In the preclinical mouse model, a higher intake of oleic acid was found to confer a significant survival advantage ($p=0.048$). **Conclusions:** Our clinical data suggests that a diet rich in plant-based unsaturated fatty acids, particularly oleic acid, and low in sucrose modulates myeloma biology and positively influences therapy outcomes in NDMM patients. These observations were supported by a preclinical in vivo model. Collectively, our study emphasizes the importance of considering dietary interventions as an indispensable adjunct in supporting and optimizing anti-myeloma therapy.

P-483

A whole foods plant-based weight loss intervention improves metabolic and immune biomarkers in MGUS/SMM patients as well as progression trajectory in a subset: the NUTRIVENTION trial

Urvi Shah[1], Andriy Derkach[2], Francesca Castro[2], Aishwarya Anuraj[2], Jenna Blaslov[2], Kinga Hosszu[2], Michael Pollak[3], Sham Mailankody[1], Neha Korde[1], Carlyn Rose Tan[1], Malin Hultcrantz[2], Hani Hassoun[1], Kylee Maclachlan[1], Gunjan Shah[2], Michael Scordo[2], Oscar Lahoud[2], David Chung[4], Heather Landau[4], Anita D'Souza[5], Ola Landgren[6], Sergio Giralt[2], Neil Iyengar[2], Saad Usmani[2], Alexander Lesokhin[2], Marcel van den Brink[2]

[1]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City NY, USA; [2]Memorial Sloan Kettering Cancer Center, New York City NY, USA; [3]McGill University; [4]Bone Marrow Transplant and Cellular Therapy, Memorial Sloan Kettering Cancer Center, New York City NY, USA; [5]Medical College of Wisconsin; [6]Myeloma Service, Sylvester Comprehensive Cancer Center, University of Miami

Introduction: Obesity, low adiponectin, high leptin, high insulin, and diets lacking plant-based foods are all risk factors for plasma cell disorders (PCDs). Therefore, there is a rationale to study a whole food plant-based dietary (WFPBD) intervention to improve modifiable biomarkers and disease trajectory. **Methods:** This was a pilot, single-arm dietary intervention trial of a WFPBD for 12-weeks (w) and health coaching for 24w (by Plantable) in patients (pts) with myeloma precursor disease (MGUS/SMM) and body mass index (BMI) ≥25 (NCT04920084). The primary endpoint was feasibility at 12w; secondary endpoints included metabolic markers (insulin, adiponectin leptin ratio via ELISA at 12w), peripheral blood immune profiling by flow cytometry at 12w, and change in monoclonal (M)-spike concentrations. Rate of change of M-spike per year (y) measured by slope with 95% CI was calculated for up to 20 months (m) pre-intervention and for up to 20m from intervention start (baseline). A p-value for difference in M-spike rates was calculated. **Results:** The median age was 62y with 43% male, 43% non-White, 52% MGUS, 74% obese, and 26% prediabetic/diabetic. At time

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P-483

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of analysis 20 pts completed the 12w WFPBD intervention and 12 completed 1y of follow-up. The study met feasibility endpoints with 92% median dietary adherence, leading to 7.4% median BMI reduction, improvement in insulin levels (median decrease 0.791 mU/L; p=0.01) and adiponectin leptin (AL) ratio (median increase 0.09; p=0.0002) at 12w. There was a reduction in total innate lymphoid cells (ILCs) (p=0.03) and early NK cells (p=0.03) and an increase in classical monocytes (p=0.04) and CD33+ classical monocytes (p=0.03) (n=14). Among 12 pts followed for 1y, 2 with significant BMI reduction on trial had a statistically significant improvement in the M-spike trajectory: The first patient with Mayo Int Risk IgGκ/IgGλ MGUS achieved a 1y BMI reduction of 19%. Pre-intervention M-spike changed +0.28g/dL/y (6 M-spike values in 20m), and during intervention M-spike changed +0.02g/dL/y (11 M-spike values in 20m); p=0.0001. Baseline M-spike 1.2g/dL and bone marrow plasma cells (BM PC) < 5%; 1.5y BM PC 5-9%. The second patient with IMWG Int Risk IgGκ SMM achieved a 1y BMI reduction 13%. Pre-intervention M-spike changed +0.12g/dL/y (8 M-spike values in 20m), and during intervention M-spike changed -0.05g/dL/y (8 M-spike values in 16m); p=0.009. Baseline M-spike 1.2g/dL and BM PC 20-30%; 1y BM PC 10-15%. Two pts without significant BMI reduction (-4% and -1% at 1y) had rising M-spikes. The remaining 8 pts had median 8% BMI reduction at 1y with stable M-spike levels. **Conclusions:** This is the first trial in PCDs to show a WFPBD improves metabolic profile (BMI, insulin resistance) with an early signal of potentially slowing progression trajectory in a subset of patients. Preliminary immune profiling data supports an effect on ILC and myeloid cell quantity suggestive of diet-mediated immune modulation. Additional analysis in larger sample sets is planned (NCT05640843).

P-484

Successful incorporation of ePRO using PROMIS-29 into standard of care after hematopoietic stem cell transplant and chimeric antigen receptor T cell therapy for plasma cell dyscrasias

Gunjan Shah[1], Stephanie Lobaugh[1], Sean Devlin[1], Thomas Atkinson[1], Neha Korde[2], David Chung[3], Parastoo Dahi[1], Heather Landau[3], Oscar Lahoud[1], Malin Hultcrantz[2], Alexander Lesokhin[1], Sham Mailankody[2], Hani Hassoun[2], Urvi Shah[2], Kylee Maclachlan[2], Carlyn Rose Tan[1], Saad Usmani[1], Peter Stetson[1], Sergio Giralt[1], Michael Scordo[1]

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Introduction: Autologous hematopoietic stem cell transplant (AHCT) and chimeric antigen receptor T cells (CAR T) are mainstays of treatment for multiple myeloma (MM), but often have significant and prolonged side effects. Patient-reported outcome (PRO) measures allow for self-reporting of symptoms to the care team and are more comprehensive and reliable than provider-based assessments. Using our center's electronic platform, we aimed to integrate PRO collection into standard-of-care to improve the clinical experience after HCT and CAR T. **Methods:** Patients received the PROMIS-29 survey through a patient portal. Baseline surveys were automatically generated by a chemotherapy order, and follow-up surveys on Day 0 (infusion), weekly for the first month, monthly for the first year, and every 3 months for the second year were generated based on the date of the cell infusion order. Survey responses in pre-identified severe ranges prompted instructions to call the clinician's office and for the clinical team to call the patient. Scores are standardized against US normative population data producing T scores with a mean of 50 and a standard deviation of 10. **Results:** From November 2020 to December 2022, 335 patients underwent a commercial cell therapy at MSK (326 MM, 9 AL amyloidosis, 309 AHCT infusions, 33 CAR T) with overall median age of 64 (range 27-81) and 46% female. At least one survey was completed by 85% of patients with AHCT, with response rates at baseline, Day 0, week 1, week 2, week 3, week 4, and Day 90 of 61%, 38%, 39%, 34%, 38%, 40%, and 36%, respectively. PROMIS-29 physical health summary scores at baseline, Day 0, week 1, week 2, week 3, week 4, and Day 90 were 47 [21-59], 45 [23-59], 44 [22-59], 42 [21-59], 41 [22-59], 42 [22-59], and 46 [29-59], respectively. Mental health summary scores were 51 [31-64], 49 [30-64], 49 [31-64], 48 [27-64], 48 [31-64], 49 [30-64], and 52 [26-64], respectively. For the CAR T patients, 64% answered at least one survey, with response rates at baseline, Day 0, week 1, week 2, week 3, week 4, and Day 90 of 39%, 12%, 21%, 27%, 24%, 21%, and 9%, respectively. PROMIS-29 physical health summary scores at baseline, Day 0, week 1, week 2, week 3, week 4, and Day 90 were 43 [27-57], 40 [27-46], 45 [38-59], 44 [35-59], 51 [35-59], 45 [34-58], and 37 [34-58], respectively. Mental health summary scores were 48 [36-59], 46 [40-50], 49 [45-63], 51 [38-62], 52 [36-64], 52 [48-62], and 45 [39-63], respectively. **Conclusions:** We demonstrate the feasibility of incorporating patient-reported outcomes into standard-of-care practice after AHCT and CAR T. Missing surveys were more common while inpatient, which may be due to toxicity and/or less frequent use of the patient portal while admitted. Additional work is ongoing to improve the response rates at all time points. Importantly, the electronic system allowed us to capture later timepoints when patients have less frequent visits and may be followed locally. Full survey results will be presented.

P-485

Novel observation of the negative effects of persistent chronic opioid use on myeloma survival: a retrospective urban-based cohort study and ongoing prospective HealthTree survey study

Karen Sweiss[1], Pritesh Patel[1], Jennifer Ahlstrom[2], Jay Hydren[2], Jorge Arturo Hurtado Martinez[2], Ana Maria Avila Rodriguez[1], John Quigley[1], Lisa Sharp[3], Gregory Calip[4], Damiano Rondelli[1], Douglas Sborov[5], Craig Hofmeister[6]

of analysis 20 pts completed the 12w WFPBD intervention and 12 completed 1y of follow-up. The study met feasibility endpoints with 92% median dietary adherence, leading to 7.4% median BMI reduction, improvement in insulin levels (median decrease 0.791 mU/L; p=0.01) and adiponectin leptin (AL) ratio (median increase 0.09; p=0.0002) at 12w. There was a reduction in total innate lymphoid cells (ILCs) (p=0.03) and early NK cells (p=0.03) and an increase in classical monocytes (p=0.04) and CD33+ classical monocytes (p=0.03) (n=14). Among 12 pts followed for 1y, 2 with significant BMI reduction on trial had a statistically significant improvement in the M-spike trajectory: The first patient with Mayo Int Risk IgGκ/IgGλ MGUS achieved a 1y BMI reduction of 19%. Pre-intervention M-spike changed +0.28g/dL/y (6 M-spike values in 20m), and during intervention M-spike changed +0.02g/dL/y (11 M-spike values in 20m); p=0.0001. Baseline M-spike 1.2g/dL and bone marrow plasma cells (BM PC) < 5%; 1.5y BM PC 5-9%. The second patient with IMWG Int Risk IgGκ SMM achieved a 1y BMI reduction 13%. Pre-intervention M-spike changed +0.12g/dL/y (8 M-spike values in 20m), and during intervention M-spike changed -0.05g/dL/y (8 M-spike values in 16m); p=0.009. Baseline M-spike 1.2g/dL and BM PC 20-30%; 1y BM PC 10-15%. Two pts without significant BMI reduction (-4% and -1% at 1y) had rising M-spikes. The remaining 8 pts had median 8% BMI reduction at 1y with stable M-spike levels. **Conclusions:** This is the first trial in PCDs to show a WFPBD improves metabolic profile (BMI, insulin resistance) with an early signal of potentially slowing progression trajectory in a subset of patients. Preliminary immune profiling data supports an effect on ILC and myeloid cell quantity suggestive of diet-mediated immune modulation. Additional analysis in larger sample sets is planned (NCT05640843).

P-484

Successful incorporation of ePRO using PROMIS-29 into standard of care after hematopoietic stem cell transplant and chimeric antigen receptor T cell therapy for plasma cell dyscrasias

Gunjan Shah[1], Stephanie Lobaugh[1], Sean Devlin[1], Thomas Atkinson[1], Neha Korde[2], David Chung[3], Parastoo Dahi[1], Heather Landau[3], Oscar Lahoud[1], Malin Hultcrantz[2], Alexander Lesokhin[1], Sham Mailankody[2], Hani Hassoun[2], Urvi Shah[2], Kylee Maclachlan[2], Carlyn Rose Tan[1], Saad Usmani[1], Peter Stetson[1], Sergio Giralt[1], Michael Scordo[1]

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Introduction: Autologous hematopoietic stem cell transplant (AHCT) and chimeric antigen receptor T cells (CAR T) are mainstays of treatment for multiple myeloma (MM), but often have significant and prolonged side effects. Patient-reported outcome (PRO) measures allow for self-reporting of symptoms to the care team and are more comprehensive and reliable than provider-based assessments. Using our center's electronic platform, we aimed to integrate PRO collection into standard-of-care to improve the clinical experience after HCT and CAR T. **Methods:** Patients received the PROMIS-29 survey through a patient portal. Baseline surveys were automatically generated by a chemotherapy order, and follow-up surveys on Day 0 (infusion), weekly for the first month, monthly for the first year, and every 3 months for the second year were generated based on the date of the cell infusion order. Survey responses in pre-identified severe ranges prompted instructions to call the clinician's office and for the clinical team to call the patient. Scores are standardized against US normative population data producing T scores with a mean of 50 and a standard deviation of 10. **Results:** From November 2020 to December 2022, 335 patients underwent a commercial cell therapy at MSK (326 MM, 9 AL amyloidosis, 309 AHCT infusions, 33 CAR T) with overall median age of 64 (range 27-81) and 46% female. At least one survey was completed by 85% of patients with AHCT, with response rates at baseline, Day 0, week 1, week 2, week 3, week 4, and Day 90 of 61%, 38%, 39%, 34%, 38%, 40%, and 36%, respectively. PROMIS-29 physical health summary scores at baseline, Day 0, week 1, week 2, week 3, week 4, and Day 90 were 47 [21-59], 45 [23-59], 44 [22-59], 42 [21-59], 41 [22-59], 42 [22-59], and 46 [29-59], respectively. Mental health summary scores were 51 [31-64], 49 [30-64], 49 [31-64], 48 [27-64], 48 [31-64], 49 [30-64], and 52 [26-64], respectively. For the CAR T patients, 64% answered at least one survey, with response rates at baseline, Day 0, week 1, week 2, week 3, week 4, and Day 90 of 39%, 12%, 21%, 27%, 24%, 21%, and 9%, respectively. PROMIS-29 physical health summary scores at baseline, Day 0, week 1, week 2, week 3, week 4, and Day 90 were 43 [27-57], 40 [27-46], 45 [38-59], 44 [35-59], 51 [35-59], 45 [34-58], and 37 [34-58], respectively. Mental health summary scores were 48 [36-59], 46 [40-50], 49 [45-63], 51 [38-62], 52 [36-64], 52 [48-62], and 45 [39-63], respectively. **Conclusions:** We demonstrate the feasibility of incorporating patient-reported outcomes into standard-of-care practice after AHCT and CAR T. Missing surveys were more common while inpatient, which may be due to toxicity and/or less frequent use of the patient portal while admitted. Additional work is ongoing to improve the response rates at all time points. Importantly, the electronic system allowed us to capture later timepoints when patients have less frequent visits and may be followed locally. Full survey results will be presented.

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[1]University of Illinois at Chicago; [2]HealthTree Foundation; [3]Department of Biobehavioral Nursing Science, University of Illinois at Chicago; [4]Flatiron Health; [5]University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA; [6]Winship Cancer Institute of Emory University

Introduction: Overuse of opioids has been associated with a significant public health crisis, yet these drugs remain critical as adjunctive treatment for pain in multiple myeloma (MM). Prolonged survival with the use of autologous stem cell transplant (ASCT) and maintenance therapy validates the need to examine chronic opioid use (COU) patterns and the effects of COU on clinical outcomes. **Methods:** A retrospective cohort study of MM patients (n=174) who received ASCT at an urban inner-city transplant center treating mostly Black patients was undertaken. Given the findings of this study, in collaboration with HealthTree Foundation, through a prospective survey-based study, we sought to identify other predictors of COU and gain insight into patient attitudes towards opioids. COU was defined as an active prescription for 3 consecutive months and daily opioid doses were converted to MME. **Results:** At baseline, COU was observed in 92 (52.9%) patients, 27 (29.3%) of whom did not have a history of bone disease. Baseline average MME was 65.3 mg (SD=69.97 mg). COU rates and average MME/day were similar between those with and without bone disease. Previous illicit drug use was associated with higher baseline COU, while use of non-opioid analgesics, being retired, or employed were associated with lower baseline COU. 142 (81.6%) patients received opioids during ASCT, while 105 (60.3%) were discharged on opioids and 72 (41.4%) met criteria for COU at 6 months. In the 105 patients discharged on opioids, COU remained high over time, with 63 (60%) having COU at 6 months after ASCT. In baseline non-opioid users, 30 (36.6%) patients became new opioid users on discharge. Opioid use at hospital discharge was associated with a higher 6-month COU (p=0.008). Median OS in patients with 6-month COU was 48 months vs not reached (p=0.004; Fig 1). 6-month COU independently predicted for worse OS (p=0.006). Given these findings, we developed a 36-item survey addressing demographics like race and SES, disease markers, and experience with pain, use of opioids, opioid risk, and barriers to patient-provider communication. The survey is hosted on the HealthTree Cure Hub (healthtree.org). Between May 15th when the survey went live to May 24th, 230 patients have participated. Surveys will remain open for 3 months with an expected accrual of up to 750 patients. Descriptive data and association between baseline patient/disease-related characteristics and survey answers will be analyzed. **Conclusions:** Here we describe high rates of baseline COU in MM unrelated to the presence of bone disease and highlight a high rate of opiate use after ASCT including a number of new users post-ASCT, which result in ongoing COU at 6 months. We demonstrate a negative impact of COU at 6 months on OS but not on PFS suggesting that opioid-related morbidity may play a role. These data highlight the need to improve our understanding and management of pain in MM. Results from our prospective HealthTree survey study will be presented at the Congress.

P-486

Clinical significance of baseline body mass index and its trajectory during triplet induction therapy in newly diagnosed multiple myeloma

Ram Prakash Thirugnanasambandam[1], Ross Firestone[1], Andriy Derkach[1], Kylee Maclachlan[2], Malin Hultcrantz[2], Sham Mailankody[2], Oscar Lahoud[1], Heather Landau[3], David Chung[3], Gunjan Shah[1], Michael Scordo[1], Hani Hassoun[2], Alexander Lesokhin[1], Sergio Giralt[1], Neha Korde[2], Saad Usmani[1], Carlyn Rose Tan[1], Urvi Shah[2]

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Introduction: Elevated body mass index (BMI) is a known risk factor for newly diagnosed multiple myeloma (NDMM); however, the prevalence and clinical significance of BMI changes (gain and loss) during induction therapy in NDMM has not been explored. **Methods:** We conducted a retrospective study of 188 NDMM patients (pts) receiving induction therapy with carfilzomib, lenalidomide and dexamethasone (KRd) from 2016 to 2022 to determine the clinical significance of baseline BMI and trajectory during induction therapy. BMI was collected at baseline and at completion of induction therapy. Pts were divided into – underweight (< 18.5), normal (18.5-24.9) and elevated BMI (≥ 25). Pts were also divided into – weight stable (BMI change < 5%), weight loss (BMI decrease ≥5%) and weight gain (BMI increase ≥5%) based on BMI change post induction from baseline. High risk cytogenetics was defined by the presence of +1q, del(17p), t(4;14), t(14;16) or t(14;20). Progression free survival (PFS) was defined as time from beginning induction therapy to disease progression or death. Univariate analysis was performed by unpaired two-sided t-tests or Cox proportional hazards for survival analyses. Multivariate analysis was performed using Cox proportional hazards regression analysis and model was adjusted for baseline BMI, cytogenetics, age, ECOG and ISS. **Results:** Baseline BMI for pts were 1% underweight, 22% normal, 76% elevated, and 1% unknown. No differences in age, cytogenetics, or ISS stage were noted across baseline BMI categories. During induction, BMI for pts were 14% lost weight, 62% weight stable, and 21% gained weight. For pts with high-risk cytogenetics, 17% lost weight and 18% gained weight, whereas for pts with standard-risk cytogenetics, 13% lost weight and 25% gained weight. Pts with weight gain had a lower median age than weight stable pts (58 years (y) vs 61y, p=0.073) and pts with weight loss had a significantly higher age than weight stable pts (66y vs 61y, p=0.008). On univariate analysis, PFS trended worse for pts with BMI >25 (median PFS NR for both groups, p=0.07). On multivariate analysis, pts with baseline BMI >25 (HR 3.2, p=0.05), high-risk cytogenetics (HR 2.0, p=0.04), and ISS stage 3 disease (HR 2.9, p=0.03) had worse PFS with no difference identified for patient age or ECOG. No differences were observed in post-induction PFS when comparing weight stable pts to those gaining or losing weight (p=0.27). **Conclusions:** Most pts in our dataset had an elevated BMI

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P-486

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that was maintained during induction therapy. The increased risk for weight gain in younger pts and for weight loss in older pts should be considered for pt counseling, although this did not affect PFS. An elevated BMI tracks with inferior PFS. Data on a similar cohort of pts treated with bortezomib, lenalidomide, and dexamethasone along with long-term BMI trajectories post-induction from both cohorts will be presented at the meeting.

P-487

Adherence to patient-reported symptom monitoring and subsequent clinical interventions for patients with multiple myeloma in outpatient care: a longitudinal observational study

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Introduction: Background: Use of software to monitor Patient-Reported Outcome Measures (PROMs) can improve outcomes for cancer patients receiving anticancer therapy; however, evidence from applications used in routine clinical practice is lacking. **Objective:** We aimed to investigate adherence to, and patient perceptions of a weekly, web-based PROM symptom monitoring in routine clinical practice for patients with Multiple Myeloma. Moreover, we aimed to capture how clinical alerts prompted by the system influenced clinical care. **Methods:** Methods: We conducted a single-center longitudinal observational study to evaluate patient adherence to and perceptions of the PROM monitoring software in routine practice. Patients with Multiple Myeloma remotely completed weekly treatment-specific PROMs to monitor key symptoms via a dedicated web-based platform. Alarming symptoms triggered clinical alerts in the application for the treatment team who could initiate clinical interventions. The primary outcomes were the online assessment completion rate and patients' perceptions of the monitoring program assessed by an evaluation questionnaire. Moreover, clinical alerts prompted by the system and consequential clinical interventions were analyzed. **Results:** Results: Between July 2021 and June 2022, 55 patients were approached for participation; 39 patients participated (24 male [61%], mean age: 63.2 years, SD 9.2). The median assessment completion rate out of all weekly scheduled assessments was 70.3% (IQR 41.2-89.6). Most patients (77%) felt that the healthcare team was better informed on their health status due to the online assessments. Clinical alerts were triggered for 1758/14639 (12.0%) of reported symptoms. For 548/1758 (31.2%) of alerts, the symptom had been registered before and no further action was required; for 348/1758 (19.9%) of alerts, telephone consultation and self-management advice sufficed. Higher-level interventions were seldom needed in response to alerts: referral to a doctor or specialist (88/1758 of alerts, 5.0%), medication changes (22/1758, 1.3%), scheduling additional diagnostics (9/1758, 0.5%), or unplanned emergency visits (7/1758, 0.4%). Most patients (55%) reported the calls in response to alerts gave them "quite a bit" or "very much" of an added feeling of security during therapy. **Conclusions:** Our study shows that high adherence to regular and tailored PROM monitoring can be achieved in routine clinical care. The findings provide valuable insight into how the PROM monitoring program and the clinical alerts and resulting interventions shaped clinical practice. Trial Registration: NCT05036863 (https://clinicaltrials.gov/).

P-488

Expert in the loop - AI assisted generation of real-world-evidence

Wolfgang Willenbacher[1,2], Roman Weger[2], Ella Willenbacher[1], Stefanie Tipelius[2], Jens Lehmann[3], Mario Mitter[2]

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Introduction: syndena is a technology company that provides an innovative Expert-in-the-Loop (EITL) data extraction tool to extract data from electronic health records (EHRs) and medical files. The EITL tool aims to improve patient outcomes in various medical fields e.g. hematology, oncology, neurology, cardiology, and nephrology by generating real-world evidence and preventing misdocumentaions, as well as relieving medical staff of the burden of managing large and complex data sets. **Methods:** Syndena's EITL technology utilizes advanced natural language processing (NLP) and machine learning algorithms to extract relevant data points from unstructured medical records with expert oversight. Healthcare professionals can leverage the technology to gain insights from a broad range of data sources, including lab results and clinical notes. Syndena is already able to structure and find relevant clinical information in EHRs of patients with various medical conditions, making the technology applicable across multiple medical fields. The EITL tool has been successful in extracting and analyzing large and complex data sets from EHRs and medical files at much higher speeds than traditional methods. The data gathered is saved in the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) automatically, which provides several advantages, including a standardized, widely accepted, data structure. **Results:** syndena's EITL technology can lead to improved patient outcomes by timely generating real-world evidence for all medical fields including hematology. The technology

that was maintained during induction therapy. The increased risk for weight gain in younger pts and for weight loss in older pts should be considered for pt counseling, although this did not affect PFS. An elevated BMI tracks with inferior PFS. Data on a similar cohort of pts treated with bortezomib, lenalidomide, and dexamethasone along with long-term BMI trajectories post-induction from both cohorts will be presented at the meeting.

P-487

Adherence to patient-reported symptom monitoring and subsequent clinical interventions for patients with multiple myeloma in outpatient care: a longitudinal observational study

Ella Willenbacher[1], Wolfgang Willenbacher[1,2], Kelly M de Ligt[3], Stefanie Tipelius[2], Johannes Giesinger[4], Monika Sztankay[4], Sandra Voigt[1,2], Lonneeke van de Polse[5,6,7], Gerhard Rumpold[4], Roman Weger[2], Holzner Bernhard[4], Jens Lehmann[4]

[1]Innsbruck Medical University, Internal Medicine V: Hematology & Oncology, Innsbruck, Austria; [2]syndena GmbH, connect to cure, Innsbruck, Austria; [3]Department of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, the Netherlands; [4]University Hospital of Psychiatry II, Medical University of Innsbruck, Innsbruck, Austria; [5]Department of Psychosocial Research and Epidemiology, Department of Medical and Clinical Psychology, Center of Research on Psychological and Somatic Disorders (CoRPS), Tilburg University, Tilburg, the Netherlands; [6]The Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, the Netherlands; [7]Department of Research and Development, Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands

Introduction: Background: Use of software to monitor Patient-Reported Outcome Measures (PROMs) can improve outcomes for cancer patients receiving anticancer therapy; however, evidence from applications used in routine clinical practice is lacking. **Objective:** We aimed to investigate adherence to, and patient perceptions of a weekly, web-based PROM symptom monitoring in routine clinical practice for patients with Multiple Myeloma. Moreover, we aimed to capture how clinical alerts prompted by the system influenced clinical care. **Methods:** Methods: We conducted a single-center longitudinal observational study to evaluate patient adherence to and perceptions of the PROM monitoring software in routine practice. Patients with Multiple Myeloma remotely completed weekly treatment-specific PROMs to monitor key symptoms via a dedicated web-based platform. Alarming symptoms triggered clinical alerts in the application for the treatment team who could initiate clinical interventions. The primary outcomes were the online assessment completion rate and patients' perceptions of the monitoring program assessed by an evaluation questionnaire. Moreover, clinical alerts prompted by the system and consequential clinical interventions were analyzed. **Results:** Results: Between July 2021 and June 2022, 55 patients were approached for participation; 39 patients participated (24 male [61%], mean age: 63.2 years, SD 9.2). The median assessment completion rate out of all weekly scheduled assessments was 70.3% (IQR 41.2-89.6). Most patients (77%) felt that the healthcare team was better informed on their health status due to the online assessments. Clinical alerts were triggered for 1758/14639 (12.0%) of reported symptoms. For 548/1758 (31.2%) of alerts, the symptom had been registered before and no further action was required; for 348/1758 (19.9%) of alerts, telephone consultation and self-management advice sufficed. Higher-level interventions were seldom needed in response to alerts: referral to a doctor or specialist (88/1758 of alerts, 5.0%), medication changes (22/1758, 1.3%), scheduling additional diagnostics (9/1758, 0.5%), or unplanned emergency visits (7/1758, 0.4%). Most patients (55%) reported the calls in response to alerts gave them "quite a bit" or "very much" of an added feeling of security during therapy. **Conclusions:** Our study shows that high adherence to regular and tailored PROM monitoring can be achieved in routine clinical care. The findings provide valuable insight into how the PROM monitoring program and the clinical alerts and resulting interventions shaped clinical practice. Trial Registration: NCT05036863 (https://clinicaltrials.gov/).

P-488

Expert in the loop - AI assisted generation of real-world-evidence

Wolfgang Willenbacher[1,2], Roman Weger[2], Ella Willenbacher[1], Stefanie Tipelius[2], Jens Lehmann[3], Mario Mitter[2]

[1]Innsbruck University Hospital Internal Medicine V: Hematology and Oncology &; [2]Syndena GmbH, Connect to Cure, Innsbruck, Austria; [3]Medical University of Innsbruck, Dep. of Psychiatry II & syndena, GmbH, Innsbruck, Austria

Introduction: syndena is a technology company that provides an innovative Expert-in-the-Loop (EITL) data extraction tool to extract data from electronic health records (EHRs) and medical files. The EITL tool aims to improve patient outcomes in various medical fields e.g. hematology, oncology, neurology, cardiology, and nephrology by generating real-world evidence and preventing misdocumentaions, as well as relieving medical staff of the burden of managing large and complex data sets. **Methods:** Syndena's EITL technology utilizes advanced natural language processing (NLP) and machine learning algorithms to extract relevant data points from unstructured medical records with expert oversight. Healthcare professionals can leverage the technology to gain insights from a broad range of data sources, including lab results and clinical notes. Syndena is already able to structure and find relevant clinical information in EHRs of patients with various medical conditions, making the technology applicable across multiple medical fields. The EITL tool has been successful in extracting and analyzing large and complex data sets from EHRs and medical files at much higher speeds than traditional methods. The data gathered is saved in the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) automatically, which provides several advantages, including a standardized, widely accepted, data structure. **Results:** syndena's EITL technology can lead to improved patient outcomes by timely generating real-world evidence for all medical fields including hematology. The technology

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P-489

Prolonged cytopenia after CAR T-cell therapy in multiple myeloma: results from a prospective comprehensive biomarker study

Xiang Zhou[1], Emilia Stanojkovska[1], Vivien Wagner[1], Christine Riedhammer[1], Xianghui Xiao[1], Mara John[1], Umair Munawar[1], Seungbin Han[1], Johannes Waldschmidt[1], Max Topp[1], Johannes Duell[1], Hermann Einsele[1], Angela Riedel[1], Martin Kortüm[1], Leo Rasche[1]

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Introduction: The majority of patients treated with CAR-T-cell display unexplained prolonged cytopenia. Our study aimed to explore biomarkers that correlate with cytopenia post CAR-T in multiple myeloma (MM). **Methods:** We prospectively analyzed peripheral blood (PB) of MM patients treated with idecabtagen-vicleucel at these time points: before lymphodepleting (baseline), after CAR-T on d4, 7, 14, 28, and monthly thereafter. Flow cytometry was performed with following markers: CD45, CD3, CD4, CD8, CD62L, CD45RA, CD19, CD14, CD138, CD38 and a BCMA-CAR-detection marker. **Results:** We included a total of 191 sequential PB samples of 32 MM patients. The patients were pretreated with a median of 5 therapy lines (range 2-10). 31 (97%) and 8 (25%) patients underwent autologous and allogeneic stem cell transplant, respectively. Of note, patients with allogeneic stem cell transplant or ≥5 prior therapy lines did not show longer duration of grade ≥3 cytopenia than the remaining patients. However, baseline hemoglobin and platelet count correlated with the duration of grade ≥3 anemia (r=-0.63, P< 0.001) and thrombocytopenia (r=-0.44, P=0.01), respectively. Moreover, the ferritin peak post CAR-T significantly correlated with the duration of grade ≥3 anemia (r=0.65, P< 0.001) and thrombocytopenia (r=0.69, P< 0.001), and the baseline ferritin showed a correlation with the duration of grade ≥3 anemia (r=0.54, P=0.001) and thrombocytopenia (r=0.54, P=0.001). Interestingly, the duration of grade ≥3 lymphopenia significantly correlated with CD4+ (r=0.55, P=0.004), CD8+ T-cell (r=-0.59, P=0.002) frequencies and the CD4+/CD8+ ratio (r=0.55, P=0.004) at baseline. We then divided the patients into two groups: early (< d60) vs prolonged (≥d60) cytopenia. In both groups, high baseline ferritin level indicated severe anemia (< d60: r=-0.50, P< 0.001; ≥d60: r=-0.64, P< 0.001) and thrombocytopenia (< d60: r=-0.61, P< 0.001; ≥d60: r=-0.74, P< 0.001). In the ≥d60 group, the frequency of T-cells showed a negative correlation with hemoglobin (r=-0.52, P=0.001) but a positive correlation with lymphocyte count (r=0.62, P< 0.001), suggesting that prolonged lymphopenia post CAR-T was mainly attributed to the lack of T-cell. The frequency of naïve CD4+ T-cells correlated with neutrophil count (r=0.57, P< 0.001), hemoglobin (r=0.44, P=0.009) and leukocyte count (r=0.48, P=0.004). In prolonged lymphopenia, we found a significant correlation between lymphocyte count and the frequencies of CAR+CD4+ (r=-0.52, P=0.002), CAR+CD8+ (r=0.53, P< 0.001), CAR-CD4+ (r=-0.63, P< 0.001), CAR-CD8+ (r=0.73, P< 0.001) T-cells as well as the ratio of CAR+CD4+/CAR+CD8+ (r=-0.54, P=0.001) and CAR-CD4+/CAR-CD8+ (r=-0.69, P< 0.001). **Conclusions:** Together, high ferritin level and preexisting cytopenia were associated with prolonged cytopenia post CAR-T in MM. Patients with high CD4+/CD8+ ratio, e.g. newly diagnosed MM, are at risk of prolonged T-cell lymphopenia, which may be an issue for infectious complications and later T-cell based immunotherapies.

NURSING SYMPOSIUM ORAL PRESENTATIONS

NSO-01

Real world experience of teclistamab using a prompt management strategy for cytokine release syndrome

Donna Catamero[1], Victoria Dai[2], Mohammad Rattu[1], Sundar Jagannath[3], Cesar Rodriguez[4]

[1]Mount Sinai Hospital; [2]Mount Sinai School of Medicine, New York, NY, USA; [3]Mount Sinai Medical Center, New York, NY, USA; [4]Icahn School of Medicine at Mount Sinai

Introduction: Cytokine release syndrome (CRS) is a systemic inflammatory response commonly associated with T-cell engagers. Teclistamab is the first B-cell maturation antigen bispecific antibody approved for the treatment of relapsed/refractory multiple myeloma (RRMM). In the MajesTEC-1 study, 72.1% of patients experienced CRS; most events were grade 1 (50.3%) but 21.2% were grade 2 and one grade 3. The CRS management guidelines recommended tocilizumab use for grade 2 events but could be considered in certain grade 1. CRS was managed with tocilizumab (36.4%), steroids (8.5%), supplemental oxygen (12.7%), and vasopressors (0.6%) (Moreau et al, NEJM, 2022). Here, we aim to describe the real world experience (RWE), which historically includes

has been tested in various healthcare settings and has been successful in extracting and analyzing large amounts of complex data from source files (EHRs) at high speeds with expert oversight. The EITL tool can also prevent misdocumentations by identifying and correcting data inconsistencies and errors in EHRs and medical files, using plausibility controls. Moreover, the automatic saving of data in the OMOP CDM provides several advantages, including a standardized data structure that allows for efficient and effective data analysis, data normalization, and interoperability across different data sources. **Conclusions:** syndena's EITL technology is a significant advancement in the use of technology to optimize the timely generation of real-world data from large medical data sets and primary source files in a highly compatible fortmat (OMOP CDM) Resulting in standardized data sets that allow for efficient and effective data analysis, data normalization, and interoperability across different data sources. Syndena's EITL technology has demonstrated its potential to improve QoL and understanding of outcomes across multiple medical fields. By facilitating personalized medicine and improving clinical trial design, the EITL tool can inform healthcare policies and drive evidence-based decision-making. Fubased data sets. rthermore syntetic data can easily be generated from EITL based data sets.

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NURSING SYMPOSIUM ORAL PRESENTATIONS

NSO-01

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patients who would not have been eligible for clinical trials, using a more proactive teclistamab use to manage CRS. **Methods:** This retrospective study analyzed data from RRMM patients who were treated with commercial teclistamab at our center as of December 1, 2022. Patients were identified using the pharmacy's database and data was abstracted from electronic medical records. Information on treatment administration, disease profile, toxicities including CRS and management were collected. Per institutional policy, the use of tocilizumab was used at first onset of fever during the initial step-up doses of teclistamab. **Results:** As of May 30, 2023, 35 patients were treated. Data from 26 patients has been analyzed and data from all patients will be presented at the meeting. Overall, 78% of patients experienced any grade CRS. Among patients with CRS, 85% of patients experienced a grade 1 CRS and 15% had a grade 2. There were no grade 3 events. Seventy percent of CRS events occurred with step-up dose (SUD) 1, 35% with SUD2 and 20% with cycle 1 day 1. Two patients had CRS after cycle 1 day 1. Of these two, one had plasma cell leukemia and the other significant extramedullary disease. All patients presented with fever (38.5C) and were administered tocilizumab and acetaminophen with first at first occurrence. Other supportive measures included steroids (25%) and intravenous fluids (5%). Four patients had subsequent CRS after initial dose of tocilizumab; all events were grade 1. **Conclusions:** Our RWE is comparable to the MajesTEC-1 in terms of overall CRS incidence, despite a patient population which would not have been eligible for clinical. We expected this population to be more vulnerable to higher grades of CRS yet data showed a more benign course. We attribute this to aggressively managing CRS with use of tocilizumab and acetaminophen at first sign of CRS to prevent further escalation. CRS episodes were seen less in subsequent teclistamab doses and severity was never above grade 1, making it more manageable in a potential outpatient setting. A proactive management approach to reduce severity and increase predictability could facilitate adoption of outpatient when treatment and escalation are needed, to ensure successful administration of teclistamab.

NSO-02

Characteristics of multiple myeloma patients with central nervous system involvement

Jessica Chen[1], Tiffany Richards[1], Christy Allen[1], Yue Jiang[1], Courtney Bendig[1], Ashley Morphey[1], Elizabeth Cuellar[1], Sarah Knight[1], Efe Ighovoyivwi[1], Rebecca Lu[1], Pei Lin[1], Behrang Amini[1], Mahmoud Gaballa[1], Hans Lee[1], Elisabet Manasanch[1], Krina Patel[1], Sheeba Thomas[1], Jing Christine Ye[1,2], Bouthain Dabaja[1], Chelsea Pinnix[1], Penny Fang[1], Jill Gunther[1], Robert Orlowski[1], Donna Weber[1], Melody Becnel[1]

[1]MD Anderson Cancer Center; [2]University of Michigan, Rogel Cancer Center, Ann Arbor, MI, USA (during study)

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NSO-03

Impact of myeloma and amyloidosis on young patients

Emma Dowling[1], Nuno Correia[2], Ashutosh Wechelaker[3]

[1]HCA Healthcare UK; [2]HCA healthcare at UCH, Private Care; [3]National Amyloidosis Centre, University College London, London, United Kingdom

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patients who would not have been eligible for clinical trials, using a more proactive teclistamab use to manage CRS. **Methods:** This retrospective study analyzed data from RRMM patients who were treated with commercial teclistamab at our center as of December 1, 2022. Patients were identified using the pharmacy's database and data was abstracted from electronic medical records. Information on treatment administration, disease profile, toxicities including CRS and management were collected. Per institutional policy, the use of tocilizumab was used at first onset of fever during the initial step-up doses of teclistamab. **Results:** As of May 30, 2023, 35 patients were treated. Data from 26 patients has been analyzed and data from all patients will be presented at the meeting. Overall, 78% of patients experienced any grade CRS. Among patients with CRS, 85% of patients experienced a grade 1 CRS and 15% had a grade 2. There were no grade 3 events. Seventy percent of CRS events occurred with step-up dose (SUD) 1, 35% with SUD2 and 20% with cycle 1 day 1. Two patients had CRS after cycle 1 day 1. Of these two, one had plasma cell leukemia and the other significant extramedullary disease. All patients presented with fever (38.5C) and were administered tocilizumab and acetaminophen with first at first occurrence. Other supportive measures included steroids (25%) and intravenous fluids (5%). Four patients had subsequent CRS after initial dose of tocilizumab; all events were grade 1. **Conclusions:** Our RWE is comparable to the MajesTEC-1 in terms of overall CRS incidence, despite a patient population which would not have been eligible for clinical. We expected this population to be more vulnerable to higher grades of CRS yet data showed a more benign course. We attribute this to aggressively managing CRS with use of tocilizumab and acetaminophen at first sign of CRS to prevent further escalation. CRS episodes were seen less in subsequent teclistamab doses and severity was never above grade 1, making it more manageable in a potential outpatient setting. A proactive management approach to reduce severity and increase predictability could facilitate adoption of outpatient when treatment and escalation are needed, to ensure successful administration of teclistamab.

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NSO-03

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NSO-02

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NSO-03

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Introduction: Multiple myeloma (MM) and Amyloid (AL) is a treatable plasma cell cancer with no cure1. The average age of

diagnosis of these malignancies is 70 years old2. The overall survival of younger patients is drastically longer than of their older cohorts3, and with this comes a unique set of challenges and obstacles to live with at such a young age. The young MM and AL patients and their survivorship is not a common area of exploration. We performed this study to understand the impact of these diagnoses on our patients from a physical, psychological and social perspective and assess their need for increased education and psychological support as a result. We asked patients to retrospectively grade their top areas of concern at time of diagnosis and then further grade these concerns again in the present day. **Methods:** An online, questionnaire designed by the authors via Microsoft Forms. This questionnaire surveyed MM/AL patients who were diagnosed at the age of 55 or under. **Results:** We surveyed 57 young patients (under the age of 55) and obtained 29 completed surveys, in a period of 7days. We expect more surveys to be completed. Our patients average age at diagnosis was 45, ranging from 30 to 55 years of age. We obtained responses from 19 male and 10 female patients. Only 4 (14%) had heard of the disease before diagnosis. When questioned on their biggest fear the overwhelming response from these patients was early death. Their biggest areas of concern at diagnosis were "anxiety about their future" and "the impact on their children's lives". And although these concerns are still present today, they are reduced in comparison to the time of diagnosis. Interestingly 13 (45%) of our patients have not received any counselling support, of these some site "exercise, meditation, family and friends, myeloma nurse and support groups", as their strategy to cope with their illness. Some patients have developed comorbidities throughout their treatment journey, mainly 5 (17%) with cardiac complications and 4 (14%) with thyroid related issues. **Conclusions:** This survey is a unique opportunity to explore the areas of most concern of this young patient population. Many of these patients will live for many years, meaning more focus is needed on survivorship and quality of life. From our findings we can conclude the disease has an enormous psychological impact on patients' lives. Their greatest fears are dying young and not seeing their kids grow up. Conversely, despite this huge impact on their mental health, only half of them have received counselling. This highlights space for improvement and perhaps counselling could be standardised as part of their plan of care from diagnosis. With greater treatment options and longer life expectancy, this patient group, requires more tailored specialised care to adequately meet their unique needs.

NSO-04

Characterising sleep disturbances with actigraphy in those receiving steroids for the treatment of multiple myeloma: findings from a pilot study

Tracy King[1,2], Kerri Melehan[1,2], Gislaine Gauthier[1], Chantale Boustany[2], Louise Acret[2], Kate White[2,3]

[1]Royal Prince Alfred Hospital; [2]The University of Sydney; [3]Sydney Local Health District

Introduction: Glucocorticosteroids (steroids), central to the treatment of multiple myeloma (MM), have multiple deleterious side effects (SE). Our team found that disturbed sleep was the most frequently reported SE, identified in up to 95% of patients (King et al 2019), with 67% of patients reporting severe sleep disturbances. This pilot study, funded by a grant from Sydney Blood Cancer Institute, is the first to characterise sleep disturbances associated with steroid treatment in MM using objective measures of sleep quality. **Methods:** 10 MM participants currently taking steroids for MM, with associated disturbed sleep and an ECOG ≤ 2 were recruited. Participants were assessed for risk of obstructive sleep apnoea (OSA), and those found to be at high risk of OSA excluded from the study. Sleep duration, sleep efficiency and wake bouts were measured over the three weeks of monitoring using actigraphy, a validated method of objective long-term sleep monitoring using a watch-like device, and sleep diaries to document subjective sleep experience. Actigraphy data was analysed in a blinded fashion, utilising light, and activity levels to determine attempted sleep periods, with sleep diaries to confirm these. Semi-structured interviews were undertaken post monitoring period. **Results:** To date 8 participants have been recruited, 4 male and 4 female. Enrolled participants were median of 60.5 (53-71) years of age, receiving median of 100 mg range (24-160) of dexamethasone per cycle of treatment and had received up to 4 lines of previous treatment. We report actigraphy data on 3 participants with completed data. Sleep duration was reduced in 2/3 of participants by 33%, and 43% on dexamethasone nights. There was a reduction in average sleep efficiency (% time asleep when in bed) and a lowering of wake bouts with dexamethasone, 83.0% vs 75.3%, and 29.5 vs 21.0, respectively. The average fragmentation index (a measure of sleep disturbance) slightly increased from 17.2 to 19.8 on dexamethasone nights. **Conclusions:** This pilot study has shown the approach to data collection is feasible. It is the first study to objectively characterise sleep disturbances associated with dexamethasone treatment in MM. Our preliminary results indicate a reduction in sleep duration and sleep efficiency on nights participants took dexamethasone. Sleep was more disturbed on these nights, with less, though longer, periods of wakefulness. Data on the full cohort is pending and will be further informed by the qualitative interviews.

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NSO-05

Specialist physiotherapy post-autologous stem cell transplant improved functional outcomes with high patient satisfaction in multiple myeloma patients

Joanne Land[1], Jotham Marfil[1], Jackie Horder[1], Fiona Newrick[1], Charalampia Kyriakou[1], Jonathan Sive[1], Neil Rabin[1], Xenofon Papanikolaou[1], Abi Fisher[2], Kwee Yong[2], Orla McCourt[1]

[1]NHS University College London Hospital, London, United Kingdom; [2]University College London, United Kingdom

Introduction: Autologous stem cell transplantation (ASCT) is offered as a front-line treatment for eligible multiple myeloma

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[1]NHS University College London Hospital, London, United Kingdom; [2]University College London, United Kingdom

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diagnosis of these malignancies is 70 years old2. The overall survival of younger patients is drastically longer than of their older cohorts3, and with this comes a unique set of challenges and obstacles to live with at such a young age. The young MM and AL patients and their survivorship is not a common area of exploration. We performed this study to understand the impact of these diagnoses on our patients from a physical, psychological and social perspective and assess their need for increased education and psychological support as a result. We asked patients to retrospectively grade their top areas of concern at time of diagnosis and then further grade these concerns again in the present day. **Methods:** An online, questionnaire designed by the authors via Microsoft Forms. This questionnaire surveyed MM/AL patients who were diagnosed at the age of 55 or under. **Results:** We surveyed 57 young patients (under the age of 55) and obtained 29 completed surveys, in a period of 7days. We expect more surveys to be completed. Our patients average age at diagnosis was 45, ranging from 30 to 55 years of age. We obtained responses from 19 male and 10 female patients. Only 4 (14%) had heard of the disease before diagnosis. When questioned on their biggest fear the overwhelming response from these patients was early death. Their biggest areas of concern at diagnosis were "anxiety about their future" and "the impact on their children's lives". And although these concerns are still present today, they are reduced in comparison to the time of diagnosis. Interestingly 13 (45%) of our patients have not received any counselling support, of these some site "exercise, meditation, family and friends, myeloma nurse and support groups", as their strategy to cope with their illness. Some patients have developed comorbidities throughout their treatment journey, mainly 5 (17%) with cardiac complications and 4 (14%) with thyroid related issues. **Conclusions:** This survey is a unique opportunity to explore the areas of most concern of this young patient population. Many of these patients will live for many years, meaning more focus is needed on survivorship and quality of life. From our findings we can conclude the disease has an enormous psychological impact on patients' lives. Their greatest fears are dying young and not seeing their kids grow up. Conversely, despite this huge impact on their mental health, only half of them have received counselling. This highlights space for improvement and perhaps counselling could be standardised as part of their plan of care from diagnosis. With greater treatment options and longer life expectancy, this patient group, requires more tailored specialised care to adequately meet their unique needs.

NSO-04

Characterising sleep disturbances with actigraphy in those receiving steroids for the treatment of multiple myeloma: findings from a pilot study

Tracy King[1,2], Kerri Melehan[1,2], Gislaine Gauthier[1], Chantale Boustany[2], Louise Acret[2], Kate White[2,3]

[1]Royal Prince Alfred Hospital; [2]The University of Sydney; [3]Sydney Local Health District

Introduction: Glucocorticosteroids (steroids), central to the treatment of multiple myeloma (MM), have multiple deleterious side effects (SE). Our team found that disturbed sleep was the most frequently reported SE, identified in up to 95% of patients (King et al 2019), with 67% of patients reporting severe sleep disturbances. This pilot study, funded by a grant from Sydney Blood Cancer Institute, is the first to characterise sleep disturbances associated with steroid treatment in MM using objective measures of sleep quality. **Methods:** 10 MM participants currently taking steroids for MM, with associated disturbed sleep and an ECOG ≤ 2 were recruited. Participants were assessed for risk of obstructive sleep apnoea (OSA), and those found to be at high risk of OSA excluded from the study. Sleep duration, sleep efficiency and wake bouts were measured over the three weeks of monitoring using actigraphy, a validated method of objective long-term sleep monitoring using a watch-like device, and sleep diaries to document subjective sleep experience. Actigraphy data was analysed in a blinded fashion, utilising light, and activity levels to determine attempted sleep periods, with sleep diaries to confirm these. Semi-structured interviews were undertaken post monitoring period. **Results:** To date 8 participants have been recruited, 4 male and 4 female. Enrolled participants were median of 60.5 (53-71) years of age, receiving median of 100 mg range (24-160) of dexamethasone per cycle of treatment and had received up to 4 lines of previous treatment. We report actigraphy data on 3 participants with completed data. Sleep duration was reduced in 2/3 of participants by 33%, and 43% on dexamethasone nights. There was a reduction in average sleep efficiency (% time asleep when in bed) and a lowering of wake bouts with dexamethasone, 83.0% vs 75.3%, and 29.5 vs 21.0, respectively. The average fragmentation index (a measure of sleep disturbance) slightly increased from 17.2 to 19.8 on dexamethasone nights. **Conclusions:** This pilot study has shown the approach to data collection is feasible. It is the first study to objectively characterise sleep disturbances associated with dexamethasone treatment in MM. Our preliminary results indicate a reduction in sleep duration and sleep efficiency on nights participants took dexamethasone. Sleep was more disturbed on these nights, with less, though longer, periods of wakefulness. Data on the full cohort is pending and will be further informed by the qualitative interviews.

Reference: King T, Jagger J, Fethney J, Boustany C, Joshua D, White K (2019). The Steroid Symptom Questionnaire Multiple Myeloma (SSQ-MM): Feasibility, acceptability, reliability and internal consistency. Clinical Lymphoma, Myeloma and Leukemia, 19(10): e341-e341.

NSO-05

Specialist physiotherapy post-autologous stem cell transplant improved functional outcomes with high patient satisfaction in multiple myeloma patients

Joanne Land[1], Jotham Marfil[1], Jackie Horder[1], Fiona Newrick[1], Charalampia Kyriakou[1], Jonathan Sive[1], Neil Rabin[1], Xenofon Papanikolaou[1], Abi Fisher[2], Kwee Yong[2], Orla McCourt[1]

[1]NHS University College London Hospital, London, United Kingdom; [2]University College London, United Kingdom

Introduction: Autologous stem cell transplantation (ASCT) is offered as a front-line treatment for eligible multiple myeloma

(MM) patients due to its efficacy at increasing progression-free survival. However, it is also associated with high symptom burden and reduced quality of life (QoL) which are greatest in the first-month post-ASCT. Whilst most symptoms improve by the third month, pain and reduced QoL remain prevalent for up to one year. Indicating a need for supportive care to aid recovery. Patients who complete exercise programs pre and post-ASCT report a greater trajectory of recovery. Therefore, we evaluated the implementation of specialist physiotherapy provision introduced at 100 days (D100) post-transplant aimed to optimize patient recovery through exercise. **Methods:** At University College London Hospital we conducted a service improvement project within the MM ASCT pathway. Patients seen within the D100 clinic between November 2021–December 2022 were assessed by a specialist MM physiotherapist and prescribed tailored exercises. Outcomes included a measure of functional capacity (1-minute timed sit-to-stand test (STS-1min)), self-reported (PA) (GODIN), VAS for pain (0=no pain to 10=worst pain) and QoL (EQ5D-5L). These measures were collected at their D100 appointment (baseline) and 3 months post-D100 appointment (follow-up). In addition, an anonymous patient satisfaction survey was emailed to consenting patients upon completion of the programme. **Results:** Over 1 year, 78 patients were assessed at baseline (68% male; mean age 58 years (range 42-77)). 13/78 (17%) had previous surgery and 27/78 (35%) had worn a spinal brace for MM-related bone disease. 38 patients completed a follow-up assessment within the funded time frame of the project and were included in the analysis. There was a significant and clinically meaningful increase in functional capacity. Mean STS-1min score increased by 13 repetitions (Baseline: 23 reps, Follow-up: 36 reps; p<.001). Significant improvements were found in PA levels (Median mod-vig PA Baseline: 0 mins per week [IQR 0–0] Follow-up: 180 mins per week [IQR 50–270] p<.001). Pain significantly reduced from 4/10 to 1/10 (p<.0 01). From baseline to follow-up, 18 (75%) of patients had an improved QoL status, 3 (13%) had a mixed change and 3 (13%) had no change. QoL domains related to mobility and pain showed the largest improvements. The patient satisfaction questionnaire was returned by 31/38 (81%) patients, 91% strongly agreed and 9% agreed that they felt more confident to self-manage their functional concerns after their physiotherapy consultation and it had been a valuable part of their recovery. There were no adverse events. **Conclusions:** This service evaluation demonstrates the benefit of a physiotherapist assessment and individually tailored rehabilitation input as part of the ASCT pathway in MM. Results show that rehabilitation post-transplant is safe, improves patients functional capacity, PA levels, pain and QoL with high levels of patient satisfaction.

NSO-06

'Just one thing': patient, nurse and haematologist priorities for myeloma services

Monica Morris[1], Suzanne Renwick[1], Jessica Turner[1]

[1]Myeloma UK

Introduction: Myeloma services that are responsive to individual need are vital to supporting a positive patient experience. The Myeloma UK Clinical Service Excellence Programme (CSEP) supports hospitals to deliver optimum care to myeloma patients through a process of assessment and accreditation. During CSEP, patient feedback is gathered using a survey that includes the question 'If you could change one thing about your myeloma treatment and care, what would it be?' An earlier analysis of responses to this question prompted the authors to pose a similar question to healthcare professionals (HCPs). The aim was to compare responses to further inform how service development could improve patient experience. **Methods:** Using email and Microsoft Teams calls, feedback was collated from specialist nurses and haematologists in reply to the question 'If you could change one thing about your myeloma service, what would it be?' Further responses from patients collected since the first analysis were added to the existing patient data and re-analysed. **Results:** Between 2015 and 2023, over 1000 responses were gathered from patients, nurses and haematologists from more than 60 hospitals. Patient responses including negative feedback or suggested changes were included in the analysis, as were all HCP responses. As a result, over 500 responses were analysed and thematically organised. HCP responses were grouped into seven themes: clinic waiting time, community treatment delivery, dedicated hospital space, holistic care, research and treatment, staffing, and other resources integral to the service. Patient responses were grouped into eight themes: clinic and pharmacy waiting time, communication, continuity of care, coordination of care, holistic care, hospital facilities, travel, and access to treatment. Themes from patients and HCPs on issues of hospital space and facilities, waiting times, staffing, resources, and travel for treatment and care, intersect to highlight systemic logistical problems within UK health services. Themes of holistic care, community delivery, communication and continuity of care suggest the need for services to be more patient-centred for this often elderly, frail, patient cohort. For HCPs, having adequate staffing (particularly clinical nurse specialists) was the key concern. Pressure on nurse time reflects recent advances in myeloma treatment and survival which has translated into larger caseloads and more patients being on treatment needing review. Consequently, patients are impacted by longer waits and HCPs struggle to manage patients' individual needs. **Conclusions:** Broadening this analysis to include HCPs provides increased insight into which service changes are needed to improve patient experience. By combining the voice of both patients and the staff caring for them, a stronger case for change can be made.

NSO-07

Management considerations for dermatologic toxicities associated with talquetamab, a GPRC5D×CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma

Kiah Purcell[1], Donna Catamero[2], Victoria Dai[1], Julia Feuer[1], Leora Giacoia[1], Yan Leon[1], Alaina Lurie[1], Emily Mitchell[1], Chloe Ray[1], Annel Urena[1]

[1]Mount Sinai School of Medicine, New York, NY, USA; [2]Mount Sinai Health System, New York, NY, USA

(MM) patients due to its efficacy at increasing progression-free survival. However, it is also associated with high symptom burden and reduced quality of life (QoL) which are greatest in the first-month post-ASCT. Whilst most symptoms improve by the third month, pain and reduced QoL remain prevalent for up to one year. Indicating a need for supportive care to aid recovery. Patients who complete exercise programs pre and post-ASCT report a greater trajectory of recovery. Therefore, we evaluated the implementation of specialist physiotherapy provision introduced at 100 days (D100) post-transplant aimed to optimize patient recovery through exercise. **Methods:** At University College London Hospital we conducted a service improvement project within the MM ASCT pathway. Patients seen within the D100 clinic between November 2021–December 2022 were assessed by a specialist MM physiotherapist and prescribed tailored exercises. Outcomes included a measure of functional capacity (1-minute timed sit-to-stand test (STS-1min)), self-reported (PA) (GODIN), VAS for pain (0=no pain to 10=worst pain) and QoL (EQ5D-5L). These measures were collected at their D100 appointment (baseline) and 3 months post-D100 appointment (follow-up). In addition, an anonymous patient satisfaction survey was emailed to consenting patients upon completion of the programme. **Results:** Over 1 year, 78 patients were assessed at baseline (68% male; mean age 58 years (range 42-77)). 13/78 (17%) had previous surgery and 27/78 (35%) had worn a spinal brace for MM-related bone disease. 38 patients completed a follow-up assessment within the funded time frame of the project and were included in the analysis. There was a significant and clinically meaningful increase in functional capacity. Mean STS-1min score increased by 13 repetitions (Baseline: 23 reps, Follow-up: 36 reps; p<.001). Significant improvements were found in PA levels (Median mod-vig PA Baseline: 0 mins per week [IQR 0–0] Follow-up: 180 mins per week [IQR 50–270] p<.001). Pain significantly reduced from 4/10 to 1/10 (p<.0 01). From baseline to follow-up, 18 (75%) of patients had an improved QoL status, 3 (13%) had a mixed change and 3 (13%) had no change. QoL domains related to mobility and pain showed the largest improvements. The patient satisfaction questionnaire was returned by 31/38 (81%) patients, 91% strongly agreed and 9% agreed that they felt more confident to self-manage their functional concerns after their physiotherapy consultation and it had been a valuable part of their recovery. There were no adverse events. **Conclusions:** This service evaluation demonstrates the benefit of a physiotherapist assessment and individually tailored rehabilitation input as part of the ASCT pathway in MM. Results show that rehabilitation post-transplant is safe, improves patients functional capacity, PA levels, pain and QoL with high levels of patient satisfaction.

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NSO-07

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NSO-07

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[1]Mount Sinai School of Medicine, New York, NY, USA; [2]Mount Sinai Health System, New York, NY, USA

Introduction: Talquetamab is a T-cell redirecting bispecific antibody that targets a novel antigen, GPRC5D, on myeloma cells. Data from the MonumenTAL-1 study in patients with relapsed/refractory multiple myeloma (RRMM) showed overall response rates of >71% and durable responses at talquetamab weekly (QW) and every other week (Q2W) dosing. Talquetamab is associated with a distinct group of GPRC5D-related adverse events (AEs), including dermatologic (skin and nail) AEs. Here we describe the presentation and management of dermatologic AEs in patients from MonumenTAL-1 treated at a single center. **Methods:** MonumenTAL-1 (NCT03399799/NCT04634552) is an open-label, single-arm, phase 1/2 study of patients who had progressed on or could not tolerate established MM therapies (phase 1) or were exposed to ≥3 prior lines of therapy (phase 2; including a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody). Patients included in the current analysis received subcutaneous talquetamab at the recommended phase 2 doses (RP2Ds) of 0.4 mg/kg QW or 0.8 mg/kg Q2W. AEs were graded according to CTCAE v4.03. **Results:** Talquetamab has demonstrated 12-month PFS rates of 35% and 54% and OS rates of 76% and 77% with QW and Q2W dosing in the MonumenTAL-1 study. Dermatologic AEs in MonumenTAL-1 included skin (eg, dry skin, exfoliation), rash, and nail (eg, thinning, peeling) AEs. Among patients (N=24) receiving the talquetamab RP2Ds in our center, 87.5% had skin (grade 3, 4.2%), 45.8% had rash (grade 3, 33.3%), and 58.3% had nail (grade 3, 0%) AEs. Median time to onset of dermatologic AEs was ~4.6–15 weeks following first talquetamab dose. Most dermatologic AEs resolved, except nail AEs: only 28.6% of events resolved, with a median time to resolution of ~16 weeks; this is potentially due to timing of nail regrowth. Management of dermatologic AEs included a heavy moisturizer for general dryness; ammonium lactate 12% lotion twice daily (BID) for hand and foot peeling; loratadine 10 mg oral tablet daily for 3–5 days post dose and triamcinolone 0.1% cream BID for pruritus, injection-site reaction, and rash; and nail hardeners, topical vitamin E oil, and triamcinolone 0.025% ointment for nail thinning and peeling. Methylprednisolone taper and betamethasone 0.05% cream BID were considered for grade 3 rash. Other grade 3 dermatologic AE mitigation approaches included dose holds. In general, patients were encouraged to take short lukewarm showers, use a heavy lotion or moisturizer throughout the day on skin and cuticles, and keep nails short and clean. Patients considered the AEs generally tolerable, and no patient from our center discontinued the study due to dermatologic AEs. **Conclusions:** Talquetamab is an effective therapy for patients with RRMM. Skin and nail AEs are common but are primarily low grade with no discontinuations. Appropriate management, education, and supportive care ensure that patients can stay on treatment to receive optimal benefit from talquetamab.

NURSING SYMPOSIUM POSTER PRESENTATIONS

NSP-01

Update to nursing care pathway for infection risk and prophylaxis in RRMM receiving novel therapy

Carrie Bellerive[1], Matthew Whooley[1], Sarah Stice-Goff[1], Steven Bleak[1], Kristi Bailey[1], Briana Peterson[1], Zachary Francom[1], Ishwarya Balasubramanian[1], Charlotte Wagner[2], Baylee Bryan[2], Kelley Julian[2], Lindsay Maxwell[3], Meghan Vigil[3], Samuel Shewan[3], Mary Steinbach[3], Hannah Imlay[4], Douglas Sborov[1]

[1]Huntsman Cancer Institute at the University of Utah; [2]Department of Pharmacy, University of Utah Hospitals and Clinics, Huntsman Cancer Institute; [3]Division of Hematology, Department of Internal Medicine, University of Utah Huntsman Cancer Institute; [4]Division of Infectious Diseases, Department of Internal Medicine, University of Utah Huntsman Cancer Institute

Introduction: New BCMA-targeted drugs have been FDA approved for relapsed and refractory multiple myeloma (RRMM). These new treatments provide excellent responses but also have side effects of prolonged neutropenia and increased risk for infection. Pneumocystis jirovecii pneumonia (PJP) fungal infection can cause life-threatening pneumonia in MM. Similarly, cytomegalovirus (CMV) is now more commonly seen in RRMM. In 2022, nurses at the Huntsman Cancer Institute (HCI) developed a nursing care pathway for monitoring PJP risk in patients receiving stem cell transplants, Chimeric antigen receptor T-cell (CarT) therapy, and bispecific antibodies (BsABs). Herein we present our experience after updating the nursing care pathway to reflect new recommendations and real-world exposures. **Methods:** A rolling report of MM patients post-autologous transplant, post-CarT, or receiving BsABs was updated to include patient information for monitoring (including CD4 count, CMV NAAT, prophylaxis, and next lab appointment). Based on the report, nurses either (1) begin monitoring CD4 and/or CMV, (2) discontinue monitoring CD4 and/or CMV, (3) begin PJP prophylaxis (CD4 200 for two consecutive months). Monitoring BsAbs patients for CMV via NAAT titers was added to the report and algorithm in October 2022. If CMV NAAT is detected but not quantifiable, weekly monitoring is performed until undetected. If CMV titer is quantifiable at >100 IU/mL, appropriate induction treatment is initiated with weekly monitoring. Therapy is continued until CMV NAAT is undetected or until 14 days. If a patient on CMV treatment has no clinical symptoms, therapy is discontinued once CMV NAAT is undetectable. Monthly monitoring of these patients continues. If CMV turns positive and the patient is symptomatic, an ID consult is initiated to streamline intervention(s). **Results:** After closer monitoring of high-risk patients for a year, HCI has had no new PJP infections. Of the patients meeting the need for CMV viral load monitoring per algorithm, twelve are on bispecific therapy and two are post-CarT and received >1 dose of tocilizumab or dexamethasone (≥ 10 mg for 3 days) with baseline CMV IgG seropositivity. Only 14% (1 out of 14) required induction

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Carrie Bellerive[1], Matthew Whooley[1], Sarah Stice-Goff[1], Steven Bleak[1], Kristi Bailey[1], Briana Peterson[1], Zachary Francom[1], Ishwarya Balasubramanian[1], Charlotte Wagner[2], Baylee Bryan[2], Kelley Julian[2], Lindsay Maxwell[3], Meghan Vigil[3], Samuel Shewan[3], Mary Steinbach[3], Hannah Imlay[4], Douglas Sborov[1]

[1]Huntsman Cancer Institute at the University of Utah; [2]Department of Pharmacy, University of Utah Hospitals and Clinics, Huntsman Cancer Institute; [3]Division of Hematology, Department of Internal Medicine, University of Utah Huntsman Cancer Institute; [4]Division of Infectious Diseases, Department of Internal Medicine, University of Utah Huntsman Cancer Institute

Introduction: New BCMA-targeted drugs have been FDA approved for relapsed and refractory multiple myeloma (RRMM). These new treatments provide excellent responses but also have side effects of prolonged neutropenia and increased risk for infection. Pneumocystis jirovecii pneumonia (PJP) fungal infection can cause life-threatening pneumonia in MM. Similarly, cytomegalovirus (CMV) is now more commonly seen in RRMM. In 2022, nurses at the Huntsman Cancer Institute (HCI) developed a nursing care pathway for monitoring PJP risk in patients receiving stem cell transplants, Chimeric antigen receptor T-cell (CarT) therapy, and bispecific antibodies (BsABs). Herein we present our experience after updating the nursing care pathway to reflect new recommendations and real-world exposures. **Methods:** A rolling report of MM patients post-autologous transplant, post-CarT, or receiving BsABs was updated to include patient information for monitoring (including CD4 count, CMV NAAT, prophylaxis, and next lab appointment). Based on the report, nurses either (1) begin monitoring CD4 and/or CMV, (2) discontinue monitoring CD4 and/or CMV, (3) begin PJP prophylaxis (CD4 200 for two consecutive months). Monitoring BsAbs patients for CMV via NAAT titers was added to the report and algorithm in October 2022. If CMV NAAT is detected but not quantifiable, weekly monitoring is performed until undetected. If CMV titer is quantifiable at >100 IU/mL, appropriate induction treatment is initiated with weekly monitoring. Therapy is continued until CMV NAAT is undetected or until 14 days. If a patient on CMV treatment has no clinical symptoms, therapy is discontinued once CMV NAAT is undetectable. Monthly monitoring of these patients continues. If CMV turns positive and the patient is symptomatic, an ID consult is initiated to streamline intervention(s). **Results:** After closer monitoring of high-risk patients for a year, HCI has had no new PJP infections. Of the patients meeting the need for CMV viral load monitoring per algorithm, twelve are on bispecific therapy and two are post-CarT and received >1 dose of tocilizumab or dexamethasone (≥ 10 mg for 3 days) with baseline CMV IgG seropositivity. Only 14% (1 out of 14) required induction

treatment, and remains on maintenance therapy for ongoing CMV viremia. This asymptomatic patient was on a BsAB clinical trial; the other patients being surveilled did not cross the treatment threshold. **Conclusions:** Given the evolution of safety data and monitoring for novel treatments in RRMM, we updated our algorithm. As a result, nursing practice has elevated to quickly identifying patients at highest risk for developing PJP and CMV viremia and intervening appropriately. Prolonged treatment holds have been reduced due to this algorithm as evidenced by no new PJP infections and a small proportion of patients with mild CMV. In the future, we hope to refine best practices for CD4 and CMV titer monitoring and frequency in RRMM.

NSP-02

Clinical trial enrollment at a national cancer institute cancer center in the US Mountain West

Carrie Bellerive[1], Kelley Julian[1], Ryan Lombardi[1], Catherine Cromar[1], Mary Steinbach[1], Douglas Sborov[1]

[1]University of Utah, Huntsman Cancer Institute

Introduction: Despite advances in the treatment of multiple myeloma (MM) through clinical trials, equitable trial enrollment which accurately reflects the landscape of the disease remains challenging. Research in MM has uncovered disparities with regard to patient age, race/ethnicity, rural-urban residence, socioeconomic status, insurance type, and underrepresentation in clinical trials. Huntsman Cancer Institute (HCI) located in Salt Lake City, Utah, is the only NCI-Designated Cancer Center in the Mountain West and a critical access point for clinical trials. Our catchment area includes six states and 525,000 square miles. Travel to large centers can be associated with financial toxicity and social stress which adversely affect health-related quality of life in MM. Beyond Salt Lake City boundaries is mostly considered rural for health access; additionally, patients living in these areas are at risk for being uninsured or underinsured. Herein we describe our enrollment for clinical trials as it pertains to rurality with consideration of insurance status. **Methods:** A list of enrolled subjects in MM or AL-amyloid clinical trials from January 2018 to April 2023 was compiled to evaluate geographical and rural enrollment patterns among these niche patient populations at HCI. A randomized identifier was created and patient information appended, including: zip code and residence distance to HCI, age, sex, and insurance status. Zip codes were used to determine county and deemed rural versus not rural according to the Federal Office of Rural Health Policy (FORHP). Descriptive statistics were utilized. **Results:** A total of 97 patients were enrolled in clinical trials; a majority being males (57%) and only 3% of enrollees having AL-amyloidosis. Medicare or Medicaid comprised 43%, private insurance 53%, and 4% were uninsured. Based on county of residence, 18% were rural while 82% were not. A majority of rural patients (65%) had Medicare and the remainder had private insurance. Amongst the 97 patients enrolled, the majority (52%) lived within 20 miles of the cancer center, and 73% of patients lived within 40 miles. Twelve percent of patients lived within 41-80 miles of the cancer center, whereas only 15% of patients enrolled on trials lived over 80 miles away. **Conclusions:** Our study shows that most patients with MM or AL-amyloid enrolled on trials at our NCI-designated cancer center in the Mountain West live within an 80-mile radius. With an understanding of historical patient demographics, we aim to improve access to our clinical trials in the next five years. This will be accomplished by increasing patient support group topic frequency about open clinical trials, expanding our trial portfolio, testimonies from existing trial patients within existing support groups, and increased utilization of our existing Rural Patient Navigator in trial screening processes. Future directions include research to better understand the reasons rural patients decline participation in clinical trials.

NSP-03

Practical management of patients with relapsed/refractory multiple myeloma receiving talquetamab, a GPRC5D×CD3 bispecific antibody: experience in monumenTAL-1

Donna Catamero[1], Kiah Purcell[2], Chloe Ray[2], Leora Giacoia[2], Sheryl Leahey[3], Patricia Born[4], Sandy Kruyswijk[5]

[1]Mount Sinai Health System, New York, NY, USA; [2]Mount Sinai School of Medicine, New York, NY, USA; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]University Hospital Würzburg, Würzburg, Germany; [5]Amsterdam University Medical Center, Amsterdam, The Netherlands

Introduction: Talquetamab (tal) is a T-cell redirecting bispecific antibody targeting a novel antigen, G protein–coupled receptor family C group 5 member D (GPRC5D). Tal has shown overall response rates of >71% in patients with relapsed/refractory multiple myeloma (RRMM) in the MonumenTAL-1 study. Adverse events (AEs) reported with tal include those associated with T-cell redirection therapies as well as GPRC5D-related AEs. Here we provide guidance for administering tal and strategies for monitoring and managing AEs based on our experience in the MonumenTAL-1 study. **Methods:** MonumenTAL-1 (NCT03399799/NCT04634552) is an open-label, single-arm, phase 1/2 study of patients with RRMM evaluating the recommended phase 2 doses of subcutaneous tal at 0.4 mg/kg weekly and 0.8 mg/kg every other week. **Results:** Administration of tal includes initial "step-up" doses prior to the first full dose to mitigate risk of high-grade cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Similar to other bispecifics, these AEs appear early with tal and are generally mild to moderate. Patients should be premedicated appropriately and monitored closely for CRS/ICANS during step-up dosing and the first full dose. Infections are a common complication of MM; patients should be screened for infections before starting tal, receive prophylaxis as needed, and be monitored throughout treatment for infections. GPRC5D-related AEs, including dermatologic and oral toxicities, also tend to appear early, after the first few doses of tal. Dermatologic AEs (incidence ~30–73%), including rash and skin peeling, are relatively benign, not painful, self-limiting, and manageable with emollients; nail AEs (incidence ~54–63%), including nail thinning and loss, are mostly aesthetic but take time to resolve. Oral AEs (incidence ~71–77%),

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NSP-02

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NSP-03

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including dysphagia (difficulty swallowing), dry mouth, and taste changes, tend to have longer duration and can affect patients' quality of life; patients generally experience taste alteration with dry mouth that may lead to difficulty swallowing, which in turn can lead to weight loss. Supportive measures may be utilized (eg, NaCl mouth rinse, artificial saliva spray, diet modification) but oral AEs are most successfully managed with dose modification. A multidisciplinary team, including dermatologists, dentists, and nutritionists, can be consulted to provide additional guidance on managing GPRC5D-associated AEs. Educating patients about what to expect and ensuring they report symptoms promptly is also key to managing AEs appropriately. In general, patients respond well to treatment, and GPRC5D-associated AEs improve over time, becoming more tolerable; notable reduction in AEs is seen with dose modification. **Conclusions:** Tal demonstrates responses in >71% of patients with RRMM, with a safety profile that can be clinically managed with appropriate identification, monitoring, and treatment to ensure patients receive optimal benefit of tal.

NSP-04

Managing infections, hypogammaglobulinemia, and neutropenia during treatment with teclistamab in relapsed/refractory multiple myeloma: nurse-led experience from the MajesTEC-1 study

Donna Catamero[1], Patricia Blázquez Benito[2], Samantha Shenoy[3], Katherine Chastain[4], Arnob Banerjee[5], Keqin Qi[6], Sheri Skerget[5], Margaret Doyle[7], Sandy Kruyswijk[8]

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Introduction: Patients with relapsed/refractory multiple myeloma (RRMM) are at an increased risk of infection, which may compromise quality of life and treatment outcomes. Teclistamab is the only approved BCMA×CD3 bispecific antibody with a personalized, weight-based, and flexible dosing schedule for the treatment of triple-class exposed RRMM. In the MajesTEC-1 study, prophylaxis and management of infections with teclistamab were per institutional guidelines. We share our experience in managing patients treated with teclistamab to support nurses on the front line of patient care. **Methods:** Patients in MajesTEC-1 were screened for hepatitis B and C, and must have had no evidence of serious bacterial, viral, or fungal infections to initiate treatment with teclistamab, which was administered subcutaneously at a dose of 1.5 mg/kg once weekly after the approved step-up dosing schedule. At our institutions, all patients treated with teclistamab were up to date with vaccinations (eg, COVID-19, influenza, and pneumococcal) and received acyclovir or valacyclovir prophylaxis; additional antimicrobials (eg, sulfamethoxazole/trimethoprim for Pneumocystis jirovecii pneumonia prophylaxis) were given per individual center guidelines. We regularly assessed all patients for infection prior to each weekly teclistamab dose and performed complete blood counts, cytomegalovirus testing, and COVID antibody testing as needed. Patients were also asked to self-report any signs or symptoms of infection (eg, fever, chills, cough) to the hospital team. Infections were managed with antimicrobials and teclistamab dose delays as appropriate. Immunoglobulin G (IgG) levels were monitored every 4 weeks at our centers with intravenous IgG (IVIG) given every 3–6 weeks if levels fell below 400 mg/dL. Treatment-emergent neutropenia was managed with granulocyte colony-stimulating factor (G-CSF), although this was avoided during periods of high risk for cytokine release syndrome, eg, teclistamab step-up dosing. **Results:** In MajesTEC-1, infections occurred in 80.0% of patients, with grade 3/4 in 55.2% (most commonly COVID-19, respiratory infections, Pneumocystis jirovecii pneumonia, and viral infections) and deaths in 12.7%. Approximately 70% of patients had IgG < 400 mg/dL (overall, 46.1% received at least one dose of IVIG); 65.5% of patients had grade 3/4 neutropenia and 54.5% used G-CSF. **Conclusions:** Teclistamab should not be given in case of any active infection; therefore, partnership between nurses, physicians, and patients is essential to facilitate prompt identification, monitoring, and management of infections, including appropriate use of antimicrobial prophylaxis, IVIG, and G-CSF. In particular, we recommend that patients are educated on the importance of reporting early signs and symptoms of infections, and that nurses and care teams are prepared and trained to implement appropriate infection management strategies.

NSP-05

Managing cytokine release syndrome in relapsed/refractory multiple myeloma: experience with teclistamab in the MajesTEC-1 study

Donna Catamero[1], Patricia Blázquez Benito[2], Samantha Shenoy[3], Katherine Chastain[4], Sandy Kruyswijk[5]

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including dysphagia (difficulty swallowing), dry mouth, and taste changes, tend to have longer duration and can affect patients' quality of life; patients generally experience taste alteration with dry mouth that may lead to difficulty swallowing, which in turn can lead to weight loss. Supportive measures may be utilized (eg, NaCl mouth rinse, artificial saliva spray, diet modification) but oral AEs are most successfully managed with dose modification. A multidisciplinary team, including dermatologists, dentists, and nutritionists, can be consulted to provide additional guidance on managing GPRC5D-associated AEs. Educating patients about what to expect and ensuring they report symptoms promptly is also key to managing AEs appropriately. In general, patients respond well to treatment, and GPRC5D-associated AEs improve over time, becoming more tolerable; notable reduction in AEs is seen with dose modification. **Conclusions:** Tal demonstrates responses in >71% of patients with RRMM, with a safety profile that can be clinically managed with appropriate identification, monitoring, and treatment to ensure patients receive optimal benefit of tal.

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including dysphagia (difficulty swallowing), dry mouth, and taste changes, tend to have longer duration and can affect patients' quality of life; patients generally experience taste alteration with dry mouth that may lead to difficulty swallowing, which in turn can lead to weight loss. Supportive measures may be utilized (eg, NaCl mouth rinse, artificial saliva spray, diet modification) but oral AEs are most successfully managed with dose modification. A multidisciplinary team, including dermatologists, dentists, and nutritionists, can be consulted to provide additional guidance on managing GPRC5D-associated AEs. Educating patients about what to expect and ensuring they report symptoms promptly is also key to managing AEs appropriately. In general, patients respond well to treatment, and GPRC5D-associated AEs improve over time, becoming more tolerable; notable reduction in AEs is seen with dose modification. **Conclusions:** Tal demonstrates responses in >71% of patients with RRMM, with a safety profile that can be clinically managed with appropriate identification, monitoring, and treatment to ensure patients receive optimal benefit of tal.

NSP-04

Managing infections, hypogammaglobulinemia, and neutropenia during treatment with teclistamab in relapsed/refractory multiple myeloma: nurse-led experience from the MajesTEC-1 study

Donna Catamero[1], Patricia Blázquez Benito[2], Samantha Shenoy[3], Katherine Chastain[4], Arnob Banerjee[5], Keqin Qi[6], Sheri Skerget[5], Margaret Doyle[7], Sandy Kruyswijk[8]

[1]Mount Sinai Health System, New York, NY, USA; [2]University Hospital of Salamanca, Salamanca, Spain; [3]University of California, San Francisco, San Francisco, CA, USA; [4]Janssen Research & Development, Raritan, NJ, USA; [5]Janssen Research & Development, Spring House, PA, USA; [6]Janssen Research & Development, Titusville, NJ, USA; [7]Janssen Sciences Ireland, Dublin, Ireland; [8]Amsterdam University Medical Center, Amsterdam, The Netherlands

Introduction: Patients with relapsed/refractory multiple myeloma (RRMM) are at an increased risk of infection, which may compromise quality of life and treatment outcomes. Teclistamab is the only approved BCMA×CD3 bispecific antibody with a personalized, weight-based, and flexible dosing schedule for the treatment of triple-class exposed RRMM. In the MajesTEC-1 study, prophylaxis and management of infections with teclistamab were per institutional guidelines. We share our experience in managing patients treated with teclistamab to support nurses on the front line of patient care. **Methods:** Patients in MajesTEC-1 were screened for hepatitis B and C, and must have had no evidence of serious bacterial, viral, or fungal infections to initiate treatment with teclistamab, which was administered subcutaneously at a dose of 1.5 mg/kg once weekly after the approved step-up dosing schedule. At our institutions, all patients treated with teclistamab were up to date with vaccinations (eg, COVID-19, influenza, and pneumococcal) and received acyclovir or valacyclovir prophylaxis; additional antimicrobials (eg, sulfamethoxazole/trimethoprim for Pneumocystis jirovecii pneumonia prophylaxis) were given per individual center guidelines. We regularly assessed all patients for infection prior to each weekly teclistamab dose and performed complete blood counts, cytomegalovirus testing, and COVID antibody testing as needed. Patients were also asked to self-report any signs or symptoms of infection (eg, fever, chills, cough) to the hospital team. Infections were managed with antimicrobials and teclistamab dose delays as appropriate. Immunoglobulin G (IgG) levels were monitored every 4 weeks at our centers with intravenous IgG (IVIG) given every 3–6 weeks if levels fell below 400 mg/dL. Treatment-emergent neutropenia was managed with granulocyte colony-stimulating factor (G-CSF), although this was avoided during periods of high risk for cytokine release syndrome, eg, teclistamab step-up dosing. **Results:** In MajesTEC-1, infections occurred in 80.0% of patients, with grade 3/4 in 55.2% (most commonly COVID-19, respiratory infections, Pneumocystis jirovecii pneumonia, and viral infections) and deaths in 12.7%. Approximately 70% of patients had IgG < 400 mg/dL (overall, 46.1% received at least one dose of IVIG); 65.5% of patients had grade 3/4 neutropenia and 54.5% used G-CSF. **Conclusions:** Teclistamab should not be given in case of any active infection; therefore, partnership between nurses, physicians, and patients is essential to facilitate prompt identification, monitoring, and management of infections, including appropriate use of antimicrobial prophylaxis, IVIG, and G-CSF. In particular, we recommend that patients are educated on the importance of reporting early signs and symptoms of infections, and that nurses and care teams are prepared and trained to implement appropriate infection management strategies.

NSP-05

Managing cytokine release syndrome in relapsed/refractory multiple myeloma: experience with teclistamab in the MajesTEC-1 study

Donna Catamero[1], Patricia Blázquez Benito[2], Samantha Shenoy[3], Katherine Chastain[4], Sandy Kruyswijk[5]

[1]Mount Sinai Health System, New York, NY, USA; [2]University Hospital of Salamanca, Salamanca, Spain; [3]University of California, San Francisco, San Francisco, CA, USA; [4]Janssen Research & Development, Raritan, NJ, USA; [5]Amsterdam University Medical Center, Amsterdam, The Netherlands

Introduction: Cytokine release syndrome (CRS) is a systemic inflammatory response commonly associated with T-cell engagers. In the MajesTEC-1 study of teclistamab, the only approved BCMA×CD3 bispecific antibody with a personalized, weight-based, and flexible dosing schedule for the treatment of triple-class exposed relapsed/refractory multiple myeloma, CRS was effectively managed with pre-medication, step-up dosing, and prompt diagnosis and intervention (Martin et al, Cancer, 2023). As nurses are on the front line of patient care, recognizing CRS and responding with appropriate treatment are critical to mitigate risk of severe/life-threatening CRS. Here, we aim to support nurses with guidance on CRS diagnosis, monitoring, and management in patients receiving

teclistamab, based on the MajesTEC-1 experience. **Methods:** A step-up dosing schedule (0.06 and 0.3 mg/kg step-up doses before first treatment dose of 1.5 mg/kg subcutaneous teclistamab), requiring premedication with a corticosteroid, histamine-1 receptor antagonist, and antipyretic, was used to mitigate risk of high-grade CRS. Frequent vital sign observations (every 2–4 hours per institutional guidelines) by the inpatient nursing team during step-up dosing were required to monitor for CRS. CRS management was dependent on CRS severity but included tocilizumab (36.4% of patients), intravenous fluids (13.9%), low-flow oxygen (12.7%), steroids (8.5%), single vasopressor (0.6%), and other supportive measures, including antipyretics. **Results:** Overall, 72.1% of patients experienced CRS; all events were grade 1/2, except for one grade 3 event that occurred in the setting of an infection. Among patients with CRS, 96.6% experienced CRS during step-up dosing; thus, frequent monitoring during this period is critical. As common CRS symptoms (fever, hypoxia, chills, hypotension) can present with other conditions, a differential diagnosis is important to ensure that CRS is properly diagnosed and treated. CRS was monitored inpatient with vital signs checked frequently (every 2–4 hours) or continuously through wearable devices. Partnering with patients and physicians to recognize and report CRS symptoms early allowed for rapid intervention and transfer to intensive care where necessary. As infections can exacerbate CRS, patients should be examined for signs of infection, and all infections should be resolved before initiating teclistamab. In MajesTEC-1, tocilizumab could be considered for grade 1 CRS and was recommended for grade 2 events. At our institutions, tocilizumab was given for grade 1 CRS (either generally or if persistent), and no patient had recurrent CRS. **Conclusions:** Practical guidance is needed for nurses to recognize and monitor CRS and to anticipate when treatment and escalation are needed to ensure successful administration of teclistamab. Data previously presented at the 2023 Oncology Nursing Society (ONS) Annual Meeting.

NSP-06

Scrambler therapy for neuropathic pain: a systematic review of evidence in plasma cell disorders

Beth Faiman[1], Ruth Lagman[1], Susan McInnes[1], Kyle Neale[1], Chirag Patel[1], Laura Shoemaker[1], Renato Samala[1]

[1]Cleveland Clinic

Introduction: Research into the prevention and treatment of peripheral neuropathy (PN) is evident in other cancers and disease states but strategies are conspicuously absent in patients with plasma cell disorders (PCDs), such as multiple myeloma, and amyloidosis. Peripheral neuropathy occurs in PCD patients with prolonged exposure to neurotoxic therapies, such as bortezomib, and/or because of disease progression. This condition is often managed with medications (such as gabapentinoids and antidepressants) and non-pharmacologic treatments (such as transcutaneous electrical nerve stimulation and spinal cord stimulation) with varying degrees of efficacy. High-quality studies into PN treatments are desperately needed due to the major adverse impact these poorly understood complications have on the quality of life (QOL) and control of the disease. In recent years, Scrambler Therapy (ST) has emerged as an alternative non-pharmacologic intervention for treatment of neuropathic pain but emerging evidence supports its use in pain from other sources. ST is approved by the FDA as a non-invasive electro-analgesia device that aims to transform the information of pain into non-pain signals using the same pathways, ultimately resulting in remodulation of the pain system and retraining of the brain. The newest version is ST-5A with 5 channels that deliver low-intensity stimuli (max. 5 mA) generated by a completely automated treatment program. Previous studies have demonstrated ST efficacy, including in the treatment of chronic, opioid-resistant cases and chemotherapy-induced peripheral neuropathy (CIPN). Recently, our Department of Palliative and Supportive Care acquired an ST unit and began treating patients in January 2023. Thus, the aim of this systematic review was to detect gaps in the literature regarding the efficacy of ST for PCD pain and formulate recommendations for research. **Methods:** PubMed with MeSH was used to identify studies that met inclusion criteria using a pre-determined search strategy. A reference list of retrieved studies, Google Scholar, and clinicaltrials.gov database were used to verify that no relevant studies had been omitted. Data were extracted from the studies with a data extraction sheet. Qualitative analyses of the extracted data were undertaken. **Results:** Eighty-two references to ST were identified. Of these, 13 full-text papers including clinical trials were reviewed. Only one study reported findings in patients with amyloidosis, using the older MCA-5 device model, but no studies were conducted specifically in PCD using the newer ST-5A scrambler model. **Conclusions:** Peripheral neuropathy symptoms plague patients with chronic, but incurable conditions, such as PCD. This review sheds initial light on the need for further research of ST in PCD and specifically using the newest technology. Caution is needed in that due to the small sample sizes of the studies included, these findings cannot be generalized, yet provide direction for future symptom science studies.

NSP-07

A comparison of reach and effectiveness of live versus virtual case-based education for nurses

Beth Faiman[1], Donna Catamero[2], Tiffany Richards[3], Kimberly Noonan[4], Diane Moran[5], Michelle Faber[5], Joyce Divine[5]

[1]Cleveland Clinic Taussig Cancer Institute, Department of Hematology and Medical Oncology; [2]Mount Sinai Health System, New York, NY, USA; [3]University of Texas MD Anderson Cancer; [4]Dana-Farber Cancer Institute; [5]International Myeloma Foundation

Introduction: The expanding landscape of multiple myeloma (MM) treatment options, coupled with an emphasis on advocacy, highlights the need for nurses to have access to up-to-date education. To address the distinct educational needs of both in-person and e-education learners, 4 expert MM faculty developed educational content for a 1.5-hour symposium held in person at the Oncology Nursing Society Annual Congress in Los Angeles, California on April 28, 2022, and later available via a virtual, enduring format.

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NSP-07

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NSP-07

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Here we present a comparative analysis of reach and effectiveness between the 2 formats for a case-based MM treatment continuing education intervention. **Methods:** To develop content, faculty participated in 13, 1-hr planning sessions from Jan 1-Apr28 2022. Faculty conducted literature reviews to include the most updated information, adopting a case study-based learning format and integrated updated educational content. Demographics, practice information, pre-/post-education surveys, and intent to change were administered to the 477 in-person attendees, and to 10,556 virtual enduring program participants from Jul 1–Dec 31, 2022. **Results:** The live program attendees were split between academic and community practice settings while more virtual attendees practiced in the community. The average number of patients with MM seen per month was 10.2 in-person vs 4.5 virtual. The virtual program attendees were estimated to impact 21,332 patients with MM per month, compared with 3,453 patients for the in-person program. Learning gains were reported across all domains in diagnosis, disparities, relapse workup, and immunotherapies (Figure 1). Of respondents polled during the in-person program 73% (N=371) reported, "Yes" they plan to make clinical changes to improve their effectiveness. 85% (N=327) reported a 'strong' or 'very strong' commitment to making planned changes, while 85% (N=318) of those reported a change plan to "be more mindful of my influence on myeloma patients" outcomes. In the virtual program (N=4087), 72% reported "Yes, I plan to make changes to improve my effectiveness as a healthcare team member" while 78% reported a 'strong' or 'very strong' commitment to change and 60% reported they plan to "be more mindful of my influence on myeloma patients' outcomes." **Conclusions:** While most learners at the in-person meeting were from the US and divided between academic and community practice, the virtual format was utilized by a higher % of community-based learners and attendees from outside the US. Results indicate both formats effectively reached audiences with learning gains across domains. A similar % of respondents in both groups intended to make changes to their practice. Both formats showed comparable levels of knowledge acquisition and competency development, suggesting the virtual enduring format is complementary to in-person education. Results underscore the effectiveness of live continuing education and the importance of e-education to meet the evolving educational needs of nurses.

NSP-08

Co-designing a pilot patient support program (PSP) for a multiple myeloma (MM) therapy prior to listing on the pharmaceutical benefits scheme

Emma-Jane Furphy[1], Hayley Beer[1,2], Laura Jones[1], Gareth Davidson[3], Nathan O'Donnell[3], Nirmal Lorensuhewa[4], Joanne Farrell[4], Tamara Etto[4], Michele Robbins[4]

[1]Myeloma Australia; [2]Peter MacCallum Cancer Centre; [3]Atlantis Health; [4]Antengene

Introduction: Myeloma Australia (MA), a non-profit support organisation, identified poor uptake of traditional pharmaceutical company facilitated patient support programs (PSPs) when the program is designed with a single drug focus and does not follow the patient beyond progression. MA together with Antengene (AUS) Pty Ltd, a biopharmaceutical company, co-designed a PSP for patients with relapsed/refractory MM (RRMM) who were prescribed XPOVIO® (selinexor) in combination with dexamethasone (Xd). Given that XPOVIO is a novel anti-myeloma drug available in Australia, the PSP aimed to enhance patient education and support their hospital-based treating teams for achieving optimal patient outcomes. **Methods:** Review of existing PSPs was conducted, including multi-disciplinary advisory boards including haematologists, nurses and pharmacists. MA and Antengene worked together with a behavioural change organisation, Atlantis Health, to review patients' key needs at the time of XPOVIO® therapy. The program designed would support patients at key time points throughout their treatment and beyond, that would be complimentary to the care provided by their hospital-based treating team. **Results:** 14 RRMM patients (8 male and 6 female) prescribed Xd via an access program were enrolled into the X-TEND program (age range 47-85 yrs). Patients received contact from a specialist MA nurse at baseline and at defined intervals. Average call duration was 20 mins. Topics discussed included management of adverse events, general physical wellbeing, and psychosocial support. Average time on XPOVIO was 141 days and patients could remain on the program once therapy has ceased. **Conclusions:** X-TEND is a comprehensive PSP that provides one-on-one bespoke support to patients on Xd regimen. It provides education on side-effect management, ensures the patient has a better understanding of their disease and offers unlimited emotional and psychosocial supportive care. The PSP has filled gaps that the hospital system is not able to fill. MA has plans to replicate this model with other myeloma therapies.

NSP-09

Clinical validation of the steroid symptom questionnaire multiple myeloma (SSQ-MM) in a multi-centre study

Tracy King[1,2], Jacqueline Jagger[3], Claudia Rutherford[2], Louise Acret[2], Margaret-Ann Tait[2], Julija Sipavicius[4], Georgia McCaughan[5], Susan Stapleton[5], Kate White[2,6]

[1]Royal Prince Alfred Hospital; [2]The University of Sydney; [3]Central Coast Local Health District; [4]Royal North Shore Hospital; [5]St Vincent's Hospital, Sydney; [6]Sydney Local Health District

Introduction: Steroids remain a mainstay in multiple myeloma (MM) treatment, with significant side effects (SE). As no tool existed to monitor steroid SE in this population, we developed the SSQ-MM to inform clinical care. Pilot testing of the SSQ-MM demonstrated high levels of feasibility, acceptability, repeatability, and internal consistency. This paper presents preliminary findings of a multi-site study to test the clinical validity and reliability of the final version SSQ-MM. **Methods:** Clinical validity of the SSQ-MM was tested in a prospective, multi-centre, cross sectional study. MM patients attending participating haematology departments and taking steroids as part of MM treatment were invited to participate. The SSQ-MM, EORTC quality of life and MM Patient Reported Outcome Measures (PROM) (QLQ-C30 & MY20) were

Here we present a comparative analysis of reach and effectiveness between the 2 formats for a case-based MM treatment continuing education intervention. **Methods:** To develop content, faculty participated in 13, 1-hr planning sessions from Jan 1-Apr28 2022. Faculty conducted literature reviews to include the most updated information, adopting a case study-based learning format and integrated updated educational content. Demographics, practice information, pre-/post-education surveys, and intent to change were administered to the 477 in-person attendees, and to 10,556 virtual enduring program participants from Jul 1–Dec 31, 2022. **Results:** The live program attendees were split between academic and community practice settings while more virtual attendees practiced in the community. The average number of patients with MM seen per month was 10.2 in-person vs 4.5 virtual. The virtual program attendees were estimated to impact 21,332 patients with MM per month, compared with 3,453 patients for the in-person program. Learning gains were reported across all domains in diagnosis, disparities, relapse workup, and immunotherapies (Figure 1). Of respondents polled during the in-person program 73% (N=371) reported, "Yes" they plan to make clinical changes to improve their effectiveness. 85% (N=327) reported a 'strong' or 'very strong' commitment to making planned changes, while 85% (N=318) of those reported a change plan to "be more mindful of my influence on myeloma patients" outcomes. In the virtual program (N=4087), 72% reported "Yes, I plan to make changes to improve my effectiveness as a healthcare team member" while 78% reported a 'strong' or 'very strong' commitment to change and 60% reported they plan to "be more mindful of my influence on myeloma patients' outcomes." **Conclusions:** While most learners at the in-person meeting were from the US and divided between academic and community practice, the virtual format was utilized by a higher % of community-based learners and attendees from outside the US. Results indicate both formats effectively reached audiences with learning gains across domains. A similar % of respondents in both groups intended to make changes to their practice. Both formats showed comparable levels of knowledge acquisition and competency development, suggesting the virtual enduring format is complementary to in-person education. Results underscore the effectiveness of live continuing education and the importance of e-education to meet the evolving educational needs of nurses.

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Introduction: Myeloma Australia (MA), a non-profit support organisation, identified poor uptake of traditional pharmaceutical company facilitated patient support programs (PSPs) when the program is designed with a single drug focus and does not follow the patient beyond progression. MA together with Antengene (AUS) Pty Ltd, a biopharmaceutical company, co-designed a PSP for patients with relapsed/refractory MM (RRMM) who were prescribed XPOVIO® (selinexor) in combination with dexamethasone (Xd). Given that XPOVIO is a novel anti-myeloma drug available in Australia, the PSP aimed to enhance patient education and support their hospital-based treating teams for achieving optimal patient outcomes. **Methods:** Review of existing PSPs was conducted, including multi-disciplinary advisory boards including haematologists, nurses and pharmacists. MA and Antengene worked together with a behavioural change organisation, Atlantis Health, to review patients' key needs at the time of XPOVIO® therapy. The program designed would support patients at key time points throughout their treatment and beyond, that would be complimentary to the care provided by their hospital-based treating team. **Results:** 14 RRMM patients (8 male and 6 female) prescribed Xd via an access program were enrolled into the X-TEND program (age range 47-85 yrs). Patients received contact from a specialist MA nurse at baseline and at defined intervals. Average call duration was 20 mins. Topics discussed included management of adverse events, general physical wellbeing, and psychosocial support. Average time on XPOVIO was 141 days and patients could remain on the program once therapy has ceased. **Conclusions:** X-TEND is a comprehensive PSP that provides one-on-one bespoke support to patients on Xd regimen. It provides education on side-effect management, ensures the patient has a better understanding of their disease and offers unlimited emotional and psychosocial supportive care. The PSP has filled gaps that the hospital system is not able to fill. MA has plans to replicate this model with other myeloma therapies.

NSP-09

Clinical validation of the steroid symptom questionnaire multiple myeloma (SSQ-MM) in a multi-centre study

Tracy King[1,2], Jacqueline Jagger[3], Claudia Rutherford[2], Louise Acret[2], Margaret-Ann Tait[2], Julija Sipavicius[4], Georgia McCaughan[5], Susan Stapleton[5], Kate White[2,6]

[1]Royal Prince Alfred Hospital; [2]The University of Sydney; [3]Central Coast Local Health District; [4]Royal North Shore Hospital; [5]St Vincent's Hospital, Sydney; [6]Sydney Local Health District

Introduction: Steroids remain a mainstay in multiple myeloma (MM) treatment, with significant side effects (SE). As no tool existed to monitor steroid SE in this population, we developed the SSQ-MM to inform clinical care. Pilot testing of the SSQ-MM demonstrated high levels of feasibility, acceptability, repeatability, and internal consistency. This paper presents preliminary findings of a multi-site study to test the clinical validity and reliability of the final version SSQ-MM. **Methods:** Clinical validity of the SSQ-MM was tested in a prospective, multi-centre, cross sectional study. MM patients attending participating haematology departments and taking steroids as part of MM treatment were invited to participate. The SSQ-MM, EORTC quality of life and MM Patient Reported Outcome Measures (PROM) (QLQ-C30 & MY20) were

Here we present a comparative analysis of reach and effectiveness between the 2 formats for a case-based MM treatment continuing education intervention. **Methods:** To develop content, faculty participated in 13, 1-hr planning sessions from Jan 1-Apr28 2022. Faculty conducted literature reviews to include the most updated information, adopting a case study-based learning format and integrated updated educational content. Demographics, practice information, pre-/post-education surveys, and intent to change were administered to the 477 in-person attendees, and to 10,556 virtual enduring program participants from Jul 1–Dec 31, 2022. **Results:** The live program attendees were split between academic and community practice settings while more virtual attendees practiced in the community. The average number of patients with MM seen per month was 10.2 in-person vs 4.5 virtual. The virtual program attendees were estimated to impact 21,332 patients with MM per month, compared with 3,453 patients for the in-person program. Learning gains were reported across all domains in diagnosis, disparities, relapse workup, and immunotherapies (Figure 1). Of respondents polled during the in-person program 73% (N=371) reported, "Yes" they plan to make clinical changes to improve their effectiveness. 85% (N=327) reported a 'strong' or 'very strong' commitment to making planned changes, while 85% (N=318) of those reported a change plan to "be more mindful of my influence on myeloma patients" outcomes. In the virtual program (N=4087), 72% reported "Yes, I plan to make changes to improve my effectiveness as a healthcare team member" while 78% reported a 'strong' or 'very strong' commitment to change and 60% reported they plan to "be more mindful of my influence on myeloma patients' outcomes." **Conclusions:** While most learners at the in-person meeting were from the US and divided between academic and community practice, the virtual format was utilized by a higher % of community-based learners and attendees from outside the US. Results indicate both formats effectively reached audiences with learning gains across domains. A similar % of respondents in both groups intended to make changes to their practice. Both formats showed comparable levels of knowledge acquisition and competency development, suggesting the virtual enduring format is complementary to in-person education. Results underscore the effectiveness of live continuing education and the importance of e-education to meet the evolving educational needs of nurses.

NSP-08

Co-designing a pilot patient support program (PSP) for a multiple myeloma (MM) therapy prior to listing on the pharmaceutical benefits scheme

Emma-Jane Furphy[1], Hayley Beer[1,2], Laura Jones[1], Gareth Davidson[3], Nathan O'Donnell[3], Nirmal Lorensuhewa[4], Joanne Farrell[4], Tamara Etto[4], Michele Robbins[4]

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administered together, with the SSQ-MM repeated 1-week later. Internal consistency reliability was tested with Cronbach's alpha >0.8 for individual patient decision-making. Test-retest using intraclass correlation coefficient >0.7 to test scale stability reliability. An estimated 200 patients are required to achieve statistical requirements. Clinical and demographic characteristics were collected. **Results:** To date, 109/200 patients have been recruited across four hospitals in Sydney, Australia. Participants were 45-86yrs, 57% male, with average 4yrs (range, 1mth to 22yrs) since diagnosis. More than half (65/109; 59.6%) completed the PROMs electronically. Average dexamethasone dose was 28mg weekly (range, 4 to 80), or 124mg per cycle (range, 12 to 180). The most common regimens were Lenalidomide & Bortezomib (29/109, 26.6%), Lenalidomide (24/109, 22%), Daratumumab & Bortezomib (15/109, 13.8%), or Carfilzomib (15/109, 13.8%) based. Cronbach's alpha at time points 1 (0.83) and 2 (0.84) showed internal consistency, and test-retest indicated the scale was stable (ICC: 0.844, 95%CI: 0.779 to 0.892; p< 0.001). The most frequently reported symptoms were disturbed sleep 100/109 (91.7%), loss of energy/fatigue 88/109 (80.7%), and trouble concentrating 87/109 (79.8%). Patients typically experienced 10 symptoms concurrently (range, 1 to 19), with 4 symptoms rated as severe (range, 0 to 12). Most frequently reported severe symptoms included disturbed sleep 73/109 (67 %), loss of energy/fatigue 55/109 (50.5%), and fragile skin/easy bruising 50/109 (45.9%), with disturbed sleep rated as most bothersome 53/109 (48.6%). **Conclusions:** The SSQ-MM currently demonstrates high levels of feasibility, acceptability, and reliability and is suitable for clinical use to manage steroid toxicity and improve treatment outcomes for MM patients. The study continues to evaluate convergent and discriminant validity by exploring relationships between similar and dissimilar constructs within EORTC QLQ-C30 and QLQ-MY20, enabling the SSQ-MM to be used in future clinical trials of steroid treatments for MM. A study characterising sleep disturbance in this patient group is underway.

NSP-10

Addressing the complex care needs of the individual with multiple myeloma (MM) and their family: contribution of advanced practice myeloma nurses

Kate White[1,2], Tracy King[1]

[1]Royal Prince Alfred Hospital, The University of Sydney; [2]Sydney Local Health District

Introduction: Australia has the highest incidence of multiple myeloma (MM) internationally, with a projected increase of 42% by the year 2040. This projected increase combined with changes to approaches to treatment, management of associated toxicities, in a predominantly older patient cohort has highlighted a need to examine new approaches to the delivery of care for this incurable disease. To inform the development of new models of care delivery, a MM Specialist Group commissioned the development of a White Paper. **Methods:** A systematic review of advance nurse practice roles in cancer and haematology was undertaken. Indepth interviews with haematology health care professionals (HCP) explored their perspective of gaps in current delivery of care models, potential approaches to address these, and current challenges in delivery clinical MM care. Fifteen haematology medical and nursing specialists participated in the telephone interviews. These were thematically analysed. **Results:** Systematic review of studies of advanced practice nurse (APN) roles consistently report positive findings. Studies focused on three areas: comparison of medical versus nurse delivery of care (replacing component of a medical role); development of new nursing role to improve patient outcomes; and nurse led models of care. While the quality of the research was variable, studies consistently report positive findings in support of APN roles benefiting patient outcomes and improved service delivery. Improvements were reported in patient symptom management, emotional wellbeing, being informed, earlier referral to palliative care, increased communication with primary care. The review highlighted the need to establish consistent nomenclature and scope of nursing practice in line with APN roles. Interviews with stakeholders highlighted the perception addressing the increasingly complex nature of MM patients, treatment optimization needed to be a priority, and that currents service delivery approaches were not designed or resourced to meet the increasingly complexity associated with the care of those impacted by MM. HCP identified the heterogeneous and unpredictable nature of the disease establishing MM as a complex disease to treat with transition to lifelong active treatments, a compounding toxicity profile, and comorbidities associated with an older population. **Conclusions:** Drawing on these findings the patient centred Model for Complex Myeloma Care incorporates components to optimize care; MM supportive care, tailored education, advocacy, coaching, access, assessment, and monitoring been developed. The MM White Paper recommends establishment of MM specific APN roles to provide tailored specialist care and need for service planning to address the growing incidence in MM. Further exploration of older MM specific needs as recommended, and this work is currently underway.

NSP-11

Haematology society of Australia & New Zealand myeloma specialists practice network (MSPN) Consensus recommendations on supportive care for patients with multiple myeloma receiving selinexor

Tracy King[1,2], Jacqueline Jagger[3], Carmel Woodrow[4], Jessica Demajo[5], Hayley Beer[5,6], Daniela Klarica[7], Alicia Snowden[8], Kate White[2,9], Donna Catamero[10], Hang Quach[11]

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Introduction: Selinexor is a first in class, oral, selective inhibitor of nuclear export (SINE) that is approved for the treatment of relapsed refractory multiple myeloma (RRMM). Selinexor has a

administered together, with the SSQ-MM repeated 1-week later. Internal consistency reliability was tested with Cronbach's alpha >0.8 for individual patient decision-making. Test-retest using intraclass correlation coefficient >0.7 to test scale stability reliability. An estimated 200 patients are required to achieve statistical requirements. Clinical and demographic characteristics were collected. **Results:** To date, 109/200 patients have been recruited across four hospitals in Sydney, Australia. Participants were 45-86yrs, 57% male, with average 4yrs (range, 1mth to 22yrs) since diagnosis. More than half (65/109; 59.6%) completed the PROMs electronically. Average dexamethasone dose was 28mg weekly (range, 4 to 80), or 124mg per cycle (range, 12 to 180). The most common regimens were Lenalidomide & Bortezomib (29/109, 26.6%), Lenalidomide (24/109, 22%), Daratumumab & Bortezomib (15/109, 13.8%), or Carfilzomib (15/109, 13.8%) based. Cronbach's alpha at time points 1 (0.83) and 2 (0.84) showed internal consistency, and test-retest indicated the scale was stable (ICC: 0.844, 95%CI: 0.779 to 0.892; p< 0.001). The most frequently reported symptoms were disturbed sleep 100/109 (91.7%), loss of energy/fatigue 88/109 (80.7%), and trouble concentrating 87/109 (79.8%). Patients typically experienced 10 symptoms concurrently (range, 1 to 19), with 4 symptoms rated as severe (range, 0 to 12). Most frequently reported severe symptoms included disturbed sleep 73/109 (67 %), loss of energy/fatigue 55/109 (50.5%), and fragile skin/easy bruising 50/109 (45.9%), with disturbed sleep rated as most bothersome 53/109 (48.6%). **Conclusions:** The SSQ-MM currently demonstrates high levels of feasibility, acceptability, and reliability and is suitable for clinical use to manage steroid toxicity and improve treatment outcomes for MM patients. The study continues to evaluate convergent and discriminant validity by exploring relationships between similar and dissimilar constructs within EORTC QLQ-C30 and QLQ-MY20, enabling the SSQ-MM to be used in future clinical trials of steroid treatments for MM. A study characterising sleep disturbance in this patient group is underway.

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significantly different toxicity profile to other MM treatments yet has not been included in current supportive care guidelines. Patients receiving selinexor may be heavily pre-treated, with significant disease and treatment related morbidities, and have comorbidities of an older patient group. Early recognition and implementation of supportive care interventions is critical to minimise selinexor-related toxicities and reduce risk of subsequent discontinuation of therapy. **Aim:** To provide guidance for nurses to deliver best supportive care to those receiving selinexor through development of living consensus recommendations. **Methods:** The approach to developing consensus recommendations when there is limited research evidence was followed. A Selinexor Expert Advisory Group (SEAG) was established, all available published research, including selinexor licensing clinical trial data and papers focused on dosing, toxicity and management were examined. In addition, optimal supportive care, national and international guidelines associated with cancer supportive care were identified and reviewed. Draft consensus recommendations were developed, and a formal consensus process followed with SEAG. Draft recommendations were reviewed by an international MM nurse leader with experience in managing selinexor toxicities, a haematologist, and an academic nurse researcher prior to presentation to the M-SPN membership. Feedback from members was minor and incorporated into the final document. **Results:** Consensus Recommendations: Three core areas: 1. Patient and carer education prior to commencing treatment focusing on different symptom profile, importance of recognising and early reporting of symptoms, adherence to medications to reduce toxicities, concurrent supportive medications in an often medically fragile population. 2. Prompt and proactive symptom management in the first few cycles of therapy can reduce the risk of treatment discontinuation due to toxicity. 3. Prompt dose reduction in presence of therapy-related adverse events (TRAEs) with a 'go slow and low' approach can further help patients better adjust to therapy. The recommendations include brief information about selinexor indication, dosing/reductions, TRAE incidence and management of common toxicities, treatment checklist, links to 3rd party consumer information and patient treatment calendars, previously developed by our group https://rego.interact.technology/myetx/. **Conclusions:** Such level IV evidence that provides grade C recommendations provides useful evidence where data is lacking. This consensus guideline is important particularly as selinexor is reimbursed for the treatment of RRMM in Australia and will be updated regularly. Access @ www.hsanz.org.au.

NSP-12

Multiple myeloma and disparate populations: the path forward

Rebecca Lu[1], Joseph Tariman[2], Donna Catamero[3], Michaela Hillengass[4], Kimberly Noonan[5]

[1]MD Anderson; [2]Rutgers University; [3]Mount Sinai Health System, New York, NY, USA; [4]Roswell Park Comprehensive Cancer Center; [5]Dana-Farber Cancer Institute

Introduction: It is a well-known and disturbing fact that racial and ethnic minority populations with multiple myeloma (MM) are often underrepresented, especially in clinical trials. In fact, some studies report less than 4% of patients of African American descent will enroll in therapeutic trials1 and though there is opportunity to receive novel standard of care treatments, minority populations are still underserved. With this knowledge, an international group of MM nursing experts convened in September 2021 to discuss barriers that hinder equitable access to care and provide strategic solutions. Better understanding of diverse populations is critical for nurses and advanced practice providers to effectively provide care. **Methods:** In order to identify the prevalent groups impacted by disparity and barriers to equitable treatments, a literature review through PubMed was conducted using the search terms of myeloma, bias, diversity, inequity, clinical trial, sexual orientation, and disparity. A total of 180 articles were identified and from those, 54 were excluded as they did not involve MM patients and 37 were excluded as they did cover disparity in MM. **Results:** The search identified key disparities that affect patient access to treatment and care including race, age, socioeconomic status, and sexual preference/orientation. These disparities profoundly affect patient care and the effect of clinical trials, especially as investigational drugs are administered in real world setting. Based on literature review, authors synthesized the information to provide recommendations to better inform the nurse and advanced practice provider of strategies to increase trial participation for diverse populations. **Gap and proposed intervention:** Lack of healthcare provider education regarding existing disparities: 1. Provide ongoing education. 2. Identify and address barriers. 3. Provide resources on diversity and implicit bias. Lack of community awareness of clinical trials: 1. Provide clinical trial education directly to communities. 2. Establish relationships to foster trust. 3. Consider logistical challenges for patients. Lack of access to clinical trials for rural communities: 1. Develop outreach programs. 2. Utilize local laboratories and facilities to decrease travel burden. 3. Collaborate with sponsors to provide greater financial assistance. Lack of inclusivity in clinical trials: 1. Incorporate gender-neutral terminologies through consent and questionnaires. **Conclusions:** The lack of representation from various ethnic backgrounds in clinical trials ultimately impacts the treatment for all MM patients. Identifying and creating realistic strategies to address barriers to diversity in trial enrollment is a crucial step to advancing equity among MM patients. Based on the review the group developed evidenced based recommendations to equip health care providers to create an equitable therapy plan for MM patients with plans to publish full recommendations in a peer-reviewed journal.

NSP-13

Multiple myeloma: validation of the values and preferences elicitation questionnaire – cure and survival preference scale (VPEQ-CSPS)

Anastasiia Savchenko[1], Alexandria Kohon[1], Joseph Tariman[2], Shannon Simonovich[1], Thomas Dahan[2], Jessica Bishop-Royse[3]

[1]DePaul University; [2]Rutgers University; [3]Rush University

Introduction: With the emergence of many novel therapies, the treatment decisions for multiple myeloma (MM) are increasingly

significantly different toxicity profile to other MM treatments yet has not been included in current supportive care guidelines. Patients receiving selinexor may be heavily pre-treated, with significant disease and treatment related morbidities, and have comorbidities of an older patient group. Early recognition and implementation of supportive care interventions is critical to minimise selinexor-related toxicities and reduce risk of subsequent discontinuation of therapy. **Aim:** To provide guidance for nurses to deliver best supportive care to those receiving selinexor through development of living consensus recommendations. **Methods:** The approach to developing consensus recommendations when there is limited research evidence was followed. A Selinexor Expert Advisory Group (SEAG) was established, all available published research, including selinexor licensing clinical trial data and papers focused on dosing, toxicity and management were examined. In addition, optimal supportive care, national and international guidelines associated with cancer supportive care were identified and reviewed. Draft consensus recommendations were developed, and a formal consensus process followed with SEAG. Draft recommendations were reviewed by an international MM nurse leader with experience in managing selinexor toxicities, a haematologist, and an academic nurse researcher prior to presentation to the M-SPN membership. Feedback from members was minor and incorporated into the final document. **Results:** Consensus Recommendations: Three core areas: 1. Patient and carer education prior to commencing treatment focusing on different symptom profile, importance of recognising and early reporting of symptoms, adherence to medications to reduce toxicities, concurrent supportive medications in an often medically fragile population. 2. Prompt and proactive symptom management in the first few cycles of therapy can reduce the risk of treatment discontinuation due to toxicity. 3. Prompt dose reduction in presence of therapy-related adverse events (TRAEs) with a 'go slow and low' approach can further help patients better adjust to therapy. The recommendations include brief information about selinexor indication, dosing/reductions, TRAE incidence and management of common toxicities, treatment checklist, links to 3rd party consumer information and patient treatment calendars, previously developed by our group https://rego.interact.technology/myetx/. **Conclusions:** Such level IV evidence that provides grade C recommendations provides useful evidence where data is lacking. This consensus guideline is important particularly as selinexor is reimbursed for the treatment of RRMM in Australia and will be updated regularly. Access @ www.hsanz.org.au.

NSP-12

Multiple myeloma and disparate populations: the path forward

Rebecca Lu[1], Joseph Tariman[2], Donna Catamero[3], Michaela Hillengass[4], Kimberly Noonan[5]

[1]MD Anderson; [2]Rutgers University; [3]Mount Sinai Health System, New York, NY, USA; [4]Roswell Park Comprehensive Cancer Center; [5]Dana-Farber Cancer Institute

Introduction: It is a well-known and disturbing fact that racial and ethnic minority populations with multiple myeloma (MM) are often underrepresented, especially in clinical trials. In fact, some studies report less than 4% of patients of African American descent will enroll in therapeutic trials1 and though there is opportunity to receive novel standard of care treatments, minority populations are still underserved. With this knowledge, an international group of MM nursing experts convened in September 2021 to discuss barriers that hinder equitable access to care and provide strategic solutions. Better understanding of diverse populations is critical for nurses and advanced practice providers to effectively provide care. **Methods:** In order to identify the prevalent groups impacted by disparity and barriers to equitable treatments, a literature review through PubMed was conducted using the search terms of myeloma, bias, diversity, inequity, clinical trial, sexual orientation, and disparity. A total of 180 articles were identified and from those, 54 were excluded as they did not involve MM patients and 37 were excluded as they did cover disparity in MM. **Results:** The search identified key disparities that affect patient access to treatment and care including race, age, socioeconomic status, and sexual preference/orientation. These disparities profoundly affect patient care and the effect of clinical trials, especially as investigational drugs are administered in real world setting. Based on literature review, authors synthesized the information to provide recommendations to better inform the nurse and advanced practice provider of strategies to increase trial participation for diverse populations. **Gap and proposed intervention:** Lack of healthcare provider education regarding existing disparities: 1. Provide ongoing education. 2. Identify and address barriers. 3. Provide resources on diversity and implicit bias. Lack of community awareness of clinical trials: 1. Provide clinical trial education directly to communities. 2. Establish relationships to foster trust. 3. Consider logistical challenges for patients. Lack of access to clinical trials for rural communities: 1. Develop outreach programs. 2. Utilize local laboratories and facilities to decrease travel burden. 3. Collaborate with sponsors to provide greater financial assistance. Lack of inclusivity in clinical trials: 1. Incorporate gender-neutral terminologies through consent and questionnaires. **Conclusions:** The lack of representation from various ethnic backgrounds in clinical trials ultimately impacts the treatment for all MM patients. Identifying and creating realistic strategies to address barriers to diversity in trial enrollment is a crucial step to advancing equity among MM patients. Based on the review the group developed evidenced based recommendations to equip health care providers to create an equitable therapy plan for MM patients with plans to publish full recommendations in a peer-reviewed journal.

NSP-13

Multiple myeloma: validation of the values and preferences elicitation questionnaire – cure and survival preference scale (VPEQ-CSPS)

Anastasiia Savchenko[1], Alexandria Kohon[1], Joseph Tariman[2], Shannon Simonovich[1], Thomas Dahan[2], Jessica Bishop-Royse[3]

[1]DePaul University; [2]Rutgers University; [3]Rush University

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Introduction: With the emergence of many novel therapies, the treatment decisions for multiple myeloma (MM) are increasingly

guided by concerns of quality of life, achievement of cancer-free remission, living a longer overall survival, and a relentless search for a cure; however, the impact of these various treatment options on patients' choices and lives is mainly unknown. Oncology clinicians face the challenge of uncovering their patient's preferences and values and putting them into the actual treatment decision-making. **Purpose:** This study examined the psychometric properties of the Values and Preferences Elicitation Questionnaire-Cure and Survival Preference Scale (VPEQ-CSPS) instrument. **Methods:** The VPEQ-CSPS instrument was deployed using an anonymous Qualtrics online survey to patients diagnosed with MM within the network of International Myeloma Foundation (IMF) online patient support groups across the US. One hundred seventy-four (N=174) valid responses were obtained and used to examine the validity and reliability of the VPEQ-CSPS. **Results:** Exploratory factor analysis (EFA) revealed a Kaiser-Meyer-Olkin value of 0.72 indicating excellent sample adequacy and a statistically significant Bartlett's test of sphericity ($p < 0.001$) indicating significant correlations among the variables of the dataset to conduct the EFA. The internal consistency coefficients indicated high reliability of the instrument with Cronbach's alpha value at 0.80. The EFA and parallel analysis revealed the 5-item VPEQ-CSPS as a valid and reliable unidimensional scale that can be used by oncology clinicians to elicit their patient's personal values and preferences and achieve shared decision-making for myeloma treatment decisions. **Conclusions:** This study has demonstrated that VPEQ-CSPS is a 5-item unidimensional instrument with strong psychometric properties designed to elicit patient values and preferences for remission, survival, and cure. It addresses the communication gap during cancer treatment decision-making for MM. The information and data that the VPEQ-CSPS can elicit are essential to SDM and patient-centered care in patients with MM.

NSP-14

Project to improve volume of treatment and satisfaction (PIVOTS): optimizing physician and advanced practice provider workflow

Samuel Shewan[1], Mary Steinbach[1], Kelley Julian[2], Matthew Whooley[3], Carrie Bellerive[3], Zachary Francom[3], Douglas Sborov[3]

[1]Division of Hematology, Department of Internal Medicine, University of Utah Huntsman Cancer Institute; [2]Department of Pharmacy, University of Utah Hospitals and Clinics, Huntsman Cancer Institute; [3]Huntsman Cancer Institute at the University of Utah

Introduction: Huntsman Cancer Institute Plasma Cell Dyscrasia (PCD) Program is the primary referral center in the Mountain West. In 2021, we reported on a project to improve our care model to optimize clinical efficiency. Here we provide an update on this quality improvement project. We hypothesized that utilizing a contemporary clinical model would improve efficiency and Relative Value Unit (RVU) generation, enhance job satisfaction for all clinical team members while maintaining high patient satisfaction scores. This model, called Project to Improve Volume of Treatment and Satisfaction (PIVOTS) is focused on 4 fundamental pillars: 1) Modifying physician and APP clinic templates to optimize daily clinic volumes; 2) Establishing specific "divisions of labor" for patient follow-up; 3) Standardization of post-autologous transplant follow-up; and 4) Standardization of documentation practices via standardized note templates and intelligent text. The goal of this project was to improve our practice model to optimize patient care, productivity and team morale. **Methods:** Clinic template adjustments: Physician schedule templates included all New Patient Visits (NPV), follow-up visits with disease reassessment or treatment change, and visits per patient request. We eliminated the ability to double book on the MD schedule. There were defined instances for shared MD/APC visits: NPV with active MM, transplant consent, and treatment change or progression. Independent APP schedule templates included surveillance visits, clinical trial visits, and post-ASCT. The general approach is that patients with well controlled myeloma alternate between the MD and APP schedule on a 2 and 4-month or 3 and 6-month basis. To maximize efficiency, note templates and intelligent text were standardized for all physicians and APPs in the 6 months prior to starting PIVOTS. **Results:** Three outcome measures were defined before the start of the project based on our hypothesis: 1) Employee Satisfaction Rating; 2) APP wRVUs; and 3) Patient Satisfaction. Each outcome was assessed quarterly between May 2021 and May 2022. As measured from a survey, employee satisfaction improved from 50% to 71%. APP wRVUs increased from 1427 to 2397 per APC. Patient satisfaction scores based on the likelihood to recommend practice from the Press Ganey survey improved from 93% to 98%. **Conclusions:** Implementing PIVOTS has increased clinical efficiency, improved workforce satisfaction, and improved patient satisfaction scores. Importantly, these successes occurred during the COVID pandemic and during a period of growth in which clinic volumes increased > 100% between 2019 and 2022. While PIVOTS was piloted for a single physician schedule template, we now use this model for all clinical faculty in the PCD Program. Our outcomes justify the ongoing application of PIVOTS and we believe that "pivoting" patients between independent physician and APP schedules allows for significant workflow flexibility and allows our APPs to function at the top of their licensure.

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AUTHOR INDEX