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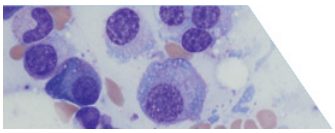

KEY:
OAB = oral presentation
P = poster presentation
NS = nursing symposium

OAB-001

Potentiating T cell activity against multiple myeloma through SUMOylation inhibition

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Introduction: Multiple myeloma (MM), the second most common blood cancer, is characterized by abnormal plasma cell growth in the bone marrow. MM cells can create an immunosuppressive milieu in the bone marrow that promotes immune escape and T cell dysfunction, which is associated with MM disease progression and immunotherapy failure. Chimeric antigen receptor (CAR) T cell therapy has demonstrated impressive response rates in MM. However, few patients experience long-term disease control, due to therapeutic resistance associated with T cell dysfunction. Thus, there is an urgent need for new therapies that enhances CAR T efficacy. We propose inhibition of SUMOylation as a novel therapy with the potential to address this need. SUMOylation regulates protein function by covalently attaching Small Ubiquitin-like MOdifier (SUMO) proteins to target proteins via an enzymatic cascade. Our study aims to evaluate the effects of SUMOylation inhibition on T cell function and CAR T activity against MM.
Methods: Using T cells isolated from MM patients and healthy donors, we evaluated the effects of knockdown of SUMO E1 (SAE2) or using TAK-981, a novel and specific SUMO E1 inhibitor, on T cell effector function by flow cytometry, degranulation assay, cytotoxicity assay, qPCR, ELISA and western blot. Xenograft mouse models were generated to determine the in vivo anti-MM effects of TAK-981 as a single agent and in combination with CS1-CAR T cells. RNA-seq, GSEA analysis and ChIP assay were utilized for evaluating key factors mediating T cell function.
Results: TAK-981 significantly suppressed MM tumor growth in an immuno-competent mouse MM model, demonstrating anti-MM effect of TAK-981 as a single agent in vivo. TAK-981 significantly increased PBMC immune-mediated MM killing. TAK-981 induced T cell activation in PBMCs from both MM patients and healthy donors. We observed TAK-981 treatment during T cell expansion significantly decreased T cell exhaustion and significantly increased IL2, IFNγ and Granzyme B levels in both T cells from healthy donors and patients with MM, proving SUMOylation inhibition promotes T cell effector function. Knockdown of SUMO E1 in active T cells showed similar effects as decreased exhaustion and enhanced effector function. SUMOylation inhibition induces IL2 and IFNγ expression through upregulating c-Jun. Overexpression of c-Jun has been reported to prevent exhaustion and promote effector function in CAR T cells. We found addition of TAK-981 to CS1-CAR T cells significantly potentiated MM killing efficacy in vitro. More importantly, TAK-981 in conjunction with a single CS1-CAR T cell infusion significantly reduced MM tumor growth and prolonged survival in a pre-clinical mouse model.
Conclusions: Our study proves SUMOylation inhibition potentiates CAR T cell efficacy against multiple myeloma (MM) by enhancing CAR T effector function and preventing exhaustion, presenting TAK-981 as an efficient regimen to advance CAR T therapy in MM, with relevance to other blood cancers and solid tumors.

OAB-002

The preexisting T cell landscape determines response to T cell-engagers therapy in multiple myeloma

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Introduction: Adaptive immunotherapy by T Cell Engagers (TCE), such as bispecific antibodies, is emerging as one of the most promising therapeutic strategies in various cancers. However, detailed understanding of molecular mechanisms of action, predictors of response, and mediators of resistance remains largely elusive.
Methods: We employed primary multiple myeloma (MM) samples due to its close association with the bone marrow immune microenvironment, the impressive activity of TCEs, and the availability of serial bone marrow biopsies from patients on experimental single agent BCMAxCD3 bispecific antibody treatment. We defined transcriptional gradients of bone-marrow associated immune cells from a total of 32 healthy bone marrow donors, newly diagnosed MM patients and relapsed/refractory MM patients receiving BCMAxCD3 bispecific antibody monotherapy. Longitudinal site-matched bone marrow biopsies were performed to allow for comparisons of the immune repertoire pre-treatment and at two timepoints on-treatment. By tracing T cell clones over time using their TCR amino acid sequence as individual barcode, we further integrated longitudinal data with global and individual repertoire-level analyses.
Results: Here, we identify conserved behaviors of bone marrow residing CD4+ and CD8+ T cells in multiple myeloma patients undergoing TCE therapy. We show that the bone marrow immune landscape reacts to malignant disease progression as well as T cell-targeting immunotherapy with clonal expansion of T cells and phenotype diversification. We discover a response-driving population of CD8+ T cells in continuous progression from an early effector into a dysfunctional T cell state. Clonal replacement by circulating T cells in peripheral blood sustains this dynamic process, while high abundance of dysfunctional CD8+ T cells before therapy initiation predetermines clinical response failure. We further identify mediators of primary as well as acquired resistance and immune evasion to TCE.
Conclusions: This is the first study to provide a deep interrogation of the human T cell repertoire and its dynamics in response to TCE and our dataset provides a valuable resource of real-time T cell fates and their modulation by multiple myeloma and immunotherapy. Together, our work provides: 1) a new conceptual framework for understanding the effects of T cell-activating immunotherapy approaches, and 2) identifies conserved behaviors of bone marrow residing CD4+ and CD8+ T cells that may be purposefully engaged to improve antitumor immunity. By demonstrating the mechanism of TCE treatment in humans as well as specific mechanisms of immune evasion, we provide the rationale for predictive immune-monitoring and conditioning of the immune repertoire to guide future immunotherapy approaches in multiple myeloma.

OAB-003
Phase 1 study of CART-ddBCMA, a CAR-T therapy utilizing a novel synthetic binding domain for the treatment of subjects with relapsed and refractory multiple myeloma

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Introduction: Chimeric Antigen Receptor (CAR) T cell therapies targeting B-cell maturation antigen (BCMA) have demonstrated benefit in patients (pts) with relapsed/refractory Multiple Myeloma (RRMM). CART-ddBCMA is an autologous anti-BCMA CAR T cell therapy that utilizes a novel, synthetic binding domain, called a D-Domain, instead of a typical scFv binder. The objective of this first-in-human trial is to assess the safety & efficacy of CART-ddBCMA.
Methods: This is a Phase 1, multi-center, open label, dose escalation trial for pts with RRMM who have received ≥3 regimens or are triple refractory. Lymphodepletion is given days -5 to -3 followed by CART-ddBCMA infusion on day 0. Dose escalation was performed at 100 (DL1) & 300 (DL2) x 10^6 (± 20%) CAR+T cells, followed by expansion of DL1. The primary outcome measure is incidence of adverse events (AEs), including dose-limiting toxicities. Additional outcome measures are ORR, CR rate, DoR, MRD (clonoSEQ), PFS & OS.
Results: As of May 2, 2022, 33 pts received CART-ddBCMA, with median age 66 (range: 44-76), after a median of 5 prior lines of therapy (3-16), including 12 (39%) with extramedullary disease (EMD). Median follow-up was 12.1 mo (0.9-26.7 mo). Overall, 31 pts (25 DL1; 6 DL2) were evaluable for safety & for efficacy analysis. 28/31 (90%) pts experienced CRS, but only 1 pt (in DL2) had grade (G) 3 CRS. All other CRS cases were G≤2, with no cases of G≥3 CRS in DL1. Seven pts experienced ICANS (5, G≤2; 2, G3), with 1 G3 case in each of DL1 (4%) & DL2 (17%). All cases resolved without sequalae with standard management. The ORR was 100%, sCR/CR rate 71% & ≥VGPR rate 94%. Conversion to CR/sCR was observed with longer follow-up, as late as month 12 in this trial, & 6 pts with PR /VGPR in the DL1 have <12 months follow-up, with 5 (of 6 evaluable) negative at ≥10^{-5} for MRD. Overall, 19/22 (86%) evaluable pts have achieved best MRD response of ≥10^{-5}. Median duration of response, PFS & OS were not evaluable at the time of data-cut because 22 of 31 evaluable pts (71%) remain in ongoing response. In the patients with ≥12 months follow-up (n=16), which included 8

(50%) patients with EMD, ORR was 100%, sCR/CR rate was 81% (13/16) and ≥VGPR rate was 88% (14/16).
Conclusions: CART-ddBCMA has demonstrated clinical activity, including 100% ORR with rates of CR/sCR and ≥VGPR of 71% and 94%, respectively. No off-tumor tissue-targeted toxicity or delayed neurotoxicity or Parkinson's-like events were observed in the entire cohort.

OAB-004
Idecabtagene vicleucel chimeric antigen receptor T-cell therapy for relapsed and refractory multiple myeloma: real-world experience

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Introduction: Idecabtagene vicleucel (ide-cel) is an autologous B-cell maturation antigen (BCMA)-directed chimeric antigen receptor therapy (CAR) T-cell therapy approved for relapsed/refractory multiple myeloma (RRMM). We evaluated the real-world outcomes of patients treated with standard of care (SOC) ide-cel under the commercial FDA label.
Methods: Eleven US academic centers contributed data to this effort independent of the manufacturer. Data was retrospectively collected from RRMM patients who underwent leukapheresis as of 2/28/2022. Toxicities were graded and managed according to each institution's policies, while responses were graded based on the International Myeloma Working Group (IMWG) response criteria.
Results: As of 2/28/2022, 196 patients completed leukapheresis with intent to manufacture and receive SOC ide-cel. 12 patients (6%) experienced a first manufacturing failure, and of these, 7 manufactured successfully on a second attempt, resulting in definitive manufacturing failure of 2.5%. 159 patients were infused by data cut-off and represent the study population for this retrospective analysis. Extramedullary and penta-refractory disease were seen in 47% and 44% of patients, respectively, higher than the KarMMa trial. 77% of patients would not have met eligibility criteria for KarMMa. Common reasons for ineligibility (> 1 reason in 46% of patients) were co-morbidities (31%), cytopenias (30%), prior use of BCMA-targeted therapy (22%), poor ECOG PS of ≥ 2 (17%), and plasma cell leukemia (PCL)/polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS)/amyloidosis or nonsecretory RRMM (13%). Toxicity was comparable to that seen in KarMMa. Cytokine release syndrome (CRS) was seen in 82% (≥ grade 3: 3%) and neurotoxicity (NT) in 18% (≥ grade 3: 6%) of patients, respectively. Tocilizumab and steroids were used in 71% and 26% of patients, respectively. Infections were seen in 34% of patients. 141 patients were evaluable for best overall response rate (ORR) by day 90. Best overall and ≥ CR response were 86% and 42%, respectively. 13% of patients have died by data cut-off, 13 due to disease progression and 8 due to other causes (2 grade 5 CRS, 2 hemophagocytic lymphohistiocytosis with 1 having concomitant grade 5 CRS, 1 progressive neurological weakness, 3 COVID-19, and 1 cardiomyopathy). At a median follow-up of 5.3 months, the median progression-free survival (PFS) was 8.9 months and median overall survival (OS) was not reached. Patients with prior exposure to BCMA-targeted therapy and high-risk cytogenetics had inferior PFS on multivariable analysis.
Conclusions: The safety and efficacy of ide-cel in patients with RRMM in the SOC setting was comparable to the phase II KarMMa trial despite most patients not meeting trial eligibility criteria. High-risk cytogenetics and prior use of BCMA-targeted therapy are independent predictors of inferior outcomes. D.K.H. and S.S. contributed equally; J.M., F.L.L. and K.K.P. contributed equally

OAB-005
Point mutations in BCMA extracellular domain mediate resistance to BCMA targeting immune therapies

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Introduction: Recent studies interrogating T cells repertoires and fitness correlated resistance to these BCMA-targeting adaptive therapies with exhausted T cell states. While in lymphoma, antigen escape with CD19 loss is observed in 30% of patients with acquired resistance to adaptive therapies, in MM BCMA structural or point mutations are thought to be less prevalent in recipients of BCMA-targeting CARs or TCEs.

Further studies of the role BCMA structural or point mutations to the immune escape to these adaptive therapies are needed.
Methods: Serial BM aspirates were collected from patients treated with BCMA-targeting TCE CARs prior to therapy and at relapse. MM cells were profiled with single cell mRNA (scRNAseq), single cell copy number (scCNVseq) using the GemCode system and whole genome sequencing (WGS). Sequenced reads were aligned to hg38. Single cell reads were processed with CellRanger and downstream analyses with Seurat and Monocle R packages.
Results: WGS (n=19, 100x coverage) did not identify any structural mutations (deletions) at baseline in TNFRSF17 gene locus. In contrast to WGS, scCNV studies identified more frequent subclonal monoallelic copy number losses of TNFRSF17 in 14% of the cells (23,600 MM cells from 30 patients) prior to anti-BCMA therapy exposure with the deletions ranging 200 kb to 2.3 Mb and a homozygous deletion of TNFRSF17 was noted in 1 patient at the time of disease progression post CAR T. With regard to TNFRSF17 point mutations, WGS studies identified at baseline only one SNV in TNFRSF17 exon 1 corresponding to aa 33 [p. (P33S)] within BCMA extracellular domain. This patient harboring this mutation had a limited response to CAR T cells (PR, DOR 3 months) and failed to respond to BCMA TCE in the next line of therapy. In relapsed samples, in one patient progressing from a durable CR on BCMA TCE, we observed an acquired mono-allelic loss of BCMA (scCNV) coupled with de novo mutation in TNFRSF17 extracellular domain c.81G >C [p.(R27P)]. This point R27P mutation is predicted to be damaging to BCMA (Polyphen) with disruption of several H-bonds between R27 and C24, Q25, S29, S30 and T32 of BCMA extracellular aa residues. Importantly, molecular dynamic simulations of WT vs. mutant R27P using publicly deposited crystal structural of BCMA bound to anti-BCMA Ab (J22.9-xi) (PBD ID 4ZFO) demonstrated that this mutation disrupts all H-bonds between BCMA and the light chain of chimeric mouse/human anti-BCMA Ab (J22.9-xi). Functionally, K562 cells transduced with mutant BCMA (R27P) were resistant to BCMAxCD3 cytotoxicity compared to WT BCMA.
Conclusions: While structural alterations of BCMA remain rare, we have identified a monoallelic loss of BCMA coupled with BCMA extracellular domain point mutation (R27P) that confers resistance to BCMAxCD3 TCE in MM. Therefore, antigen escape resulting from point mutations in BCMA extracellular domain are important point to consider in MM patients receiving targeted-immunotherapies.

OAB-006
BCMA CAR T-cells secreting IL-12 to alter the tumour microenvironment in multiple myeloma

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Introduction: Chimeric antigen receptor (CAR)-T cells directed against B-cell maturation antigen (BCMA), have yielded impressive results in clinical trials for multiply relapsed/refractory multiple myeloma. However, progression free survival is short, demonstrating a need for improvements to this therapy. The immunosuppressive tumour microenvironment (TME) contains a mixed cell population that promotes MM growth and survival, and is a potential major contributor to CAR-T cell failure. Engineering BCMA CAR-T cells that can secrete IL-12 could improve the efficacy of CAR T-cells by modulating the TME to support immune-mediated tumour cell death.
Methods: Initial in vitro validation of our single-domain antibody (sdAb)-based BCMA-directed CAR T-cells using cells isolated from healthy human donors will include antigen binding, activation, cytokine release, cytotoxicity, and proliferation. Following these initial validation stages, CAR T-cells generated from mouse donor cells will then be tested in an immunocompetent mouse model of MM to dissect the interactions with the TME and the effects of the production of IL-12 on the TME and overall survival.
Results: Using T-cells isolated from human healthy donors, our sdAb-based BCMA-directed CAR T-cells can bind both human and mouse BCMA. Furthermore, in co-culture experiments, we show that these CAR T-cells can effectively lyse target cells, as well as release inflammatory cytokines, and effectively proliferate. We also provide preliminary evidence that CAR T-cells expressing an IL-12 cassette secrete detectable levels of IL-12. Finally, this CAR construct has been transduced into mouse T-cells and on-going functional characterization is underway prior to interventional studies in the Vk*MYC mouse model of myeloma.
Conclusions: We have shown that the development of sdAb-based BCMA-directed CAR T-cells from either human or mouse donor cells is feasible and that these engineered effector cells are functional. Future experiments will include the administration of these CAR T-cells to mice to understand the effects on the TME and survival.

OAB-007
Updated clinical and correlative results from the Phase I CRB-402 study of the BCMA-targeted CAR T cell therapy bb21217 in patients with relapsed and/or refractory multiple myeloma

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Introduction: bb21217 is a B-cell maturation antigen (BCMA) directed chimeric antigen receptor (CAR) T cell therapy which uses the same CAR molecule as ide-cel, the first CAR T cell therapy approved for the treatment of relapsed or refractory multiple myeloma (RRMM). The PI3K inhibitor, bb007, is used during ex vivo culture of bb21217 to enrich the drug product (DP) for memory-like T cells and decrease the proportion of highly differentiated/senescent T cells. We hypothesize that DPs enriched for memory like CAR T cells may persist and function longer than non-enriched DPs and this increased persistence may positively influence duration of response (DOR).
Methods: CRB-402 (NCT03274219) is a multi-center phase 1 trial of bb21217 in RRMM patients (pts) who received ≥3 prior lines of antimyeloma therapy, including a proteasome inhibitor and an immunomodulatory agent, or are double-refractory to both classes. In expansion, pts were required to have prior exposure to an anti-CD38 antibody and to be refractory to last line of therapy. Pts received bb21217 at 150, 300 or 450 x 10^6 CAR+ T cells. Primary endpoint is incidence of adverse events (AEs). Other endpoints include PK, response including CR/sCR, DOR, OS and correlation of outcome with the molecular characteristics of materials collected through treatment.
Results: As of Jan 20, 2022, 72 pts received bb21217; median follow up is 29.3 (16-52) months (M). Pts had a median of 6 (3-17) prior lines of therapy. At data cut off, safety is consistent with previous reports. CRS and NT were generally low grade and reported in 75% (1G3, 2G5) and 15% (2G3, 1G4) of pts, respectively. ORR is 69% with 43% sCR/CR. The median duration of response (DOR) is 23.8M (16.8-34.8) for all responding pts and 28.8M (17.6-NE) for pts with CR/sCR. At M12, OS was estimated at 73.9%. Persistent CAR+ T cells were detected in 39/42 and 24/32 pts at M6 and M12, respectively. Unsupervised analysis of the phenotypic profile of DP identified that CD4+ cell clusters expressing high levels of LEF1 and TCF1 positively associated with peak expansion and sCR/CR, while CD4+ cell clusters expressing either CD57 or TIM3, PD1 and LAG3 negatively associated with peak expansion and ≤VGPR. In PBMCs collected at apheresis, CD4+ T cells enriched for memory like markers were positively associated with response to bb21217. Multivariate random forest models for peak expansion, sCR/CR and DOR reveal a combination of PBMC, DP and clinical baseline characteristics associated with the modeled endpoint. DP enriched for memory T cells and depleted of effector/exhausted T cells in the setting of low tumor burden and low baseline inflammation are associated with optimal outcome.
Conclusions: bb21217 treatment resulted in deep durable responses. Low baseline tumor burden, low baseline inflammation, high memory like/proliferative phenotype and low exhaustion/senescence markers in PBMC and DP were associated with positive clinical outcomes.

OAB-008
Efficacy and safety of BCMA-targeted CAR-T therapy in elderly patients with multiple myeloma

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Introduction: Risks of B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR-T) therapy for patients with multiple myeloma (MM) include cytokine release syndrome (CRS), immune effector-cell associated neurotoxicity syndrome (ICANS), and infections. Older patients with MM are at higher risk of infections (Blimark 2015), and pre-existing comorbidities may complicate CRS and ICANS in these patients. While progression-free survival (PFS) was similar in older vs younger patients in the KarMMa trial of idecabtagene vicleucel (Berdeja 2020), BCMA CAR-T outcomes in the geriatric setting – including the risks of prolonged cytopenias, hypogammaglobulinemia, and infections – have not yet been analyzed.
Methods: We analyzed all patients with MM who received any autologous BCMA CAR-T therapy between 2017-2021 at our institution. Key endpoints included CRS (ASTCT criteria), ICANS incidence (ASTCT criteria), prolonged neutropenia (lasting ≥30 days from infusion), incidence of hypogammaglobulinemia (immunoglobulin G < 400 mg/dL at post-CAR-T nadir), confirmed infections within 30 days of CAR-T, PFS, and overall survival (OS). Characteristics were compared between older patients (age ≥70 at infusion) and younger patients using Fisher's and Kruskal-Wallis testing.
Results: Of 69 analyzed patients (age range 33-77), 15 (22%) were aged ≥70 at infusion. Demographics, performance status, and disease-related characteristics were similar between older and younger patients. Despite similar weights, older patients had lower creatinine clearances (medians 74.5 vs 108.7 mL/min using the Cockcroft-Gault equation, p< 0.01) and were more likely to receive reduced-dose fludarabine as part of lymphodepletion (53% vs 17%, p< 0.01). The incidences of any-grade CRS, any-grade ICANS, and prolonged neutropenia were similar between groups. Hypogammaglobulinemia occurred in 93% of older patients vs 72% of younger patients (p=0.16); however, all 5 infections occurred in the younger cohort. Median PFS was not reached (NR) in older patients (95% CI 10.6-NR) vs 13.9 months in

younger patients (95% CI 11.3-NR). Median OS was NR in older patients (95% CI NR-NR) vs 30.0 months (95% CI 24.8-NR) in younger patients, with 3-year survival probabilities of 83% and 39% respectively. There were 2 deaths before Day +100, both due to progressive MM and both in younger patients.
Conclusions: While limited by small sample size and likely selection bias in favor of healthier-functioning older adults, our analysis did not demonstrate any increases in BCMA CAR-T toxicity among patients aged ≥70.
Hypogammaglobulinemia, while possibly more common numerically in older patients, did not correspond to a higher risk of infections. Absolute fludarabine dose reductions during lymphodepletion (as expected when using age-adjusted calculations of creatinine clearance) did not impair CAR-T efficacy among older patients. CAR-T remains a safe and effective option for the geriatric MM population.

OAB-009
γ-secretase inhibitors augment efficacy of BCMA-targeting T cell engagers against multiple myeloma cells without impairing T cell effector function

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Introduction: BCMA-targeting therapy is the first efficacious mono-immunotherapy to treat patients with relapsed and refractory multiple myeloma (MM). However, membrane BCMA (mBCMA) receptor molecule is constantly cleaved by γ-secretase (GS) to release shed/soluble BCMA (sBCMA) into the circulation, which could prevent complete and durable patient MM cell lysis. We here defined the impacts of GS inhibitors (GSIs) on T-cell-dependent BCMA-specific MM cell killing and immunomodulatory effects induced by bispecific antibodies (BisAbs).
Methods: The potencies of 9 GSIs were determined to inversely correlate mBCMA with sBCMA in MM cell lines followed by the 3d-pharmacokinetic studies of GSI activity. The cytolytic activities of 4 BCMAxCD3 BisAb clones were evaluated in ex vivo MM-PBMC/T co-cultures, with pretreatment or co-treatment with GSIs. Degranulation, activation, and differentiation of T-cells from normal donors and MM patients were also determined in 3d- and 7d-co-cultures. Efficacy of GSI to deplete sBCMA and enhance anti-MM activity of BCMAxCD3 BisAb were studied in NSG mice bearing KMS11-luc tumors reconstituted with human T cells.
Results: EC50 values of 9 GSIs are comparable for mBCMA accumulation and sBCMA reduction, ranging from 0.07 to 777 nM. LY411575 is most effective, showing ~2-log greater potency than DAPT in all tested MM cell lines and patient MM cells. GSIs-induced mBCMA expression reached near maximum within 4h and sustained over 42h-study period on MM cell lines and patient MM cells. GSIs, i.e., 2 nM LY411575 or 1 μM DAPT, specifically increased mBCMA densities on CD138+ but not CD3+ patient cells, while sBCMA became undetectable in 1d-culture supernatants. In MM-T-cell co-cultures, GSIs abrogated sBCMA-inhibited MM cell lysis and further enhanced autologous patient MM cell lysis induced by BCMAxCD3 BisAbs, accompanied by upregulation in cytolytic markers (CD107a, IFNγ, IL2, TNFα) and downregulation in suppressive subsets (Treg, IL10+, TGFβ1+) in patient T cells. In longer 7d-co-cultures, LY411575 minimally affected BCMAxCD3 BisAb (PL33)-induced transient expression of checkpoint (PD1, TIGIT, TIM3, LAG3) and co-stimulatory (41BB, CD28) proteins, as well as time-dependent increments in % subsets with effector memory (CD45RA-CD62L-) plus central memory (CD45RA-CD62L+) phenotypes and CD8/CD4 ratios in patient T cells. Importantly, a single low LY41157 treatment (3 mg/kg) rapidly cleared sBCMA from sera of MM-bearing NSG mice reconstituted with human T cells and significantly augmented anti-MM efficacy of a single sub-curative PL33 treatment with prolonged host survival ($P < .01$).
Conclusions: GSI inhibits mBCMA loss from MM cells and overcomes the sBCMA decoy neutralization, leading to further improved efficacy of BCMAxCD3 BisAbs without adverse impacts on activation and differentiation of patient T cells. Rationally incorporating GSI into all BCMA-targeting immunotherapy therefore represents a promising novel combination approach to improve patient outcome in MM.

OAB-010
Atlas: a phase 3 randomized trial of carfilzomib, lenalidomide, and dexamethasone versus lenalidomide alone after stem-cell transplant for multiple myeloma

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Introduction: Treatment following autologous stem cell transplantation (ASCT) for multiple myeloma (MM) remains an area of active investigation. We have shown that extended post-ASCT treatment with carfilzomib, lenalidomide, and dexamethasone (KRd) after KRd induction improved the depth and duration of response (Jasielec et al, Blood 2020), suggesting a benefit of post-ASCT KRd therapy. In this study we aimed to directly compare extended post-ASCT KRd treatment to standard lenalidomide (R) maintenance.
Methods: This international open-label phase 3 randomized trial recruited newly-diagnosed MM patients (pts) who received any induction therapy for up to 12 months (mo) followed by single ASCT and achievement of at least stable disease within 100 days afterward. Pts were randomized to receive either KRd or R, stratified by post-transplant response (≥VGPR vs < VGPR) and cytogenetic risk [standard risk (SR) vs high [HR: presence of t(4;14), t(14;16), or del(17p)]. Pts randomized to KRd received carfilzomib 36 mg/m2 on days (D) 1,2,8,9,15,16 for 4 cycles (C) then D1,2,15,16 starting C5; R 25 mg D1-21, and dexamethasone 20 mg D1,8,15,22 in 28-day cycles. KRd pts with SR who reached IMWG-defined MRD-negativity after C6 de-escalated therapy to R alone after C8 (KRd- >R); the rest continued KRd through C36 followed by R alone until progression. Pts randomized to R received lenalidomide 10 mg C1-3 and then 15 mg daily. The primary objective was to compare progression free survival (PFS) rate between the two arms. Based on historical PFS rates, a sample size of 180 Pts was calculated to provide 85% power with 2-sided alpha 0.05.
Results: 180 pts were enrolled (R n=87; KRd n=93) through 10/21/20; data cutoff was 12/31/21. Pt characteristics in the KRd and R arms were balanced for median age (58 vs 59 yrs), ≥VGPR (88% vs 92%), and HR (23% vs 21%). After 6 cycles, 47% pts in the KRd arm and 29% in the R arm achieved MRD-negativity (p=0.017). 34 KRd pts eligible for de-escalation converted to R alone after C8 and were analyzed on the KRd arm per intention-to-treat. At median follow-up of 33.8 mo, 23 pts (25%) on the KRd arm and 38 pts (44%) on the R arm progressed; estimated median PFS was 59.0 mo for KRd vs 41.4 mo for R (Hazard Ratio 0.56, logrank p=0.026). At cutoff, 90% of KRd and 87% of R pts were alive; no deaths were treatment-related. All-grade toxicities were generally comparable between arms. The most common grade 3+ AEs and those of special interest were neutropenia (KRd 47%; R 59%), thrombocytopenia (KRd 13%; R 7%), infections (KRd 15%; R 6%), cardiovascular toxicities (KRd 4%, R 5%), and secondary malignancies (KRd 2, R 2).
Conclusions: This is the first randomized phase 3 trial demonstrating superior PFS with extended post-transplant KRd therapy compared to R maintenance. Therefore, MRD/risk-adapted post-ASCT extended KRd treatment may represent a new standard of care.

OAB-011

Predictors of unsustained negativity in minimal residual disease (MRD)-negative transplant-eligible newly diagnosed multiple myeloma (MM) patients enrolled in the FORTE trial

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Introduction: With novel therapies, a significant proportion of multiple myeloma (MM) patients (pts) achieve minimal residual disease (MRD) negativity. Nevertheless, the

identification of the factors associated with a persistence of MRD negativity remains a matter of debate. We aimed to analyze the impact of baseline prognostic factors on the risk of losing the MRD-negative status over time.
Methods: We included all pts enrolled in the FORTE trial (NCT02203643) who achieved MRD negativity by multiparameter flow cytometry (sensitivity of 10-5). MRD was assessed in the bone marrow aspirate of pts with ≥very good partial response. MRD evaluation was performed at premaintenance and repeated every 6 months during maintenance. Hemodilution of the first MRD-negative sample was ruled out. The primary endpoint of the analysis was the cumulative incidence of MRD positivity and/or progression starting from the first MRD-negative evaluation. Death without progression was considered a competing event. A multivariate Fine-Grey model was used to evaluate the risk of losing the MRD-negative status over time.
Results: 306/474 (65%) pts enrolled in the FORTE trial achieved MRD negativity and were analyzed. After a median follow-up of 50.4 months from MRD negativity, 185/306 (60%) pts were still MRD-negative and progression-free, 118 pts (39%) lost their MRD-negative status, and 3 pts (1%) died without progression. The presence of ≥2 concomitant high-risk cytogenetic abnormalities (HRCA) was associated with a higher risk of unsustained MRD negativity (HR 2.22, P=0.01), as compared with pts without HRCA. The 4-year (y) cumulative incidence of unsustained MRD negativity was 59% vs 29% in pts with ≥2 HRCA vs pts without HRCA. Pts harboring gain(1q) (HR 1.50, P=0.08) and especially amp(1q) (HR 2.12, P=0.02) showed a higher risk of unsustained MRD negativity vs normal 1q. The 4-y cumulative incidence of unsustained MRD negativity was 63% vs 49% vs 32% in pts with amp(1q) vs gain(1q) vs normal 1q. The median duration of the MRD-negative status was 27.6 months in amp(1q) pts. Pts with high circulating tumor cells (CTC) levels at baseline showed a higher risk of unsustained MRD negativity as well (HR 1.88, P=0.01). The 4-y cumulative incidence of unsustained MRD negativity according to CTC levels was 59% vs 31% in pts with high vs low CTC, with a median duration of MRD negativity of 38.1 months in the high CTC group. According to the protocol, at maintenance patients were randomized to receive carfilzomib (for up to 2 y) + lenalidomide (KR) vs lenalidomide alone (R). During the 2 y after maintenance randomization, patients receiving KR had a lower risk of unsustained MRD negativity (HR 0.58, P=0.03) vs patients receiving R alone.
Conclusions: MRD-negative pts with amp(1q), high CTC levels, or multiple HRCA were at high risk of losing their MRD-negative status over time. During the exposure to KR maintenance, patients were at lower risk of losing the MRD-negative status vs R alone.

OAB-012

Early and sustained negative minimal residual disease (MRDneg) after idecabtagene vicleucel (ide-cel) defines a subset of multiple myeloma (MM) patients in KarMMa achieving prolonged survival

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Introduction: MRD is a key prognostic factor in MM but there is limited information about its clinical meaning in patients treated with CAR T cells. Furthermore, as serological responses are often delayed compared to MRD negativity, there is uncertainty regarding the optimal time points to assess the efficacy of CAR T therapy in MM using each response criterion.
Methods: MRD was analyzed at months 1, 3, 6 and 12 after ide-cel infusion regardless of clinical response in the KarMMa phase 2 clinical trial. Of 128 patients receiving ide-cel, 125 had at least one MRD assessment. A total of 336 and 257 MRD assessments using NGF (EuroFlow) and NGS (clonoSEQ®) respectively, were performed in bone marrow (BM). Any detectable level of MRD >1x10-6 was considered positive. Median follow-up was 24.8 months.
Results: The percentage of concordant MRD status between NGF and NGS was 67%, 75%, 81.5% and 73% at months 1, 3, 6 and 12 after ide-cel, respectively. Most discordances were due to BM samples classified as hemodiluted by NGF and as MRD negative by NGS, which peaked immediately after ide-cel infusion and persisted until one year after (27.5%, 14%, 12.5% and 13% at months 1, 3, 6 and 12, respectively). That notwithstanding, NGF and NGS showed similar prognostic value at all time points. Therefore, subsequent analyses were done on the NGF dataset because a more complete dataset was available and monitoring of hemodilution was intrinsic to the method. At month 1 after ide-cel, there were no significant differences in median progression-free survival (mPFS) between patients in less than complete remission (< CR, n=103) vs those in CR (n=14) (8 vs 11 months, p=.09). By contrast, presence of MRD at month 1 (n=24) predicted dismal mPFS (2 vs 11.5 months in MRDneg patients [n=53], p< .001). At months 3, 6 and 12 after ide-cel, patients in CR and MRDneg showed significantly longer mPFS vs those in < CR and MRDneg (p≤.007). At month 12, the mPFS of patients in CR/MRDneg (n=19) vs < CR/MRDneg (n=4) vs CR/MRDpos (n=4) vs < CR/MRDpos (n=9) was 18 vs 6 vs 2 vs 0.3 months,

respectively. Patients with early and sustained MRDneg for 12 months (n=14) did not reach mPFS. Interestingly, among MRDneg patients, those with undetectable normal plasma cells (PC) that suggests ongoing function of the CAR T cells, showed superior mPFS when compared to cases with reappearance of normal PC.
Conclusions: Our results show that patients achieving early and sustained MRDneg after ide-cel have prolonged PFS. Furthermore, we unveiled the prognostic implication of different serological and MRD response dynamics; whereas only MRD (and not CR) status at month 1 after ide-cel predicted different outcomes, both CR and MRDneg at month 12 were required to identify patients with longer PFS. This study also uncovers a high frequency of hemodilution in BM aspirates after CAR T therapy, and the potential value of studying the reappearance of normal PC as a surrogate of loss of CAR T cell functionality and inferior PFS.

OAB-013
Universal loss of BCL7A allows release of its binding partner IRF4 inducing its transcriptional activity promoting MM cell growth

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Introduction: BCL7A is a tumor suppressor gene that is in the top 3% of downregulated genes in MM cells compared to normal plasma cells. Because it is part of a chromatin remodeling complex, we used ATAC-seq to assess the genome-wide changes in DNA accessibility caused by genetic modulation of BCL7A expression. We found that loss of BCL7A in MM cell lines (KMS12BM and NCI-H929) increased the accessibility of many important transcription factor motifs. Particularly affected was the IRF4 motif, as determined by querying a database of human ChIP-seq experiments (Remap 2020) and transcription factor foot-printing.
Methods: As IRF4 is central to myeloma cell proliferation, we investigated the role of BCL7A loss on its transcriptional activity. By comparative mass spectrometric analysis, we found that in addition to being in the canonical m-SWI/SNF complex, BCL7A forms a protein-protein complex with IRF4, which was confirmed by co-immunoprecipitation/GST pull-down assay. Interestingly, interaction with BCL7A prevents IRF4 from binding its target DNA sequence, as determined by a competitive electrophoretic mobility shift assay (EMSA) and validated by an in vitro reporter assay. Furthermore, we observed increased binding of IRF4 to the promoter of its target genes in BCL7A KO cells and significantly decreased binding when BCL7A expression was restored.
Results: To discover the IRF4 target genes most affected by BCL7A loss, integrated transcriptomic analysis was performed following GOF (Gain-of-function) and LOF (Loss-of-function) of BCL7A.This revealed the existence of a set of genes transcriptionally regulated by IRF4 that were significantly modulated by BCL7A. To investigate whether these genes are involved in the phenotypic and functional effects observed in MM after BCL7A depletion, we performed LOF studies (si-RNA screen) in scrambled and BCL7A KD MM cells. Among others, we observed that MM cells are highly sensitive to the inhibition of EEF1B2, RPS3A, SOX2, DCC and NDUFA1 only in the context of BCL7A loss, implicating a role as critical effector molecules downstream of the IRF4-BCL7A transcriptional network. To decipher additional gene dependencies in MM cells in the context of BCL7A loss, we utilized a customized CRISPR screen (pXPR_023) to find target genes that are synthetically lethal with BCL7A loss. We identified a set of 85 significant genes that specifically kill BCL7A-null MM cells but not control cells including GART, BCL2, MCL1, and PRMT5.
Conclusions: In conclusion, we show that the widespread loss of BCL7A in MM allows IRF4 to exert its transcriptional activity to induce MM cell growth, providing insight into the mechanism of the development of IRF4 dependency in MM and novel targets for therapeutic intervention in BCL7A-null MM cells.

OAB-014
Chemotherapy signatures reveal the evolutionary history of post-melphalan myeloid neoplasm

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Introduction: Therapy-related myeloid neoplasms (tMN) have dismal prognoses. Patients with underlying clonal hematopoiesis (CH) have a high risk of tMN, especially those undergoing autologous stem cell transplantation (ASCT). To understand this association, we used chemotherapy mutational signatures as temporal barcodes to map tumorigenesis with respect to melphalan exposure.
Methods: We assembled a cohort of 40 tMN whole genomes from patients exposed to cytotoxic chemo (and/or radiation).

For 11 of 16 patients with tMN post-melphalan/ASCT as treatment for multiple myeloma, we investigated the presence of antecedent CH using targeted sequencing (MSK-IMPACT; Bolton, Nat Gen 2020) on pre-melphalan blood samples.
Results: We compiled single nucleotide variants (SNV) and performed mutational signature analysis to identify the mutational processes in each tumor. Overall, the only chemo associated with signatures was platinum and melphalan. All 10 tMN with prior platinum exposure bore a platinum signature (SBS31/SBS35) while only 6 of 16 post-ASCT (37.5%) bore the melphalan signature (SBS-MM1). As detection of chemo signatures in bulk whole genomes is contingent on a single cell expanding to clonal dominance (Pich, Nat Gen 2019), this differential signature presence suggests that CH may escape exposure to melphalan via leukapheresis, and to be reinfused to expand to tMN. We validated this model via the detection of CH via targeted sequencing in pre-melphalan samples in 8/11 tested patients, the detection of platinum but not melphalan signatures in 3 tumors with sequential exposure to both agents, and via detection of SBS-MM1 in two tumors without an escape route (tMN post-oral melphalan and transitional cell carcinoma post-ASCT). Presence or absence of chemo signatures created a dichotomy among tMN in all of SNV, copy number variations (CNV), and structural variants (SV). The mutational burden of melphalan signature-positive tMN was higher than those without ($p = 0.009$). After importing 298 de novo AML exomes from the Beat AML study, de novo AML and tMN lacking chemo-induced mutagenesis shared a similar distribution and frequency of CNV, while tMN harboring chemo signatures preferentially included deletions of 5q, 7q, 17p, and gains in 19p13.2 (FDR< 0.01). Consistent with the CNV, complex SV (i.e., chromothripsis) were enriched in tMN with chemo signatures vs those without ($p< 0.001$). Finally, using chemo signatures among duplicated and non-duplicated mutations across chromosomal gains (i.e., trisomy 8), chromosomal aneuploidies are seen to occur late, following exposure to melphalan.
Conclusions: Using chemo-induced mutations as temporal barcodes, we detail two routes of tMN expansion post-melphalan/ASCT: one in which chemo induces mutations and complexity in pre-leukemic clones and one in which CH can escape exposure to melphalan, outright, and be reinfused to expand in a post-transplant environment, underscoring the importance of investigations into the effect of ASCT on tMN promotion.

OAB-015
Single cell multiomic analysis reveals relapsed and refractory multiple myeloma clusters associated with 1q alterations and overexpression of PHF19 that are present at diagnosis in high-risk patients

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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, gain or amplification of 1q, and TP53 abnormalities. Increasingly, other markers are also being identified that are associated with progression such as PHF19. These markers are highly prevalent at relapse, but can exist in the earlier stages of the disease.
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 underwent CD138+ sorting and single cell multiomic sequencing (RNA-seq and ATAC-seq; 10X Genomics). The single cell data were integrated using Seurat and cell clusters were evaluated for cytogenetic markers, disease progression, gene expression, and other markers of high-risk disease. In total, 335,025 high quality plasma cells were examined across the 49 patient samples.
Results: Integration of all 49 patient samples resulted in 25 clusters representing diverse subsets of malignant and normal plasma cells. We identified a subtype of plasma cells shared by most patients that were associated with RRMM disease that were denoted relapse/refractory-associated plasma cells (RRPCs). The relative proportion of this cluster across patients significantly increased from SMM to NDMM ($P=0.025$) and from NDMM to RRMM ($P< 0.001$). Patients with gain/amp(1q) or TP53 mutations had a greater proportion of RRPCs ($P=0.029$ and $P=0.023$, respectively). Consequently, RRPCs had increased expression of CKS1B in comparison to other clusters ($Log2FC=2.76$, $P< 0.001$) indicative of gain/amp(1q). RRPCs had increased expression of 16 proliferative markers including KIF15, BUB1B, CDC25C, PCNA, and BUB1. When evaluated further for regulatory mechanisms of cell cycle, the RRPCs also had increased expression of PHF19 ($Log2FC=2.79$,$P< 0.001$). Aside from the increase of PHF19 in the RRPCs, there was also upregulation of EZH2 ($Log2FC=2.46$, $P< 0.001$), a downstream effector of PHF19.
Conclusions: We have generated the largest dataset of CD138+ myeloma cell multiomics to date comprising 335,025 cells across 49 patients at different stages of progression. Based on these data, expression of high-risk markers are largely found in a subset of cells from any given patient and this subset increases during myeloma progression. These cells, denoted RRPCs, have an increased proliferative signature and increased expression of PHF19 and EZH2. Given the emergence of immuno-oncology targeting molecules in MM further studies to evaluate the prevalence of BCMA, GPRC5D, FCRL5 and checkpoint genes are underway and results across disease progression from SMM-NDMM-RRMM at single cell level will be reported.

OAB-016
High risk subclones detected at relapse are present from diagnosis in small subclones and impact the prognosis

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Introduction: Multiple myeloma is characterized by many genomic abnormalities, some of which influence patient outcome. For some patients high-risk changes are observed only at relapse(s), suggesting their acquisition during tumor evolution. However, the presence of micro subclonal populations may be missed in bulk analyses. Here, we use single-cell genomics to determine how often these high-risk variants are missed at diagnosis and selected at relapse and evaluated presence of micro subclones on patient outcome.
Methods: In this study, we analyzed single-cell DNA sequencing from 81 patients with plasma cell dyscrasias. Sixty-six patients were done at diagnosis, nine at first relapse, and six in pre-symptomatic stages. We further evaluated the impact of accumulated risk features in patients after initial treatment by using our clinical database that includes FISH and targeted sequencing data from 5659 patients.
Results: We have analyzed longitudinal samples from patients with 1q gain and showed that it was positively selected. A patient with a 1q gain micro subclone at diagnosis detected by single cell sequencing but not detected in the routine assessment, showed post-induction (thus before high-dose melphalan and autologous stem cell transplantation) 1q gain enrichment (70% of the analyzable cells), and at disease progression 92% of the cells harbored the 1q gain. To investigate whether the presence of these high-risk subclones at diagnosis impacts outcome, we used a pre-existing patient database that records information on both high-risk genotypes and survival parameters described above. We found statistically significant increase in 1q gain and 17p deletion in relapse compared to diagnosis. To further investigate this, we compared the survival curves of patients who had a high-risk subclone detectable by routine assessment at diagnosis compared to those who only had it in the first relapse. For 1q gain, PFS and OS curves were superimposable, suggesting that high-risk subclone was present at diagnosis and likely expanded to detectable levels before relapse. However del17p and del1p showed intermediate outcome for subclonal events detected only at relapse.
Conclusions: These data suggest that identifying these scarce aggressive cells using new approaches like single cell sequencing may necessitate more aggressive treatment as early as diagnosis to prevent them from becoming the dominant clone.

OAB-017

Mutations accumulated before and after hyperdiploidy reveal timing and impact of chromosomal gains on multiple myeloma

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Introduction: Nearly half of the Multiple Myeloma (MM) patients show hyperdiploidy (HMM) at diagnosis. Although HMM is early, possibly at the beginning of the oncogenic transformation, and a frequent event, processes leading to hyperdiploidy and post-hyperdiploidy are still unclear.
Methods: We used WGS data of 214 MM patients, of which 102 were HMM. We examined VAF for each mutation on the hyperdiploid chromosomes, selecting a VAF of around 67% or 33% after purity correction for pre- and post-HMM mutations. We hypothesize that through the analysis of these mutations, we may allude to the order of processes in HMM.
Results: We identified the pre-HMM and post-HMM clonal mutations at 80% confidence interval. The ratio of post-HMM mutations to pre-HMM mutations was 3.61 (±0.12 SEM), indicating that 28% of clonal mutations accumulated before hyperdiploidy. Mutational burden in hyperdiploid regions was 1.8 per Mb compared to 2.3 per Mb in diploid regions from the same patients (p-value 2.1e-5). Similarly, non-HMM MM patients had a significantly higher mutational load on odd number chromosomes than HMM (3.6 vs. 1.8 per Mb, p-value

0.02). This suggests that these odd number chromosomes are not as protected in non-HMM cases. We have evaluated mutational signatures in pre- and post-hyperdiploid mutations using NMF. NMF identified six stable signatures after permutation testing showing high cosine similarity to found signatures (0.94±0.05 SD), indicating found signatures are not highly dependent on individual samples. Exposure in pre-hyperdiploid mutations showed a high contribution of AID (34.0%), SBS17b (15.0%) and age/Clock-like signature. Exposure to post-hyperdiploid mutations showed a contribution of DNA damage (18.7%) and APOBEC (24.3%). The number of absolute mutations attributed to AID was similar for pre- and post-mutations (65 vs. 75, p-value 0.265), indicating AID was active before hyperdiploidy. The number of mutations and normalized exposure attributed to APOBEC and DNA damage increased for the post-hyperdiploid group (p-value 2.2e-16). Moreover, HMM patients with high-risk features showed more post-hyperdiploidy mutations (865 vs. 570, p-value 0.009).
Conclusions: Emerging data from our study suggest that HMM cells accumulate ~28% of mutations in the pre-hyperdiploid phase. Moreover, dominant AID presence in pre-hyperdiploid mutations suggests that hyperdiploidy happens after the somatic hypermutations process. We have previously shown that hyperdiploid patients have a lower mutational load than non-HMM patients. Here, we also found that mutational load in hyperdiploid regions is low compared to diploid regions from the same individual, suggesting a possible activation of protection on these chromosomes. Further work is necessary to validate this. Our data also confirmed the activation of APOBEC and DNA damage processes in the post-hyperdiploid stage. Although similar processes were active for all HMM, high-risk features eventually caused more mutation accumulation post-transformation.

OAB-018
From CARDAMON to CoMMpass: a mutational signature that predicts carfilzomib-specific outcomes in myeloma

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Introduction: Clinical trials provide critical evidence for myeloma therapy. However, therapeutic comparisons are limited within any one trial. Furthermore, a good response in one trial arm indicates that the majority of patients gained benefit, but less is known about those who did not, or those who may have benefited equally from a less potent, more tolerable treatment. Predictive biomarkers are therefore needed to provide more context for clinical trial data interpretation. We have previously shown that a transcriptional signature can be used to rationally select between bortezomib- and lenalidomide-based treatments. Correct therapy selection according to this signature markedly improved survival. However, transcriptional signatures are challenging to implement in the clinic. As part of the CARDAMON clinical trial, in which newly diagnosed patients received upfront carfilzomib/cyclophosphamide/dexamethasone (KCD) induction and maintenance, we implemented whole exome sequencing and applied machine learning algorithms to derive a mutational signature specific for outcome in carfilzomib-treated patients.
Methods: Patients enrolled in the CARDAMON trial underwent whole exome sequencing (WES) of selected baseline CD138+ cells. Following quality control of the data, we trained a boosted tree classification model on an 80:20 data split to identify patients with a progression-free survival (PFS) of >18 months. Model parameters were chosen to favour simplicity. Once the model was locked, independent testing was performed in the CoMMpass dataset.
Results: 141 CARDAMON patients had good quality exome sequencing data suitable for analysis. Mutation and copy number changes across the dataset were typical for a myeloma cohort. We identified a mutational signature in which absence of mutations across five genes was associated with better outcome following KCD treatment. These genes (MGAM, CCDC168, PDXDC1, ABCC1, S1PR2) were not targets of known driver mutations, nor did their mutation associate with known driver mutations or with Revised International Staging System score. In cross-validation, the signature achieved an accuracy of 72%. When applied to 154 patients in the CoMMpass study who had received upfront carfilzomib-based therapies, patients predicted as carfilzomib-responsive

had a median PFS of 58.8 months, whereas those predicted to be less responsive had a median PFS of 33.2 months (p=0.0067). The signature was carfilzomib-specific, as it did not separate patients treated with first-line bortezomib/cyclophosphamide/dexamethasone or cyclophosphamide/dexamethasone.
Conclusions: We present a simple prediction model for response to carfilzomib-based therapy in newly diagnosed myeloma. It is not a general prognostic signature, but rather is specific to carfilzomib. Absence of mutations in five genes predicts for good response to carfilzomib. Being mutation-based, it could be easily applied in the clinic by adding the genes to a targeted exome sequencing panel.

OAB-019
Proteogenomic screens reveal that RAS commandeers the amino acid sensing machinery to aberrantly activate mTORC1 in multiple myeloma

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Introduction: Oncogenic mutations within the RAS pathway are common in multiple myeloma (MM), with KRAS and NRAS each mutated in about 20% of newly diagnosed MM cases. MM is unusual in this regard, as other RAS-dependent tumor types typically rely on a single isoform of RAS. RAS can signal through a number of effector pathways, but perhaps most characteristically by activation of the classical MAP kinase (MAPK) pathway through RAF, MEK and ERK. Despite the high frequency of RAS mutations in MM, there is no clear role for classical MAPK signaling in MM pathogenesis and MEK inhibitors have little success treating MM patients harboring mutant RAS. These findings suggest that RAS-dependent activation of the classical MAPK pathway is not the sole mode of RAS signaling in malignant plasma cells and point to an unidentified role for oncogenic RAS signaling in this disease.
Methods: To uncover mechanisms of pathogenic RAS signaling in MM, we employed an unbiased proteogenomic approach to dissect RAS signaling in MM by combining genome-wide CRISPR-Cas9 screening with quantitative mass spectrometry focused on RAS biology.
Results: This approach revealed the "essential interactome" of mutant RAS and highlighted the connection between RAS and SLC3A2. SLC3A2 (CD98, 4F2hc) is a component of several heterodimeric amino acid transporters for large neutral amino acids, including SLC3A2-SLC7A5 that serves to transport leucine and glutamine (11). Proteomic analysis of RAS and SLC3A2 interaction partners and dependent signaling networks identified that mTORC1 was activated downstream of both RAS and SLC3A2. We determined that RAS coordinated the co-localization of SLC3A2 and MTOR on LAMP1+ endolysosomes, where RAS, SLC3A2 and MTOR cooperatively activated mTORC1. RAS accomplished this by subverting nutrient sensing pathways that normally regulate homeostasis through mTORC1. Inhibition of RAS-dependent mTORC1 activity enhanced reliance on MEK and ERK signaling in MM cells, and combinations of mTORC1 and MEK inhibitors resulted in a synthetic lethal phenotype that was profoundly toxic to RAS-dependent malignant cells.
Conclusions: This study details a new concept in pathogenic RAS signaling in MM and provides a mechanistic and rational basis to target this novel mode of RAS signaling.

OAB-020
RAD51 interacts with minichromosome maintenance protein complex (MCM2–7) providing strong dependency in myeloma

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Introduction: Genomic instability, a prominent feature of cancer cells, is associated with cancer progression and drug resistance, and appears to impact cancer cell proliferation as well. Inhibiting RAD51, the key protein involved in homologous recombination (HR), reduces spontaneous and chemotherapy-induced genomic instability. A CRISPR interference-based functional screen also identified RAD51 as one of the top dependencies in MM.
Methods: RAD51 expression in normal PBMC and MM cell lines was evaluated by Western blotting. To investigate RAD51 expression in MM patient samples, GSE6477 dataset (MGUS = 22, SMM = 24, MM = 73, and Relapse = 28) was used. RAD51 expression was suppressed using shRNA. DNA replication was assessed by EdU incorporation assay. RAD51 protein complexes were identified using mass spectrometry (MS) as well as chromatin interacting protein-mass spectrometry (ChIP-MS).
Results: To validate RAD51 as a dependency and investigate mechanisms by which it impacts proliferation of MM cells, we assayed RAD51 expression and found that it was undetectable in normal PBMC, whereas it was substantially increased in MM cell lines. We also found increased expression in patients with SMM, MM, and relapsed MM (p values ≤ 0.008). Transduction of MM cell lines (H929 and JJN3) with shRNAs, caused a 70−80% reduction in RAD51 expression and led to near complete inhibition of growth. To understand the mechanisms by which RAD51 impacts MM cell proliferation, we investigated RAD51 protein complexes using MS and ChIP-MS in MM cells (H929 and JJN3). In the absence of DNA, the RAD51 protein complex consisted of 56 proteins including ATR, NBN, RPA3 and WRN, which have roles in the initial phases of the DNA repair process. Interestingly, in the presence of DNA, the RAD51 complex had several DNA replication proteins including PCNA and members of the minichromosome maintenance protein complex (MCM2–7), which assembles the replication machinery at genomic origins of DNA replication. Inhibiting MCM2 not only inhibited the growth of MM cells but also that of RAD51-overexpressing normal human fibroblasts. Importantly, using a flow cytometry–based EdU incorporation assay, we found that RAD51 knockdown inhibited DNA

replication in MM cells. Consistent with the physical association of RAD51 with the replicative complex (MCM2-7), coimmunoprecipitation experiments demonstrated that RAD51 also interacts with key proteins involved in the signaling networks for growth stimulation and cytokinesis. These include AKT (phosphorylated at S473), FOXM1, phosphorylated FOXM1, E2F1 and ALIX. FoxM1 is a key downstream gene of the Akt/FoxM1 signaling cascade, whereas transcription factor E2F is a component of the downstream proliferative machinery regulated by Akt, and ALIX is an important component of the protein complex mediating cytokinesis.
Conclusions: Our data provide initial evidence for the requirement of RAD51 for assembly and/or regulation of replication machinery at the origins of genome replication in MM cells.

OAB-021
High-risk multiple myeloma due to extramedullary disease-like gene expression induced by bone marrow stromal cells

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Introduction: Bone marrow stromal (BMS) cells induce chromatin remodeling and gene expression in multiple myeloma (MM) cells through cell-cell contacts and soluble factors. These stromal interactions protect MM cells against cytotoxic therapies and immunotherapies through several mechanisms including altered gene expression. Here, we investigated the predictive and prognostic implications of BMS-induced gene expression in newly diagnosed MM.
Methods: By integrating ATAC-seq and RNA-seq data, we identified genes characterized by increased expression and accessibility of associated cis-regulatory elements (CREs) in MM cells (INA6, MM1S, RPMI) upon co-culture with BMS cells (H5). Using proportional hazards regression and automated feature selection we developed a 10-gene expression classifier. We evaluated the classifier's independent prognostic significance (PFS and OS) and predictive power (therapeutic resistance and extramedullary disease dissemination) in newly diagnosed MM.
Results: BMS cells induced chromatin remodeling and associated changes in gene expression in MM cells. We identified 68 overexpressed genes with increased accessibility of associated CREs (p=1.05x10-13). Gene set enrichment analysis demonstrated that the expression of these 68 BMS-induced genes is akin to the transcriptional program of extramedullary MM cells (5376 circulating MM cells, NES 1.41, FDR=0.027; 477 MM cells from malignant effusions, NES 1.37, FDR=0.029). The expression of 10 of these 68 genes was independently associated with PFS in UAMS TT2/3. The 10-gene expression classifier identified adverse stromal interactions (ASI+) in approximately 30% of patients. ASI+ was associated with OS in three independent patient cohorts with newly diagnosed MM: UAMS TT2/3 (29% ASI+, HR 1.93, 95% CI 1.43-2.62, p< 0.001, n=559), IFM 2009 (32% ASI+, HR 2.61, 95% CI 1.67-4.10, p< 0.001, n=214), and MMRF IA16 (30% ASI+, HR 1.69, 95% CI 1.29-2.24, p< 0.001, n=635). Its prognostic significance was independent of age, sex, ISS stage, elevated LDH, high-risk cytogenetics, UAMS-70, and EMC-92. ASI+ predicted resistance to first-line therapy in general and to VRd induction in particular (OR 1.64, 95% CI 1.10-2.43, p=0.015, MMRF IA16, n=211). This extramedullary-like gene expression pattern (ASI+) also translated into a higher prevalence of circulating plasma cells among newly diagnosed patients (54% versus 35%, p=1.65x10-5, MMRF IA16, n=629) and a higher incidence of bone disease and plasmacytoma progression during follow-up (HR 2.24, 95% CI 1.51-3.31, p< 0.001, MMRF IA16, n=622).
Conclusions: We identified an extramedullary disease-like transcriptional program in MM cells induced by BMS cells. In newly diagnosed MM patients, this was associated with therapeutic resistance, accelerated disease dissemination, and impaired long-term survival. These transcriptional changes may allow MM cells to sustain extramedullary growth and the development of novel therapies to overcome such adverse stromal interactions remains an unmet need.

OAB-022
The role of bone marrow adipocyte-modulated aryl hydrocarbon receptor activity in multiple myeloma cellular growth and survival

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Introduction: Obesity is a major risk factor for incidence and progression of monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) to multiple myeloma (MM); however, the mechanisms driving obesity-associated progression are currently unknown. Epidemiologic data demonstrates that exposure to environmental aryl hydrocarbon receptor (AhR) agonists such as dioxin, benzene and polyaromatic hydrocarbons increases the rates of MGUS and MM. While the AhR is a ligand-activated transcription factor that controls a diverse set of genes, we describe a novel role for the AhR in obesity-mediated MM progression.
Methods: To evaluate the functional effects of bone marrow adipocytes on AhR expression in myeloma cell lines, we used AhR expressing myeloma cells, MM.1S, and AhR-null cells, U266B1, in direct co-cultures with bone marrow stromal cells differentiated to adipocytes in vitro. Additional computational approaches were utilized to interrogate publicly available gene expression and clinical outcome data

to determine the translational significance of AhR expression in myeloma patients.
Results: Our data demonstrate higher expression levels of AhR in obese myeloma patients and that elevated AhR is associated with poor clinical outcome. These patient studies are complemented by our in vitro studies which show that bone marrow adipocytes secrete factors to elevate AhR expression in MM cell lines. The increased expression of the AhR in MM cell lines led to subsequent changes in AhR activity and transcriptional regulation/protein production of the pro-myelomagenic factor, IL-6. In concordance with AhR's regulatory role on cell cycle progression, treatment with adipocyte conditioned media promoted an enhanced proliferative phenotype in MM cells expressing AhR. Pathway analysis of genes positively associated with high AhR expression levels across myeloma cell lines, revealed an enrichment of genes connected to KRAS signaling, suggesting a link between AhR levels and KRAS activity. Importantly, myeloma cells co-cultured with adipocytes have elevated phosphorylation of target proteins downstream of RAS, suggesting adipocyte-driven RAS activation in myeloma cells, a process exacerbated in AhR expressing cells. Additionally, MM cells exposed to adipocyte-derived factors became more resistant to Bortezomib treatment in vitro.
Conclusions: Collectively, MM cells exposed to bone marrow adipocytes have elevated AhR levels, augmented production of IL-6, increased RAS activity, and functionally display subsequent enhanced proliferation and chemoresistance. These findings suggest the AhR as a potential link between environmental and dietary/lifestyle risk factors in MM and further strengthen the rationale for targeting the AhR in MM therapy.

OAB-023
Single-cell analysis reveals disease induced perturbations of CD8+T-cell subsets in the bone marrow and peripheral blood of newly diagnosed multiple myeloma patients

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Introduction: CD8+T-cells have a well-established role in myeloma control. We examined the impact of multiple myeloma (MM) on CD8+T-cells isolated from the bone marrow (BM) and peripheral blood (PB) using age-matched individuals without MM as a control.
Methods: Purified CD8+T-cells were isolated from BM and PB mononuclear cells of MM patients and subjected to scRNA-seq, inclusive of paired TCR-seq. Transcriptomic maps generated from paired BM and PB samples were compared with public data from age-matched controls in both resting and TCR-activated states. [1] Samples from MM, MGUS and age-matched controls were further assessed by high-dimensional flow and mass cytometry. Analysis was performed using custom bioinformatics pipelines, publicly available tools (TCRMatch and ERGO-II) and FlowJo.
Results: Unsupervised clustering revealed effector memory (TEM) cells as the dominant subset in BM. BM-TEM from MM patients reflected the transcriptional profile of TCR activated cells from age-matched controls, demonstrating significant ($p< 0.0001$) enrichment in several AP-1 associated genes (e.g. FOS, JUN and JUNB) and other markers of activation. Clonal CD8+T-cells, evident in BM and PB, potentially specific for common peptides previously reported as over-expressed in MM, [2] were observable in multiple individuals and demonstrated evidence of restricted gene usage, possibly suggestive of public clonotypes. Differences between BM and PB were apparent by cluster restricted expression of Granzyme B (GZMB) and Granzyme K (GZMK), with the latter predominantly evident within the BM and largely co-expressing CD69. CD69 expression was restricted to the BM and delineated two independent CD8+T-cell subsets. There were no differences in the proportion of CD8+T-cells expressing CD69 in any cohort, however MM patients demonstrated significantly higher CD38 and CD69 expression ($p< 0.01$) within the CD69+ subset along with marked differences in Granzyme expression in the CD69- subset compared to age-matched controls. BM-CD8+CD69- T-cells from MM patients appeared to mimic cells from the PB, in which Granzyme B is more highly expressed compared to BM, demonstrating a near BM:PB 1:1 ratio, which was significantly higher ($p< 0.05$) than that in age-matched controls. CD8+ TEM analysis by mass cytometry confirmed the relative phenotypic homogeneity of the CD69+ subset, contrasting the highly heterogeneous CD69- subset.
Conclusions: While BM-CD8+CD69- T-cells cells appear phenotypically diverse and demonstrate markedly higher levels of Granzyme B expression in MM compared to age-matched controls, BM-CD8+CD69+ T-cells are relatively homogeneous. The MM-associated changes are largely restricted to elevated levels of CD38 and CD69 and increased transcriptional activity of early effector genes, suggestive of chronic activation of these cells in myeloma. References: [1] Szabo et al., Nat Commun 10, 4706, [2] Walz et al., Blood. 2015 22;126(17):2072-3.

OAB-024
T cell differentiation in the bone marrow during disease evolution: insights from COSMOS and integrative analysis of 317,000 single-cell transcriptomes

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Introduction: The immune microenvironment in myeloma is reported to be increasingly dysfunctional during progression

from SMM to symptomatic disease. T cells reside homeostatically in the BM, where tumour-reactive clones may be recruited to mediate tumour destruction. Phenotypic alterations to BM T cells may therefore serve as a proxy for tumour-promoting niche remodelling or immune fitness, with the potential to stratify SMM patients by risk of progression. We present the first T cell-sorted scRNAseq dataset of a SMM cohort and re-analyse published healthy and myeloma scRNAseq to place smouldering T cells into the continuum of progression.
Methods: We performed scRNAseq with scTCRseq on fresh BMMNCS from 14 SMM patients using 10X Genomics 5' kit. Analysis and integration were performed in scanpy and scVI. In an independent cohort we analysed 941k T cells from 11 SMM and 9 MM patients by CyTOF with a 40-marker T cell panel.
Results: In our 75k cell scRNAseq dataset we describe a range of T cell phenotypes in SMM patients, ranging from naïve to terminal memory. We identified PD1-expressing activated CD8+Tem, but could not resolved exhausted cells. Within CD4s, we identified Th17 and cytotoxic cells. TCR clonality increased linearly with differentiation, most clonal expansions seen in GZMB+ subsets. CyTOF described similar phenotypes in SMM; PD1+ activated CD8+Tem were identified but similarly lacked other exhaustion markers. Differential abundance and expression testing between SMM risk groups showed minimal differences, suggesting the T cell compartment varied independent of existing SMM risk groups. We extended our dataset with BM T cells from published data, creating an integrated atlas of 317k T cells from samples of healthy(n=58), MGUS(16), SMM(19) and MM donors(38). Our T cell phenotypic landscape was re-capitulated in this larger dataset. We saw marked similarity in T cell phenotypes across patient groups, with no T cell populations uniquely found in MM or healthy donors. CyTOF also showed no phenotypic differences between SMM and MM. We observed an increase in the proportion of late-stage GMZB+ CD8 terminal effector T cells (CD8+Tte) in the BM in SMM or MM patients vs healthy donors(vs HD: in SMM P=0.001, MM P< .001), with a concomitant fall in naïve cells(vs HD: CD4Tn in MM P=.002; CD8Tn in SMM P< .001 and in MM P=.002). These results were independent of age. This proportional shift described cross-sectionally was recapitulated longitudinally in paired SMM-MM samples, suggesting this compositional dynamic occurs from SMM to progression.
Conclusions: Our analysis provides the first in-depth description of the SMM T cell landscape and a unification of BM T cell phenotypes. We show myeloma evolution is accompanied by enrichment of CD8+Tte and loss of naïve cells. We noted no clear emergence of an exhausted subset, suggesting distinct immune evolutionary processes to those reported in solid tumours. We plan to make our atlas available for MM researchers.

OAB-025

The role of checkpoint inhibitor PD-1H/VISTA in osteoclast activation and bone disease in multiple myeloma

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Introduction: Multiple myeloma bone disease (MMBD) is caused by increased bone resorption coupled with impaired bone formation. MM cells produce osteoclast-activating factors that induce osteoclast (OCL) activation and extensive bone resorption. Our previous work demonstrated that MMP-13 is a critical osteoclastogenic factor that is highly secreted by MM cells. Checkpoint inhibitor, programmed death-1 homolog (PD-1H/VISTA), serves as the MMP-13 receptor in OCLs and mediates its osteoclastogenic function. While the inhibitory role of PD-1H in T-cells is described, its cellular binding proteins remain unclear, and its role in OCL activation and MMBD has not been addressed.
Methods: PD-1H binding proteins were pulled down by Ni-NTA agarose from PD-1H-His6 overexpressing mouse BMMNC lysates and identified by mass spectrometry. PD-1H and F-actin cellular localizations were detected by IF confocal microscopy. The in vivo role of PD-1H in MMBD was evaluated by micro-CT analysis on the intratibial 5TGM1 MMBD model.
Results: Functional annotation charting of the proteins enriched in PD-1H pull-down samples indicated that ~30% of the interacting targets were cytoskeleton or associated proteins. F-actin cytoskeleton undergoes dynamic reorganization and plays a critical role in bone resorption. We found that PD-1H co-localizes with F-actin podosome clusters, rings, and sealing belts during OCL differentiation. Pd-1h-/- leads to the disruption of podosome clusters at early stages relative to WT controls, while at later stages, Pd-1h-/- OCLs exhibited significantly fewer F-actin rings and belts. Further, the binding of MMP-13 to PD-1H increased the number of OCLs forming F-actin rings and belts, and the size of F-actin belts, which was blocked in Pd-1h-/- OCLs. The in vivo role of PD-1H in the development of MMBD was examined by the intratibial 5TGM1 MMBD model using Pd-1hwtRag2-/- vs Pd-1h-/-Rag2-/- mice (n=10). Quantitative histomorphology analyses by micro-qCT of the trabecular and cortical bones confirmed that Pd-1h-/- reduced bone destruction with significantly less decrease in trabecular bone volume, trabecular bone number, trabecular bone thickness, as well as less increase in trabecular bone spacing and bone specific surface compared to Pd-1hwtRag2-/- mice. Similar effects were observed in cortical bone with less decrease in cortical bone thickness, cortical bone area fraction, and cortical tissue mineral density in 5TGM1 bearing Pd-1h-/-Rag2-/- mice vs Pd-1hwtRag2-/- mice.
Conclusions: Taken together, our study reveals the novel role of checkpoint inhibitor, PD-1H/VISTA, in osteoclast and multiple myeloma bone disease. PD-1H associates with cytoskeleton proteins and regulates the F-actin cytoskeleton

reorganization which is critical for OCL bone resorption activity. Further, PD-1H mediates MMP-13-induced OCL fusion, F-actin belts formation, and OCL activation. Pd-1h-/- in recipient mice significantly impairs MM-induced bone loss, demonstrating that PD-1H/VISTA plays a critical role in MMBD.

OAB-026

Humoral immune reconstitution after quadruplet therapy, autologous hematopoietic cell transplant (AHCT) and measurable residual disease adapted treatment cessation in newly diagnosed myeloma (NDMM)

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Introduction: Quadruplet induction, AHCT, and measurable residual disease (MRD) response-adapted consolidation yields unprecedented depth of response in NDMM. Immune reconstitution (IR) in patients (pts) receiving limited duration intensive therapy is unknown.
Methods: NDMM pts treated on MASTER (NCT03224507) received induction with daratumumab, carfilzomib, lenalidomide, and dexamethasone (DKRd; 4 cycles), followed by AHCT and 0, 4 or 8 cycles of DKRd consolidation guided by serial assessments of bone marrow MRD by next-generation sequencing (NGS, ClonoSEQ®). Pts with two serial MRD< 10-5 stopped therapy and entered active surveillance for MRD resurgence (MRD-SURE). The primary objective of this study was to evaluate humoral IR of MRD-SURE pts by characterizing quantitative changes in the repertoire of immunoglobulin (Ig) genes (IgH, IgK and IgL) by NGS and serum gamma globulin levels.
Results: After induction, the IgH repertoire was small and lacked diversity (median unique sequences (mus) 11,330/106, IQR 5,711-23,143). Of 63 evaluable pts who received AHCT and ³ 4 cycles of consolidation, a substantial expansion of the IgH repertoire was seen 90 days after AHCT (75,375 mus/106, IQR 49,361-113,305, P< 0.001) with a contraction after consolidation (15,795 mus/106, IQR 5,571-33,732, P< 0.001). Pts who received post-AHCT consolidation (N=27) had a smaller IgH repertoire at MRD-SURE entry compared to pts entering MRD-SURE after AHCT (N=28) (15,082 v 76,266 mus/106, p< 0.001), with near but incomplete recovery after 6 months (mo) of treatment cessation (83,954 v 107,715 mus/106, p=0.037) and no difference at 18 mo (109,989 v 115,246 mus/106, P=0.72). Similar findings were seen for IgK and IgL. The serum protein gamma fraction was depressed (median 0.3 g/dL) in pts entering MRD-SURE post-AHCT, but rose off therapy (medians at 2, 6, 10, and 18 mo 0.33, 0.48, 0.65, and 0.75 g/dL, respectively). Of those receiving consolidation, the gamma fraction remained low and increased after 6 mo (medians at 0, 2, 6, 10, and 18 mo 0.29, 0.25, 0.28, 0.41, and 0.60 g/dL, respectively).
Conclusions: Quadruplet, anti-CD38 mAb-containing therapy leads to profound hypogammaglobulinemia and quantitative reduction in Ig gene repertoire. We report a delayed IR in pts who received post-AHCT consolidation as compared to those who did not, a rapid expansion in Ig repertoire with a plateau at 6 mo for both groups, and no statistically significant difference 18 mo after treatment cessation. Recovery of the Ig repertoire occurred before recovery of gamma globulin levels. These findings may have implications for the timing of post-AHCT immunizations and the risk of infection in pts who stop therapy. Further evaluation of IR after MRD-adapted therapy is warranted as new immunotherapeutic agents are incorporated in treatment regimens.

OAB-027

Discovery of tumor-reactive T cell receptors in multiple myeloma

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Introduction: Novel immunotherapeutic approaches including cell therapy are believed to be the next generation of paradigm-changing treatment options in hematological malignancies. Cell therapy using CAR-T cells or expanded autologous T cells (TILs) has shown promising results in non-solid and solid malignancies. However, acquired resistance to immunotherapy or rapid disease progression represent major clinical challenges in multiple myeloma and tumor-infiltrating T cells are often dysfunctional and inert to reactivation. Patient-autologous lymphocytes with genetically engineered T cell receptors (TCR) to recognize tumor antigens can induce remarkable and durable regression of refractory solid tumors. However, a bona fide population of myeloma reactive TCRs is yet to be identified.
Methods: We performed single-cell profiling coupled with functional TCR testing of tumor-infiltrating lymphocytes (TILs) in multiple myeloma patients to understand diversity, phenotype dynamics and specificity of T cells and to translate these findings into a workflow for the development of personalized adoptive T cell therapy. To this end, we utilized samples from patients with newly diagnosed multiple myeloma. From these patients we matched single-cell RNA/TCR/CITE sequencing data with mutational load and functional validation of TCR : anti-tumor reactivity by testing TCR reactivity against malignant plasma cells and synthetic neoepitopes. Furthermore, we have established a multiplexed optical barcoding assay to allow for single-cell profiling of individual bone marrow resident T cells with reactivity against isolated autologous patient myeloma cells to identify patient-specific myeloma-reactive TCRs.
Results: In our proof of principle patient cohort, we have performed whole-genome sequencing (WGS), single-cell RNA/TCR-Seq in malignant bone marrow plasma cells from 18 newly diagnosed multiple myeloma patients. TCR clonality analysis revealed that the patients exhibiting the highest tumor mutational load acquired hyperexpanded T cell clones in both bone marrow and peripheral blood. By performing downstream neoepitope prediction and functional in vitro testing of neoepitope- and anti-tumor reactivity in both, patient-specific TILs and TCR-transgenic T cells, we provide proof of principle of tumor-reactive T cell receptors in multiple myeloma. We furthermore identified a previously unknown subset of Thymocyte selection-associated high mobility group box protein (TOX)-expressing dysfunctional myeloma-associated T cells that is associated with limited response to induction immunochemotherapy.
Conclusions: Our results demonstrate significant antitumor reactivity in a subset of bone marrow-derived TILs against malignant plasma cells and provide the rationale for future personalized cell therapy approaches in myeloma patients. More broadly, the generated resources from this project might contribute to identifying and monitoring tumor-reactive T cell responses targeting hematological neoplasms.

OAB-028

Single-cell dissection of bone marrow and peripheral blood immune cells in a large cohort of patients with smoldering multiple myeloma at diagnosis and post-therapy

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Introduction: Patients with Smoldering Multiple Myeloma (SMM) already exhibit hallmarks of immune dysregulation, as well as suboptimal response to immune challenges, such as vaccination for SARS-CoV-2. Preliminary evidence suggests that early therapeutic intervention may prolong progression-free survival in patients with high-risk SMM, however it is unclear how underlying immune dysregulation may impact risk and outcomes. Immune profiling of large cohorts of patients may help to independently identify subsets at risk of progression and/or suboptimal response to therapy.
Methods: Here, we performed single-cell RNA-sequencing (scRNA-seq) on 149 samples, drawn from 34 patients with high-risk SMM who were enrolled on a Phase II clinical trial of Elotuzumab, Lenalidomide, and Dexamethasone (E-PRISM), and 32 healthy donors. Specifically, we profiled 117 patient samples, including 57 bone marrow (BM), and 60 peripheral blood (PB) samples, drawn at baseline, during, or at the end of treatment (EOT). For 24 patients and 40 samples, data was generated from matched BM and PB immune cells to enable head-to-head comparisons. Furthermore, we profiled BM immune cells from 22 healthy donors and PB immune cells from 10 healthy donors.
Results: In patients with high-risk SMM, we observed increased abundance of: naïve and memory CD4+ T-cells, and in particular, regulatory T-cells, Th2, Th17, and Th1 cells, GZMB+ effector CD8+ T-cells and cytotoxic NK cells, memory B-cells, marginal-zone B-cells, CD16+ monocytes, macrophages expressing the complement component C1q, and canonical type 2 dendritic cells (DCs). Furthermore, we observed decreased abundance of: progenitor cells, central memory and GZMK+ effector memory CD8+ T-cells, mucosa-associated invariant T-cells, CD160+ GZMK+ NK cells, CD14+ monocytes expressing L-Selectin, pro-inflammatory cytokines and chemokines, and plasmacytoid DCs. Immune composition in the PB strongly correlated with that of matched BM samples (median Pearson's r=0.73). In principal component (PC) analysis, diagnostic BM and PB patient samples clearly separated from normal BM and PB samples (Wilcoxon p=3.9e-10, and p=3.2e-4, respectively), demonstrating that both BM and PB immune cells reflect the presence of SMM. Moreover, BM samples drawn at EOT were more closer to normal BM in PC space compared to diagnostic samples, providing evidence of post-therapy immune normalization, which could have prognostic implications.

Conclusions: To our knowledge, this is the largest to date study of immune scRNA-seq profiling in patients with SMM, and the first systematic attempt of this scale to assess the feasibility of using PB for immune profiling in patients with myeloma. Here, we present a comprehensive dissection of alterations in the composition of the BM immune microenvironment, demonstrate that PB mirrors the composition of the BM immune compartment, and provide evidence of post-therapy immune normalization, which could have prognostic implications.

OAB-029

Single-cell transcriptomic analysis reveals reduction of cytotoxic NK cells in a subset of newly diagnosed multiple myeloma patients impacting outcome after daratumumab therapy

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Introduction: Anti-CD38 antibody-based therapies in multiple myeloma (MM) rely to a large degree on natural killer (NK) cell-mediated antibody-dependent-cellular cytotoxicity. Classically, NK cells are divided into cytotoxic CD56dim and cytokine-producing CD56bright subsets. However, accumulating evidence suggests a larger degree of heterogeneity in the NK cell compartment and we hypothesized that changes in NK cell subset composition would impact responses to NK cell-driven immunotherapies in MM. Here, we used single-cell RNA sequencing to investigate the heterogeneity of the NK cell compartment in the bone marrow of newly diagnosed MM (NDMM) patients, and the effects of altered NK cell subset composition on therapy response in patients undergoing first-line daratumumab-containing therapy.

Methods: We performed single-cell RNA sequencing of the CD38+ immune cell compartment in 19 NDMM patients. NK cells were identified in silico resulting in a single-cell transcriptomic dataset of 24,664 BM NK cells.
Results: UMAP dimensionality reduction identified 5 transcriptomic distinct NK cell clusters, present in all NDMM patients. MM bone marrow was characterized by heterogeneity in the ratio of cytotoxic vs cytokine-producing NK cell cluster composition, with a subset of patients (3/19) presenting with a relative decrease in cytotoxic NK cell clusters. The reduction in cytotoxic NK cell subsets in this patient subgroup was reflected in an altered overall transcriptome of the total BM NK cell population, with enrichment for inhibitory receptors such as KLRB1 and KLRC1, and a relative loss of activating receptors such as FCGR3A (CD16), NCR3 (NKp30) and CD226 (DNAM-1), and cytotoxic effector genes including NKG7 and GNLY. Flow cytometric analyses of 246 NDMM patients from 2 independent clinical cohorts revealed reduced frequencies of cytotoxic CD56dim NK cells, determined as < 90% CD56dim NK cells, in 17.9 % of 162 transplant-eligible treatment-naïve NDMM and in 28.6% of 84 treatment-naïve frail or unfit transplant ineligible MM patients. To test whether such relative decrease in cytotoxic NK cells would negatively impact responses to daratumumab, we associated BM NK cell composition with clinical outcome in the context of first-line daratumumab therapy in a cohort of frail NDMM patients ineligible for transplant from the HO143 trial (n=43). Multivariate cox regression analyses revealed that reduced frequencies of CD56dim NK cells in the BM correlated with significantly shorter progression-free survival (PFS) (hazard ratio 1.38; 95% confidence interval: 1.057 – 1.803; P = 0.018).
Conclusions: Here, we show that about 20% of NDMM patients have a relative reduction in cytotoxic NK cells, which was correlated with significantly shorter PFS following daratumumab-containing therapy in a frail cohort of NDMM patients. Our data suggest that defining BM NK cell composition could stratify patients and identify a subgroup less likely to benefit from therapies driven by NK cell-mediated ADCC.

OAB-031

PHF19 promotes multiple myeloma cell resistant to daratumumab/isatuximab via upregulation in immunosuppressive microenvironment and reduced CD38 target expression

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Introduction: We here investigated whether Polycomb-like protein (PHF19), an epigenetic gene recently identified in high-risk multiple myeloma (MM), influences MM cell response to anti-CD38 immunotherapies and further defined cellular and molecular mechanisms underlying these processes.
Methods: Ex vivo cocultures were used to determine the percentage, viability, proliferation, and function of PHF19-overexpressing (PHF19-OE) vs control (ctrl) MM cell-induced regulatory T (iTreg), in parallel with immune checkpoint markers on conventional T cells (Tcon). Immunosuppressive cytokines and MM antigens (BCMA and CD38) were evaluated in PHF19-OE vs -knockdown (KD) MM cells, followed by NK cell-mediated daratumumab (dara)- or isatuximab (isa)-induced MM cytolysis in vitro and in vivo.
Results: PHF19 OE in MM cells (n=5) induced 2-4-fold higher % iTregs conversion from Tcon, either from PBMCs or purified CD3+ Tcon (n=5, d4). Compared with paired ctrl cells, PHF19-OE MM cells continued to increase % iTreg at later time points (d7), associated with upregulation in cell proliferation (CCND1, CCND2), anti-apoptosis (BCL2, BCL2L1), and Treg-related genes (TGFβ1, IL-10, Foxp3) (P < .0001). Meanwhile, enhanced checkpoint marker (PD1, TIM3, LAG3) expression was prolonged on Tcon co-cultured with PHF19-OE vs ctrl MM cells. IL-10 and TGFβ1 levels were higher in supernatants of PHF19-OE MM cells, alone and in co-cultures. BCMA expression was also increased in PHF19-OE vs ctrl MM cells and APRIL further increased % iTreg in cocultures. PHF19-OE MM cells further augmented Treg-blocked Tcon proliferation determined by CTV-diluted fractions, which was partially neutralized by anti-IL-10 or -TGFβ1 antibodies. Furthermore, CD38 molecule density on MM cell membrane was significantly reduced on PHF19-OE vs ctrl MM cells. CD38 and STAT1 downregulation was next confirmed in PHF19-OE vs ctrl AMO1 tumors developed in mice, together with elevated human κ light chain, soluble BCMA, and TGFβ 1 in matched serum samples. PHF19-OE MM cells became less susceptible to NK-mediated lysis by dara or isa, correlated with decreased % CD107a+ and IFNγ+ NK effector cells. Conversely, PHF19 KD enhanced CD38 expression and rendered MM cells more sensitive to CD38 targeting. In the PHF19-OE vs ctrl AMO1 xenografted NSG mice reconstituted with human NK cells, effects of dara were diminished with PHF19-OE AMO1 tumor regrowth expressing low CD38 and STAT1 and significantly decreased host survival. IFN-related genes remained negatively enriched in PHF19-OE tumor regrowth vs ctrl AMO1 tumors. Moreover, transcript expression of PHF19 was negatively related to CD38 in patient MM cells (Spearman's γ= -0.38 and - 0.2 for GSE5900 and GSE31161, P < .004).
Conclusions: Taken together, PHF19 contributes to MM cell immune evasion thereby immunotherapeutic responses via enhancing iTreg and immune suppressive cytokines while inhibiting IFN-related CD38 and STAT1. These results further support PHF19 as a new therapeutic target in MM.

OAB-033
Pre-clinical models of genetically heterogeneous multiple myeloma reveal mechanisms of immune escape and predict clinical immunotherapy outcomes

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Introduction: Advancing therapeutic discoveries in multiple myeloma (MM) has been historically hampered by the lack of mouse models reflecting the genetic heterogeneity of the disease.
Methods: To circumvent this limitation, we performed a cre-LoxP-based screen in genetically engineered mice carrying eight common MM lesions: NF-κB activation, KRAS-G12D, MYC expression, P53 deletion, BCL2 expression, and translocations t(11;14), t(4;14), and t(14;16). These changes were combinatorially activated at germinal center B cells by a cγ1-cre allele.
Results: Among 42 mouse strains carrying varied genetic combinations, 15 developed bone marrow (BM) tumors fulfilling the key pathogenic elements in human MM: presence of precursor-like states before clinically active disease, genetic diversity within the genetic-risk groups, and the interplay between tumor and immune cells during progression. Integrative multi-OMIC and single-cell analyses of ~500 mice and ~1,000 MM patients revealed a MAPK-MYC genetic pathway that accelerated time to progression across genetically heterogeneous tumors. MYC-dependent

time to progression conditioned immune evasion mechanisms, which remodeled the BM microenvironment and divided MM into immune-cold and inflamed categories. Rapid progressors with early MYC activation exhibited inflamed phenotypes with highly activated/exhausted CD8+ T and NK cells. In contrast, late acquisition of oncogenic MYC in slow progressors promoted an immune-cold MM microenvironment. To determine whether such immunological differences modulate immunotherapy outcomes, pre-clinical trials were conducted in MIcγ1 and BIcγ1 mice, which recapitulate early and late MYC-driven progression, respectively. PD1/PD-L1 blockade therapy extended survival in MIcγ1 mice but not in BIcγ1 mice. Critically, an increased number of cytotoxic CD8+ T cells vs. immunosuppressive CD4+CD25+Foxp3+ regulatory T (Treg) cells underlie immune checkpoint blockade (ICB) efficacy in MIcγ1 mice, while a lower CD8/Treg-cell ratio characterized BIcγ1 mice. In smoldering MM patients, a high CD8/Treg-cell ratio was associated with early progression (2-year PFS, 38% vs. 88%; p=0.005), suggesting that ICB therapy may have a role in high-risk SMM. In newly diagnosed MM patients, a high CD8/Treg-cell ratio characterized only 13% of cases, explaining clinical MM refractoriness to PD-1 blockade, and correlated with early progression under Len/Dex therapy (median PFS, 18 months vs. not reached; p=0.011). In mouse models of ICB-refractory MM, increasing CD8+ T-cell cytotoxicity by simultaneous PD-1 and TIGIT inhibition, or depleting Treg cells with an anti-CD25 antibody yielded prolonged MM control.
Conclusions: Our pre-clinical models enabled integrative analyses of MM genetic and immunological traits at unprecedented levels, allowing to predict clinical immunotherapy responses. We expect that their broad use by the MM scientific community will accelerate clinical translation of curative immunotherapy.

OAB-034
External validation of the simplified score to predict early relapse in multiple myeloma (S-ERMM) in the MMRF CoMMpass dataset

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Introduction: Despite recent advances in the treatment of newly diagnosed multiple myeloma (NDMM), a subset of patients have rapid disease progression. A clinical risk score for early relapse could allow providers to tailor care for those identified as high-risk. Zaccaria et al recently proposed the Simplified Score to Predict Early Relapse in Multiple Myeloma (S-ERMM), which uses clinically available variables to predict relapse by 18 months (ER18) in NDMM (CCR 2021). However, it has not been externally validated and only 14% of the derivation cohort received both proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs) as part of induction. Hence, we sought to validate the S-ERMM in a prospective cohort of patients receiving modern triplet regimens and compare its performance to the R-ISS.
Methods: The MMRF CoMMpass study (NCT01454297) prospectively collected outcomes for 971 patients diagnosed with MM between 2011 and 2015. Bone marrows were assessed centrally; chromosomal abnormalities (CAs) were assessed on CD138-selected samples by sequential Fluorescence In Situ Hybridization (seqFISH) using a 20% cutoff. Given laboratory variation, the ULN for LDH was defined as 300 IU/L. R-ISS was calculated as described by Palumbo et al. S-ERMM was calculated using bone marrow plasma cells (BMPCs) (3 points), albumin (3), del17p (3), t(4;14) (3), LDH (5) and light chain isotype (2) and classified patients as low (≤ 5), intermediate (6 – 10) or high risk (≥ 11) as described by Zaccaria et al. The accuracy of risk model at predicting ER18 was assessed by logistic regression and comparison of the resulting ROC curves.
Results: After review, 112 patients were excluded due early mortality in remission or follow up < 18 months; 414 were excluded for missing data. 440 patients were included in the analysis. The median age was 62 (IQR 55-68); 59% were male; 74% were white. 24% had high-risk CAs. 80% of patients received a PI and IMID-containing triplet as first-line therapy. 63% received front-line ASCT. 31%, 61% and 9% of patients were classified as R-ISS Stage 1, 2, and 3 risk, respectively. 65%, 25% and 10% had S-ERMM Low, Int, and High-risk disease, respectively. Overall, 17% of patients had ER18. The rate of ER18 by R-ISS risk was 7%, 20% and 34%, respectively. The rate of ER18 by S-ERMM risk was 14%, 20% and 30%, respectively. There was no statistically significant difference in area under the curve (AUC) between R-ISS (0.63) or S-ERMM (0.59) (P = 0.16).
Conclusions: In the CoMMpass dataset, the S-ERMM was comparable to the R-ISS in predicting ER18. Consequently, S-ERMM is not an improvement in clinical risk stratification for early relapse over existing risk scores in patients receiving modern triplet regimens. Notably, the AUC for both scores was relatively low, indicating poor discrimination between high and low risk patients. Better risk scores are needed to identify patients at high risk of early relapse.
OAB-035
Characterising risk and biology Of smouldering myeloma for early detection of symptomatic myeloma: COSMOS, a prospective observational study in smouldering myeloma

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Introduction: Trial in progress. Recommendation to treat SLiM-CRAB and new insights into disease biology has necessitated generation of updated risk models for MGUS and smouldering myeloma (SMM). Current models use single window assessments primarily based on disease bulk, ignoring dynamic changes over time and the influence of host fitness and immunity. Understanding disease trajectories and tracking determinants of progression over time will refine our risk models, and aid trial design. The COSMOS study aims to track disease and host features longitudinally, focussing on tumour genome and clonal dynamics, immune function and exploring the utility of serial liquid biopsies.
Methods: COSMOS is a multi-centre observational study running in England and Wales. Patients are recruited at diagnosis or from clinic; clinical, radiological and laboratory features recorded longitudinally, and blood and BM are regularly sampled to track intra-patient changes. A basic flow cytometry panel to characterise tumour and immune cell types is performed on all samples, with subsequent processing for deep immune profiling, scRNASeq (with VDJ), bulk sequencing and sequencing of tumour genome and epigenome.
Results: 75 patients have been enrolled from 7 sites. 40(53%) were male with median age of 67.5y(range 27-85). Median paraprotein, SFLC ratio and BM PC at entry were 19.5g/L, 7.4, 15% respectively. 34% of patients had high risk cytogenetics and 72% had immunoparesis. Mayo 2018 criteria identified 37%, 31% and 31% of SMM patients as low, medium and high risk, whilst 33%, 28%, 25% and 15% were low, low-intermediate, intermediate and high risk using IMWG SMM criteria. 5/6 patients who progressed were Mayo intermediate or high risk. Correlative analysis identified a negative correlation between haemoglobin and trephine BM PC%($p=0.04$) and paraprotein levels($p< 0.001$). We found a positive correlation between trephine BM PC% and tumour CD138+ cells by flow($p< 0.001$). BM CD3+ T cells negatively correlated with CD11b+ myeloid cells($p< 0.001$) and CD4 cells positively correlated with total NK cells($p=0.02$). There was no clear correlation of any immune subset with risk group. Initial single cell RNA sequencing of T cells and integration with published data are presented in another abstract.
Conclusions: Our initial experience with COSMOS indicates good uptake in UK SMM patients into a prospective observational study that will provide us with longitudinal data on clinical, laboratory and biological parameters to build dynamic risk models. In an unselected SMM patient population 15% are high risk by IMWG criteria. Our baseline data suggest haemoglobin levels correlate with disease burden, despite patients not meeting myeloma defining criteria and we will explore this relationship over time. Strengths of our study include the prospective design, high predicted enrolment partnered with longitudinal deep immune phenotyping, tumour genomics and tracking of blood borne markers.

OAB-036

The PANGEA model: dynamic modeling for personalized prediction of precursor disease progression to multiple myeloma

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Introduction: Precursor multiple myeloma (MM) patients are dichotomized into monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM (SMM) based on a threshold of 10% plasma cells in the bone marrow (BM) or 3.0 g/dL of monoclonal protein. Current risk stratification of MGUS (2014 IWMG criteria) and SMM (IMWG 2/20/20 criteria) depend on static laboratory measurements at diagnosis and fail to incorporate changes in clinical variables. Furthermore, the separation between MGUS, SMM, and overt MM relies on clinical values and subjective endpoints. Improvements to clinical cytogenetics and the limitations of current risk criteria advocate for models that incorporate dynamic changes and redefine the disease states of MGUS and SMM.
Methods: We assembled a retrospective cohort of MGUS and SMM patients with clinical and biological variables measured at baseline and serial timepoints to model risk of progression to MM. The PANGEA (Precursor Asymptomatic Neoplasms by Group Effort Analysis) cohort is composed of 6441 patients with 4931 (77%) MGUS and 1510 (22%) SMM patients at baseline. 1060 (16%) of these patients progressed to MM. The model was validated in independent cohorts of precursor patients from Greece, the United Kingdom, and the Czech Republic.
Results: We built the PANGEA Model, a dynamic, multivariate Cox model with time-varying and trajectory biomarkers, to

estimate the risk of precursor disease progression to MM for individual patients. We trained the PANGEA Model with or without BM-specific variables in addition to time-varying biomarkers (monoclonal protein, free light chain, age, creatinine, bone marrow plasma cell percentage) and dynamic trajectories (hemoglobin, creatinine). The PANGEA Model (BM) and PANGEA Model (No BM) outperform previous models as demonstrated by a 43% or 30% higher C-statistic values compared to the 20/2/20 model, respectively, in a validation cohort. When we included cytogenetic variables as the PANGEA Model (FISH), we found an increased risk of progression in patients with chromosome 17/17p deletion, chromosome 1q gain, chromosome 13/13q deletion, and, for a sub-cohort, MYC alterations.
Conclusions: The PANGEA Models are novel, dynamic models that improve clinical predictions of precursor progression by using time-varying biomarkers as risk predictors, and we provide a simple, interactive website which implements them together for simplified clinical use. Together, the PANGEA Model (BM), PANGEA Model (No BM), and PANGEA Model (FISH) reform current MGUS and SMM risk criteria by either allowing incorporation of cytogenetic information or estimating risk without BM data. We also define a spectrum of risk of progression that replaces MGUS/SMM dichotomization with personalized risk estimates for individual patients.

OAB-037

Detection of abnormal plasma cells by multiparameter flow cytometry in a screened cohort of patients with monoclonal gammopathy of undetermined significance

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Introduction: Multiparameter flow cytometry (MFC) is not routinely used in diagnosis of patients with multiple myeloma (MM) and its precursors. The advantage of using MFC is the ability to differentiate between normal and abnormal plasma cells (abPC) based on immunophenotype. In the present study, we evaluated the frequency of abPC detection in the bone marrow (BM) using MFC in a screened cohort of patients with monoclonal gammopathy of undetermined significance (MGUS) and in relation to other diagnostic factors at baseline and during follow-up.
Methods: Participants were enrolled from the Iceland Screens, Treats, or Prevents MM (iStopMM) study, a population-based screening study (N=80,759) for MM precursors and randomized trial of follow-up strategies. In a subset of participants with abnormal screening test, BM samples were analyzed by MFC for the detection of abPCs using the EuroFlow MM-Minimal Residual Disease panel. Participants with a non-IgM MGUS diagnosis at baseline and a follow-up of ≥12 months were included. The Mann-Whitney U test was used to assess statistical significance of differences between groups.
Results: A total of 92 individuals have been included in the study so far with a median (range) follow-up of 44.5 (12-57) months. An abPC population was detected (abPCpos) in 67 cases (72.8%) by MFC, of those, 60 (89.6%) had heavy-chain (HC) MGUS (61.7% IgG, 33.3% IgA, and 5.0% biclonal) and 7 (10.4%) had light-chain (LC) MGUS. In 25 (27.2%) cases an abPC population was not detected (abPCneg), of those, 16 (64%) had HC-MGUS (81.3 IgG, 0% IgA, and 18.8% biclonal) and 9 (36%) had LC-MGUS. At baseline the abPCpos group had a significantly ($p< 0.01$) larger M-protein compared to the abPCneg group [median (range): 1.9 g/L (0.1-14.0 g/L) vs 0.5 g/L (0.1-2.0 g/L)], a significantly ($p< 0.05$) higher FLC ratio [involved/uninvolved median (range): 2.0 (0.8-32.9) and 1.4 (1.0-5.0)], and significantly ($p< 0.01$) higher number of MGUS risk factors [average (range): 0.83 (0-2) vs 0.13 (0-1)]. In 7/16 abPCneg HC-MGUS the M-protein was of IgG isotype and persisted during follow-up, 8/16 had a transient M-protein, and in one case, M-protein of IgG isotype was detected in the screening sample whereas IgM was detected during follow-up. 2/9 abPCneg LC-MGUS had a constantly pathological FLC ratio whereas in 7/9 cases the FLC ratio was within normal range in ≥1 measurements during follow-up.
Conclusions: We detected an abPC population in the BM by MFC in 72.8% of individuals with MGUS at diagnosis. A majority of cases in which an abPC population was not detected were found to have either a transient M-protein or a normal FLC ratio in repeated measures during follow-up. The findings suggest that MFC may identify individuals with clinically insignificant MGUS or individuals with a false positive MGUS diagnosis. Further studies with longer follow-up are needed.

OAB-038

Physiotherapist-led exercise prehabilitation embedded within the multiple myeloma autologous stem cell transplantation pathway: a feasibility randomised controlled trial

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Introduction: Autologous stem cell transplant (ASCT) is first line treatment for newly diagnosed myeloma patients considered 'fit' enough but often results in loss of function. It is known that patients with myeloma who are more physically

active have better quality of life (QOL), less fatigue and reduced morbidity. This pilot trial aimed to investigate the feasibility of a physiotherapist-led exercise intervention delivered across the continuum of the myeloma ASCT pathway at a UK centre. Initially designed and delivered as a face-to-face trial, the study protocol was adapted in response to the COVID-19 pandemic and delivered virtually.
Methods: A pilot randomised controlled trial of partly supervised exercise with incorporated behaviour change techniques delivered before, during and for 3 months following admission for ASCT compared to usual care. Face to face delivery of the pre-ASCT intervention was adapted to virtual supervised group classes via video conferencing. The intervention was delivered by a physiotherapist. Primary outcomes related to feasibility; recruitment rate, attrition and adherence. Secondary outcomes included measures of functional capacity (six minute walk test (6MWT), timed sit to stand (TSTS), self-report and objective physical activity (PA), QOL (EORTC C30, FACT-BMT, EQ5D), and fatigue (FACT-F).
Results: Over 11 months 50 participants were enrolled and randomised (Intervention n=23; Control n=27). Overall, uptake to the study was 46%. The attrition rate was 34%, with the main cause being failure to undergo ASCT (20%). Loss of follow up for other reasons was low with 85% of participants who underwent ASCT completing the final study assessment (n=33/39). Between baseline and admission for ASCT, improvement beyond minimally important differences (MID) were evident in intervention group outcomes for fatigue and QOL. Significant effects in favour of the intervention were evident in the pre-ASCT phase for TSTS (Intervention: +5.9, 95% CI 2.5, 9.3; Control: +0.2, 95% CI -3.1, 2.8). Overall, between baseline and 3 months post-ASCT intervention group scores in lower limb strength improved by 40% compared to 3% in the control group. The intervention group improved 6MWT beyond MID whereas the control group deteriorated between pre-ASCT baseline and three months post-ASCT (intervention: +57.1m; control: -33.1m). There were also promising indications of increased objective and self-reported PA pre- and post-ASCT in intervention participants but reduced levels of PA among controls.
Conclusions: This trial demonstrates acceptability and feasibility of delivering exercise prehabilitation, in person and virtually, within the ASCT pathway in myeloma. Promising results were evident for the benefit of exercise prior to, during and after ASCT with improvements in functional capacity, PA, QOL and fatigue evident on admission for ASCT and 3 months post-ASCT. The effects of prehabilitation and rehabilitation provision as a component of the ASCT pathway warrants further investigation.

OAB-039
Treatment duration and long-term outcomes with daratumumab in transplant-ineligible newly diagnosed multiple myeloma from the phase 3 MAIA study

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Introduction: In the phase 3 MAIA study (NCT02252172), daratumumab plus lenalidomide and dexamethasone (D-Rd) treatment until progression improved progression-free survival (PFS) and overall survival (OS) versus lenalidomide and dexamethasone (Rd) alone in patients with transplant-ineligible newly diagnosed multiple myeloma. Given the cost of long-term disease control with D-Rd, physicians may look to limit treatment while maintaining clinical benefit. However, randomized practice-informing data are lacking.
Methods: To determine the impact of treatment duration on long-term clinical outcomes, a post hoc analysis of OS was conducted based on D-Rd treatment duration (< 18 vs ≥18 months), excluding patients who discontinued therapy due to disease progression during the first 18 months. Post hoc analyses were also performed in D-Rd patients who discontinued only D or only R±d but continued remaining treatment to evaluate the impact of discontinuing individual D-Rd–regimen components. To assess the impact of treatment duration and response on PFS and OS, a post hoc analysis was conducted in patients who received D-Rd or Rd treatment for ≥9 or ≥18 months.
Results: Median follow-up time was 56.2 months. OS benefit was observed in D-Rd patients who received treatment for ≥18 versus < 18 months (HR, 0.16; 95% CI, 0.1-0.25; P< 0.0001). For D-Rd patients who discontinued R±d at any time but continued D±d treatment (n=48), 60-month PFS and OS rates were 97.9% and 100%, respectively, compared with 52.5% and 66.3% in the intent-to-treat population (n=368). PFS and OS benefits of D-Rd versus Rd were observed in

patients who received treatment for ≥18 months (PFS HR, 0.57; 95% CI, 0.43-0.76; P< 0.0001/OS HR, 0.68; 95% CI, 0.47-0.98; P=0.0379) and ≥9 months (PFS HR, 0.49; 95% CI, 0.38-0.62; P< 0.0001/OS HR, 0.63; 95% CI, 0.47-0.85; P=0.0025). Among patients treated for ≥18 months, responses with D-Rd deepened over time; complete response or better (≥CR) rates increased from 9.2% by 6 months, to 19.1% by 9 months, to 49.8% by 18 months. For patients with treatment ≥18 months, D-Rd significantly prolonged PFS and OS versus Rd in patients who achieved a best response of very good partial response by 6 months and deepened to ≥CR by 9 months (PFS HR, 0.15; 95% CI, 0.05-0.45; P< 0.0001/OS HR, 0.25; 95% CI, 0.07-0.86; P=0.0175) or by 18 months (PFS HR, 0.34; 95% CI, 0.19-0.62; P=0.0002/OS HR, 0.33; 95% CI, 0.17-0.65; P=0.0006). No new safety concerns were identified, and grade 3/4 hematologic treatment-emergent adverse events with D-Rd generally decreased over time.
Conclusions: At a median follow-up of >4.5 years, D-Rd improved clinical outcomes versus Rd in patients who received ≥18 months of treatment. For D-Rd patients, discontinuation of R±d did not appear to compromise efficacy. Our findings support D-Rd treatment for at least 18 months to achieve deep clinical responses and that stopping D-Rd earlier based on response level may compromise long-term patient outcomes.

OAB-040
BUMEL vs MEL-200 prior autologous transplant for patients with newly diagnosed multiple myeloma previously treated with bortezomib, lenalidomide and dexamethasone: final results of a phase 3 trial

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Introduction: Since the results of the IFM 9502 trial in 2002, melphalan 200 mg/m2 (MEL200) is the standard conditioning for newly diagnosed multiple myeloma (NDMM) transplant-eligible patients. Attempts to improve this conditioning have included TBI plus melphalan 140 mg/m2, and particularly the busulfan plus melphalan combination (BUMEL), among others. Previous reports indicated that BUMEL could be superior to MEL200. The aim is to compare the safety and efficacy of BUMEL (iv. BU cumulative dose 9,6 mg/kg) plus MEL140 vs. MEL200 as conditioning for autologous stem cell transplant (ASCT) in NDMM patients, preceded by 6 cycles of lenalidomide, bortezomib and dexamethasone (VRD), and followed by two VRD consolidation cycles.
Methods: This is an open label, randomized phase 3 study followed by a maintenance trial that compared lenalidomide-dexamethasone +/- ixazomib (Rosiñol L. et al. ASH 2021 reported no differences between arms) with a 2-by-2 factorial design and a 1:1:1:1 assignation ratio at diagnosis.
Results: From the 458 initial patients, 397 received ASCT (BUMEL n=203, MEL200 n=194). Patients randomized to MEL200 vs. BUMEL were similar respect to baseline features. In ASCT, the median CD34+ cells infused was 3.06x106 cells/kg with no differences between arms. No differences were observed in the recovery times of granulocytes, platelets or hospitalization periods. There were 4 deaths due to infection by day 100 in the BUMEL group (no deaths in the MEL200 group). Grade 2–3 mucositis was observed in 25% in the BUMEL versus 16% in the MEL200 arms. Respect to VOD, 4 patients in the BUMEL arm had this complication. One patient in the BUMEL group had a graft failure successfully treated with cyclosporin. After induction the responses were 16.8% PR, 31.9% VGPR and 36,2% sCR/CR, without differences between the arms. There were also no differences in the rates of MRD-ve (sensitivity 3x10-6): MRD-ve post-induction 30.4% and 27.2%, MRD-ve pos-ASCT 43.9% and 40.4%, for BUMEL and MEL200, respectively. With a median follow-up of 72 months at February 2021 cut-off, median PFS was not reached in the BUMEL and 76 months in

the MEL200 arms; 6-year PFS was 58% (95%CI: 51-64) in BUMEL and 52% (45-58) in the MEL200 arms. The comparison of PFS between arms did not show a clinical benefit [HR (95%CI): 0.85 (0.65-1.1)]; 6-year OS was 75% (69-81) in the BUMEL arm and 77% (71-82) in the MEL200 arm [HR 1.03 (0.70-1.50)]. In risk subgroups, including cytogenetics-risk, ISS, LDH, extramedullary disease and conventional and MRD responses, conditioning regimens did not show differences, except for ISS 3 patients in which 6 years PFS increased from 26% (14-39) in the MEL200 arm to 51% (37-63) in the BUMEL arm [HR 0.57 (0.35-0.93)]
Conclusions: This randomized trial indicate that MEL200 should remain as the standard of care based on efficacy and toxicity, except for high-risk ISS patients, in which BUMEL provides a clear PFS benefit.

OAB-041
Daratumumab carfilzomib lenalidomide and dexamethasone as induction therapy in high-risk transplant eligible newly diagnosed myeloma patients: results of the phase 2 study IFM 2018-04

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Introduction: High-risk (HR) cytogenetic is associated with poor outcome in transplant eligible (TE) newly diagnosed myeloma multiple myeloma (NDMM). The triplet combination carfilzomib lenalidomide and dexamethasone (KRD) plus transplantation demonstrated high efficacy with favorable safety profile in TE-NDMM patients (FORTE). The addition of daratumumab (Dara) to frontline therapy also improved response rate and progression free-survival in TE-NDMM patients (CASSIOPEIA, GRIFFIN). Double transplant also improved outcome of HR TE NDMM patients (EMN02, STAMINA). The phase 2 trial 2018-04 from the Intergroupe Francophone du Myelome (IFM) is evaluating an intensive strategy with Dara-KRD induction and consolidation plus double transplant in HR TE NDMM (NCT03606577).
Methods: HR MM was defined by the presence of del17p, t(4;14) and/or t(14;16). Stategy includes Dara-KRD induction (6 cycles), autologous stem cell transplantation (ASCT), Dara-KRD consolidation (4 cycles), second ASCT, Dara-lenalidomide maintenance. The primary endpoint was the feasibility of this intensive strategy. Here, we report efficacy and safety analysis of Dara-KRD induction.
Results: Fifty patients with previously untreated NDMM were included from july 2019 to march 2021 in 11 IFM centers Median age was 57 (range 38 -65). ISS stage 3 was present in 12 (24%) patients. Based on inclusion criteria, all patients had HR cytogenetic, including 17p deletion (n=20, 40%), t(4;14) (n=26, 52%) or t(14;16) (n=10,20%). Forty-six patients completed Dara-KRD induction. Two patients discontinued treatment due to severe adverse event (COVID-19 infection, n=1 ; drug-induced hepatitis, n=1) and 2 patients discontinued treatment due to disease progression. Grade 3-4 treatment related adverse event (>5% of patients) were neutropenia (38%), anemia (14%), thrombocytopenia (8%), infection (6%), renal insufficiency (6%) and deep-vein thrombosis (6%). Two patients (6%) experienced stem-cell collection failure. Overall response rate was 96%, including 92 % > very good partial response. Among 37/46 evaluable patients post induction, Minimal Residual Disease negativity rate (NGS, 10-5) was 62%.
Conclusions: Dara-KRD as induction prior ASCT is safe and allows deep responses in TE NDMM patients with high-risk cytogenetic profile. IFM 2018-04 study is ongoing and longer follow-up is needed to evaluate safety and efficacy of the overall strategy with Dara-KRD induction and consolidation plus double transplant in this subset of HR patients.

OAB-042
The impact of marginalization on treatment receipt and overall survival in newly diagnosed multiple myeloma patients in Ontario: a population-based cohort study

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Introduction: Despite therapeutic advancements, multiple myeloma (MM) remains an incurable malignancy. Prior studies have shown conflicting results regarding the association between socioeconomic status (SES) and MM outcomes. It is unknown whether SES affects management and prognosis of MM within Canada's public-payer healthcare system.
Methods: In this retrospective population-based study, administrative health data from the Institute of Clinical

Evaluative Sciences (ICES) was used to evaluate the association between the Ontario Marginalization index (ONMARG), as a surrogate measure of SES, and treatment receipt as well as overall survival (OS) among newly diagnosed patients with MM. ONMARG is a composite score accounting for material deprivation (%low income), dependency (%seniors, %unemployed), ethnic concentration (%recent immigrants, %visible minorities), and residential instability (%renters, %living alone) based on census tract data. Logistic regression was used to assess the association between ONMARG and receipt of treatment (alkylators, immunomodulatory drug (IMID), or proteosome inhibitors (PI) which reflects the available and reimbursed therapeutic drugs). Cox proportional hazards regression was used to assess the association between ONMARG and OS. Regression models were adjusted for sex, age at diagnosis, Charlson comorbidity index, diagnosis time-period, and community size. The OS analyses also adjusted for receipt of IMID/PI or upfront autologous stem cell transplant (ASCT).
Results: Overall, we included 9777 patients with MM diagnosed between January 2007 to December 2018 in Ontario, Canada. We found patients with higher ON-MARG scores (poor marginalized status) were less likely to receive treatment after adjusting for confounders (ONMARG quintile 5 v. 1: OR 0.71, 95% CI 0.60-0.84, p< 0.001; ONMARG quintiles 2-4 v. 1: OR 0.88, 95% CI 0.77-1.01, p=0.065). Among treated patients (n=7535), receipt of PI/IMID induction was similar between ONMARG quintiles 1 vs 2-4 vs 5 (76% vs 74% vs 73%, respectively, p=0.233), however more marginalized patients were less likely to receive an upfront ASCT (46% vs 39%, vs 30%, p< 0.001). ASCT recipients residing in more marginalized areas had improved OS after adjusting for confounding (ONMARG quintile 5 vs 1: HR 0.82, 95% CI 0.67-1.01, p=0.057; ONMARG quintiles 2-4 vs 1: HR 0.74, 95% CI 0.64-0.85, p< 0.001). ONMARG was not significantly associated with OS among ASCT-ineligible patients.
Conclusions: In the Ontario, a universal healthcare system, poor socioeconomic status is associated with reduced treatment receipt among patients with MM. Counterintuitively, marginalized patients who receive an upfront ASCT have improved OS, which may be indicative of a transplant referral bias. Structural barriers to care, such as reduced health literacy or lack of access to referral centers, need to be identified and addressed to reduce inequities within our universal healthcare system.

OAB-043

Ciltacabtagene autoleucel (cilta-cel) in patients with multiple myeloma and early relapse after initial therapy: biological correlative analyses and updated clinical results from CARTITUDE-2 Cohort B

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Introduction: The efficacy and safety of cilta-cel are being evaluated in CARTITUDE-2 (NCT04133636) Cohort B, which enrolled patients (pts) with multiple myeloma (MM) and early relapse after initial therapy. These pts have functionally high-risk disease and an unmet medical need, as early relapse post autologous stem cell transplantation (ASCT) is a poor prognostic factor. Here we report updated data.
Methods: Eligible pts had MM, 1 prior line of therapy (proteasome inhibitor and immunomodulatory drug required), disease progression per International Myeloma Working Group criteria (≤12 months after ASCT or ≤12 months after initiation of anti-myeloma therapy for pts without ASCT) and were naive to CAR-T/anti-BCMA therapies. Pts received a single cilta-cel infusion (target dose 0.75×10^6 CAR+ viable T cells/kg) after lymphodepletion. The primary endpoint was minimal residual disease (MRD) negativity at 10^-5. Management strategies were used to reduce the risk of movement/neurocognitive adverse events (MNTs). The following analyses are being conducted: pharmacokinetics (PK) (Cmax/Tmax of CAR+ T-cell transgene levels in blood), levels of cytokine release syndrome (CRS)-related cytokines (eg, IL-6) over time, peak cytokine levels by response and CRS, association of cytokine levels with immune effector cell-associated neurotoxicity syndrome (ICANS), and CAR+ T cell CD4/CD8 ratio by response, CRS, and ICANS.
Results: 19 pts (median age 58.0 years; 74% male) received cilta-cel as of January 2022, with a median follow-up of 13.4 months (range 5.2–21.7). 79% of pts had prior ASCT. Overall response rate was 100% (90% ≥complete response and 95% ≥very good partial response). Median time to first response was 0.95 months (range 0.9–9.7) and median time to best response was 5.1 months (range 0.9–11.8). 93% (14/15) of

MRD-evaluable pts achieved MRD 10^-5 negativity. Median duration of response was not reached. At 12 months, the event-free rate was 88.9% and the progression-free survival rate was 90%. 16 pts (84.2%) had CRS (1 gr 4); median time to onset was 8 days (range 5–11). CRS resolved in all pts. 1 pt had ICANS (gr 1); 1 pt had MNT (gr 3, previously reported). 1 pt died after cilta-cel due to progressive disease at day 158. Based on preliminary PK analyses, peak expansion of CAR-T cells occurred on day 13.1 (range 8.96–209.9), with a median persistence of 76.9 days (range 40.99–221.8).
Conclusions: A single infusion of cilta-cel resulted in deep and durable responses and manageable safety in a functionally high-risk pt population with early clinical relapse/treatment failure to initial therapy. Cilta-cel led to responses in this pt population with ineffective or insufficient response to ASCT. Follow-up is ongoing and responses continue to deepen. We will present updated and detailed PK, cytokine, and CAR-T subset analyses as well as clinical correlation to provide novel insights into biological correlates of efficacy and safety in this pt population.

OAB-044

Efficacy and safety of cilta-cel in patients with progressive multiple myeloma after exposure to BCMA-targeting antibody-drug conjugate treatment

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Introduction: With the availability of multiple therapy classes targeting B-cell maturation antigen (BCMA) for multiple myeloma (MM), data are needed to understand effective treatment sequencing. CARTITUDE-2 (NCT04133636) is a phase 2, multicohort study evaluating the efficacy and safety of cilta-cel, an anti-BCMA CAR-T therapy, in several MM patient populations. We present results on cohort C patients with previous exposure to a BCMA-targeting antibody-drug conjugate (ADC).
Methods: Cohort C patients had progressive MM after treatment with a proteasome inhibitor, immunomodulatory drug, anti-CD38 antibody, and non-cellular BCMA-targeting agent. A single cilta-cel infusion (target dose: 0.75×106 CAR+ viable T cells/kg) was administered 5–7 days post lymphodepletion. The primary endpoint was minimal residual disease (MRD) negativity at 10-5. Secondary endpoints included overall response rate (ORR; assessed by IMWG criteria), duration of response (DOR), and adverse events (AEs).
Results: As of October 8, 2021, 13 ADC-exposed patients (62% male, median age 66 y [range, 44–81]) were treated with cilta-cel; 2 additional patients underwent apheresis but did not receive cilta-cel due to low cellular yield (n=1) or death (n=1). All 13 who received cilta-cel had prior belantamab mafodotin (as last line of therapy [LOT] in 4 patients); 1 had also received MEDI2228 and 1 had also received BCMA-targeting bispecific antibody (REGN5459). Patients had received a median of 8 (range, 4–13) prior LOT, 11/13 (85%) were triple-class refractory, and 11/13 (85%) were refractory to prior anti-BCMA therapy. The median time between ADC termination and cilta-cel infusion was 180 d (range, 62–944). At a median follow-up of 11.8 mo (range, 2.0–16.0), 5 of 13 (38.5%; 95% CI: 13.9–68.4) patients were MRD negative (5 of 7 [71.4%; 95% CI: 29.0–96.3] in the MRD-evaluable subset). ORR was 61.5% (95% CI: 31.6–86.1). Median DOR and progression-free survival were 11.5 (95% CI: 7.9–NE) and 9.5 (95% CI: 1.0–NE) mo, respectively. Patients who responded to cilta-cel had a shorter median duration of last ADC exposure (23 d, range 1–277) than non-responders (63 d, range 22–527). Responders also had a longer median time between last ADC treatment and apheresis (150 d, range 26–695) than non-responders (56 d, range 40–895). No correlation was seen between baseline serum BCMA levels and response. CAR-T cell expansion kinetics were consistent with previous studies. The most common AEs were hematologic. CRS occurred in 6 (46%) patients (all grade 1/2); 2 had ICANS (1 gr 3/4) that resolved; none had parkinsonism. There were 4 deaths: 3 due to progressive disease and 1 due to COVID-19 pneumonia (not treatment-related per investigator).
Conclusions: MM patients who had previous exposure to an anti-BCMA ADC therapy had favorable responses, DOR, and PFS following cilta-cel. These results may inform treatment

plans, including sequencing and washout period between BCMA-targeting agents.

OAB-045

Updated clinical data and biological correlative analyses of ciltacabtagene autoleucel (cilta-cel) in lenalidomide-refractory multiple myeloma after 1–3 prior lines of therapy: CARTITUDE-2 Cohort A

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Introduction: CARTITUDE-2 (NCT04133636) Cohort A is evaluating the safety and efficacy of cilta-cel in patients (pts) with multiple myeloma (MM) who received 1–3 prior lines of therapy (LOT) and were lenalidomide (len)-refractory – a difficult-to-treat population with poor prognosis. Here we present updated results.
Methods: Eligible pts had progressive MM after 1–3 prior LOT (including a proteasome inhibitor and immunomodulatory drug) and were len-refractory with no prior exposure to B-cell maturation antigen-targeting agents. Pts received a single infusion of cilta-cel (target dose 0.75×10^6 CAR+ viable T cells/kg) after lymphodepletion. The primary endpoint was minimal residual disease (MRD) negativity at 10^-5. Management strategies were used to reduce the risk of movement/neurocognitive AEs (MNTs). Analyses are being conducted to assess pharmacokinetics (PK) (Cmax and Tmax of CAR+ T-cell transgene levels in blood), levels of cytokine release syndrome (CRS)-related cytokines (eg, IL-6) over time, peak levels of cytokines by response and CRS, association of cytokine levels with ICANS, and CAR+ T cell CD4/CD8 ratio by response, CRS, and ICANS.
Results: 20 pts (65% male; median age 60 years [range 38–75]) received cilta-cel as of January 2022, with a median follow-up (MFU) of 17.1 months (range 3.3–23.1). Pts had a median of 2 (range 1–3) prior LOT; median time since MM diagnosis was 3.5 years (range 0.7–8.0). 40% of pts were triple-class refractory and 95% were refractory to last LOT. Overall response rate was 95% (90% ≥complete response and 95% ≥very good partial response). Median time to first response was 1.0 month (range 0.7–3.3) and median time to best response was 2.6 months (range 0.9–13.6). All MRD-evaluable pts (n=16) achieved MRD negativity at 10^-5. Median duration of response was not reached. At 12 months, the event-free rate was 79% and the progression-free survival rate was 75%. 95% of pts had CRS (gr 3/4: 10%); median time to onset was 7 days (range 5–9) and median duration was 3 days (range 2–12). 30% of pts had neurotoxicity (5 gr 1/2; 1 gr 3/4). 15% of pts had ICANS (all 3 gr 1/2); 1 pt had gr 2 facial paralysis. No MNTs were observed. 1 death occurred due to COVID-19 (treatment-related per investigator), 2 due to progressive disease, and 1 due to sepsis (not related to treatment). Based on preliminary PK analyses, peak expansion of CAR-T cells occurred at day 10.5 (range 8.7–42.9) and median persistence was 153.5 days (range 57.1–336.8).
Conclusions: At a longer MFU of 17.1 months, a single infusion of cilta-cel resulted in deep and durable responses in pts with MM who were len-refractory and had 1–3 prior LOT. Follow-up is ongoing. We will present updated and detailed PK, cytokine, and CAR-T subset analyses, as well as clinical correlation to provide novel insights into biological correlates of efficacy and safety in this pt population, which is being further evaluated in the CARTITUDE-4 study (NCT04181827; enrollment complete).

OAB-046

Depth of response of isatuximab plus carfilzomib and dexamethasone in relapsed multiple myeloma: IKEMA updated analysis

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Introduction: Achievement of minimal residual disease negativity (MRD–) status in multiple myeloma (MM) is associated with improved progression-free survival (PFS) and overall survival. Isatuximab (Isa) is an anti-CD38 monoclonal antibody approved in combination with carfilzomib (K) and dexamethasone (d) for relapsed MM patients (pts) after ≥1 prior therapy, based on the primary interim analysis of the Phase 3 IKEMA study (NCT03275285). Here, we report updated, longer-term depth of response results from IKEMA, including MRD– status.
Methods: IKEMA was a randomized, open-label, multicenter Phase 3 study investigating Isa-Kd (n=179) vs Kd (n=123) in relapsed MM pts who received 1-3 prior lines of therapy. Intravenous (IV) Isa 10 mg/kg was given weekly for 4 weeks and then every other week. Both arms received the approved schedule of K (IV) and d (oral or IV). This prespecified analysis evaluated PFS (primary endpoint) at 159 events and secondary endpoints of ≥complete response ([CR] + stringent CR), MRD–, and ≥CR + MRD– rates, as determined by Independent Response Committee (IRC) based on central laboratory data and IRC review of local radiology. MRD status was assessed by next-generation sequencing at 10-5 sensitivity level at least in bone marrow aspirates from pts achieving ≥very good partial response. The HYDRASHIFT Isa immunofixation (IFE) test removing interference of Isa in IFE was used to update the ≥CR rate. Secondary endpoints were compared between treatment arms using the Cochran-Mantel-Haenszel test. One-sided descriptive p-value is provided. All randomized pts not reaching MRD– or without MRD assessment were considered as MRD+.
Results: As of Jan 14, 2022 (cutoff), at a median follow-up of 44 months, deeper responses were observed in Isa-Kd vs Kd, with ≥CR rates being 44.1% vs 28.5%, respectively (odds ratio [OR]: 2.09; 95% CI: 1.26–3.48; descriptive p=0.0021). MRD– (10-5) occurred in 33.5% vs 15.4% of Isa-Kd vs Kd pts (OR: 2.78; 95% CI: 1.55–4.99; descriptive p=0.0002), with 26.3% vs 12.2% of Isa-Kd vs Kd pts reaching ≥CR + MRD– (10-5; OR: 2.57; 95% CI: 1.35–4.88; p=0.0015). MRD– at 10-6 sensitivity level occurred in 10.6% vs 3.3% of Isa-Kd vs Kd pts. MRD– pts (10-5) had longer median PFS than MRD+ pts in both arms: not calculable ([NC]; 95% CI: NC–NC) for Isa-Kd MRD– pts and 21.7 (95% CI: 16.4–27.1) months for Isa-Kd MRD+ pts vs NC (95% CI: 29.2–NC) for Kd MRD– pts and 16.2 (95% CI: 13.4–19.5) months for Kd MRD+ pts.
Conclusions: These results demonstrate clinically meaningful improvement in depth of response with Isa-Kd vs Kd. The impressive ≥CR rates and ≥CR + MRD– (10-5) rates of 44.1% and 26.3% in Isa-Kd vs 28.5% and 12.2% in Kd are the highest reported for a proteasome inhibitor-based regimen in relapsed MM. Achieving MRD– led to better outcomes in both treatment arms, with Isa-Kd pts having a more than 2-fold higher likelihood of achieving MRD–. Additionally, isatuximab improved the outcomes of MRD+ patients.
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OAB-047

Clinical and translational results of the myeloma developing regimens using genomics (MyDRUG) sub-protocol C1 targeting RAS mutations

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Introduction: Multiple myeloma (MM) is characterized by somatic mutations involving cancer-associated genes. The most common mutations are in NRAS or KRAS, and their prevalence increases with progression. Previous data suggest efficacy of targeting the MAPK pathway in RAS-mutated MM. The MyDRUG trial was initiated to explore the efficacy of molecularly-targeted therapies in combination with standard therapies in MM.
Methods: MyDRUG (NCT03732703) is a genomically-guided umbrella trial for patients with functional high-risk MM defined as early relapse following primary therapy (3 years for transplant with maintenance, 18 months without). Subjects undergo molecular profiling of their MM cells and are assigned to a targeted arm if an actionable mutation with variant allele frequency (VAF) over 25% is identified. Subjects

with mutations in NRAS, KRAS, or BRAF were assigned to sub-protocol C1 with cobimetinib, a MEK inhibitor approved for melanoma. Patients receive single agent investigational drug for 2 cycles followed by combination with ixazomib, pomalidomide and dexamethasone (IPd). Limited dose escalation was performed with the single agent followed by dose assessment in combination with IPd. High dimensional immunophenotyping of the bone marrow microenvironment at screening and during treatment by single-cell RNA-sequencing (scRNA seq) and bioinformatic analysis
Results: Eleven subjects with RAS/BRAF mutations were screened between August 2019 and October 2020, with 4 screen failures. Seven were enrolled, 5 males, median age 65 years, and median time from diagnosis of 30 months. NRAS, KRAS or BRAF mutations were seen in 4, 2, and 1 subjects, respectively, with VAF ranging from 33-93%. Median number of prior lines of therapy was 1 (1-3), 3 patients had extramedullary disease, and 1 patient had high-risk cytogenetics. Median duration of therapy was 12 months. One patient was not evaluable for dose limiting toxicity. All but 1 patient had at least one cycle delayed due to adverse events (AEs), but no dose reductions were required. No dose limiting toxicities were observed across the cycles, either during single agent therapy (Cycles 1-2) or in combination with IPd (Cycles 3 and 4). Six patients responded to therapy (4 PR, 2 VGPR). One patient was not response evaluable. Fatigue was the most common non-hematological AE followed by diarrhea.
Conclusions: Here we report on the feasibility of genomically-guided, precision medicine therapy in NRAS/KRAS/BRAF-mutated MM. The MEK inhibitor cobimetinib in combination with IPd appears safe in functionally high-risk patients. The study is ongoing at the established Ph2 combo dosing.

OAB-048
An interim analysis of a phase I/II single arm study of belantamab mafodotin, carfilzomib and dexamethasone in patients with relapsed multiple myeloma: AMaRC 19-02 BelaCarD study

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Introduction: Belantamab Mafodotin (Belamaf; B), a first in class anti-B-cell maturation antigen (BCMA) antibody-drug conjugate, is efficacious in patients with triple-class exposed/refractory multiple myeloma (RRMM). Combining B with carfilzomib and dexamethasone (Kd) is potentially synergistic through direct myeloma-cell kill and immune response against myeloma. This planned interim analysis aims to characterize the safety, tolerability, and preliminary efficacy of B-Kd in patients with early relapsed MM.
Methods: BelaCarD is an ongoing, two-part, single-arm, multicentre phase I/II study evaluating B every 8 weeks in combination with Kd in pts with RRMM after 1-3 prior lines of treatment. Prior refractoriness to proteasome inhibitors was allowed. Analysis of safety run-in phase conducted (first 10 patients) who completed at least 1 treatment-cycle: Belamaf (2.5mg/kg) administered on D1 of every 2nd 28-day cycle, K 70mg/m2 iv D1 (20mg/m2 on C1D1), D8 and D15 of every cycle and dexa 40mg weekly (20mg for patients >75 years). Treatment continued until progression. Adverse events (AEs) were graded per CTCAEv4, except corneal AEs - graded by pre-specified keratopathy and visual acuity (KVA) scale. Response was assessed by the IMWG criteria.
Results: At cut-off (03Feb22), 19 patients had received B-Kd. Median age of the 10 safety run-in patients was 65 yo (range, 48-77); One, five and four patients had 3, 2 and 1 prior lines of therapy respectively including (exposed/refractory %) Bort (100/30%), carfilzomib (10/0%) Len (60/50%), Pom (10/10%), ASCT (70/0%), anti-CD38 monoclonal Ab (mAb) (40/40%). Median number of treatment-cycles was 7 (5-11). Median number of cycles commenced was 9 (range, 2-13). Most frequent AE during cycle 1 was thrombocytopenia (All Gr 30%, Gr 3/4 20%) and blurred vision (All Gr 20%, Gr 3/4 0%) One patient experienced Gr 4 neutropenia. From cycle 2 onwards, the most frequent AEs included blurred vision (all grade 40%, Gr 3/4 20%), peripheral neuropathy (all grade 30%, Gr 3/4 10%), URTI (all grade 30%, Gr 3/4 20%), dry eyes (all grade 20%, Gr 3/4 0%), neutropenia (all grade 20%, Gr 3/4 10%) and nausea (all grade 20%, Gr 3/4 0%). Six patients had an SAE, one was related to Belamaf (Gr 1 infusion reaction). Keratopathy occurred in 8 patients; grade 1, 20%; grade 2, 0%; grade 3, 60%. Decline in best corrected visual acuity (BCVA) by at least 2 lines occurred in 8 patients (Gr 3 n=6, Gr 2 n=2). One patient discontinued therapy due to corneal toxicity. Two patients died (progressive disease n=1, unrelated n=1). Of the 10 patients in the safety run-in, 9 achieved a PR or better (CR=3, VGPR=3, PR=3); 2 have subsequently progressed. At estimated median potential follow-up of 9.95 months, median PFS had not been reached (95%CI: 1.08 –NR).
Conclusions: B-Kd with an extended B schedule, has a safety profile that is in keeping with that expected for each individual drug. Deep responses were seen. Recruitment is ongoing in an expansion phase based on the preliminary safety and efficacy.

OAB-049

Impact of baseline ocular conditions (BOCs) on belantamab mafodotin (belamaf)–related corneal events in patients (pts) with relapsed or refractory multiple myeloma (RRMM)

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Introduction: Belantamab mafodotin (belamaf), a B-cell maturation antigen-targeted antibody-drug conjugate, has demonstrated deep and durable responses in heavily pretreated pts with RRMM. Reversible changes to the corneal surface of the eye (keratopathy), which can lead to decreased or blurred vision and dry eye, are associated with belamaf due to the known toxic effect of the monomethyl auristatin F payload. Pts with RRMM may have impaired ocular health due to comorbidities or effects of prior myeloma therapies. The impact of these BOCs and the incidence and severity of belamaf-related ocular symptoms are important to understand in order to counsel the pt. Here we report an analysis of pooled data from DREAMM-2 to examine the association between BOCs, belamaf treatment (Tx) duration, and resulting ocular symptoms.
Methods: DREAMM-2 evaluated belamaf (2.5 or 3.4 mg/kg every 3 weeks) in pts with RRMM after ≥3 lines of therapy. Exclusion for baseline ocular conditions was limited to corneal epithelial disease (except mild punctate keratopathy). Baseline and subsequent eye examinations were done prior to each dose. Dose modifications were allowed for toxicity. In this analysis, ocular symptoms (pt reported, not solicited by investigator) were analyzed via the presence or absence of the most common BOCs for all pts and according to belamaf Tx duration (≤3 or >3 months) to assess the impact of drug exposure. Differences were defined as a ≥20% variance in ocular symptoms between pts with/without each BOC.
Results: Of 218 pts who received belamaf, most had BOCs (198 with vs 20 without). Cataracts (66%) and cornea-related conditions, including keratopathy (52%) and dry eye (22%), were the most common reported BOCs. Among pts with BOCs, blurred vision and dry eye were the most common ocular symptoms with belamaf Tx overall. There were no differences (≥20% variance) in ocular symptoms in pts with/without conditions associated with the lens (cataract), optic nerve (glaucoma), or eyelids (blepharitis) at baseline. Blurred vision was more common in pts with dry eye (44% vs 21%) and, although confounded by small numbers, in pts with age-related macular degeneration at baseline (38% vs 14%). Differences in ocular symptoms by the presence or absence of BOCs were not observed in pts exposed to belamaf for 3 months; n=95), a difference in blurred vision was seen in pts with dry eye (65% vs 40%) and keratopathy (56% vs 36%) at baseline.
Conclusions: BOCs are very common in pts with RRMM; however, only pts with cornea-related BOCs were likely to have more ocular symptoms with belamaf, predominantly blurring of vision. There was little evidence that other BOCs, such as cataract, glaucoma, or blepharitis, had any effect on Tx-emergent ocular symptoms. These findings inform risk/benefit decision-making with belamaf and indicate that belamaf can be a Tx option for pts with RRMM despite BOCs.

OAB-050

Randomized phase 2 study of weekly carfilzomib 70 mg/m2 and dexamethasone plus/minus cyclophosphamide in relapsed and/or refractory multiple (MM) patients (GEM-KyCyDex)

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Introduction: Carfilzomib dosed at 56 mg/m2 twice a week in combination with dexamethasone (Kd) is a standard of care for RRMM after 1-3 prior lines (PL) based on the ENDEAVOR study. Later on, the ARROW study showed Kd dosed at 70 mg/m2 weekly to be superior to Kd dosed at 27 mg/m2 twice a week in RRMM patients after 2-3 PL. On the other side, Cyclophosphamide (Cy) is an alkylating agent that has been widely combined with proteasome inhibitors in MM, improving their efficacy with a good safety profile.
Methods: In this phase 2 randomized study we have compared Kd plus cyclophosphamide with Kd in RRMM after 1-3PL, both with K dosed weekly at 70 mg/m2. RRMM after 1-3 PL of therapy were included in the trial. Patients (pts) were randomized 1:1 to receive K 70 mg/m2 iv on days 1, 8 and 15 plus dex 20 mg po the day on and the day after K plus/minus Cy 300 mg/m2 iv on days 1, 8 and 15 of each 28 days-cycle until progressive disease or unacceptable toxicity. The primary end-point was PFS and secondary end-points included response rates, safety profile and OS.
Results: Between January 2018 and February 2020, 197 RRMM were included. Ninety-seven pts were randomized to KyCyDex and 100 to Kd. Median age was 70 years and the median number of PL was 1 (1-3). 95% and 91% of patients had been exposed to PI in the KyCyDex and Kd, respectively. 75% and 66% of patients had been exposed to IMiD's and 33% and 38% of them were IMiD's-refractory in the KyCyDex and Kd, respectively. 50% of the patients in both groups were refractory to their last line of therapy and lenalidomide was the drug in 33% of patients in KyCyDex and 38% in Kd. After a median f/u of 37 months, median PFS was 18.4 m and 16.5 m in KyCyDex and Kd, respectively (p=0.6). Of note, in the IMiD-refractory population, the addition of Cy to Kd resulted in a significant benefit in terms of PFS: 18.4 months (mo) vs 11.3 mo in the Kd arm (p=0.015). The same benefit was observed in the population refractory to the last line of therapy (19 vs 11 mo, p=0.013). At 36 months, 56% and 66% of patients in KyCyDex and Kd remain alive, respectively (p = NS). The ORR was 69% for both groups and 19.3 and 20% of patients achieved at least complete response in KyCyDex and Kd, respectively. As far as toxicity is concerned, neutropenia was the most frequent hematological adverse event (AE) reported in KyCyDex compared with Kd, (G3-4: 15% vs 6%). Regarding non-hematological AEs: G3-4 infections were reported in 13% of patients in KyCyDex and 7% in Kd; cardiovascular AEs in 12 and 16 % in KyCyDex and Kd arms. Hypertension was the most common in both arms.
Conclusions: In conclusion, Cy added to Kd 70 mg/m2 weekly in RRMM pts after 1-3 PL is not different to Kd but in the lenalidomide-refractory population a significant benefit was observed. The administration of K at a dose of 70 mg/m2 weekly was safe and more convenient, and, overall, the toxicity profile was manageable in both arms.

OAB-051

Salvage therapies and clinical outcomes after relapse following BCMA CAR-T in patients with relapsed/refractory multiple myeloma

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Introduction: Chimeric antigen receptor T-cell (CAR-T) therapies targeting B-cell maturation antigen (BCMA) have been shown to be effective in the treatment of patients with relapsed/refractory multiple myeloma (RRMM), leading to rapid and deep clinical responses. However, most patients treated with BCMA CAR-T eventually have progressive disease (PD), and much is unknown about their outcomes and post-CAR-T therapies.
Methods: We performed a single-center retrospective analysis of all patients with RRMM who received any BCMA CAR-T therapy between January 2017 and December 2021, including patients treated on clinical trials and those who received standard-of-care idecabtagene vicleucel. Demographic and disease-related characteristics prior to CAR-T infusion were collected. Progression-free survival (PFS) of the total cohort was evaluated, and patients who had PD after BCMA CAR-T were selected for further analysis. Key endpoints included types of salvage therapy received, overall response rate (ORR) [defined as partial response or better by IMWG criteria], duration of response per line of therapy, and overall survival (OS) from time of PD. Time-to-event analysis was conducted via Kaplan-Meier method.
Results: We identified 64 patients who received BCMA CAR-T therapy. Median age was 62.5 years. Median prior lines of therapy was 6 (range: 1- 14). 39 patients (63%) had high-risk cytogenetics, and 41 patients (64%) were triple-class refractory. With median follow-up of 2 years, 2-year PFS was 44% (95% CI: 33 – 59%) and median PFS was 20.4 months (95% CI: 11.6% to not reached). Of 44 patients with post-CAR-T PD, 41 (93%) received ≥1 subsequent therapy with a median of 2 (range: 1-8) lines of subsequent therapy. Patients who received subsequent BCMA CAR-T, anti-CD38 antibodies, alkylators, BCMA-targeted bispecific antibodies (bsAb), immunomodulatory drugs (IMiDs), or proteosome inhibitors (PI) as salvage therapy had ORR 75%, 64%, 51%, 50%, 47%, and 43%, and median durations of treatment of 8.1, 2.9, 1.5, 5.0, 2.8, and 1.9 months, respectively. Re-treatment with drug classes often led to responses even after prior refractoriness: 6 of 9 patients with CD38-refractory disease responded to daratumumab, while 4 of 9 patients with PI-refractory disease responded to carfilzomib. 7 patients were treated with belantamab mafadotin, with 2 patients (29%) achieving a response. Median OS for the 41 patients who received any post-CAR-T therapy was 14.8 months (95% CI: 10-23 months). Among 8 patients who received subsequent

BCMA CAR-T or BCMA-targeted BsAb within 6 months of CAR-T failure, median OS was 18 months (95% CI: 17.8% – NR).
Conclusions: Patients with RRMM who relapse after BCMA CAR-T have poor outcomes. Subsequent BCMA-directed immunotherapies may be effective in these patients. Other conventional treatments may also elicit clinical responses, but durations of responses appear limited. Novel therapies are needed for this patient population.

OAB-052

Isatuximab plus pomalidomide/low-dose dexamethasone versus pomalidomide/low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (ICARIA-MM): final overall survival analysis

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Introduction: The anti-CD38 monoclonal antibody isatuximab (Isa) combined with pomalidomide and dexamethasone (Pd) is approved in several countries for patients (pts) with relapsed and refractory multiple myeloma (RRMM) who have received ≥2 prior treatments (tx), including lenalidomide and a proteasome inhibitor, based on the primary analysis of the Phase 3 ICARIA-MM study (NCT02990338). Here, we report the final overall survival (OS) analysis.
Methods: Isa 10 mg/kg was administered weekly for the first 4-week cycle and then every 2 weeks thereafter. Both arms received pomalidomide 4 mg (days 1-21) and weekly dexamethasone 40 mg (days 1, 8, 15, and 22) of each cycle. This final OS analysis of ICARIA-MM (Isa-Pd, n=154; Pd, n=153) was planned when 220 death events occurred. Safety was assessed in patients receiving ≥1 study dose.
Results: At the operational cutoff (Mar 14, 2022), 16 (10.4%; Isa-Pd) pts and 3 (2.0%; Pd) pts were still on tx; 101 (65.6%) and 117 (76.5%) pts, respectively, discontinued due to progressive disease. Median tx duration was longer with Isa-Pd vs Pd (47.6 vs 24.0 weeks). After a median follow-up of 52.4 months, a clinically meaningful OS benefit was observed in favor of Isa-Pd vs Pd after 220 events (Jan 27, 2022; median OS: 24.6 vs 17.7 months; hazard ratio [HR] 0.776 [95% CI: 0.594–1.1015]; one-sided P=0.0319; significance level: P=0.02). Consistent results were seen in a sensitivity analysis censoring COVID-19 deaths (HR 0.759; 95% CI: 0.580–0.994; one-sided P=0.0023). Time to next tx (median 15.5 vs 8.9 months; HR 0.548 [95% CI: 0.417–0.718]) and progression/death on subsequent tx (PFS2; median 17.5 vs 12.9 months; HR 0.735 (95% CI: 0.569–0.950) were longer with Isa-Pd vs Pd. The safety profiles in both arms were consistent with prior ICARIA-MM findings; most adverse events (AEs) were reported at the interim OS analysis (Oct 2020). Grade ≥3 and serious tx-emergent AEs (TEAEs) were higher with Isa-Pd (90.8% and 73.7%) vs Pd (75.8% and 61.1%); however, TEAEs leading to tx discontinuation or death were not increased with Isa-Pd (12.5% and 9.9%) vs Pd (14.8% and 10.7%). The most common non-hematological TEAEs with Isa-Pd were infusion reactions (37.5%), upper respiratory tract infections (35.5%), diarrhea (31.6%), pneumonia (27.6%), and bronchitis (27.0%). More pts receiving Isa-Pd vs Pd reported Grade 3-4 neutropenia (84.9% vs 71.4%) and thrombocytopenia (34.2% vs 25.2%). The incidence of second primary malignancies (SPM) was higher with Isa-Pd vs Pd (relative risk 3.27; 95% CI: 0.92–11.64); most cases were localized non-melanoma skin cancers. Notably, no new patient developed SPM since the interim OS analysis, and SPM did not negatively impact OS.
Conclusions: This final OS analysis demonstrates a clinically meaningful benefit with a 6.9-month improvement in median OS and significantly improved time to next tx and PFS2, with a manageable safety profile, which further supports Isa-Pd as a standard-of-care therapy for pts with RRMM. Funding: Sanofi.

OAB-053

Mezigdomide (MEZI; CC-92480) in combination with dexamethasone (DEX) and bortezomib (BORT) or carfilzomib

(CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM)

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Introduction: MEZI is an oral novel cereblon E3 ligase modulator (CELMoD®) with enhanced tumoricidal and immune-stimulatory effects compared to IMiD® agents, which induces maximal degradation of Ikaros/Aiolos leading to increased apoptosis in MM cells. MEZI is being evaluated in the phase 1/2 study CC-92480-MM-002 (NCT03989414) plus standard treatments in pts with RRMM. A dose of 1.0mg of MEZI plus BORT was selected for further investigation in a dose-expansion cohort. We report results from the MEZI+BORT+DEX (MeziVd) and MEZI+CFZ+DEX (MeziKd) dose-escalation and the MEZI+BORT+DEX dose-expansion (MeziVd-1.0mg) cohorts.
Methods: Eligible pts had RRMM, 2–4 (MeziVd and MeziKd cohorts) or 1–3 (MeziVd-1.0mg cohort) prior regimens including prior treatment with lenalidomide (LEN), and documented progressive disease (PD) during or after their last myeloma therapy. MEZI was given at escalating doses or at the 1.0mg dose on days (D)1–14 of each 21-D cycle with BORT and DEX; or at escalating doses on days D1–21 of each 28-D cycle with CFZ and DEX. Primary objectives were to determine the recommended dose and regimen, and evaluate safety and preliminary efficacy.
Results: As of March 15, 2022, 22 pts received MeziVd, 34 MeziVd-1.0mg, and 17 MeziKd. Median (range) age was 66 (50–83), 64 (43–83), and 70 (45–76) y, median time since diagnosis was 4.8 (1.9–17.1), 4.5 (0.9–20.5), 6.5 (0.7–15.7) y, and median number of prior regimens was 3 (2–4), 1 (1–3), and 2 (2–4), respectively. Exposure to prior regimens was heterogeneous; 10 (45.5%), 6 (17.6%), and 8 (47.1%) pts were refractory to a proteasome inhibitor, and 18 (81.8%), 21 (61.8%), and 13 (76.5%) to LEN. Seven (31.8%), 24 (70.6%), and 10 (58.8%) pts continue on treatment, with 11, 6.5, and 6 median cycles received. The main reason for discontinuation was PD in the MeziVd cohort (9/15 pts); and adverse events (AEs) in the MeziVd-1.0mg (5/10 pts) and MeziKd (3/7 pts) cohorts, with most frequent being asthenia (40.0%) and COVID-19 pneumonia (66.7%), respectively.Hematologic grade (Gr) 3–4 treatment-emergent AEs (TEAEs) of interest included neutropenia (36.4%) and thrombocytopenia (18.2%) with MeziVd; neutropenia (29.4%), all infections (29.4%), and thrombocytopenia (26.5%) with MeziVd-1.0mg; and neutropenia (41.2%) and all infections (29.4%) with MeziKd; no Gr 3–4 peripheral neuropathy was observed in all cohorts. No pt experienced dose-limiting toxicity (DLT) with MeziVd and 1 pt had a DLT with MeziKd (pulmonary embolism). There were 6 (27.3%), 11 (32.4%), and 5 (29.4%) pts with ≥1 MEZI dose reduction due to TEAEs in the MeziVd, MeziVd-1.0mg, and MeziKd cohorts, respectively.ORR was 72.7% (MeziVd), 70.6% (MeziVd-1.0mg), and 76.5% (MeziKd), with 36.4%, 50.0%, and 35.3% very good partial responses or better.
Conclusions: MeziVd and MeziKd demonstrated a manageable safety profile and promising efficacy in pts with RRMM. These results support further evaluation of these MEZI combinations in phase 3 studies. Updated data will be presented at the meeting.

OAB-054
Comparative efficacy of teclistamab versus real-world physician's choice of therapy in the prospective LocoMMotion study in patients with triple-class exposed relapsed/refractory multiple myeloma

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Introduction: Patients (pts) with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM) who have been exposed to ≥3 lines of therapy (LOT) have a poor prognosis and limited treatment (tx) options. Teclistamab is a B-cell maturation antigen × CD3 bispecific antibody being evaluated in MajesTEC-1 (NCT04557098), a single-arm, phase 1/2 study in pts with RRMM who were TCE to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody and received ≥3 LOT. Since MajesTEC-1 lacks a control arm, we assessed the comparative efficacy of teclistamab vs real-world (RW) physician's choice of therapy by creating an external control arm from LocoMMotion (NCT04035226), a RW prospective study in pts with TCE RRMM who received ≥3 LOT.
Methods: An external control arm for MajesTEC-1 was created from pts in LocoMMotion (N=248, enrolled between Aug 2019 and Oct 2020; clinical cutoff May 21, 2021) who met MajesTEC-1 eligibility criteria. Individual pt-level data from MajesTEC-1 were included from 150 pts treated with teclistamab (1.5 mg/kg weekly) at a clinical cutoff of Nov 9, 2021. Inverse probability of tx weighting with average tx effect on the treated was used to adjust for imbalances in baseline covariates of prognostic significance (refractory status, International Staging System stage, time to progression on prior LOT, extramedullary disease, number of prior LOT, time since diagnosis, average duration of prior LOT, age, hemoglobin, lactate dehydrogenase, creatinine clearance, ECOG performance status, gender, type of MM, and prior transplant). Comparative effectiveness of teclistamab vs RW physician's choice of therapy was estimated for overall response rate (ORR), very good partial response (VGPR) rate, complete response or better (≥CR) rate, overall survival (OS), progression-free survival (PFS), and duration of response (DOR). For ORR, VGPR, and CR, relative effect of teclistamab vs RW physician's choice of therapy was estimated with an odds ratio, transformed into a response-rate ratio (RR) and 95% confidence interval (CI), derived from weighted logistic regression. A weighted Cox proportional hazards model was used to compute hazard ratios (HRs) and 95% CIs for OS, PFS, and DOR.
Results: Baseline characteristics were well balanced between the 2 cohorts after reweighting the external control arm. Pts treated with teclistamab had significantly improved outcomes vs RW physician's choice of therapy: ORR (RR [95% CI] 2.34 [1.78–2.90]; P< 0.0001), VGPR rate (RR 5.61 [3.42–7.79]; P< 0.0001), ≥CR rate (RR 102.14 [14.16–736.61]; P< 0.0001), OS (HR 0.66 [0.44–0.99]; P=0.04), PFS (HR 0.48 [0.34–0.66]; P< 0.0001), and DOR (HR 0.23 [0.13–0.43]; P< 0.0001).
Conclusions: Teclistamab showed significantly improved efficacy over RW physician's choice of therapy for all outcomes, highlighting its clinical benefit as a highly effective tx option for pts with TCE RRMM who have been exposed to ≥3 LOT.

OAB-055

Updated results of a phase 1, first-in-human study of ABBV-383, a BCMA × CD3 bispecific T-cell redirecting antibody, in patients with relapsed/refractory multiple myeloma

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Introduction: Prognosis is poor for patients (pts) with relapsed/refractory multiple myeloma (RRMM) with a high unmet clinical need, where B-cell maturation antigen (BCMA) is emerging as a promising therapeutic target. ABBV-383, a BCMAxCD3 T-cell engager, has demonstrated promising activity in RRMM. Herein, the updated results from the ongoing first-in-human phase 1 study are reported including patients treated from the 60mg escalation (ESC)/expansion (EXP) cohort.
Methods: This phase 1, ESC/ EXP study (NCT03933735) is enrolling pts with RRMM (≥3 prior lines), eGFR ≥30 mL/min, and ECOG PS ≤2. Primary objectives include safety/tolerability and pharmacokinetics; secondary objectives include clinical activity assessed per IMWG 2016 criteria. The study uses 3+3 dose escalation and dose expansion to determine RP2D. ABBV-383 is administered intravenously once every 3 weeks (Q3W). Pts are treated until progression, unacceptable toxicity, or other discontinuation criteria are met. Adverse events (AEs) including cytokine release syndrome (CRS) are graded according to NCI CTCAE v5.0.
Results: As of 8Jan2022, a total of 124 pts are treated: 73pts in ESC (0.025mg-120mg) and 51pts in EXP at 60mg; a 40mg dose expansion cohort is enrolling currently. The median age is 68 years with median of 5 prior therapies received, and 82% were triple class refractory. The median follow-up (f/u) is 10.8 months(mo), with 36% continuing study drug. Of the 124pts treated with ABBV-383, with 121 (98%) experienced an AE with most common being CRS (57%; 54% G1/G2). Among pts treated at 60mg (n=60; ESC+EXP), CRS occurred in

72% of the pts (48% G1; 22% G2; 2% G3) with the first dose, with median time to onset and resolution of 1 day (0% recurrence). Other AEs observed in >20% of all pts are fatigue (30%; G3-4, 1%), anemia (29%; G3-4, 16%), nausea (29%; G3-4, 2%), diarrhea (27%; G3-4, 2%), vomiting (24%; G3-4, 0%), and neutrophil count decreased (22%; G3-4, 19%). In all patients (n=122), the ORR (≥ PR), ≥VGPR, and ≥CR rates are 57%, 43%, and 29%, respectively. Of the 11 MRD-evaluable patients with ≥CR, 8 (73%) were MRD-negative (≤10-5). At 60mg (ESC+EXP; n=58), the ORR, ≥ VGPR and ≥CR rates were 60%, 43%, and 29%,respectively, with median time to first confirmed response of 0.8mo and median time to sCR/CR of 2.8mo. Median duration of response (DOR) was not reached with the 12-month Kaplan-Meier (KM) estimate of 79.9%; median PFS was not reached with 12-month KM estimate of 57.0% in this EXP cohort.
Conclusions: ABBV-383 monotherapy demonstrates an acceptable and manageable safety with promising efficacy indicated by deep and durable responses with ORR of 60% (at 60mg) and median DOR not reached, supporting the development of ABBV-383 monotherapy in a heavily pre-treated RRMM population with a high unmet need. Enrollment in the dose-expansion arm is ongoing with additional dose level of 40mg currently under exploration.

OAB-056
Early, deep, and durable responses, and low rates of cytokine release syndrome with REGN5458, a BCMAxCD3 bispecific antibody, in a Phase 1/2 study in patients with relapsed/refractory multiple myeloma

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Introduction: Despite recent advances in treatment options, multiple myeloma (MM) remains incurable. REGN5458 is a BCMAxCD3 bispecific antibody currently under investigation in relapsed/refractory MM (RRMM) in an ongoing Phase 1/2 trial (NCT03761108). Preliminary data suggest that REGN5458 has a manageable safety profile with early, deep, and durable responses in heavily pretreated patients (pts). Updated Phase 1 data are reported here.
Methods: Pts with progressive RRMM who are double- or triple-refractory, or intolerant to, prior lines of systemic therapy, including a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody, are treated with REGN5458. The Phase 1 primary objectives are to assess safety, tolerability, and occurrence of dose-limiting toxicities, and to determine a recommended Phase 2 dose regimen. The objective response rate by modified International Myeloma Working Group criteria is a key secondary objective.
Results: At data cut-off (September 30, 2021), 73 pts were treated with REGN5458 in the dose-escalation cohort, with full doses ranging from 3 to 800 mg. The median age at enrollment was 64 years (range, 41–81) and 20.5% pts were ≥75 years. As per the Revised International Staging System, stages were 1, 2, or 3 in 15.0%, 57.5%, and 23.3% of pts, respectively. Pts had a median of 5 prior lines of systemic therapy (range, 2–17), with 89.0% of pts being triple-refractory. The median duration of follow-up was 3.0 months (range, 0.7–22.1). The most frequent treatment-emergent adverse events (TEAEs) were fatigue in 33 pts (45.2%), grade (Gr) 1/2 in 31 pts (42.5%), Gr 3 in 2 pts (2.7%); cytokine release syndrome (CRS) in 28 pts (38.4%), Gr 1 in 25 pts (34.2%), Gr 2 in 3 pts (4.1%). No pt had Gr ≥3 CRS or discontinued treatment due to CRS. There were no Gr ≥3 neurotoxicity events. Nausea was reported in 24 pts (32.9%), Gr 1 in 17 pts (23.3%), Gr 2 in 7 pts (9.6%). Gr 3 and 4 TEAEs were reported in 31 pts (42.5%) and 24 pts (32.9%), respectively. The most common Gr 3/4 TEAEs were hematologic (39.0%). Responses were observed at all dose levels. Among all responders, 86.5% (n=32/37) achieved at least a very good partial response and 43.2% (n=16/37) achieved complete, or stringent complete, responses. Amongst pts treated at the 200–800 mg dose levels, the response rate was 75.0% (n=18/24). The Kaplan–Meier estimated probability of responders being in response for ≥8 months was 90.2% (95% confidence interval: 72.6–96.7), and median duration of response was not reached.
Conclusions: REGN5458 shows a manageable safety and tolerability profile, with Gr 2 CRS in only 4.1% of pts and no Gr ≥3 CRS or neurotoxicity events. No new safety signals were observed during the additional follow-up period. Early, deep, and durable responses were seen in triple- to penta-refractory pts with RRMM, with a 75.0% response rate at the combined 200–800 mg dose levels. The Phase 2 portion of the study is currently recruiting.

OAB-057
Daratumumab (DARA) + Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients (Pts) With Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Final

Analysis of GRIFFIN

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Introduction: DARA is a human IgGκ monoclonal antibody approved across lines of therapy for myeloma. In the primary analysis of the phase 2 GRIFFIN study (NCT02874742), DARA+RVd (D-RVd) improved the stringent complete response (sCR) rate by the end of consolidation vs RVd (42.4% vs 32.0%; 1-sided *P*=0.068, which met the prespecified 1-sided α of 0.1). With longer median follow-up (38.6 mo), response rates deepened and improved for D-RVd vs RVd, as did minimal residual disease (MRD)-negativity rates (10^{-5}; 64.4% vs 30.1%). Here, we present the final GRIFFIN analysis (median follow-up, 49.6 mo) after all pts completed ≥1 year of long-term follow-up after end of study treatment or withdrawal.
Methods: Transplant-eligible NDMM pts were randomized 1:1 to 4 D-RVd/RVd induction cycles, autologous stem cell transplant, 2 D-RVd/RVd consolidation cycles, and 2 years of maintenance with R ± DARA. For induction/consolidation (21-day cycles), pts received R (25 mg PO Days [D]1-14), V (1.3 mg/m^2 SC D1/4/8/11), and d (40 mg PO QW) ± DARA (16 mg/kg IV on D1/8/15 of Cycles 1-4 and D1 of Cycles 5-6). During maintenance (28-day cycles), pts received R (10 mg PO D1-21; if tolerated, 15 mg Cycles 10+) ± DARA (16 mg/kg IV Q8W or Q4W, or 1800 mg SC Q4W per protocol amendments). Following completion of study therapy, pts could continue R maintenance. The primary endpoint was sCR rate by end of consolidation. This predefined final analysis occurred after patients completed ≥1 year of long-term follow-up, died, or withdrew.
Results: 207 pts were randomized (D-RVd, n=104; RVd, n=103). At the time of final analysis, sCR rates were higher for D-RVd vs RVd (67.0% vs 48.0%; *P*=0.0079), as were rates of MRD negativity (10^{-5}: 64.4% vs 30.1%, *P*< 0.0001; 10^{-6}: 35.6% vs 15.5%, *P*=0.0013) and durable MRD negativity lasting ≥12 months (10^{-5}: 44.2% vs 13.6%, *P*< 0.0001; 10^{-6}: 9.6% vs 3.9%, *P*=0.1646). At median follow-up of 49.6 months, there was a 55% reduction in the risk of disease progression or death for D-RVd vs RVd (HR: 0.45, 95% CI: 0.21-0.95; *P*=0.0324); estimated 48-month PFS rates were 87.2% for D-RVd and 70.0% for RVd. In total, 14 pts died (D-RVd, n=7; RVd, n=7). No new safety concerns occurred with extended follow-up. Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in 85.9% (85/99) of D-RVd pts and 79.4% (81/102) of RVd pts. In an analysis of infections by 4-cycle intervals, the highest incidence during maintenance therapy occurred in earlier cycles (D-RVd, Cycles 7-10: 55.1% [49/89] of pts; RVd, Cycles 11-14: 39.1% [27/69] of pts). Deaths due to TEAEs occurred in 2 pts (D-RVd, n=1; RVd, n=1); none were related to study drug.
Conclusions: In the final analysis of GRIFFIN (median follow-up, 49.6 mo), addition of DARA to RVd led to a clinically meaningful PFS benefit favoring the D-RVd arm. No new safety concerns occurred with longer follow-up. These data support use of D-RVd induction/consolidation and D-R maintenance as a new standard of care in transplant-eligible NDMM.

OAB-058
Lenalidomide-bortezomib-dexamethasone (RVd) ± autologous stem cell transplantation (ASCT) and R maintenance to progression in patients with newly diagnosed multiple myeloma (NDMM), by cytogenetic risk

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Introduction: In the IFM 2009 trial, there was a progression-free survival (PFS) benefit (median 47.3 vs 35.0 mos) with RVd+ASCT vs RVd-alone plus R maintenance for 1 y but no overall survival (OS) benefit (8-y OS: 62% vs 60%, median follow-up 89.8 mos), with 77% of RVd-alone pts receiving ASCT at 1st relapse. (Attal M et al, N Engl J Med 2017; Perrot A et al, ASH 2020). We report data from our US phase 3 DETERMINATION trial, utilizing R maintenance until progression.
Methods: Pts aged 18-65 y were randomized (stratified by ISS stage and cytogenetic risk) to receive 3 RVd cycles, stem cell mobilization, and then 5 more RVd cycles (RVd-alone), or melphalan 200 mg/m^2 + ASCT and 2 more RVd cycles (RVd+ASCT). In both arms, pts then received R until progression or intolerance. The primary endpoint was PFS. Data cut-off was Dec 10, 2021.
Results: 357 vs 365 pts were randomized to RVd-alone vs RVd+ASCT (median age: 57 vs 55 y; ISS stage III: 13.7% vs 12.9%; high-risk cytogenetics [t(4;14), t(14;16), del17p]: 19.8% vs 19.4% of evaluable pts); 291 and 289 pts received R maintenance for a median of 36.4 and 41.5 mos. After median follow-up of 76 mos and 328 events, median PFS was 46.2 vs 67.5 mos with RVd-alone vs RVd+ASCT (HR 1.53; 95% CI 1.23–1.91; p< 0.0001) – 17.1 vs 55.5 mos (HR 1.99; 95% CI 1.21–3.26) in pts with high-risk and 53.2 vs 82.3 mos (HR 1.38; 1.07–1.79) in pts with standard-risk cytogenetics. Overall best response rate (≥partial response) was 95.0% vs 97.5% (high-risk: 98.5% vs 97.0%; standard-risk: 94.4% vs 97.8%), with 42.0% vs 46.9% ≥complete responses (high-risk: 36.4% vs 53.0%; standard-risk: 43.3% vs 46.7%). Preliminary analyses of minimal residual disease (MRD) at the start of maintenance in 108 and 90 pts showed MRD-negative (10^{-5}) rates of 39.8% vs 54.4% (odds ratio 0.55). With 90 vs 88 pts having died, 5-y OS rates were 79.2% vs 80.7%, respectively (HR 1.10; 95% CI 0.73–1.65): 54.3% vs 63.4% (HR 1.25; 95% CI 0.75–2.08) in pts with high-risk and 86.2% vs 86.0% (HR 0.99; 0.66–1.47) in pts with standard-risk cytogenetics. With RVd-alone and RVd+ASCT, 78.2% and 94.2% had grade ≥3 related adverse events (AEs); 60.5% vs 89.9% had grade ≥3 related hematologic AEs (p< 0.0001); 10.4% vs 10.7% had secondary malignancies (ALL 7 vs 3 pts, ns; AML/MDS 0 vs 10 pts, p=0.002). 79.9% vs 69.6% of pts who had discontinued study treatment have received subsequent non-protocol therapy; of 279 RVd-alone pts who had discontinued, 28% had received ASCT as part of any subsequent therapy.
Conclusions: RVd ± ASCT and R maintenance to progression resulted in the longest median PFS reported for each approach, and a highly significant PFS benefit with RVd+ASCT, notably in pts with high-risk cytogenetics, for whom novel therapies are needed. No OS advantage has been observed to date.

OAB-059
Enhancing SLAMF7 CAR T cell production by prevention of fatricide

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Introduction: The SLAMF7 antigen is highly and uniformly expressed on malignant plasma cells and under investigation as a target for antibody-based and cellular immunotherapy in multiple myeloma. We are pursuing the clinical development of SLAMF7 CAR T cell therapy in an ongoing phase I/IIa trial (CARAMBA EudraCT: 2019-001264-30).
A particular challenge with generating SLAMF7 CAR T cells is the physiologic expression of SLAMF7 on T cells which induces fratricide and submaximal SLAMF7 CAR T cell expansion during manufacturing. Here, we determined the effect of using an anti-SLAMF7 antibody (aSF7-mAb) to shield SLAMF7 on T cells on the yield and potency of SLAMF7 CAR T cells in preclinical campaigns.
Methods: We generated SLAMF7 CAR T cells following the cGMP-compliant manufacturing protocol of the CARAMBA

trial. Different concentrations of aSF7-mAb were added to the culture medium after SLAMF7 CAR gene-transfer, replenished every 2nd day and removed either mid-way or at the end of the manufacturing process. We performed n=4 manufacturing and release campaigns with extensive phenotyping and functional testing.
Results: We found that the addition of aSF7-mAb had a profound and consistent positive effect on SLAMF7 CAR T cell manufacturing. At the end of the manufacturing campaign, the total expansion factor of T cells treated with aSF7-mAB was 9.3 instead of 2.0 with the conventional process, and both methods resulted in a comparable gene transfer rate. aSF7-ab addition exerted the strongest effect (in preventing fratricide) immediately after gene-transfer, evidenced by a higher proportion of viable T cells.
At the end of manufacturing, SLAMF7 CAR T cells had a SLAMF7-negative phenotype, suggesting that fratricide had still occurred but at a pace and extent that was compatible with productive proliferation and expansion. Phenotypic analysis showed that a sizeable fraction of SLAMF7 CAR+ T cells had lower expression of PD-1, TIM-3 and LAG-3 after treatment with aSF7-mAb.
Of particular note, we observed strong anti-myeloma efficacy of SLAMF7 CAR T cells that had been treated with aSF7-mAb: In particular, we found greater proliferation of SLAMF7 CAR T cells after stimulation with multiple myeloma target cell lines, indicating substantially improved T cell fitness.
Conclusions: Taken together, the data show that the addition of aSF7-mAb to shield SLAMF7 on T cells substantially facilitates the manufacturing of SLAMF7 CAR T cells for adoptive therapy of multiple myeloma. The prevention (or rather: the steering of controlled fratricide) leads to increased yield, augmented phenotype and anti-myeloma function in pre-clinical models.
These data suggest that SLAMF7 CAR T cells produced with this improved protocol will also confer superior anti-myeloma efficacy in a clinical setting. The aSF7-mAb is available in pharmaceutical grade and be seamlessly incorporated into cGMP manufacturing processes for the next generation of trials under the CARAMBA IND.

OAB-060

Changes in bone marrow tumor and immune cells correlate with durability of remissions following BCMA CAR-T therapy in myeloma

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Introduction: Chimeric antigen-receptor (CAR)-T cells targeting B-cell maturation antigen (BCMA) can induce deep responses in relapsed/refractory myeloma, but most patients relapse. We previously reported results from a phase 1 trial of a BCMA-targeted CAR T cell product (CART-BCMA) (Cohen et al, J Clin Invest 2019), with responses in 48% (12/25). Here we combined several high-dimensional single cell approaches to study tumor and immune cells in the bone marrow (BM) microenvironment pre- and post-CART-BCMA therapy, in order to identify features associated with shorter versus longer duration of response.
Methods: Serially-collected, cryopreserved BM mononuclear cells (BMMC) were available from 11 responders to CART-BCMA, 4 with long progression-free survival (PFS) (median 752+ days) and 7 with short PFS (median 125 days). BMMC were analyzed using mass cytometry (CyTOF), as well as by CITE-Seq and TCR-seq (10x Genomics). Total of 28 specimens were analyzed, of which 23 underwent CITE-seq and single cell transcriptomics (yielding 151,054 single cells meeting pre-defined quality control criteria), and 24 underwent CyTOF.
Results: CAR vector copy number in peripheral blood at peak expansion and at Day 28 in bone marrow did not differ significantly between patients with short versus long PFS. Response durability was associated with dynamic changes in BM T cell and myeloid/dendritic cell (DC) compartments. In particular, a lower diversity of pre-therapy T-cell-receptor (TCR) repertoire, presence of hyperexpanded T-cell clones with an exhaustion phenotype, and higher proportion of Baff+PD-L1+ myeloid cells at Day 28 correlated with shorter PFS following CAR-T therapy. In contrast, long PFS was associated with increased proportion of Clec9a+ DCs, and CD27+TCF1+ T-cells with diverse T-cell receptors, followed by emergence of T cells expressing BM-residence genes (eg. CXCR4 and CD69). Analysis of shared TCRs revealed that CAR-T therapy leads to in-situ expansion of specific tumor-infiltrating lymphocytes (TILs) with pre-activated phenotype at baseline. Baseline myeloma cells in patients with long PFS had higher expression of mature plasma cell genes (eg. SDC1, BCMA/TNFRSF17, XBP1) and interferon response genes, while those with short PFS had higher expression of genes associated with less mature B cells (eg. PBXIP) consistent with a less differentiated phenotype. Post-treatment residual tumors from different patients clustered together, suggesting the emergence of a shared transcriptional signature in residual disease, including upregulation of genes (eg. SPARC and MYL9) implicated in epithelial-mesenchymal transition and stemness. Late tumor recurrence in patients with long PFS was associated with emergence of new dominant clones.
Conclusions: These data illustrate dynamic interplay between endogenous TILs, infused CAR-T, myeloid/DC and tumor compartments that impacts durability of response following BCMA CAR-T therapy in myeloma.

OAB-061

Altered composition of CD8 T cells subsets over time in the bone marrow of multiple myeloma patients with long- and short-term disease control

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Introduction: Survival in multiple myeloma (MM) is highly variable ranging from aggressive disease with overall survival (OS) of a few months to patients with a chronic disease for more than two decades. Whereas many clinical variables and tumor genomic aberrations are associated with risk, little is known about how adaptive immune cells interact with the tumor cells and affect tumor progression. In this study we focus on CD8 T-cell subtypes present in the BM in longitudinal samples from patients with long-term disease control (LTDC) versus short-term disease control (STDC).
Methods: We defined patients with survival less than 2 years as STDC (n=5) and patients with either more than 5 years between diagnosis and first relapse or OS more than 8 years as LTDC (n=8). All patients had at least 2 samples collected throughout their disease course (sample total=45). The first and last BM samples from each patient were used for comparison of the two groups at early and late disease stage. The samples were analyzed using mass cytometry on a Helios cytometry by time-of-flight (CyTOF) system (Fluidigm, USA), using a panel with 37 markers designed to identify T-cell subsets, activation status and effector function. Analyses, including dimension reduction and clustering algorithms tSNE-CUDA and FlowSOM, were performed using the Cytobank software (Cytobank, USA). TCR sequencing to determine clonality was also performed.
Results: FlowSOM analysis of the CD8 T cells revealed that a senescent CD8 T cell population high in CD57 was enriched in STDC patients at late disease stage. Zelle-Rieser et al. have previously found an increase in senescent CD8 T cells in MM patients compared to healthy controls (J Hematol Oncol, 2016). Here we show a difference in CD8 T cell senescence between patient groups at late disease, suggesting that the CD8 T cell responses may be less efficient in the STDC patients over time. FlowSOM analysis also revealed that a TCF1hi memory CD8 T cell population was significantly more abundant in LTDC patients compared to STDC patients at late disease stage. TCF1hi T cells are more proliferative and long-lived than differentiated effector T cells and have been linked to anti-tumor immunity and improved tumor control. Dhodapkar et al. have demonstrated an enrichment in TCF1hi cells in the memory cell compartment in MGUS patients compared to myeloma patients, suggesting a connection between loss of stem-like cells and loss of immune surveillance (JCI Insight, 2019). Here we demonstrate a difference in TCF1hi memory T cell abundance within myeloma patients with different disease control and survival.
Conclusions: Our data suggests that CD8 T cell populations in the BM change over time in myeloma patients. At late disease stage, TCF1hi memory CD8 T cells are more abundant in LTDC patients, and they have fewer senescent CD8 T cells compared to STDC patients. This indicates that LTDC patients have a tumor microenvironment richer in proliferative, functional, long-lived CD8 T cells.

OAB-062

Efficacy and safety of cilta-cel in patients with progressive multiple myeloma after exposure to BCMA-targeting bispecific antibody treatment

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Introduction: Cilta-cel is an approved BCMA-targeting CAR-T therapy for multiple myeloma (MM). Bispecific antibodies (BsAbs) targeting BCMA are in development, but few data are available on treatment sequencing with multiple anti-BCMA agents. CARTITUDE-2 (NCT04133636) is a phase 2, multicohort study evaluating efficacy and safety of cilta-cel in several MM patient populations, including those with prior exposure to BCMA-targeting BsAbs (cohort C).
Methods: Cohort C patients had progressive MM after treatment with a proteasome inhibitor, immunomodulatory drug, anti-CD38 antibody, and non-cellular BCMA-targeting agent. A single cilta-cel infusion (target dose: 0.75×106 CAR+

viable T cells/kg) was given 5–7 d post lymphodepletion. The primary endpoint was minimal residual disease (MRD) negativity at 10-5. Secondary endpoints included overall response rate (ORR; by IMWG criteria), duration of response (DOR), and adverse events (AEs).
Results: As of October 8, 2021, 7 BsAb-exposed patients (57% male, median age 60 y [range, 49–71]) were treated with cilta-cel; 2 additional patients underwent apheresis but did not receive cilta-cel due to low cellular yield (n=1) or death (n=1). Of the patients who received cilta-cel, 3 had prior teclistamab, and 1 each had prior AMG 420, AMG 701, PF-06863135, and WVT078. Patients had received a median of 8 (range, 6–12) prior lines of therapy, all were triple-class refractory, and 5 (71%) were refractory to prior anti-BCMA therapy. The median time from BsAb termination to cilta-cel infusion was 227 d (range, 84–329). At a median follow-up of 10.9 mo (range, 0.6–11.5) post cilta-cel, 2 of 7 (28.6%; 95% CI: 3.7–71.0) patients were MRD negative (2 of 3 [66.7%; 95% CI: 9.4–99.2] in the MRD-evaluable subset). ORR was 57.1% (95% CI: 18.4–90.1; 2 patients died prior to confirmed response). Median DOR and progression-free survival (PFS) were 8.2 (95% CI: 4.4–NE) and 5.3 (95% CI: 0.6–NE) mo, respectively. Patients who responded to cilta-cel had a shorter median duration of last BsAb exposure (54 d, range 23–127) than non-responders (130 d, range 15–260). Responders also had a longer median time between last BsAb treatment and apheresis (221 d, range 28–281) than non-responders (84 d, range 77–251). No correlation was seen between baseline serum BCMA levels and response. BsAb-exposed patients had an increased proportion of effector memory T cells at apheresis. CAR-T expansion kinetics were consistent with previous studies. CRS occurred in 6 (86%) patients (all grade 1/2); 2 had ICANS (1 gr 3/4); none had parkinsonism. There were 3 deaths due to COVID-19 pneumonia (not treatment-related per investigator), C. difficile colitis (related), and subarachnoid hemorrhage (not related).
Conclusions: Cilta-cel induced favorable responses, DOR, and PFS in heavily pretreated MM patients with prior anti-BCMA BsAb exposure. These initial results may inform treatment plans, including sequencing and washout periods between agents targeting BCMA.

P-001
RNA-sequencing reveals transcriptomic similarity of AL amyloidosis and MGUS aberrant plasma cells along with several potential ALA target candidate genes

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Introduction: Light-chain amyloidosis (ALA) is a rare and fatal monoclonal gammopathy (MG) causing organ and tissue damage resulting from the deposition of misfolded immunoglobulin free light-chains in the form of amyloid fibrils. Mutation landscape of ALA seems to be similar to monoclonal gammopathy of undetermined significance (MGUS) but expression profile by RNA-seq is still poorly studied and understood. We investigated the gene expression profiles in clonal aberrant PC (aPC) in order to better understand ALA, MM and MGUS etiology to clarify the expression differences between individual MG diagnoses.
Methods: Analysis of 5 newly diagnosed histologically proven ALA samples, 9 MM samples, 5 MGUS and 5 healthy donors (HD) samples was performed. Furthermore, we also added paired normal plasma cell samples from 3 ALA and 3 MGUS samples. We isolated RNA from clonal bone marrow PC sorted using CD45-PB, CD38-FITC, CD19-PECy7 and CD56-PE fluorescent antibodies. Isolated RNA served for library preparation using SMARTer Stranded Total RNA-Seq Kit v2 and sequencing aiming at 30 M pair-end reads/sample. Reads were mapped and quantified by Salmon v1.4.0. Differential gene expression was evaluated using Deseq2 v1.30.0.
Results: Principle component analysis of aberrant plasma cells (aPC) from ALA, MGUS and their polyclonal plasma cells (nPC) counterparts, MM and plasma cells from HD revealed that ALA aPC samples cluster together mainly with MGUS aPC, while all nPC and HD form a distinct non-overlaping cluster. We performed differential expression analysis of each pathology group (ALA, MGUS, MM) with transcriptomes of plasma cells from HD. We identified 299 significantly deregulated genes in ALA, 715 in MGUS and 320 in MM. All diagnoses differed from HD by a set of 55 shared genes, which mainly belonged to a neurogenesis pathway, hypothetically pointing towards undifferentiated characteristics of malignant cells. One of the most deregulated and highly expressed genes in MGs was NDNF (Neuron Derived Neurotrophic Factor) gene. Furthermore, ALA deregulated genes belong to an adhesion KEGG pathway which is activated, while oxidative phosphorylation, ribosome and spliceosome pathways that are suppressed. Among most upregulated genes were known markers as SRC, CD28, CCND1 (and its regulator SYF2 that is downregulated) and also gene MAML2, which is a prion-like transcription factor that can mediate amyloid formation. Comparison of ALA and MGUS aPC versus nPC identified 58 unique deregulated genes in ALA and 360 in MGUS. ALA aPC genes belonged mainly to processes of cell cycle and cell division (E2F1, BUB1, BUB1B, RAD51).
Conclusions: Our study represents one of the first ALA RNA-seq projects. Comparison of ALA expression profile with other monoclonal gammopathies and nPCs showed a close relationship of ALA and MGUS. Our search revealed several novel interesting ALA genes, which can serve as candidates for closer translational studies.

P-002

Clinical outcomes and effectiveness of heart transplantation in patients with systemic light-chain cardiac amyloidosis

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Introduction: In systemic light-chain (AL) amyloidosis, cardiac involvement is a major determinant of survival. However, cardiac response is limited even after systemic treatment in a majority of patients, and some require heart transplantation. In addition, limited information is available on specific indications for heart transplantation. We aimed to explore clinical outcomes of cardiac amyloidosis and its association with heart transplantation, including identifying factors favoring heart transplantation amenability.
Methods: We retrospectively analyzed data from patients diagnosed with AL amyloidosis with cardiac involvement between January 2007 and December 2020 at a tertiary referral center.
Results: Among 73 patients, 72 (99%) received systemic treatment, and 12 (16%) underwent heart transplantation. Characteristics at diagnosis were similar between heart transplant recipients and non-recipients, although left ventricular ejection fraction tended to be lower in recipients (median 48% versus 57%, P = 0.085). Eight weeks after systemic treatment, 67% and 12% of patients achieved hematologic and brain natriuretic peptide responses. Overall survival was longer among heart transplantation recipients than non-recipients, with 5-year survival rates of 61.1% (95% confidence interval [CI], 25.5-83.8%) versus 32.0% (95% CI, 20.3-44.4%) (P=0.022), respectively. Among the 34 with identifiable causes of death out of 51 deaths, 21 non-recipients (62%) died of cardiac problems compared with none in the heart transplant recipients. In addition, survival outcomes favored heart transplant recipients in most subgroups, including patients with higher Mayo 2004 European stage at diagnosis and with extracardiac involvement of amyloidosis. Seven patients among the heart transplant recipients had extracardiac involvement but without severe debilitating symptoms related to that. None of them experienced definite extracardiac progression after HTPL.
Conclusions: Heart transplantation can achieve long-term survival in appropriately selected patients with AL cardiac amyloidosis. Limited extracardiac involvement of amyloidosis per se may not be a contraindication for HTPL.

P-003

A first-in-human phase 1 study of oral LOXO-338, a selective BCL2 inhibitor, in patients with advanced hematologic malignancies (trial in progress)

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Introduction: B-cell lymphoma 2 (BCL2) is a key regulator of apoptosis and provides protection from cell death in many hematological malignancies. LOXO-338 is a novel, orally bioavailable small molecule inhibitor of BCL2, designed to achieve selectivity over BCL-xL and thus avoid dose-limiting thrombocytopenia associated with BCL-xL inhibition. In preclinical studies, LOXO-338 showed a favorable pharmacological profile, selectively inhibited BCL2, and was well-tolerated in vivo. LOXO-338 also demonstrated dose-dependent tumor growth inhibition in various murine xenograft models, and showed improved efficacy in combination with pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor (Brandhuber et al. Cancer Res 2021; 81, 13 Supplement, 1258).
Methods: LOXO-BCL-20001 is an ongoing global, open-label, multi-center, first-in-human phase 1 study of oral LOXO-338 in patients (pts) with relapsed B-cell malignancies who have previously received standard therapy (NCT05024045). The study is being conducted in 2 parts. Part 1 evaluates LOXO-338 as monotherapy, exploring different dosing strategies. Part 2 will evaluate LOXO-338 in combination with pirtobrutinib. Part 1 dose escalation portion of the study will follow an i3+3 design. Each cycle is 28 days. Eligible pts may have any one of the following B cell malignancies: CLL/SLL, mantle cell lymphoma, or Waldenström macroglobulinemia (WM), and must have received standard therapy. Pts with other B-cell non-Hodgkin lymphomas (NHL), including diffuse large B-cell, follicular and marginal zone lymphoma, who have no known potentially beneficial options are also eligible, as are pts with active or suspected Richter transformation, transformed lymphoma, Burkitt or Burkitt-like lymphoma, and multiple myeloma. Pts with AL amyloidosis are eligible in monotherapy dose expansion. Pts must not have progressed while receiving a prior BCL2 inhibitor; those with WM or AL amyloidosis must not have received a prior BCL2 inhibitor. Key exclusion criteria include a history of CNS involvement, prior stem cell transplantation or CAR-T therapy within 60 days, and clinically significant cardiovascular disease. The primary objectives of Part 1 are to determine the RP2D of oral LOXO-338 monotherapy and LOXO-338 in combination with pirtobrutinib for previously treated pts and to evaluate the antitumor activity in pts with WM and AL amyloidosis. Secondary objectives include assessment of the safety profile and tolerability, pharmacokinetic characteristics, and antitumor activity of LOXO-338 monotherapy and in combination with pirtobrutinib based on investigator-assessed overall response rate (ORR), progression-free survival (PFS), time to progression (TTP) and duration of response (DOR) as per disease-specific response criteria.

P-004

Successful ex-plantation of left ventricular assist device after cardiac recovery with daratumumab therapy in a patient with end stage heart failure due to immunoglobulin light-chain (AL) amyloidosis

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Introduction: The ANDROMEDA study has informed that daratumumab-based therapy is the current optimal standard of care for patients with newly diagnosed AL amyloidosis. It induces more rapid and higher hematologic and cardiac response rates. However, severe cardiac failure, the major cause of death amongst AL amyloidosis patients was a major exclusion criterion and it remained the primary cause of death amongst study patients. As such, management of AL amyloidosis patients with severe cardiomyopathy is the greatest unmet need for the disease.
Methods: A 46-years old female teacher presented with end-stage heart failure due to biopsy-proven systemic AL amyloidosis. Echocardiogram and cardiac MRI demonstrated moderate biventricular hypertrophy, moderately impaired left ventricular ejection fraction with severe diastolic dysfunction. Serum high-sensitive troponin-T was 279 pg/ml, NT-proBNP was 24,800 pg/ml and serum lambda and kappa free light chains were 400 mg/L and 11 mg/L respectively. Her expected survival based on the revised Mayo staging system was 6 months. She responded poorly to medical therapy but declined palliative therapy in favour of undergoing left ventricular assist device (LVAD) implantation. Due to the small left ventricular cavity size, we implanted the LVAD via a modified left atrium-to-aorta configuration technique. As she could not tolerate standard therapy for AL amyloidosis, she was treated with daratumumab.

Results: She attained sustained complete hematologic response after 3 months of treatment. Post-LVAD implantation, she did not experience any significant heart failure symptom, and returned to teaching after 6 months of rehabilitation. After 12 months, her NT-proBNP decreased to 808 pg/ml while troponin-T dropped to 55 pg/ml. Interestingly, the LVAD pump flow started to drop progressively in the second year due to competing flow from the recovering left ventricle where ejection fraction improved from 28% immediately post-LVAD implantation to 55%. The patient declined heart transplantation. In view of her cardiac recovery and to avoid potential complications from prolonged LVAD in-situ, we decided to ex-plant the LVAD after she passed several dynamic screening tests 26 months post-implantation. From the fourth month post-ex-plantation, the patient reports no significant symptom of heart failure and is back teaching again. She is currently 12 months out

Conclusions: Prognosis of end-stage heart failure remained poor despite advent of bortezomib induction. To our knowledge, this is the first reported case of successful ex-plantation of LVAD used as a bridge to cardiac recovery while treating AL amyloidosis with daratumumab. While prospective studies exploring this approach are unfeasible, the mechanistic basis of our anecdotal experience could suggest the reproducibility of such a favorable outcome in the era of novel therapeutics for AL amyloidosis. This will potentially avert early cardiac mortality for many patients presenting with severe heart failure.

P-005

Dual specific bivalent CS1 bispecific antibody for cellular immunotherapy against multiple myeloma

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Introduction: Multiple myeloma (MM) is the second most common hematological malignancy in the US with an estimated 34,000 cases annually. Although the adoptive transfer of MM-specific chimeric antigen receptor (CAR) T cell therapy has achieved incredible response rates, engineered T cells generally fail to maintain durable anti-tumor responses and present limitations in cost and manufacturing times. Alternatively, bispecific T cell engaging antibodies (bsAbs) which simultaneously bind T cells and tumor-specific antigens, represent a novel therapeutic option for hematological tumors, including MM, with demonstrated efficacy and advantages of immediate availability for patients. CS1 is a cell surface glycoprotein and member of the signaling lymphocyte activating molecule receptor (SLAM) family that has been implicated in uncontrolled proliferation and survival of MM cells. However, unlike other well studied targets such as BCMA and CD38 or the recently identified orphan G protein receptor (GPRC5D), CS1 maintains uniform and robust expression in MM cells with low level expression on other circulating immune cells, making it an attractive target for bsAb therapy. Nevertheless, with the surge in bsAb trials against MM, it is worth noting that there are no ongoing patient trials for CS1-targeting.

Methods: Here, we have developed a dual specific bivalent CS1-OKT3 bsAb (CS1-dbBiTE) using an efficient Click chemistry approach for conjugation of intact humanized antibodies, by fusing both the clinical anti-CS1 monoclonal antibody (Elotuzumab) and anti-OKT3 antibody at their respective hinge regions. Furthermore, we ensured that the specificities for CS1 and OKT3 were retained in the bispecific antibody molecule by titrating varying concentrations of the CS1-dbBiTE against specific targets in binding assays. Considering applying the CS1-dbBiTE as a cell-based immunotherapy modality, CS1-dbBiTEs were coated on T cells prior to co-culturing with MM tumor lines for functional analysis.

Results: Accordingly, our data indicates that CS1-dbBiTE coating induced T cell activation as well as long-term tumor lysis (LTK) and exhibited potent cytotoxic activity against CS1-bearing MM tumors in degranulation and intracellular cytokine assays, demonstrated by significant expression of CD107a as well as IFN-γ and TNF-α secretion. As expected, coated T cells showed significantly reduced effector function in the presence of CS1KO MM tumors highlighting specificity of the dbBiTE antibody. Similarly, in MM mouse xenograft studies, coated T cells exhibited effective anti-tumor efficacy highlighted by reduced tumor burden in CS1-expressing tumor bearing mice compared to controls and CS1KO MM bearing mice.

Conclusions: On the basis of these findings and rationale for CS1 targeting, human T cells coated with our generated CS1-dbBiTEs present a potentially effective therapeutic approach for targeting MM.

P-006

Real world experience of patients treated with idecabtagene vicleucel: a BCMA-directed chimeric antigen receptor T-cell therapy for multiple myeloma

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Introduction: Idecabtagene vicleucel (ide-cel) was approved by the US FDA in March 2021 for treatment of relapsed and refractory multiple myeloma (RRMM) in patients who have received ≥ 4 lines of therapy. Currently, the real-world experience of commercial ide-cel is lacking mainly due to

product availability. We report our initial experience with commercial ide-cel use at the Dana-Farber Cancer Institute/Brigham and Women's Hospital.

Methods: Patients treated with ide-cel until March 2022 were included in the analysis. Data was retrospectively collected under IRB approved institutional protocol utilizing a REDCap database. Data was collected for baseline demographics, prior therapies, efficacy including response rates (ORR), progression free survival (PFS) and overall survival (OS) and safety variables such as rates of cytokine release syndrome (CRS), neurological toxicity (NT), and cytopenias.

Results: Twenty patients were treated with ide-cel from August 2021 to March 2022. The median age was 64 (range 35-79), with 5 females (25%) and 15 males (75%). Median prior lines of therapy was 8 (range 3-12) with 90% of patients having had a prior stem cell transplant. Nine patients had high-risk FISH with breakdown as follows: Del 17p: 2, t(4;14): 2, t(14;16): 2, 1q21 gain: 8. Three patients had a GFR of less than 60, 2 of which were treated with dose reduced fludarabine for lymphodepletion (LD) and 2 patients were treated under an out of specification protocol. The most common treatment prior to ide-cel included quadruplet combinations and cytotoxic regimens including DCEP (3 patients) and cyclophosphamide. There were 3 patients treated with belantamab mafodotin and 7 patients were previously treated with selinexor. Bridging therapy was used in 18 patients and was commonly DCEP (4 patients) and CyBorD (4 patients). Hematologic toxicity included anemia (n=16, 80%, grade 3; 25%), neutropenia (n=10, 50%, grade 3; 35%), and thrombocytopenia (n=9, 45%, grade 3; 25%). CRS was reported in 14 patients (70%), 8 with grade 1 (40%), 6 with grade 2 (30%) and none with grade 3 or higher. Tocilizumab was used in 8 patients (40%) and dexamethasone was used in 7 patients (35%). Grade 1 NT was assessed in 1 patient (5%). At a median follow-up of 29 weeks, ORR is 70%, with 7 patients (35%) achieving a complete response (CR), and 50% achieving VGPR or greater. Two patients with GFR < 60 who received dose reduced LD achieved a CR. Nine patients have had disease progression (PD, 45%) with median PFS of 23 weeks. In patients with CR, median PFS has not been reached and median OS has not been reached.

Conclusions: Overall, we observed that ide-cel treatment in a commercial setting generated comparable responses to the previously reported clinical trials without any new toxicity signals. However, the responses appear to be less durable with median PFS of only 23 weeks. Additional follow up with commercial ide-cel use in the real-world is needed to validate these results.

P-007

Proposed clinical factors scoring system for chimeric antigen receptor T-cell (CAR T) patient selection in relapsed and refractory multiple myeloma (RRMM)

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Introduction: Chimeric antigen receptor T–cell (CART) trials have shown impressive response and remission rates in patients (pts) with relapsed refractory multiple myeloma (RRMM). Two innovative CART products are approved for use in the US yet are in high demand with short supply. Many CART candidates are not eligible for clinical trials (CTs) due to cytopenias, organ dysfunction, or lack of measurable disease, which makes approved therapies most desirable. Careful patient selection is essential. Stringent selection criteria used in CTs led to approval of the agent, but additional pts with different characteristics are eligible for CART in the commercial setting. At our institution, multidisciplinary teams regularly convene to adjudicate selection of pts based upon objective factors in consideration of limited supply. Thus, we aimed to develop a clinical factor score model for CART selection in pts with RRMM while facing a lack of access.
Methods: We conducted a systematic literature review in search of studies in PubMed with a focus on pt selection of cellular therapies. No validated instruments to aid in pt selection in RRMM within the last 5 years were identified. Based on this review, clinical experience, and expert opinion, a scoring system was created. Through weekly discussions, the current recommendation is that CART preference would be based on acute need, approved prescribing indication, and clinical considerations outlined in Table 1.
Results: From February 8, 2022-May 11, 2022, a score was obtained on 43pts considered in highest need of CART. Of these, 7pts were selected for CART and 5 infused; 2 were scheduled for infusion. In this scored cohort, 24/43 (55.8%) pts were deemed as the greatest in need with score >10, while 19/43 (44.2%) had a score of <9.

Table 1. Six criteria CART scoring system
Each item scored range 1-3. Max score __/18

1. Penta-refractory disease

2. Recent aggressive relapse with the extramedullary disease, substantial tumor burden

3. Bridge therapy requiring salvage chemotherapy

4. Lack of effective therapy or clinical trials, life expectancy < 1y as determined by the MM tumor board

5. Not in remission w/clinically active or extramedullary relapse

6. Clinically stable with life expectancy to receive future CART therapy
Conclusions: Due to a lack of validated clinical factors including risk scores or biomarkers to predict efficacy and toxicity, choosing candidates for CART provides a clinical challenge & currently relies on expert opinion. Multidisciplinary team members share the common goal of providing the best care for all pts. The limited availability of CART forces one to strike the balance between potentially life-extending therapy against clinical phenotype characteristics of performance status and disease control, towards optimizing selection. Our recently implemented scoring system represents an innovative and clinically relevant first effort towards addressing a clinical need: how to allocate slots in this time of limited approved CART product supply.

P-008

Single center, real-world, retrospective assessment of outcomes with idecabtagene vicleucel (ide-cel) for relapsed/refractory myeloma after prior treatment with a BCMA-targeted therapy

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Introduction: Patients who received prior anti-BCMA therapies were excluded from the KarMMa-1 trial (Munshi et al, NEJM 2021) that led to FDA approval of ide-cel. We assessed outcomes for patients who had received a prior anti-BCMA therapy followed by standard of care (SOC) ide-cel at our institution.
Methods: All patients at our institution treated with a prior anti-BCMA therapy who later received SOC ide-cel between 8/30/21-4/15/22 were included in this analysis to allow for ≥30 days of follow up. Response outcomes and progression were evaluated using IMWG criteria (Kumar et al, Lancet Oncol 2016) and cytokine release syndrome (CRS)/immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by ASTCT consensus guidelines (Lee et al, Biol Blood Marrow Transplant 2019). Statistics were descriptive in nature.
Results: A total of 6 patients of median age 68 received SOC ide-cel after prior anti-BCMA therapy (ADC 3; bispecific 2; CAR-T 1). Patients were heavily pretreated with a median of 14 prior lines of therapy (range 6-18), 83% triple-class refractory, 67% penta-refractory, and 83% had received prior

autologous stem cell transplant. High-risk cytogenetics defined by del17p, t(4;14), or t(14;16) were present in 67%, and 33% had extramedullary disease. The median time between anti-BCMA therapies was 8.2 months, with best ORR to the prior anti-BCMA therapy of 1/6 (17%) and median time to progression on the prior anti-BCMA therapy of 2.8 months. CRS was present in 67% (3 G1, 1 G2), with median time to max CRS of 1 day and 33% requiring tocilizumab use. No ICANS was observed. At day 30 after infusion, 33% of patients had grade 3/4 neutropenia and 50% had grade 3/4 thrombocytopenia. Infection at any time post-infusion and prior to progression was noted in 5/6 (83%). One patient died of COVID-19 ARDS and another died from cardiac arrest with unclear precipitating factors at 43 and 71 days post-infusion respectively.With a median follow up duration of 5.2 months, best ORR was 67% (2 sCR, 1 CR, 1 PR), which was numerically lower than the ORR for patients treated at our institution who had not received prior anti-BCMA therapy (ORR 80%, n=15). Stratified by prior BCMA therapy, ORR was 100% for prior CAR-T (n=1), 67% for prior ADC (n=3), and 50% for prior bispecific (n=2). All 4 responses were MRD-negative by flow cytometry. Responses are ongoing for 3 of 4 patients at 8.1, 8, and 1.1 months of respective follow up. The 3 patients who had BCMA expression testing on pre-lymphodepletion bone marrow had 2+ or greater BCMA expression by IHC.
Conclusions: In this real-world analysis of heavily pretreated RRMM patients who had received a prior anti-BCMA therapy, meaningful clinical responses were observed after treatment with SOC ide-cel, albeit at a numerically lower rate than for patients who had not gotten anti-BCMA treatment. A multicenter retrospective analysis of these outcomes is planned to provide further insight into sequencing of BCMA therapies.

P-009
Busulfan and cyclophosphamide as a conditioning regimen for autologous transplantation in patients with multiple myeloma after treatment with proteasome inhibitors and/or immunomodulatory drugs

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Introduction: Due to the coronavirus disease 2019 pandemic, there have been issues of inadequate melphalan (MEL) supply in some regions of the world including the Republic of Korea. In this situation, busulfan (BU) and cyclophosphamide (CY) may be considered as an alternative conditioning regimen for autologous transplantation in patients with multiple myeloma (MM). However, most studies on the efficacy of the BU/CY regimen were conducted before the introduction of proteasome inhibitors (PIs) or immunomodulatory drugs (IMIDs) for the MM treatment. Therefore, this study evaluated the efficacy of the BU/CY regimen compared with that of the MEL regimen in patients with MM after treatment with PIs and/or IMIDs.
Methods: We retrospectively analyzed patients with MM from July 2009 to July 2022. Patients who met the following criteria were included: (1) patients who had undergone autologous transplantation, (2) patients treated with PIs and/or IMIDs before transplantation, and (3) patients who received conditioning chemotherapy with the MEL or BU/CY regimen. MEL regimen comprised of intravenous MEL administration at a dose of 100 mg/m2 on days -3 and -2. BU/CY therapy consisted of intravenous CY at a dose of 60 mg/kg on days -6 and -5, followed by intravenous BU at a dose of 3.2 mg/kg from day -4 to -2.
Results: A total of 137 patients were analyzed (MEL: 113 patients and BU/CY: 24 patients). The proportion of patients treated with PIs and/or IMIDs was higher in the BU/CY group than in the MEL group (MEL: 59.3%, and BU/CY: 87.5%, p= 0.027). Additionally, very good partial response (VGPR) or complete remission (CR) at transplant and the proportion of post-transplant maintenance therapy was higher in the BU/CY group than in the MEL group (MEL: 58.4%, and BU/CY: 91.7%, p= 0.034, and MEL: 15.9%, and BU/CY: 62.5%, respectively, p< 0.001). There were no differences in other baseline characteristics such as age, gender, subtype, performance score, International Staging System (ISS) stage, presence of high-risk chromosomal abnormalities, and the time from diagnosis to autologous transplantation. Median progression-free survival from the time of transplantation (PFS) was 29.7 months and 46.8 months in the MEL and BU/CY groups, respectively (p= 0.018). Multivariate analysis for PFS showed that the BU/CY regimen (hazard ratio (HR): 0.313, 95% CI: 0.128–0.765, p= 0.011), ISS stage I (HR: 0.4523, 95% CI: 0.253–0.806, p= 0.007) and VGPR or CR at transplant (HR: 0.108, 95% CI: 0.230–0.501, p= 0.004) were significantly associated with good prognosis. No treatment-related mortality was noted in either group by day 100.
Conclusions: In patients treated with PI and/or IMID before autologous transplantation, BU/CY may represent an alternative conditioning regimen to the MEL regimen.

P-010
Exploring the feasibility of CD38-targeting CAR-NK therapy for multiple myeloma by harnessing features of cytokine-expanded NK cells

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy, that currently remains incurable. During the past years, targeted immunotherapeutics have changed the treatment paradigm and have significantly prolonged the survival of relapsed/refractory patients. Chimeric antigen receptor (CAR)-NK cell therapy is also increasingly investigated in this context. Here we aim to explore the feasibility of CD38-targeting CAR-NK cells in an autologous setting.
Methods: First, we use a retroviral approach to introduce a high affinity CD38-targeting CAR construct to CD38low cytokine-expanded peripheral blood NK cells of healthy donors. We show a reproducible transgene expression ranging between 40-60% and assess the functionality of the CAR-NK cells in in vitro assays.
Results: CD38-CAR-NK show up to a 3-fold increase in degranulation and a 2-fold higher specific target cell lysis of CD38+ MM cell lines, compared to unmodified NK cells. Moreover, the specific cytotoxicity of the CD38-CAR-NK cells was confirmed against CD38- MM target cell lines generated with the CRISPR/ Cas9 technology. Translating the approach to expanded PB-NK cells of three newly diagnosed MM patients, that later showed to be refractory to anti-CD38 antibody treatment, we show a 5-25% transduction efficacy and increased cytotoxic potential of the CAR-expressing NK cells against autologous CD138+ -containing bone marrow samples.
Conclusions: Altogether, our findings suggest that CD38-CAR NK cells are strong candidates for the immunotherapy of MM and that autologous NK cells could be a feasible and safe approach.

P-011
A randomized phase 2 study of modakafusp alfa (TAK-573) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) with a pilot diversity, equity, and inclusion (DEI) strategy

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Introduction: Trial in Progress.Modakafusp alfa is a first-in-class immune-targeting attenuated cytokine that delivers interferon alpha-2b to innate and adaptive immune cells. In Parts 1 (dose escalation) and 2 (expansion) of this study, the maximum tolerated dose of modakafusp was 3 mg/kg every 4 weeks (Q4W). A dose of 1.5 mg/kg Q4W (n=30, 5 in escalation, 25 in expansion) had a manageable safety profile and single-agent anti-myeloma activity with an overall response rate (ORR) of 43% in pts with RRMM after a median follow-up of 5.2 months (Kaufman EHA 2022, #S181). Based on population pharmacokinetics and dose/exposure-response analyses, a switch from weight-based to fixed dosing was considered appropriate for future assessments. Here, we describe the randomized phase 2 extension part of this study to determine the optimal, fixed dose of modakafusp for future clinical development and characterize its safety and efficacy profile in a larger pt population (NCT03215030). We have incorporated a DEI operational strategy into our trial's plan of execution in the US to increase representation of Black, American Indian/Alaska Native, and Hispanic pts, among whom the incidence of MM is 2.3, 1.3, and 1.1 times higher than in White pts (Cancer Statistics Center), but represent 18%, < 1%, and 6% of pts enrolled in the US in MM trials (Kanapuru, Blood Adv 2022).
Methods: We plan to enroll 236 pts in 16 countries who have progressive disease (PD) after ≥3 prior lines of treatment and who are refractory to ≥1 immunomodulatory drug, ≥1 proteasome inhibitor, and ≥1 anti-CD38 mAb. Pts will be randomized 1:1 to receive modakafusp 120 or 240 mg Q4W (fixed dose equivalents of 1.5 and 3 mg/kg). Randomization will be stratified by cytogenetic risk [del17, t(4;14) and/or t(14;16) vs standard risk] and myeloma type (IgA vs other). Pts may receive modakafusp until PD, intolerance to treatment, or withdrawal. The primary objective for Part 3 is ORR by Independent Review Committee assessment; secondary objectives include clinical benefit rate and duration, progression-free survival, rate of minimal residual disease negativity in patients achieving a complete response, and further characterization of the safety, PK, and immunogenicity of modakafusp. Enrollment goals will be set based on MM incidence and historic trial enrollment rates to ensure patients historically under-represented are represented in our trial. Our DEI strategy is embedded into the trial operations including protocol and study design, site feasibility and selection, and pt engagement. Diversity was factored into site selection which allowed for the inclusion of community sites and expansion into the US territory of Puerto Rico.
Results: Not applicable – trial in progress.
Conclusions: This phase 2 study aims to determine the single-agent modakafusp dose with an optimal benefit/risk profile in pts with RRMM. The study design incorporates a DEI strategy with the goal of enrolling a pt population representative of real-world pt demographics.

P-012
Cevostamab is efficacious and well tolerated in patients aged < 65 and ≥65 years with relapsed/refractory multiple myeloma (RRMM)

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Introduction: Most patients (pts) with multiple myeloma are aged ≥65 years (yrs). Advancing age is associated with a decline in immune function and an increase in comorbidity and vulnerability to treatment-related toxicities. These factors may impact the safety and efficacy of anti-myeloma agents. Cevostamab is an FcRH5xCD3 bispecific antibody that mediates T-cell directed killing of myeloma cells. In a Phase I study (NCT03275103) in pts with RRMM, cevostamab demonstrated target dose (TD)-dependent efficacy, with a higher response rate observed at the 132–198mg dose level (Trudel et al. ASH 2021). Treatment-related (TR) adverse events (AEs) leading to discontinuation were uncommon. We evaluated the safety and efficacy of cevostamab at the 132–198mg TD level in pts aged < 65 and ≥65 yrs.
Methods: All pts had RRMM for which no established therapy was available or appropriate. Cevostamab was administered IV in 21-day cycles for 17 cycles unless progressive disease or unacceptable toxicity occurred. In Cycle (C) 1, single or double step-up dosing was followed by the 132–198mg TD

(depending on the assigned cohort), which was continued from C2 onwards. Cytokine release syndrome (CRS) was reported using ASTCT criteria (Lee et al. Biol Blood Marrow Transplant 2019).
Results: As of August 25, 2021, 60 pts had received cevostamab at the 132–198mg TD level; 31 were < 65 yrs and 29 were ≥65 yrs (median age: 57 and 70 yrs; ECOG PS 1 at entry: 65% and 66%). Among pts with an available result at baseline, 14/18 (78%) aged < 65 yrs and 8/16 (50%) aged ≥65 yrs had high-risk cytogenetics (aberrations in 1q21, t(4;14), t(14;16) and/or del(17p)). Both age groups received a median of 6 prior therapies. Most pts had triple-class refractory disease (97% and 90%). AEs occurred in all pts in both age groups. CRS was most common (age < 65 vs ≥65 yrs: 84% vs 83%, respectively) and was predominantly low Grade (Gr; Gr 1: 45% vs 38%; Gr 2: 36% vs 45%); one patient (aged < 65 yrs) had a Gr 3 CRS event. Serious AEs (SAEs) of infection occurred in 29% of pts < 65 yrs and 17% of pts ≥65 yrs. Rates of any Gr neutropenia and thrombocytopenia were 36% vs 35% and 16% vs 28%, respectively. Febrile neutropenia (all Gr 3 and all considered TR) occurred in 3 older pts only. Rates of Gr 3–4 AEs (71% vs 72%) and SAEs (58% vs 62%) were comparable in both age groups. TR AEs leading to cevostamab discontinuation occurred in 3 pts (all ≥65 yrs). The overall response rate was comparable in both age groups (< 65 vs ≥65 yrs: 58% vs 55%). A best response of VGPR or better was achieved in 35% of younger pts and 28% of older pts. Among responders, 56% (95% CI: 31–82) of those aged < 65 yrs and 59% (95% CI: 28–90) of those aged ≥65 yrs maintained their response for at least 12 months.
Conclusions: Cevostamab is efficacious in older and younger pts with heavily pre-treated RRMM. The safety profile was consistent with the cevostamab MOA and target. Baseline biomarker data will be presented.

P-013
Safety and efficacy of daratumumab-based chemoimmunotherapy in multiple myeloma or AL amyloidosis patients with advanced renal failure

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Introduction: Daratumumab (Dara) is a monoclonal antibody (MAB) against CD38 with activity either as a monotherapy or in combination with other agents in multiple myeloma (MM) and AL amyloidosis (AL). In MM and AL, anti-CD38 MAB based regimen has the potential to prevent progression of renal failure. MM or AL patients with advanced renal failure are often excluded from clinical trials. There is paucity of data on efficacy, safety and outcome of Dara-based therapy in this population.
Methods: Here, we present a single-center retrospective analysis of (N=15) patients with MM (n=12) or AL(n=3) who were treated with Dara-based regimen in the setting of stage IV chronic kidney disease (CKD, n=7) or end-stage renal disease (ESRD, n=8): 40% were newly diagnosed MM who presented with acute renal failure (ARF) and 60% were relapsed/refractory (RR) at the time of initiation of Dara-based therapy. All patients (100%) received Dara in combination with either a proteasome inhibitor (PI) or an immunomodulatory drug (IMiD).
Results: Response assessment per IMWG criteria exhibited 54% complete hematologic response (CR), 20% very good partial response (VGPR), 13% partial response (PR), 6.5% each with progressive and stable disease, respectively. The treatment was well-tolerated with no tumor lysis syndrome, serious infections, critical cytopenia, or significant infusion reaction. Three patients (20%) had non-life-threatening COVID-19 infections. Three patients (20%) died during therapy: two from cardiac conditions and one from progressive myeloma. Dara-based therapy was associated with improvement in renal function leading to prevention of ESRD and dialysis in all 7 patients (47%) who presented with acute-on-chronic renal failure due to underlying MM or AL. However, Dara-based therapy was not able to achieve dialysis independence in 8 patients (53%) with established ESRD despite excellent anti-myeloma response.
Conclusions: In conclusion, Dara-based therapy was found to have high response rate (73% VGPR or better) in MM or AL patients with advanced CKD. Hematologic response was associated with improvement in renal function, particularly in patients who presented with acute renal failure due to underlying MM or AL. Anti-CD38 MABs daratumumab and isatuximab need to be investigated further in clinical trials in MM or AL patients who present with advanced renal failure.

P-014
High function, but low level stem cell memory T cells in multiple myeloma: a potential tumor targeted and long lived cell therapy population

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Introduction: Immune dysfunction play a vital role in MM progression. Although myeloma-targeted and immunomodulatory agents improve the survival of MM it still remains incurable, the majority of patients eventually end in progressive disease. Further studies to prolong survival time and improve quality of life deserved more exploration. Recently, a rare subset of memory lymphocytes which is termed "T memory stem cells" (Tscm) has been thought a more potential immunotherapy after T-cell therapy as its characteristics of Long-lived, self-renewing, and antitumor effects of strong immune-mediated
Methods: Based on previous data, 5 markers were used to define the gating strategy. The CD4+ and CD8+ T cells were divided into four subgroups according to the CCR7 and CD45RA expression pattern: T-naïve and Tscm cells (CCR7+CD45RA+), central memory T(Tcm) cells (CCR7+CD45RA-), T effector memory (Tem) (CCR7−CD45RA-),

and T terminal effector (Tef) cells (CCR7−CD45RA+). Eventually, the Tscm population was defined by double-positive CD95 and CCR7 expression. The expression of Tscm, Tcm, Tem, and Tef cells in CD4 + and CD8+ T cells in PB and BM samples from MM patients including 29 newly diagnosed MM (NDMM), 28 MM in complete remission(MM-CR), and 7 MM in recurrenced (MM-R) and 20 healthy people (HC) were detected by polychromatic flow cytometry. Furthermore, the expression of PD-1 and TIGIT and perforin and granzyme B on T cells was also detected after stimulated by anti-CD3CD28 for 72 hours

Results: The percentage of Tscm on CD8+ T cells were decreased in NDMM (0.41□0.27%, $p < 0.001$) than HC (0.96□0. 39%) as well as Tcm,Tem increased significantly in NDMM (59.74□11.56, $p < 0.05$) than HC (51.21□10.98%). It seems that Tscm and Tcm cells tend to differentiate into Tem and Tef cells in MM. Meanwhile, Tscm cells are expressed more in PB than BM, especially in CD8+T cells. For the functional study, the expression of Tigit on Tscm increased in NDMM (96.5739□4.6476%, $p < 0.05$) than HC (93.0421□5.67807), but perforin and granzyme B in Tscm were notably higher than CD3+, CD4+, and CD8+T cells

Conclusions: The dramatically increased effective function of Tscm but low level in vivo showed that improving the frequencies of Tscm from MM patients may as a potential tumor target long lived T cell therapy tool, which prolongs the survival of MM

P-015

Comprehensive comparison of allogenic CAR NK cells for MM treatment

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Introduction: Despite the arrival of novel therapies in the past decade, multiple myeloma (MM) remains an incurable disease and there is an unmet medical need for new treatment options to overcome therapy resistances. CAR-T cells in MM have demonstrated impressive preliminary efficacy, however, CAR-NK cells have emerged as a cost-effective, faster and safer approach. There are different sources of allogeneic NK cells that can be delivered to a large number of patients, such as NK-92 cell line and cord blood NK (CB-NK) cells. Here, we have performed a comprehensive comparison to find the best off-the-shelf CAR-NK immunotherapy based on cell source, CAR expression and their combinations. We additionally propose a pretreatment of MM cells with Bortezomib (BTZ) plus gamma secretase inhibitor (GSI) to boost NKG2D CAR efficacy in CB-NK immunotherapy for MM treatment.

Methods: NK cells from cord blood samples were purified and stimulated with an irradiated feeder cell line. NK-92 MI cell line and CB-NKs were lentivirally transduced with NKG2D or BCMA CAR containing same or different combination of co-stimulator domains, achieving similar vector copy number. In vitro antitumor activity was analyzed against a panel of MM cell lines with low and high target ligands expression, as well as against BTZ resistant MM cell lines. For in vivo experiments, effector populations were tested in U266 and a BTZ resistant BCMA knock-out ARP1 NSG mice models.

Results: The comparison between NKG2D and BCMA CAR show that they are equally effective against MM cell lines, and when combined they show a cytotoxic coverage even with different co-stimulator domains, but not a synergy. Our results reveal that CAR NK-92 and CAR CB-NK cells perform similar antitumor activity in vitro. Besides, NKG2D and BCMA CAR are equally efficient in U266 in vivo model, however, clinical 10 Gy irradiation dose completely abrogate the efficacy of CAR NK-92 cells in our treatment schedule. Of note, NKG2D CAR show less efficacy in vitro against primary MM cells. A pretreatment with BTZ+GSI (LY3039478) significantly enhances the ability of NKG2D CAR CB-NK cells to eradicate BTZ resistant MM cell lines in vitro, independently of low BCMA expression or even in BCMAKO-BTZ-resistant cell line. Mechanistically, BTZ+GSI caused a proteasome-dependent and transient senescence process, concomitant to a DNA damage response signaling pathway and upregulation of NKG2D ligands. Thus, NKG2D CAR behaves as senolytic agent resulting in a superior anti-tumor activity. Currently, this preconditioning regimen is being tested in vivo.

Conclusions: In vivo experiments show the inefficacy of irradiated CAR NK-92MI cells as therapeutic strategy in our MM model, being CAR CB-NK cells a promising immunotherapy for MM treatment. In addition, NKG2D CAR CB-NK off-the-shelf immunotherapy combined with a BTZ+GSI pretreatment regimen sensitize resistant MM cells to improve CAR-NK efficacy in MM patients.

P-016

Tumor profiling of idecabtagene vicleucel (ide-cel, bb2121) patients in KarMMa showed comparable responses in existing molecular high-risk subsets and preliminary gene signature of durable response

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Introduction: Multiple myeloma (MM) exhibits increasing prevalence of high-risk/resistance (HR/R) features with each successive relapse, leading to poorer outcomes in patients (pts). Treatment with idecabtagene vicleucel (ide-cel, bb2121), the first approved anti-BCMA CAR T therapy for late-line relapsed/refractory MM (RRMM) resulted in frequent, deep, and durable responses in the KarMMa (NCT03361748) study, including in pts with HR cytogenetic features (Munshi, N Engl J Med 2021). We assessed multiomics molecular profiles in tumors from KarMMa pts at baseline and progression to characterize known and novel molecular features associated with ide-cel outcomes.
Methods: Bone marrow aspirates were collected from pts pretreatment (n=97 RNA, n=68 DNA) and at progression (n=64 RNA, n=33 DNA). RNA sequencing and whole genome sequencing was done on CD138+ cells. Known molecular HR/R genomic (biallelic p53 inactivation, high cancer clonal fraction del17p, HR t(4,14), and cereblon dysregulation) and transcriptomic (MDMS8 signature) features were analyzed, and correlations with overall response (OR) and progression-free survival (PFS) evaluated. BCMA mutation and copy number variation were evaluated. Differential gene expression and principal component (PC) analyses explored novel transcriptomic signatures and response.
Results: Molecular HR/R features were identified in 44% (43/97) of pts pretreatment and 48% (31/64) at progression. Some tumors had multiple HR features consistent with heterogeneity in late-line RRMM. Paired pre/post–CAR T samples did not show dominant enrichment for specific HR feature(s) at progression. OR and PFS were not correlated with the molecular features analyzed. One PC (PC4) was correlated with PFS (P=0.002). The top-weighted genes in PC4 may be a preliminary signature associated with durable ide-cel responses. Loss of one BCMA copy was found in 4% (3/68) of pts pretreatment and 12% (4/33) at progression. Biallelic loss of BCMA at progression was found in 6% (2/33), one of whom had single copy number loss pretreatment.
Conclusions: Baseline multiomic–based tumor HR features were not associated with OR, suggesting ide-cel activation and expansion are critical for OR and may not be greatly influenced by tumor intrinsic features. Biallelic loss of BCMA was not found pretreatment and rarely at progression, consistent with previous reports. Baseline HR features did not correlate with PFS, and a dominant selection for any one HR feature at progression was not noted. These findings align with previous reports in non-molecularly defined HR subgroups from KarMMa and support the hypothesis that the CAR T mode of action may have a wider spectrum of clinical activity. A transcriptional signature was associated with more durable ide-cel responses that may outline a distinct suboptimal pretreatment feature for ide-cel; further exploration is ongoing. *Authors contributed equally to the abstract**At the time the study was conducted Accepted and presented at the 2022 EHA Annual Meeting

P-017

MagnetisMM-7: an open label, randomized, phase 3 study of elranatamab versus lenalidomide in patients with newly diagnosed multiple myeloma who are minimal residual disease-positive after transplant

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Introduction: Elranatamab (PF-06863135) is a humanized bispecific molecule that targets both B-cell maturation antigen (BCMA)-expressing multiple myeloma (MM) cells and CD3 on T cells to direct the T cell-mediated immune response against MM. In the ongoing phase 1, MagnetisMM-1 study, subcutaneous (SC) elranatamab has demonstrated anti-myeloma efficacy and a manageable safety profile in patients (pts) with relapsed or refractory MM.
Methods: MagnetisMM-7 (NCT05317416) is an open label, randomized, multicenter, phase 3 study of elranatamab vs lenalidomide in pts with newly diagnosed MM who are minimal residual disease (MRD)-positive after autologous stem cell transplant (ASCT). Approximately 366 pts will be enrolled with expected participation for ~5 years. Pts will either receive elranatamab SC 76mg weekly after initial step-up doses (12 and 32mg) during the first week, switching to every 2 weeks after 6 months of treatment, or lenalidomide oral 10mg once daily. The primary outcome measures are MRD negativity rate at 12 months per International Myeloma Working Group (IMWG) criteria as assessed by next generation sequencing (NGS), and progression free survival (PFS) assessed by blinded independent central review per IMWG response criteria. Key secondary outcomes are PFS assessed by investigator per IMWG criteria, overall MRD negativity rate, duration of MRD negativity, sustained MRD negativity rate, complete response (CR) rate, duration of CR, overall survival, incidence of adverse events and laboratory abnormalities, incidence of elranatamab immunogenicity, elranatamab pharmacokinetics, and health-related quality of life. Key inclusion criteria include age ≥18 years, MM diagnosis according to IMWG criteria, measurable disease at diagnosis, history of induction therapy for newly diagnosed MM followed by high dose therapy and ASCT, partial response or better at time of randomization, MRD positivity based on NGS at a sensitivity of 1×10-5, and Eastern Cooperative Oncology Group performance status ≤1. Key exclusion criteria are plasma cell leukemia, POEMS syndrome, amyloidosis, Waldenström's macroglobulinemia, known active CNS involvement or clinical signs of myelomatous

meningeal involvement, previous MM maintenance treatment, prior treatment with BCMA-targeted therapy, any other active malignancy within 3 years prior to enrollment (except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ, or Stage 0/1 with minimal risk of recurrence per the investigator), active, uncontrolled infection, and previous administration of an investigational drug or vaccine within 30 days or 5 half-lives of the first dose in the current study. Randomization must occur within 120 days from ASCT, and for participants who received consolidation therapy after ASCT randomization must occur within 60 days of consolidation and 7 months from transplant. The study is planned to be active in 23 countries.

P-018

Optimized affinity CD38 CAR-NK cells with CD38 KO show promising in-vivo activity in a multiple myeloma model

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Introduction: Autologous CAR-T cells are revolutionizing the treatment of MM. However, complex manufacturing and toxicities limit their broad application. Allogeneic natural killer (NK) cells represent an optimal "off the shelf" alternative, as unlike allogeneic T cells, they do not induce GVHD. We published preclinical data supporting the concept of an optimized affinity (OA) CAR-NK targeting CD38, using the NK cell line KHYG-1 for treatment of MM. These CAR-NK cells mediated effective CD38-dependent cytotoxicity towards primary MM cells ex vivo, while sparing non-malignant BM cells with low/int CD38 expression. Given the safety and feasibility of cord blood (CB) derived NK cells as immunotherapy for MM, we next sought to develop OA CD38 CAR-NK cells from CB. We also explored the feasibility of gene editing with CRISPR/Cas9 to knock out CD38 to overcome fratricide.
Methods: On D1, CD3 depleted CBMCs were expanded in co-culture with irradiated EBV-LCL feeder cells in the presence of NK media, Human AB serum and IL-2. On D5, cells underwent electroporation (MaxCyte) with delivery of a Cas9/RNP complex targeting the CD38 gene. On D7 cells underwent repeat electroporation, delivering Tc Buster mRNA (Bio-Techne) along with a nanoplasmid (Aldevron) carrying the OA CD38 CAR construct, Tc Buster transposon (Bio-Techne), LNGFR marker and a selection gene. Following a 2 day rest, cells were re-expanded in the presence of feeder cells, while undergoing selection. Transposition efficiency was confirmed by assessment of LNGFR positivity and vector copy number (VCN). On D22 cells were harvested and cryopreserved for future use. Prior to functional testing, cells were thawed and rested for 24 hr in culture media + IL-2. The anti-tumor efficacy of the CD38 CAR-NK was evaluated in NSG mice inoculated with MM.1S-LUC cells.
Results: The process enriched and expanded CD56 positive, CD3 negative NK cells (>96%) with minimal T cell contamination. Successful CD38 KO (> 85%), was observed, approaching 100% in CAR expressing cells. LNGFR detection confirmed > 80% transgene expression by D22. The average VCN of selected cells was between 1 and 2 copies/cell. Using G-Rex6M plates, CD38 CAR-NK cells with CD38 KO expanded approximately 400 fold by D22. In-vitro studies in the MM cell lines MM.1S, H929 and RPMI as well as the ALL cell line NALM6, showed potent CAR mediated cytotoxicity. In an ongoing in-vivo study, by D16 mice treated with cryopreserved OA CD38 CAR-NK cells are showing significant, promising tumor growth inhibition in NSG mice engrafted with MM.1S-LUC cells compared to treatment with control NK cells ($p < 0.01$) or vehicle alone ($p < 0.01$).
Conclusions: These results suggest that optimized affinity CD38 CAR-NK cells lacking CD38 expression have potent anti-tumor activity in vitro and in vivo in CD38 positive tumor models. Future work aims to confirm the favorable safety profile and potential beneficial immune modulatory effects of this approach as well as the added benefit of CISH KO.

P-019

Correlative analysis to define patient profiles associated with manufacturing and clinical endpoints in relapsed/refractory multiple myeloma patients treated with idecabtagene vicleucel (ide-cel)

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Introduction: Treatment with the anti-B-cell maturation antigen (BCMA) autologous chimeric antigen receptor (CAR) T cell therapy idecabtagene vicleucel (ide-cel, bb2121) resulted in frequent, deep and durable responses in relapsed/refractory multiple myeloma (RRMM) patients (Munshi, N Engl J Med 2021). Prior studies have described the correlation between favorable patient characteristics, drug product (DP) characteristics and clinical outcomes from CD19 CAR T cell therapy (Finney, J Clin Invest 2019; Fraietta, Nat Med 2018). We sought to define patient profiles correlated with manufacturing and clinical endpoints in RRMM patients treated with ide-cel in clinical trials using unsupervised clustering and multivariate machine learning across multiple key variable domains.
Methods: Clinical and manufacturing data were harmonized across 164 RRMM patients treated with ide-cel in KarMMa (NCT03361748) and KarMMa-2 cohort 1 (NCT03601078). Based on individual multivariate importance, 10 selected peripheral blood mononuclear cell (PBMC), DP, and in-process cell growth variables were used to define patient

clusters. Random forest classifiers were generated to identify patient characteristics associated with manufacturing and clinical endpoints. Wilcoxon rank sum and Kruskal-Wallis tests were used to compare 2 and 3+ categorical groups; Cox proportional hazards were used to compare groups with time-to-event data.
Results: Using an unsupervised method, 4 patient clusters were identified, corresponding to 10% (n=17), 57% (n=94), 15% (n=24), and 18% (n=29) of the 164 patients. Cluster 4 was the most favorable and was characterized by a higher frequency of T cells in PBMCs; increased T-cell size during manufacturing; higher DP T-cell transduction, potency, and vector copy number; and ultimately a > 3-fold higher CAR T cell yield compared with the least favorable cluster 1. Cluster 2 contained most patients and was associated with intermediate manufacturing endpoints. Compared with those in clusters 1 to 3, patients in cluster 4 had a higher complete response rate, longer progression-free survival, and lower tumor burden, including monoclonal protein levels* (median 12.08 g/L, 10.73, 7.36, and 7.00 for clusters 1 to 4, respectively). Patients in cluster 4 also had a higher absolute lymphocyte count* (median 0.50 x 109/L, 0.85, 0.67, and 0.91), and a longer washout period after alkylator treatment (47%, 31%, 29%, and 24% of patients with alkylator exposure within 6 months**).
Conclusions: The current analyses identified patient profiles in RRMM using accessible laboratory or medical history data that correlated with longitudinal outcomes. These findings may inform patients likely to achieve improved outcomes with CAR T cell therapy. *Assessment at screening time point **Time of last exposure is measured relative to date of apheresis

P-020
PD1-based chimeric-switch receptor expressing NK cells recover from immune checkpoint inhibition in cancer

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Introduction: Multiple myeloma (MM) is a currently incurable hematological cancer. The expression of programmed death protein 1 (PD1) on immune cells and its ligand PD-L1 in the tumor microenvironment (TME) were shown in patients with MM. However, phase III clinical trials, looking into immune checkpoint inhibition with monoclonal antibodies (mAb) failed, emphasizing the need to optimize this approach. NK cell-based therapies are currently in early-phase clinical trials for MM, but NK cell dysfunctionality may occur via PD1-PD-L1 interaction. PD1-based chimeric switch receptors (CSR) were designed to revert NK cell inhibition upon PD1-PD-L1 interaction and retarget immune checkpoint inhibition in patients with MM.
Methods: The NK cell line NK-92 as well as primary NK (pNK) cells from healthy donors and MM patients were transduced with lentiviral vectors, encoding PD1-DAP10 or PD1-DAP12 CSR. Killing of PD-L1- and PD-L1+ 786-O and Raji cells was measured in a 2D and 3D tumor spheroid model. Degranulation and expression of CD107a, IFNg and TNF were assessed against PD-L1- and PD-L1+ Raji cells, PD-L1- and PD-L1+ 786-O cells as well as autologous bone-marrow derived mononuclear cells (BM MNC) in a standard co-culture assay with or without the addition of Rituximab.
Results: PD1-DAP10 and PD1-DAP12 CSR were first tested in the NK-92 cell line. Compared to unmodified wild-type NK-92 (NK92-WT), PD1-DAP10 and PD1-DAP12 expressing NK-92 cells increased degranulation, cytokine secretion and target cell killing upon recognition of PD-L1+ tumor cells in 2D and 3D tumor models. pNK cells, expressing native PD1, decreased degranulation and cytokine production against PD-L1+ Raji cells by two-fold compared to PD1- pNK cells. In contrast, PD1-DAP10+ and PD1-DAP12+ pNK cells increased CD107a by 1.5-fold, IFNg by 2-fold and TNF by 2.3-fold against PD-L1+ Raji cells compared to PD1- pNK cells. A similar tendency was observed with the addition of Rituximab, emphasizing that PD1-DAP10+ and PD1-DAP12+ pNK cells reverted PD-L1-induced NK cell inhibition with or without antibody-dependent cellular cytotoxicity. Additionally, PD1-DAP10+ and PD1-DAP12+ pNK cells from patients with MM increased degranulation and cytokine expression against autologous CD138+ PD-L1+ malignant plasma cells.
Conclusions: NK cells expressing CSR targeting programmed death ligands exhibit reversed inhibition and induced degranulation, cytokine release, and target cell killing. PD1-CSR+ NK cells sustain potent anti-tumor activity in a PD-L1+ microenvironment alone or in combination with monoclonal antibodies. Thus, PD1-CSR represent a promising strategy to enhance adoptive NK cell-based immunotherapies towards PD-L1+ cancers, as exemplified in MM. In the future, PD1-CSR might become a standard modification for adoptive NK cell products.

P-021
7C6 is a novel monoclonal antibody that induces enhanced anti-myeloma activity of cytokine induced memory-like (CIML) NK cells by blocking MICA/B shedding and antibody-dependent cell cytotoxicity

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Introduction: Despite the success of novel therapies, multiple myeloma (MM) remains largely incurable. Natural killer (NK) cells are important mediators of cytotoxic immune responses against MM, and the efficacy of existing MM therapies relies substantially on NK cell function. However, MM cells develop mechanisms to escape NK cell recognition. To overcome reduced NK cell functionality, adoptive transfer of cytokine-induced memory-like (CIML) NK cells are of particular interest, as these cells acquire memory-like features resulting in greater IFN-γ and anti-tumor responses. The success of CIML NK cell-based therapies in MM is dependent on the ability of the NK cells to recognize malignant plasma cells. NKG2D, the main activating receptor on NK cells, is upregulated on CIML NK cells. NKG2D plays an important role in the immune recognition of MM cells through interaction with its ligand MICA/B. However, MM cells evade this recognition by proteolytic shedding of MICA/B from the cell surface, leading to NKG2D internalization. Rationally designed antibodies like the 7C6 monoclonal antibody (mAb) stabilize cell surface MICA/B expression and can enhance NK cell recognition and susceptibility to NK cell-mediated cytotoxicity. We hypothesized that use of the 7C6 mAb would allow simultaneous blockade of MICA/B shedding and ADCC by CIML NK cells resulting in enhanced targeting of MM cells.
Methods: N/A
Results: 7C6 mAb treatment inhibited shedding, leading to increased cell surface expression of MICA/B on MM.1S in a dose-dependent matter. The functional consequences of MICA/B stabilization were first tested in conventional NK cells. We observed enhanced NK cell function as assessed by increased CD107a degranulation, IFN-γ and TNF-α production in co-culture assays of conventional NK cells with MM.1S pre-treated with the 7C6 mAb vs isotype control. Next, we measured the activity of CIML NK cells to MM target cells. CIML NK cells exhibited enhanced CD107a in response to MM target cells when compared to control NK cells from the same donors. Furthermore, CIML NK cells demonstrated significantly higher cytotoxicity against 7C6 pretreated MM.1S, which was dependent on increased MICA/B and NKG2D levels. CIML NK cells in NSG mice treated with the 7C6 mAb were significantly more effective in controlling early MM tumor cell outgrowth compared to CIML NK cells in mice treated with isotype control antibodies.
Conclusions: Here we demonstrate that inhibition of MICA/B shedding with a novel antibody 7C6 enhances CIML NK cell-mediated function against MM in vitro and in a xenograft mouse model. Our data support the hypothesis that combination strategies to enhance NK cell activation can be effective to enhance NK cell-mediated immune surveillance in MM. This combined approach highlights their potential use as novel immunotherapy in MM.

P-022
Intensity of cyclophosphamide-based bridging regimens before BCMA-directed CAR-T therapy

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Introduction: Patients receiving autologous chimeric antigen receptor T-cell (CAR-T) therapies targeting B-cell maturation antigen (BCMA) for multiple myeloma (MM) may require bridging therapy before CAR-T infusion. Many bridging regimens include alkylating agents such as cyclophosphamide (Cy), and there is no consensus around optimal chemotherapy dose intensity in such regimens.
Methods: We performed a single-center analysis of all instances of bridging therapy before planned BCMA CAR-T between 2017-2021. We classified bridging regimens into three cohorts: (1) IV dose-dense Cy (IV_ddCy) with inpatient IV Cy every 12-24 hours and mesna support per modified hyperCVAD protocol (Narayan 2020); (2) Weekly_Cy, with weekly oral/IV Cy; and (3) No_Cy, where Cy was not used in bridging. Demographic and disease-related characteristics at time of T-cell collection, as well as post-CAR-T outcomes for patients who received CAR-T, were compared using Fisher's and Kruskal-Wallis testing
Results: There were 61 discrete instances of bridging therapy among 55 unique patients, 87% of whom were previously Cy-exposed. Of these 61 instances, 34% involved IV_ddCy (n=21), 34% Weekly_Cy (n=21), and 31% No_Cy (n=19). Most instances (89%, n=48) included high-dose dexamethasone. Age, prior lines, high-risk cytogenetics, paraprotein/involved light chain levels, bone marrow plasma cell burden, and rates of PD as best response to bridging were similar between cohorts. However, extramedullary disease (EMD) was borderline more common with IV_ddCy (33%, n=7) than Weekly_Cy (10%, n=2) (p=0.07). IV_ddCy was also associated with higher Cy exposure than Weekly_Cy: median 2100 vs 588 milligrams per square meter (p< 0.01). All 10 instances of bridging without subsequent CAR-T were due to manufacturing failures. Among 51 instances followed by CAR-T, there were no significant differences in vein-to-vein intervals: 42 days with IV_ddCy, 39 days with Weekly_Cy, and 46 days with No_Cy. There were no differences in rates of CRS or ICANS; however, platelet recovery took longer with IV_ddCy than Weekly_Cy (median 67.5 vs 40 days, p=0.01). Median PFS and OS were 5.0 and 15.3 months respectively

for CAR-T recipients bridged with IV_ddCy, versus 12.5 and 29.5 months with Weekly_Cy.
Conclusions: In our analysis, patients bridged with IV_ddCy rather than Weekly_Cy had similar measures of MM burden. Overall, IV_ddCy did not significantly prolong vein-to-vein intervals but was associated with delayed platelet recovery and a worsened survival signal. Study limitations include small sample size and confounding from measures of MM aggressiveness among patients who received IV_ddCy bridging, for example rates of EMD. However, our analysis suggests that intensive Cy-based bridging – including regimens such as V(T)D-PACE, DCEP, and modified hyperCVAD – may not offer advantages over weekly Cy-containing regimens for most patients with MM who require pre-CAR-T bridging therapy.

P-023
Successful use of split dose intravenous daratumumab in an overweight multiple myeloma patient after first dose life threatening infusion-related reaction

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Introduction: There is a paucity of data regarding the best practice to institute iv Daratumumab (D) in morbid obese patients regarding the infusion rate and duration, optimal dosing, and ideal way to cope with the infusion related reactions (IRR). We wanted to present the first split dose D infusion experience in a morbid obese MM case whose D was interrupted because of a grade 3 IRR.
Methods: A 55-year-old female with a diagnosis of R-ISS 2 IgA lambda MM was received 3 lines of therapy including high dose chemotherapy with autologous stem cell transplantation. A combination of D, Bortezomib and Dexamethasone was decided for fourth line treatment. The dose for the first iv D was 1840 mg/day regarding the weight of her which was measured as 115 kg. The infusion needed to be stopped at the rate of 80 cc/hour because of a sudden IRR presented as a shortness of breath and hypoxemia. Despite of all medications dyspnea got worse, she developed wheezing and tachycardia and transferred into the critical care unit. After 10 hours of follow up and treatment she was discharged. Uninterrupted infusion of the first D was planned to be given with a split dose schedule. She was able to tolerate full dose of the medication with no adverse events. She was also able to tolerate weekly 1840 mg of D.
Results: IRRs with D are mostly observed in first dose and only 5-10% of them are reported to be grade 3. A universal premedication is advised before the initiation of infusion. Chronic pulmonary obtructive disorders (COPD) are also well documented risk factors for the development of IRR's. Despite of the premedication, grade 3 IRR was also probably related with the history of asthma regarding our patient. In EQUULEUS (MMY1001) trial and a US Oncology Network trial showed that split dose approach was related with less and milder IRR's. A specific recommendation based on the BMI is lacking and a universal dosing of 16 mg/kg is recommended for D. The data among overweight and obese subjects are limited. A retrospective analysis reported by Rogue A et.al., revealed no significant difference regarding overall survival and adverse events among 9 (39.1%) out of 23 overweight MM patients and others. Our patient weighed 115 kg and had a BMI of 51 kg/m2 which classified her as a morbid obese MM patient. A single dose infusion intent should be a possible explanation of IRR in our patient.
Conclusions: We can conclude that, the safety data is scarce regarding the overweight and obese patients who receive D. Especially in patients who needs a higher dose of D because of morbid obesity we do not have a good idea of IRR incidence. In patients who are overweight or obese or suffering from a COPD, a split first dose application of D should be regarded as a safer alternative and possibly should be regarded as a standard of care approach with further trials designed to address this need.

P-024
Comparable toxicity and outcomes with generic and innovator melphalan in myeloma auto transplants

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Introduction: Autologous stem cell transplantation (ASCT) with high dose melphalan (HDM) is the standard consolidation treatment for transplant-eligible myeloma (MM) patients. Many countries use generic melphalan (MEL) due to the low cost and easy availability. We had earlier reported comparable pharmacokinetics and efficacy of generic and innovator MEL in a cohort of 65 patients from our center(Pai, Devasia, et al. 2020). Here we present the updated data and long-term follow-up in an extended cohort of 120 patients.
Methods: Consecutive patients with MM receiving HDM were included in the analysis. Choice of MEL was based on patients' preferences and finances. Patient demographics, peri transplant data, short and long-term outcomes data were captured from electronic medical records. MEL dose was based on renal functions as per standard guidelines.
Results: This analysis included one hundred and twenty patients (79 males and 41 females). The majority of the patients (n=96, 80%) had only one prior line of treatment before ASCT, and 93 patients (77.5%) achieved at least a very good partial response. 56.7% (n=68) received generic MEL for conditioning. Neutrophil engraftment occurred earlier in the generic MEL group (11.40 days vs. 12.13 days, p-0.01). There were no differences between the incidence or severity of mucositis, platelet engraftment, and duration of hospitalization among the two groups. There were 3 deaths

(2 in the generic group and 1 in the innovator group), all due to multidrug-resistant gram-negative infections. There were no differences in the response achieved on day 100. Progression-free and overall survival were similar among the two groups.
Conclusions: Generic MEL is comparable to innovator MEL with respect to toxicity, and long-term outcomes. It is an excellent alternative for the innovator to cut the cost of transplantation in developing countries.

P-025
Investigating the effect of irreversible proteasome inhibitor carfilzomib in in vivo models of cardiometabolic syndrome and early stage HFrEFP: prophylactic role of metformin

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Introduction: Carfilzomib (Cfz) is an irreversible proteasome inhibitor indicated for relapsed/refractory multiple myeloma (R/R MM). However, Cfz presents higher risk of cardiovascular complications, especially in patients with cardiac risk factors (aging, hypertension, diabetes) and high risk of Heart Failure (HF) manifestation. Therefore, the use of Cfz in MM patients with established HF with reduced Ejection Fraction (HFrEF) and Cardiometabolic Syndrome (CMS) is still questionable. Herein, we investigated Cfz effect on two in vivo models of HF and CMS and challenged the prophylactic potential of metformin (Met), which we have previously established as a prophylactic therapy against Cfz-induced cardiotoxicity.
Methods: Twenty and Twenty-five C57BL6/J male mice underwent a. Permanent LAD ligation surgery and were allowed to establish early-stage HFrEF for 14 days or b. High Fat Diet (HFD) for 14 weeks in order to establish CMS. After the establishment of the models, mice were randomized to: 1. Control: Normal Saline (N/S) 0.9% intraperitoneally (i.p.). 2. Cfz: Cfz 8mg/kg i.p. 3. Met: Met 140 mg/kg per os 4. Cfz+Met: Cfz 8mg/kg i.p. and Met 140 mg/kg per os (n=5-8 per group). Cfz was administered on alternate days, whereas Met was administered daily for 6 days. Mice underwent echocardiography at baseline and at the endpoint of the experiments. Subsequently, myocardium and peripheral blood mononuclear cells (PBMCs) were analysed for proteasome activity (PA) and myocardium was collected for molecular analysis.
Results: In the early-stage HFrEF model, LAD ligation severely decreased %Fractional shortening (FS%) and cardiac PA, whereas it increased PBMCs PA. Cfz did not further reduce FS% and cardiac PA, whereas it decreased PBMCs PA. Early-stage HFrEF increased NFκB phosphorylation, IL6 and iNOS expression, whereas it decreased Akt phosphorylation and Bax expression. Cfz administration, further increased NFκB phosphorylation and Phospholamban (PLB) and SERCA expression. Co-administration of Met did not alter FS%, whilst it reduced NFκB phosphorylation and IL6 expression exerting an anti-inflammatory potential. In the CMS model, 14 weeks of HFD led to increase in fasting blood glucose and serum lipids but did not decrease FS%, myocardial and PBMCs PA, whereas Cfz administration significantly decreased % FS, myocardial and PBMCs PA compared to the Controls. Cfz increased SERCA expression and PLB and PKA phosphorylation, implying an effect of Cfz on myocardial Ca2+ cycling, in compliance with the early-stage HFrEF model. Met co-administration prevented Cfz-induced decrease in FS% and reduced SERCA expression and PKA phosphorylation.
Conclusions: Cfz exacerbates HF in both early-stage HFrEF and CMS models by induction of inflammation and dysregulation of Ca2+ signalling. Met retains its prophylactic potential in both cardiac pathologies, though mitigation of inflammatory response and prevention of Ca2+ signalling dysregulation

P-026
Impact of monoclonal anti-CD38 antibody on collected myeloid and erythroid progenitor cells and clinical course of autologous stem cell transplant for patients with multiple myeloma

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Introduction: Multiple myeloma (MM) remains an incurable malignant neoplasm of terminally-differentiated, plasma cell clones that accumulate in bone marrow. Autologous stem cell transplant (ASCT) remains the cornerstone of treatment among eligible patients and offers prolonged progression free survival (PFS). The standard of care for eligible patients is to receive high-dose chemotherapy with autologous stem cell rescue after completion of induction therapy. Daratumumab (Dara) is a fully humanized monoclonal antibody that targets CD38 on MM cells. Combination regimens that incorporate Dara have demonstrated promising results in the relapsed/refractory setting and Dara is increasingly used

upfront, even in transplant-eligible patients. CD38 is also expressed on hematopoietic stem cells and upfront use of Dara may potentially impact stem cell yield and composition. Although, prior studies have reported minimal deleterious effect of planned Dara-containing induction regimen on ASCT outcome, impact of this agent when is used as part of a second pre-ASCT anti-myeloma regimen (i.e., due to toxicity or lack of desired response) on stem cell collection is unknown. Here, we investigated the effect of Dara on erythroid and myeloid progenitor cells, graft composition, stem cell yield and engraftment among MM patients undergoing ASCT.
Methods: One-hundred and eight MM patients who underwent ASCT between 2017-2020 were divided into two groups based on Dara use and compared using Chi-square statistic or Fisher exact test for categorical variables and student T-test for continuous variables. Two of committed erythroid progenitors namely Burst-Forming Unit (BFU) and Colony Forming Unit (CFU) as well as main granulocyte /macrophage progenitor cells CFU-GM were cultured from each graft. Multivariate analysis by logistic regression evaluated whether Dara was predictive of day 1 stem cell collection failure.
Results: An average of 7.18 x 106 cells/kg CD34+ stem cells was collected from the Dara group compared to 8.78 x 106 cells/kg from the non-Dara group, but the difference was not statistically significant. A similar trend was observed with day 1 CD34+ collection (defined as the CD34+ cell count/kg collected on day one of mobilization) and stem cell BFU-E, CFU-GM and CFU-C composition. After controlling for age, gender, ISS stage, lenalidomide use, number of pre-transplant therapies, disease status at transplant and plerixafor use, the odds ratio of day one collection failure with Dara was 3.5 (p-value=0.085).
Conclusions: Taken together, pre-ASCT use of Dara in combination regimens was well-tolerated without deleterious effects on graft composition or engraftment. Dara use did not adversely effect transplant outcomes, especially with plerixafor during stem cell mobilization. For ASCT eligible patients, Dara is a superior option to achieve prolonged disease-free survival.

P-027
Lenalidomide does not affect platelet function in vitro

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Introduction: Lenalidomide is an immunomodulatory drug (IMiD), which has greatly improved the prognosis of multiple myeloma (MM) patients and brought much convenience to clinical treatment. According to the results from several clinical studies,its most common side effect seems to be recognized as the thromboembolic complication. However, basic researches exploring the underlying mechanism remains largely unexplored. In this study, we assessed the effect of lenalidomide on platelet function in patients with MM in vitro.
Methods: Under informed consent, peripheral blood samples from 7 (5 male, 2 female) newly diagnosed MM patients without antithrombotic therapy were collected. Washed platelets were then isolated and incubated with lenalidomide (5μmol/l) or vehicle (0.1%DMSO) for 30 minutes in vitro. To explore the effect of lenalidomide on platelet activation in vitro, platelet aggregation, platelet spreaing, clot retraction and flow cytometry were conducted.
Results: All data is presented as mean±standard deviation (SD) and in the order of treatment group, vehicle group and P value. (1) Platelet aggregation. Upon stimulation with thrombin (0.1 U/mL) and collagen (2 μg/mL), no obvious differences were observed. First, the average platelet aggregation (%) in response to thrombin: 53.23±3.89, 52.99±3.84 ($P > 0.05$); as for collagen:54.32±1.14, 54.43±1.10 ($P > 0.05$). (2) Platelet spreading. Spreading platelets from patients were stained with rhodamine-conjugated phalloidin and the average adhering areas (Pixels) were counted. In the case of relevant data: 3116±283.2, 3022±353.1 ($P > 0.05$). (3) Clot retraction. We photographed at the specific time point and then analysed the degree of clot retraction. One hour later: 0.52±0.06, 0.51±0.03 ($P > 0.05$); two hours later: 0.44±0.07, 043±0.04 ($P > 0.05$); three hours later: 0.37±0.06, 0.37±0.05 ($P > 0.05$); four hours later: 0.33±0.06, 0.32±0.05 ($P > 0.05$). (4) P-selectin and PAC1 exposure. Surface expression of P-selectin and PAC1 in the presence of thrombin (0.1 U/mL) was evaluated and mean fluorescence intensity (MFI) was used for statistical analysis. Consistent with previous results, there was no significance between two groups. With reference to the data of P-selectin, for resting platelets:1392±361.8, 1273±321.5 ($P > 0.05$); towards to thrombin activation: 14008±3911, 15819±3765 ($P > 0.05$). Concerning PAC1 expression, with regard to resting platelets: 143.3±42.86, 111.8 ±52.37 ($P > 0.05$); after thrombin stimulation: 355.8±71.45, 485.3 ±143.9 ($P > 0.05$).
Conclusions: Comparing to the control group, there was no significant difference in the degree of platelet activation in the lenalidomide group in vitro.

P-028
Successful use of frontline daratumumab lenalidomide and dexamethasone in transplant ineligible frail patients with moderate renal failure at the time of presentation

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Introduction: Treatment of the elderly patients who have varying degrees of renal failure at the time of presentation, both due to the underlying plasma cell dyscrasia or the other comorbidities is a true challenge regarding the management of toxicities while trying to achieve the best durable responses. Daratumumab Lenalidomide and Dexamethasone (DRd) induction in transplant ineligible patient population is

approved among the appealing results of MAIA trial. Lenalidomide is an immunomodulatory agent which is eliminated through kidneys and should potentially threat kidney function. But recently, PrE1003 trial showed that even patients with severe renal insufficiency should tolerate higher doses of the drug label.
Methods: Treatment details and outcomes of three consecutive extremely elderly (over 85 years of age) patients who were presented with moderate to severe renal insufficiency and received DRd combination as a frontline therapy was presented.
Results: All of the three patients were over 80 years old (Pt.1 82, Pt.2 89 and Pt.3 84 yr-old). First two patients were diagnosed with IgG kappa multiple myeloma with a R-ISS score of 2 and an R-MCI score of 6 and Pt.3 was diagnosed with IgA kappa multiple myeloma with a R-ISS score of 3 and R-MCI score of 7. The estimated glomerular filtration rates (GFRs - Cockcroft Gault) of the patients were as follows at the time of presentation; Pt.1 24, Pt.2 48 and Pt.3 32 ml/min. Pt.1 and Pt.3 suffered from a long-standing type 2 diabetes and previous coronary artery disease and Pt.3 suffered from hypertension, obesity and mild dementia. All patients received Daratumumab with a dose of 16 mg/kg and Lenalidomide with a starting dose of 10 mgs (21 day on 7 days off) and Dexamethasone with a starting dose of 20 mgs per week. Thrombo-prophylaxis was uniformly done by Apixaban 2.5 mg twice daily and all patients received trimethoprim-sulfamethoxazole and valacyclovir. None of the patients required hemodialysis in the course. One patient suffered from a febrile neutropenic episode in the first cycle of DRd and required GCSF support in the consecutive cycles with a declining frequency. Two patients suffered from grade 2 and one patient suffered from grade 1 infusion related reactions while receiving first dose of Daratumumab which were managed with a short cessation of the infusion and additional doses of corticosteroids. All of the three patients successfully finished 4 cycles of induction, with one proceeding to the 6th cycle. Pt.1 and Pt.2 were able to achieve a VGPR after two cycles of DRd and Pt.3 was able to achieve CR even he harbored t(16;20). Lenalidomide dose was increased to 15 mgs/day in Pt.2 and Pt.3 and all the patients had a significant renal response with a final eGFRs of 42, 65 and 50 ml/min.
Conclusions: DRd combination was able to induce hematological and renal responses even in patients who were extremely elderly, frail and having restricted renal functions with manageable adverse events.

P-029
The association of microbiota composition and proteasome inhibitor-related gastrointestinal adverse effects

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Introduction: Emerging novel agents and strategy of continuous treatment are two main contributions to prolonged overall survival (OS) in patients with multiple myeloma (MM) during the past two decades. Therefore, drug tolerance has become the key factor for compliance. Serious adverse events (AEs) will lead to drug withdrawal and impair treatment response. The purpose of this study was to evaluate the correlation between microbiota and gastrointestinal (GI) toxicity related to anti-MM agents.
Methods: The clinical characteristics were prospectively collected in patients with newly diagnosed MM (NDMM) and relapsed/refractory MM (RRMM). Adverse effects, especially GI-AEs were recorded according to the CTCAE classification standard. Fecal samples before treatment were collected. 16S rRNA gene sequencing method was employed to analyze the species structure and species differences of microbiota. As to in vivo study, C57BL / 6 mice were treated with bortezomib, butyrate, butyrate plus bortezomib. During 4-week treatment, weight, fecal forms and microbiota were tested.
Results: A total of 85 patients were enrolled, among whom 15 treated with lenalidomide + dexamethasone (Rd), 23 with bortezomib + Rd (VRd), 24 with ixazomib + Rd (IRd), 23 with bortezomib + cyclophosphamide + dexamethasone (BCD). The median age was 65 years. Age, sex, paraprotein type and ISS stage were comparable in four treatment groups. 49 NDMM (57.6%) and 36 RRMM (42.4%) cases presented similar species diversity of microbiota.24 cases (28.2%) reported non-hematological AEs after treatment. GI-AEs (including nausea, vomiting, diarrhea and constipation) developed in 18 cases (21.2%). The Species diversity of gut microbiota in GI-AE group was significantly lower than that without (both $P < 0.05$). Further, the composition of microbiota in patients with or without GI-AEs were of great difference. The abundance of Firmicutes, Ruminococcaceae and F. prausnitzii in patients with GI-AEs reduced significantly ($P < 0.05$). Moreover, the abundance of F. prausnitzii in GI-AE patients treated with PIs (IRd, VRd and BCD) especially lower ($P < 0.05$) compared with non-GI-AE ones. The discrepancy in Rd group was not prominent ($P > 0.05$). Multivariate analysis showed that only low-level F. prausnitzii (defined as abundance < 0.1%) was an independent factor associated with GI-AEs ($P < 0.001$). Animal study suggested that in bortezomib treated mice, weight loss was remarkable, and species diversity of microbiota reduced and F. prausnitzii. decreased. After administration of butyrate, mouse weight recovered and the abundance of F. prausnitzii elevated.
Conclusions: Gastrointestinal adverse effects in MM patients are associated with reduced species diversity of microbiota. Low abundance of F. prausnitzii is related to GI-AEs caused by PIs. Short chain fatty acids may improve GI toxicity via alleviating bowel inflammation. The translation of these findings to bedside may improve drug tolerance and response.

P-030
Regular monitoring with whole body low-dose CT for osteolysis in multiple myeloma reveals more cases of

progressive bone disease than imaging performed by clinical indication

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Introduction: Should we monitor multiple myeloma (MM) patients with imaging at regular intervals? Former studies using sequential conventional radiography did not show clinical value hereof and current guidelines recommend imaging at clinical suspicion or biochemical signs of progression. Still, MM is a heterogeneous disease where focal progression without significant increase in biochemical, clonal markers and without symptoms have been reported. With improved imaging, it is possible that regular monitoring could find cases of progressive bone disease at an early stage.
Methods: In a study to investigate the optimal duration of zoledronic acid (ZOL) treatment, MM patients were included at diagnosis or after 2 years of ZOL treatment. After finishing 2 years of ZOL treatment, they were randomized to either 2 additional years or monitoring without additional treatment. A total of 267 MM patients were followed for up to 4 years with monthly blood samples and outpatient visits, quality of life questionnaires and monitoring by Whole-Body Low-Dose CT (WBLDCT) at 0, 12, 24, 30, 36 , 42 and 48 months and when clinically indicated. While the study was not designed to investigate effects of regular monitoring, it allowed for investigation of findings by regular monitoring in myeloma patients.
Results: In total, 26 (70.3%) of 37 progressive bone events were found by protocol planned imaging and 11 (29.7%) by WBLDCT on clinical indication ($p < 0.05$). In further exploration of the data we found that this difference could not be explained by clinicians ordering less imaging when preplanned WBLDCT was near, as the time distribution of performed WBLDCTs by clinical indication was equal over study period. Among subjects with identified bone event at preplanned WBLDCT, only one patient had developed another CRAB criteria (anemia) indicating clinical progression, whereas it was common in cases found by clinicians (3.8% vs 45.5% $p = 0.003$). We also found that patients with progressive bone disease found by clinicians compared to protocol planned imaging had more clinically relevant symptoms or lower function scores by EORCT QLQ-C30 and QLQ-MY20 questionnaires (moderate or minor difference) in 14/19 domains. While regular monitoring did reveal more bone events, the drawback was a higher number of imaging investigations per identified case. A total of 840 investigations were performed. Imaging on clinicians suspicion had a higher percentage of positive findings (9.9%) compared to preplanned imaging (3.6%) ($P = 0.04$). Corresponding to number needed to investigate of 1 in 10 and 1 in 28 respectively.
Conclusions: In conclusion, our study demonstrates that monitoring myeloma patients with WBLDCT detects early cases of progressive bone disease before symptoms or biochemical progression occur. Earlier identification of bone progression will make it possible to treat patients at an earlier stage of relapse, before bone pain and potential fractures occur. Supported by Nordic Cancer Union and Danish Cancer Society.

P-031
Artificial intelligence analysis of whole-body magnetic resonance imaging of patients with multiple myeloma to find prognostic factors

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Introduction: Background: Although radiologists' magnetic resonance imaging (MRI) and positron emission tomography/computed tomography reports are used to predict the prognosis of patients with multiple myeloma, there have been no reports to apply artificial intelligence (AI) technology for this purpose.

Methods: Whole-body diffusion-weighted MRI data of 45 patients with plasma cell diseases were collected. Poor prognosis was defined as the occurrence of progressive disease within 100 d after MRI assessment. Forty-one and four patients were categorized as nonpoor and poor prognosis, respectively. Due to the imbalance of the categories, we performed the under-sampling method to adjust patients to a 2:1 ratio (nonpoor [n = 8]:poor patients [n = 4]). Six nonpoor and two poor patients were included in the training data set, and two nonpoor and two poor patients were included in the test data set. AI methods, such as 3D convolutional neural network and gradient-weighted class activation mapping (Grad-CAM), were used to identify the explanatory prognostic factors of MRI.
Results: ISS 1 (n = 6), 2 (n = 1), and unknown (n = 1) and ISS 2 (n = 1) and 3 (n = 3) were recorded in nonpoor and poor patients, respectively. The prognostic model built using the training dataset was used to verify the prognosis of the test dataset: the sensitivity and specificity of prognosis prediction were 100%. The Grad-CAM method identified that loss of spleen was the most crucial factor for poor prognosis.
Conclusions: This AI analysis identified loss of spleen as a strong prognostic factor, which agrees with a recent report (Terao et al., Scientific Reports 2021). The expanded data (approximately n = 200) will be used to verify this result and find other prognostic factors.

P-032
Lenalidomide maintenance after autologous hematopoetic stem cell transplantation in Hungary from 2016 to 2021

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Introduction: Lenalidomide maintenance is an established pillar of the first line treatment, of the transplant-eligible newly diagnosed multiple myeloma patients. We performed a retrospective analysis of five years' data, provided by the four autologous stem cell transplantation units in Hungary.
Methods: Retrospective data collection using the individual hospitals' electronic health records and the national, cloud based health record system (EESZT). We performed descriptive statistics and survival analysis by the Kaplan-Meier method.
Results: We included 351 patients in the final analysis. The M:F ratio was 1.2:1 (p=0.36). Median age: 58 (range: 29-74). ISS and R-ISS staging data showed I.: 35% and 14% II.: 17% and 30% III.: 33% and 27% Unknown: 15% and 29%. As first line treatment, 69% recieved VTD, 9% VCD, 9% PAD, 6% various doublets, 7% various other regimens. 74% needed more than 1 line of treatment as induction, and 22% of patients had late transplants (time from diagnosis over 12 months. 98% of our patients recieved melphalan conditioning regimen. Our analysis showed a clear benefit for maintenance treatment in the whole (Median PFS: NR vs. 35 months p >0,01, OS: estimated 130 months vs 100 months p >0,01). Lenalidomide maintenance outperformed observation especially well in stage I and stage III disease (median PFS NR vs.48 months and 45.3 vs 25.1 months p >0,01). Within the maintenance group, the presence of a single high-risk cytogenetic feature (1q+, 17p-, t(4;14), t(14;16), monosomal karyotype) impacted the outcomes negatively
Conclusions: This real-world experience clearly highlights the benefit of maintenance treatment with lenalidomide. The treatment retained its positive effect in various situations that would most certainly be excluded from clinical trials. Reduced efficacy was shown in the presence of high risk cytogenetic markers, which underlines the importance of a differentiated approach in choosing the post-autologous transplant maintenance regimen.

P-033

Patient multiple myeloma cells do not express targetable levels of CD38 when in remission on daratumumab

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Introduction: Anti-CD38 monoclonal antibodies are an important component of induction and relapse treatment of multiple myeloma (MM), but their benefit as a long-term maintenance therapy is unknown. Recently, the CASSIOPEIA trial showed that daratumumab (Dara) addition was beneficial during maintenance only if patients had not received it during induction. It has also been demonstrated that anti-CD38 antibody treatment downregulates CD38, likely a key event in drug resistance development. Previously, we found that anti-CD38 antibody sensitivity is regained after one year elapsed since the last antibody dose, as MM cells gradually recover CD38. Thus, we hypothesize that discontinuing anti-CD38 antibody upon achieving remission would lead to earlier CD38 recovery, less drug resistance and better efficacy when used in later treatment lines.
Methods: Bone marrow aspirates and peripheral blood samples were obtained from patients at the University of Colorado Blood and Weill-Cornell Medicine after IRB approval and informed consent. Myeloma drug sensitivity testing (My-DST) was used to measure ex vivo sensitivity to Dara or isatuximab (Isa) after 48 h incubation in triplicate compared to untreated controls as previously described (Walker et al. Blood Advances, 2020). Ultrasensitive flow cytometry to measure CD38 on MM cells in patients in remission was performed on a BD FACSCelesta.
Results: We measured responses from 8 patients who were re-treated with an anti-CD38 antibody after a median period of 1.9 years post-Dara. Notably, one patient who had relapsed after Dara, but was not refractory, responded markedly better to re-treatment than the other patients. This patient was re-treated with Dara and achieved an ongoing complete remission that has lasted >9 months. We next studied bone marrow samples from patients who had achieved remission on Dara-based treatment. We identified MM by gating cells that were positive for CD138, BCMA and CD46. In samples with detectable MM cells, the CD38 levels were not elevated above the CD38 expression of other normal BM cells. This contrasts to the high level of CD38 overexpression on MM cells from Dara-naïve patients.
Conclusions: Since initial FDA approval, dosing of anti-CD38 antibodies has always been done continuously, starting weekly and reducing to monthly over time. This schedule may not have continued benefit after maximum response is achieved, and instead lead to drug resistant residual disease. In follow-up of patients who are re-treated with anti-CD38 antibodies, we observed a substantially better response if the patient stopped the antibody at maximum response. We also found that in patients who are in remission after responding to daratumumab, residual MM cells express CD38 within background levels. Thus, further clinical trial data is needed to optimize the approach to dosing of anti-CD38 antibodies in multiple myeloma.

P-034

Indian multicentre phase II randomized study comparing post stem cell transplantation maintenance regimens for newly diagnosed multiple myeloma patients (IMPOSe trial)

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Introduction: Autologous stem cell transplant (ASCT) remains the backbone therapeutic modality with the highest progression-free survival (PFS) and overall survival (OS) benefit even in the era of the novel agents in newly diagnosed multiple myeloma (NDMM). The survival post-transplant can be prolonged using maintenance therapies. The regimen with maximum benefit is still debated, with bortezomib showing PFS benefit even in the high-risk myeloma. This randomized phase II trial is aimed at studying the efficacy (as measured by overall survival (OS), progression-free survival (PFS)), and safety of post-ASCT different maintenance regimens in patients with NDMM.
Methods: Multicentric open-label interventional study with randomized allocation, parallel assignment, with intention-to-treat analysis. Recruitment was prospective starting 01 Jan 2017, including all NDMM patients eligible for the study. Remission status was evaluated at D100 and every 6 months for 2y post-ASCT, including MRD analysis by multicolor flow cytometry (MFC) and PET/CT. The four arms included (Arm-A) bortezomib alone (V), (Arm-B) bortezomib in combination with cyclophosphamide and dexamethasone (VCD), (Arm-C) bortezomib in combination with lenalidomide (VR), and (Arm-D) Lenalidomide starting D100 till 2y post-ASCT. Adverse events with CTACE grade < 2 were defined as non-serious and the rest as serious. JMP ver. 16.1 was used for statistical analysis and $p< 0.05$ was considered significant. Kaplan Meier statistics was used for survival analysis.
Results: A total of 123 patients have enrolled of which 92 patients completed the study protocol and the rest 31 patients were excluded because of protocol deviation due to the COVID pandemic. The patients were allocated to four arms (22,20,19,23 respectively). The median age of the study population was 54.5y (35-76y) with a male preponderance (67%). There was no statistically significant difference between the four arms on the log-rank test in the OS (p-0.99), clinical PFS (p-0.65), biochemical PFS (p-0.6), or MFC-based PFS (p-0.83). There was a statistically significant difference between the four arms on the log-rank test (p-0.0185) on

PET/CT-based PFS (PFS being in a descending order VCD > V > VR > R regimen). The all-cause mortality of the study participants was 19.57% (n-18) and the difference in deaths among the various groups was not statistically significant (p-0.85). The tolerability, serious and non-serious adverse were significantly higher amongst Arm D patients.
Conclusions: We conclude that there was no difference in OS or clinical PFS between the different maintenance regimens. The patients who were on Lenalidomide-only therapy (lack of bortezomib benefit) were found to have significantly inferior Imaging PFS (higher PET positivity during follow-up). This could be partly explained by poorer tolerability and higher adverse events (both serious and non-serious) among patients on Lenalidomide-based maintenance.

P-035
Ixazomib versus lenalidomide or ixazomib and lenalidomide combination as maintenance regimen for patients with multiple myeloma: interim analysis of a multi-center prospective study in China

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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 because of its 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 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. After 4 cycles of front-line induction therapy, patients reached partial response (PR) would receive autologous stem cell transplantation (ASCT) if eligible, or receive up to 5 cycles of front regimens if ineligible, then start MT. Patients did not reach PR would switch to 2nd-line induction for 2-5 cycles and start MT once PR was achieved. 4mg of Ixazomib was given on day 1,8,15, and 25mg of Lenalidomide every other day on days 1–21 of 28day cycles. Patients in dual drug group were administrated with both Ixazomib and Lenalidomide, dose as listed above. The primary endpoint was PFS from MT.
Results: A total of 187 patients were enrolled, including 63 in I-MT, 72 in L-MT and 52 in IL-MT. The demographic and clinical characteristics, including gender ratio, age, paraprotein isotype, ISS, R-ISS, were comparable among different MT regimen groups receiving ASCT or not at baseline. The proportions of patients with high-risk cytogenetic abnormalities (HRCAs), defined as amplification 1q21, deletion 17p, t(4,14) and t(14,16), were lower in L-MT without ASCT and I-MT with ASCT. The median follow-up duration was 11.9, 15.4 and 10.9 months in I-MT, L-MT and IL-MT non-transplant patients, while 8.8, 15.4 and 13.8 months in ASCT group, respectively. In non-transplant patients, the disease progression rate was 18.2%, 12.2% and 16.7%, whereas 12.5%, 21.7% and 0 in ASCT group. The median PFS and OS were not reached (NR) in all groups. As for safety, the prevalence of peripheral neuropathy in whole cohort was 17.5% on I-MT, 8.3% on L-MT and 23.1% on IL-MT. The incidence of gastrointestinal events was 11.1%, 2.8% and 15.4%, respectively. Hematologic toxicities developed in 3.2%, 8.2% and 9.6% patients. Infection rates were 9.5%, 2.8% and 3.8%. 3 patients had withdrawn from MT, 2 for grade 2 PN and 1 for grade 3 hematologic toxicity.
Conclusions: Due to inadequate access to melphalan and low rate of ASCT in China, the PFS of NDMM was lower than those in western countries. We design this multi-centered prospective study to evaluate if dual drug MT will further strengthen response and make up the gap. Though the primary endpoint--PFS has not been reached in all treatment groups, dual drug MT improves response most and is quite tolerable.

P-036
Bone anabolic effect of ixazomib - a third generation proteasome inhibitor – in multiple myeloma patients

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Introduction: The potential anabolic effect of proteasome inhibitors in multiple myeloma (MM) was first described in 2005, when bortezomib treatment was shown to increase alkaline phosphatase (ALP) and bone specific ALP (BAP), as well as trabecular bone volume per total volume (BV/TV). Another proteasome inhibitor (carfilzomib) was later found to show similar anabolic properties, suggesting a class effect. However, both bortezomib and carfilzomib are challenging for long term use due to side effects like peripheral neuropathy and cardiac toxicity. Ixazomib is an oral proteasome inhibitor that has shown efficacy as maintenance treatment for prolonging progression free survival in MM. Ixazomib is generally well tolerated and thus suitable for long term use. We are currently conducting a 2-year single center, open label, phase 2 clinical trial to investigate the effect of Ixazomib on bone in MM patients. Here, we present our preliminary 3-month data.
Methods: Natrium 18Fluoride (NaF) scans, trephine iliac crest bone biopsies and serum samples were collected from 30 MM patients before and upon completion of 3 full 28-day cycles of Ixazomib. Mean NaF standard uptake values (SUV) of skull, sternum, vertebrae, pelvis and femur were registered. Formalin-fixed, paraffin-embedded bone biopsies were sectioned at 3.5-µm-thickness; sections were either immunostained for TRAcP and in situ hybridized for COL1A1, or immunostained for osteopontin to visualize cement lines delimiting bone structure units (BSU). Serum biomarkers of bone metabolism were analyzed, including tartrate-resistant acid phosphatase 5b (TRAcP5b), C-terminal telopeptide (CTX), osteocalcin (OC), BAP and procollagen type 1 N-terminal propeptide (P1NP).
Results: Mean SUV remained unchanged in all skeletal sites examined in NAF scans; however, histological analyses of bone biopsies revealed a significant increase in BV/TV after treatment. The BV/TV increase was significantly higher in light chain than IgG MM patients, but was independent of translocation number. After adjusting for age, sex, R-ISS and relapse status, multiple linear regression analyses revealed an association between BV/TV increase and baseline BMI. Analyses of bone sections showed unchanged osteoclast number and COL1A1-expressing osteoblasts on bone surfaces. However, osteopontin staining revealed that following treatment significantly more superficial BSUs were enlarged (>200,000µm2) and presented a different distribution frequency of their shape (aspect ratio, width, and sphericity). Serum samples revealed significant decreases in CTX and TRAcP5b after treatment, suggesting reduced bone resorption.
Conclusions: Here we demonstrate that Ixazomib treatment has a bone anabolic effect in MM patients after just 3-full cycles. Further studies are warranted to understand the molecular and long-term effects of Ixazomib on bone formation in MM.

P-037
Chinese herbal medicine ‘Diwu’ suppresses myeloma bone disease via ERK/MAPK signaling pathway by targeting CCL3

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Introduction: Multiple myeloma (MM) associated bone disease (MBD) is largely dependent on the bone marrow microenvironment (BME). The cross-talk between MM cells, bone marrow mesenchymal cells and myeloid progenitors affects the osteoclastogenesis. Traditional Chinese medicine ‘Diwu’ is effective for patients with arthritis and inflammation, also occasionally uses as one ingredient treating MM. But the effects of ‘Diwu’ in MBD are largely unknown. The aim of this study is to investigate the role and underlying mechanism of ‘Diwu’ in regulating BME and osteoclast differentiation.
Methods: Myeloma cell lines RPMI-8226, NCI-H929, U266 and MM.1s were treated with ‘Diwu’ extract. Killing effects were evaluated by the half inhibitory dose (IC50) value and proportion of apoptosis MM cells. RNA-seq was applied in ‘Diwu’ treated myeloma cells to identify MBD associated signaling pathways. RPMI-8226 was co-cultured with mesenchymal stromal cell (MSC) line HS5. Human monocyte cell line THP-1 was treated with CCL3 and M-CSF to form osteoclasts determined by tartrate-resistant acid phosphatase (TRACP) staining. Primary human MSCs were cultured into osteogenic or adipogenic differentiation, determined by alizarin red staining and oil red staining, respectively. RNAi technology was applied to knock down CCL3. The expression of osteoclast-specific genes TRACP and MAPK pathway-related genes was tested using quantitative real-time PCR. Phosphorylation and expression of MEK1, ERK, FOS were measured by Western Blot. The myeloma-bearing NOD/SCID mice were treated with intragastric ‘Diwu’. Serum C-terminal telopeptide of type 1 collagen (CTXI) and propeptide of type I procollagen (PINP) was tested by ELISA. The tibia of mice was fixed and stained to analyze the differentiation and maturation of osteoblasts and osteoclasts. Micro-CT was used for bone destruction measurement.
Results: ‘Diwu’ inhibited MM cells proliferation (IC50, 29.22-364.7µg/ml) in a dose-dependent manner and promoted apoptosis by upregulating protein expression of CASP3, BCL2.

'Diwu' decreased the secretion of CCL3 and receptor activator of nuclear factor-kappa B ligand (RANKL) in myeloma-MSC co-cultured system by diminishing the direct attachment and interaction of these two cells. The mRNA and protein levels of osteoclast-specific genes such as TRACP, and the phosphorylation and expression of MEK1, ERK, FOS in osteoclast were all reduced after 'Diwu' treatment. We observed improved osteogenic activation rather than lipid formation in hMSC differentiation. The level of TRACP isoform 5b (TRACP-5b) was significantly downregulated in mouse serum after 'Diwu' treatment for 14 days.
Conclusions: Altogether, our results demonstrated that effective extract of Chinese herbal medicine 'Diwu' could simultaneously inhibit myeloma cells and suppress osteoclast formation, indicating an important role of 'Diwu' in regulating BM microenvironment. It is possible to translate 'Diwu' into clinical application as an oral agent for myeloma bone disease.

P-038
An atlas of the bone marrow bone proteome of patients with dysproteinemias

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Introduction: Multiple myeloma (MM) cells depend on a permissive bone marrow (BM) microenvironment for survival. MM bone disease is a significant cause of morbidity but there is a paucity of data on the impact of malignant plasma cells on adjacent trabecular bone within the BM. Here, we characterize the proteome of trabecular bone tissue from BM biopsies of patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering (SMM), newly diagnosed (NDMM), relapsed MM (RMM), and localized amyloidosis (AL) control subjects.
Methods: BM biopsy tissue from 56 patients (12 MGUS, 11 SMM, 15 NDMM, 18 RMM) and 12 localized AL controls were collected on microscope slides and trabecular bone was isolated via laser microdissection followed by label-free mass spectrometry. Protein groups with an FDR< 0.05 and an absolute log2 fold change of ≥0.5 were considered significantly differentially expressed and used for subsequent analyses. All patients with active MM had CyTOF, RNAseq and 65-plex Luminex analyses of their BM immune and malignant cells and BM plasma, respectively, from a previously published report.
Results: 1951 distinct proteins were identified. Functional enrichment via WebGestalt showed that proteins involved in extracellular matrix (ECM) organization, protein translation, and immunity were overrepresented, suggesting that trabecular bone is metabolically and immunologically active. Next, we grouped AL controls and MGUS subjects (i.e., low plasma cell burden) and compared them to SMM and active MM. Proteins involved in ECM formation and immunity pathways were decreased in SMM and active MM. Among the top proteins decreased were immunoglobulins, type IV collagen, and TIMP3, suggesting increased immunoparesis and decreasedECM remodelling within the trabecular bone of SMM/MM. Top proteins increased in SMM/MM were APP (enhances osteoclast activity), ENPP1 (enhances bone mineralization), and MZB1 (required for normal plasmablast differentiation). These findings identify novel key proteins involved in bone tissue homeostasis in MM and suggest mechanisms by which bone may directly sustain malignant PCs. Pathway analyses showed that proteins involved in γ-carboxylation, a pathway implicated in osteocalcin function, osteoblast differentiation, and normal hematopoiesis, were also overexpressed in SMM/MM. Finally, we identified no significant correlations (Pearson's R2 > 0.8) between bone proteins and previously reported BM immune subsets (CyTOF), BM plasma proteins or malignant cell genes.
Conclusions: This study is the first comprehensive proteomic atlas of the BM bone proteome in dysproteinemias. We identify new key proteins and pathways for MM bone disease and potentially impaired hematopoiesis in this disease, and show for the first time that γ-carboxylation pathways are increased in SMM/MM.

P-039
African American race as potential favorable biologic factor impacts clinical outcome for patients with multiple myeloma

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Introduction: Multiple myeloma (MM) remains an incurable malignancy characterized by plasma cells that are nurtured and proliferate within the permissive bone marrow milieu. It has greater incidence in self-identified African Americans (AA) compared to Caucasian Americans, CA (13.8 vs. 6.5/100,000). The five-year age adjusted mortality rate, according to SEER data acquired, is greater in AA compared to CA Pts (5.8 vs. 2.9/100,000), which is likely explained by a greater incidence in the AA population. However, recent reports have also shown that AAs with equal access to care have an even better survival than their CA counterparts [Fiala et al. Cancer. 2017]. Conversely, results from the CoMMpass registry database showed that OS was shorter for Blacks compared with Whites (age-adjusted hazard ratio (HR) 1.7, 95% confidence interval 1.2–2.4, P = 0.003) [Derman et al. Blood Cancer J. 2020] . Here, we report the interplay of race and other dimensions of MM care using the National Cancer Database (NCDB).
Methods: NCDB is the largest cancer database in the US including >70% of all newly diagnosed cancer patients. The International Classification of Diseases for Oncology (ICD-O)

code of 9732 was used. OS was calculated from the date of MM diagnosis.
Results: We identified 118,707 MM Pts between 2004 to 2014 in this database, of which 90,253 (76%) were CA and 23,479 (20%) self-identified as AA. For AA patients, there was a lower proportion of Medicare (48 vs. 57%), and private insurance (34 vs. 35%) and a higher percentage of Medicaid (11 vs. 4%) and uninsured Pts (6 vs. 3%) compared to Pts that self-identified as CA. A larger proportion of AAs had a Charlson score ≥1 (29 vs. 33 in CA) and lived in low-income regions (76.1 vs. 56.4% of whites; $P < 0.0001$). The percentage of Pts who underwent radiation was higher among CA compared to AA (23% vs 8%). However, unadjusted OS was greater for AA compared to CA Pts, 50.6 months vs. 46 months, respectively, ($P < 0.0001$). After adjusting for all above variables, black and white patients had similar OS.
Conclusions: Taken together, our study, utilizing largest available dataset at US, indicates AA race plays a favorable factor despite AA population suffers from lower socioeconomic status. This finding can suggest more favorable biology of the disease among AA Pts supported by lower rates of radiation in AA as the indirect measure of bony complications. MM is the most common cancer that involves bone structures and is dependent on a tumor-permissive microenvironment influenced by osteoclasts and osteoblasts. Given, AA enjoy less bone loss and fractures under physiologic and pathologic conditions, e.g., AA Pts with chronic kidney disease as well as Pts with metastatic prostate cancer receiving hormonal therapy exhibit reduced rates of bone loss and fracture in comparison to CA. Further studies to elucidate the differences in the cellular and molecular bases for discordance in the bony compartment of the MM microenvironment in AA Pts with MM are warranted.

P-040
Unusual presentation of multiple myeloma with rapidly progressing lesions of the distal bones: about a case report

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Introduction: Multiple myeloma (MM) is often suspected when a serum monoclonal immunoglobulin is detected in association with bone lesions of the axial skeleton. Involvement of distal bones, usually seen in end-stage disease, is much less common in this context.
Methods: We report the case of a newly diagnosed MM in which the initial pattern of bone involvement exclusively affects the distal bones.
Results: A 65-year-old woman with a previous history of anxio-depression and gastric by-pass surgery was referred to the emergency room for an acute pain in her left knee without any history of trauma. She complained of a progressive swelling of her knee over the last 3 months, and reported the recent identification of an IgA kappa monoclonal peak. There was no evidence of fracture or lytic lesion on x-rays. Lab tests confirmed a monoclonal IgA kappa (18.9 g/L) with an increased kappa/lambda ratio (3.35) and serum beta2-microglobulin (2.82 mg/L). Renal function, calcemia and LDH as well as 24-hour proteinuria were in the normal range. Bone marrow aspirate showed only 10% plasma cells with no plasmablasts. When waiting for additional work-up, the patient developed a bilateral painful swelling of the lower limbs that prevented her from walking, followed by the appearance of purplish nodules at the anterior aspect of the left leg, and then, over a few days, a bony tumor of her right cheek and eyebrow region. Both MRI and CT of the knees identified multiple nodular lesions replacing the medulla of the femoral condyles, associated with cortical bone osteolysis and infiltration of the surrounding soft tissues. Similar lesions were found in bones of the legs, ankles and feet. On the opposite, MRI of the spine showed only a diffusely anormal signal of the BM with few focal lesions. PET-CT confirmed multiple hypermetabolic osteomedullary lesions of the lower limbs as well as elbows, forearms and wrists, and the right frontal and zygomatic bones (SUVmax, 3.6-6.3). Diagnosis of MM was finally established on a biopsy of the left knee, by the presence of neoplastic cells diffusely expressing CD138 and kappa light chain. NGS failed to identify TP53 mutation, but noted the presence of a pathogenic variant of the NRAS oncogene (G12V, allelic frequency of 82.40%). Bone marrow FISH did not show any abnormality. Patient was started on a bortezomib-based regimen (VCD), and radiation therapy (8 Gy) was delivered on the left knee and both ankles. Cutaneous lesions disappeared within the first cycle, she achieved a VGPR and a complete metabolic response after 4 cycles. High dose melphalan followed by ASCT is planned in the near future.
Conclusions: Our case underlines the fact that MM can occasionally manifest at diagnosis with an unusual pattern of bone involvement with a predominance in the distal limbs instead of the axial skeleton. In order to start therapy in a timely manner, biopsy of the lesion should not be postponed since BM aspiration may fail to establish the diagnosis.

P-041
Is there an effect of daratumumab on litics bone lesions in patients with multiple myeloma?: a case report

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Introduction: Solitary plasmacytoma is a rare plasma cell dyscrasia, classified as solitary bone plasmacytoma or solitary extramedullary plasmacytoma. Histologically there is a monoclonal plasma cell infiltration in a single bone lesion or in a mass of soft tissues , and by definition there is no significant medullary plasma cell infiltration or other evidence of organ damage.
Methods: In May 2015, a 69-year-old man was diagnosed with solitary plasmacytoma of the right femoral bone Performed CT and MRI scans with evidence of lytic lesion in

the right femur and pathological solid tissue occupying the medullary canal The biopsy of the tissue performed showed numerous aggregates of plasma cells, CD138 +, K +, Lambda -, CD20-, CD3- negative bone marrow biopsy and only positive urinary immunofixation The patient then underwent radiotherapy of the right femur, followed by chemotherapy according to the PAD scheme (liposomal bortezomib-doxorubicin-dexamethasone). 8 cycles of therapy were performed (the last 4 without doxorubicin for haematological toxicity), obtaining CR In 2019, for pain relief in the lumbar and pelvic area, he performed: MRI of the spine showing bone lesions in D10-11-L2 L4 D12, ilic wing, ischium pubic bone, and right SI joint, confirmed by PET examination also on this occasion in the range, the haematochemical routine and only positive urinary immunofixation negative bone biopsy A biopsy of the iliac crest lesion is then performed, which confirms the diagnosis of plasmacytoma. Therapy according to the Dara Rd scheme starts from October 2019 The patient did not use bisphosphonates due to intolerance. After 5 months of starting therapy, the patient had pulmonary embolism, so we stopped lenalidomide, started NAO therapy and continued with daratumumb and dexamethasone alone. The PET re-evaluation of March 2021 confirms the complete remission of the disease

Results: In February, after 5 months of therapy, the patient presents a picture of pulmonary embolism, for this reason the use of lenalidomide is suspended and therapy with NAO is started. The pet review of March 2021 confirms the complete remission of the disease and continues with only daratumumb and dexamethasone. In March 2021 the patient presents with SARS COVID infection, overcome without complications, continues the therapy and the new re-evaluation of May 2021 confirms the remission of the disease.

Conclusions: We know how daratumumab acts on bone remodeling by inhibiting osteoclasts and increasing the production of markers of bone formation. This report wants to further underline the "curative" action on plasmacytoma bone localization, an action most likely to be attributed to daratumumab as in our patient the remission of the disease continued even after the suspension of lenalidomide and without the use of bisphonates. Obviously more studies are needed to confirm these hypotheses.

P-042

Phase 1 dose-escalation study of sotatercept in combination with lenalidomide and dexamethasone or pomalidomide and dexamethasone in relapsed/refractory multiple myeloma

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Introduction: Anemia and bone disease are hallmarks of multiple myeloma (MM). Sotatercept (ACE-011) is a novel, activin type IIA receptor fusion protein that binds with high affinity to activin A and GDF11. Sotatercept increases production of erythrocytes through a mechanism independent of erythropoietin. A similar drug, luspatercept, is approved for treatment of anemia in MDS and β thalassemia. Additionally, targeting activin A with an analog of sotatercept reverses osteoblast inhibition and improves MM bone disease in a mouse model (Vallet, PNAS 2010). Sotatercept has been studied with melphalan, prednisolone, and thalidomide in MM (Abdulkadyrov, Br J Haematol 2014). Based on these findings, we evaluated sotatercept with lenalidomide (len) and dexamethasone (dex) and then with pomalidomide (pom) and dex in relapsed/refractory MM (NCT01562405).

Methods: Patients (pts) with relapsed/refractory MM with ≥1 prior line of therapy and hgb < 13 g/dL were eligible. Sotatercept 10, 15, 30, or 45 mg was given s.c. q28 days along with len and weekly dex on a 28 day schedule, with dose escalation following a 3 + 3 design. The protocol was amended to add a dose level of pom with sotatercept 0.5 mg/kg. Sotatercept was held for hgb ≥13 g/dL or grade ≥3 hypertension. Bone mineral density (BMD) was assessed after 4 cycles. Bisphosphonates were not permitted during the study.

Results: We enrolled 33 pts with a median age of 70 (range 49-91) and a median of 2 prior lines of treatment (range 1-5). 15 pts were treated with len and escalating dose levels of sotatercept; an MTD was not reached. 18 pts were treated with pom and sotatercept 0.5 mg/kg. Hematologic adverse events (AEs) (all grade; grade 3-4) out of 33 pts included neutropenia (51%; 27%); anemia (45%; 18%); and thrombocytopenia (27%; 18%). Febrile neutropenia occurred in 2 pts. Common non-hematologic AEs included fatigue (51%; 12%); diarrhea (45%; 12%); hypertension (39%; 12%); upper respiratory infection (36%; 6%); insomnia (36%; 3%). Of the 4 grade 3 hypertension AEs, 2 were at the 45 mg dose level and 1 at 0.5 mg/kg dose level. There was one death on study unrelated to treatment. At 24 weeks, there was a mean increase in hgb by 1 g/dL (p=0.004) in the pom arm (N=12). Among patients who received pom with response, total lumbar spine BMD (N=7) increased 2.6% (p=0.37) at a median of 400 days; total hip BMD (N = 6) increased 2.4% (p=0.007) at a median of 329 days. ORR for the pom combination was 69% out of 16 patients evaluable for response (PR 6, VGPR 2, CR 3), and median PFS was 18.3 months (95% CI 8.31-not reached).

Conclusions: Sotatercept in combination with len and dex or pom and dex is tolerated well with expected toxicities related to the partner drugs. Preliminary data from this study suggest that sotatercept increases both hgb and BMD. Anemia and bone disease are significant causes of morbidity in MM, and sotatercept is one of the first agents acting on the microenvironment that may simultaneously address both problems.

P-043

Prospective assessment of myeloma tumour burden and bone disease using DW-MRI and exploratory bone biomarkers

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Introduction: Key clinical priorities for multiple myeloma (MM) are to reduce tumour burden and complications, of which lytic bone disease is the major cause of morbidity. To guide treatment, there is a pressing need for biomarkers that can accurately quantify tumour burden and bone disease in MM and monoclonal gammopathy of undetermined significance (MGUS). To this end, novel serum and imaging biomarkers - including bone turnover and plasma cell burden markers, and Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) - have been explored, although their role in prospective assessment in MM and MGUS are unclear.
Methods: A total of 67 patients were enrolled (14 newly diagnosed MM, 12 relapsed MM, 15 smouldering MM, 14 MGUS and 12 healthy volunteers) between March 2018 and March 2020. Following recruitment, all participants attended a baseline study appointment and only MGUS/MM patients had follow-up at six months. At each visit, all participants had DW-MRI scan, and MGUS/MM patients additionally had Dual-Energy X-ray Absorptiometry (DEXA) scan and phlebotomy for analysis of serum biomarkers (P1NP, CTX-1, ALP, DKK1, sclerostin, RANKL:OPG, BCMA) and standard myeloma bloods. DW-MRI scans were double reported by Radiologists for Apparent Diffusion Coefficient (ADC) measurements of lytic bone lesion(s), and Myeloma Response Assessment and Diagnosis System (MY-RADS) Response Assessment Category (RAC) scoring. Patients were classified by International Myeloma Working Group (IMWG) response criteria as a clinical correlate of therapy response.
Results: At baseline, there was moderate positive correlation between serum BCMA and paraprotein [r=0.42, p=0.03]. The longitudinal change differed between IMWG-defined therapy responders and non-responders for serum DKK1 [37% decrease vs 11% increase, p< 0.05] and serum BCMA [83% decrease vs 29% decrease, p< 0.01]. On assessment with DW-MRI, there was no correlation between single lesion DW-MRI ADC and paraprotein at baseline [p >0.05]; however, radiological MY-RADS RAC scoring correlated with conventional IMWG response criteria at follow-up [p=0.015]. There was moderate positive correlation between baseline serum sclerostin and bone mineral density at femoral neck [r=0.40, p< 0.01] and lumbar spine [r=0.54, p< 0.001].
Conclusions: Our prospective trial validates DW-MRI-based MY-RADS RAC as a radiological tool to assess therapy response. Whilst previous work has supported single lytic lesion ADC measurements as a correlate of tumour volume, small sample size and prior chemotherapy may have limited our ability to detect this. In comparison, plasma cell burden markers such as BCMA and DKK1 may provide a global measure to quantify myeloma burden at baseline and longitudinally with therapy. Additionally, our data highlight serum sclerostin as a correlate of bone mineral density. Overall, our study highlights radiological and serum biomarkers of tumour burden and bone loss in MM/MGUS, that warrant further exploration to better understand their clinical utility.

P-044

Genetically undetectable and negative minimal residual disease after induction therapy are equally important for survival in multiple myeloma

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Introduction: Cytogenetic abnormalities (CA) identified by interphase fluorescence in situ hybridization (iFISH) has been served as the cornerstone for risk stratification at diagnosis. However, iFISH analyses were generally performed in newly diagnosed and relapsed multiple myeloma (MM) patients, but CA architecture has received little attention in patients after induction therapy. Since it is not the be-all and end-all for everyone to achieve minimal residual disease (MRD)-negativity. iFISH assay may be a good tool to explore the nature of residual PCs and has proven to be a reliable complementary technique for MRD detection. We thus performed iFISH analyses after proteasome inhibitor (PI) or immunomodulatory drugs (IMiDs) induction in our prospective clinical trial.
Methods: A total of 396 newly diagnosed MM (NDMM) patients between January 2014 to March 2020 from the prospective, nonrandomized clinical trial BDH 2014/03 were enrolled in this study. A cohort of 269 patients with iFISH results after induction therapy were analyzed, with 252 of them were immunophenotyped by multiparameter flow

cytometry. Kaplan-Meier method was used to plot survival curves and compared by the 2-sided log-rank test. Multivariable Cox proportional hazard regression was used to assess the impact of variables on PFS and OS.
Results: Persistent high frequencies of CA were observed in residual plasma cells, survival of patients decreased with the increasing clonal size of unique CA. FISH-positive was observed in 118 (43.9%) patients whose any clonal size was more than 10%. FISH-positive patients or MRD-positive patients experienced significantly inferior survival than those without CA or undetectable (< 10-4) MRD. Patients were clustered into four groups according to the iFISH and flow-MRD status: (1) FISH- & MRD- (100/252, 39.7%), (2) FISH+ & MRD- (42/252, 16.6%), (3) FISH- & MRD+ (45/252, 17.9%) and (4) FISH+ & MRD+ (65/252, 25.8%). FISH+ & MRD- patients achieved deeper response depth than FISH- & MRD+ patients, but this did not translate into better survival, regardless of response depth or treatment regimens. Follow-up data suggested a higher MRD-negativity conversion rate of FISH+ & MRD- patients than FISH- & MRD- patients (43.8% vs. 34.1%, p = 0.232), and duration of MRD-negativity was also shortened by persistent CA. A more adverse clonal evolution pattern was observed in FISH+ & MRD- patients according to the longitudinal cytogenetic analyses.
Conclusions: In summary, our study underlines the importance of iFISH examination at post-induction. We demonstrate that patients still have high frequencies of CA after therapy, FISH-positive and MRD-positive confer similar prognostic significance. Repeat iFISH examination showed potential to be a complementary tool to flow-MRD for re-risk stratification of MM patients at post-induction and might be helpful in identifying the resistant clones and guide risk-adapted treatment strategies.

P-045
Minimal residual disease detected by a novel isotope labeled PET/CT combined with next-generation flowcytometry in newly diagnosed multiple myeloma

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Introduction: Minimal residual disease (MRD) plays a vital role in predicting clinical outcomes of multiple myeloma (MM) patients. The mainstream evaluation methods of MRD include next-generation sequencing (NGS), next-generation flowcytometry (NGF) and imaging-based approaches such as positron emission tomography/computed tomography (PET/CT). However, it remains to be solved which method holds the optimal sensitivity and specificity. We previously demonstrated a novel isotope, 11C-acetate (AC) labeled PET/CT was more sensitive for tumor burden in newly diagnosed MM (NDMM) patients. In our study, the sensitivity between AC-PET, traditional 18F-FDG PET and marrow NGF were evaluated in NDMM patients.
Methods: NDMM patients who received standard front-line regimens and reached at least partial response (PR) were prospectively enrolled in our center between 2015.11 to 2021.11. AC-PET, FDG-PET as well as Euroflow NGF MRD assessment, in which threshold of negativity was defined as lower than 1*105 cells, were examined. Characteristics at baseline including international staging system (ISS), cytogenetic abnormalities (CA), treatment and response were collected. Statistical analysis was conducted using SPSS 24.0, with X2 test or McNemar test for Categorical variables, and Kaplan-Meier analysis or COX regression model for survival analysis.
Results: Among the total 54 patients, 42 patients received dual-tracer PET/CT, 10 patients only with FDG-PET and 2 patients with AC-PET. 37 patients underwent PET/CTs and NGF. The median age of the whole cohort was 58.5 years, among whom 53.7% patients were in ISS III and 60.4% with high-risk CA. Autologous stem cell transplantation (ASCT) was performed in 46.3% patients and 90.7% patients reached at least very good partial response (VGPR). Positive MRD was detected in 11 patients by PET/CT. It appeared a trend of superior sensitivity by AC-PET (18.2%) compared with FDG-PET (7.7%) (p=0.14). The paired test of dual-tracer PET/CT scan revealed similar result (p=0.13). All patients receiving NGF achieved VGPR or better, of whom the MRD positivity rate was 40.5% (15/37). Paired test between NGF and PET/CTs demonstrated that NGF was more sensitive for MRD than imaging (p=0.01). Considering progression-free survival (PFS), univariate analysis showed that ISS stage II or III, response not reaching stringent complete response (sCR) and positive MRD by NGF were adverse prognostic factors, with p values of 0.019, $<$0.001 and 0.008, respectively. Cox regression analysis further determined that positive MRD by PET/CT and NGF were both independent prognostic factor.
Conclusions: The novel tracer 11C-acetate-PET is advantageous over traditional 18F-FDG-PET for MRD in NDMM patients after front-line treatment. Compared with imaging approaches, bone marrow NGF with Euroflow panel detect more positive MRD. NGF and PET/CT are both independent prognostic factors predicting PFS. Although different MRD methods are complementary, NGF is preferred to be recommended in clinical practice.

P-046
Maintenance therapy cessation for patients with three-year sustained MRD negative remissions: initial results from a phase II study

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Introduction: Lenalidomide (len) is currently FDA approved drug for maintenance therapy in multiple myeloma (MM). A meta-analysis done by McCarthy et al. confirms an OS benefit with len maintenance vs. observation in MM patients (pts) after ASCT, median OS not reached vs. 86.0 months (HR 0.75; 95% CI, 0.63 to 0.90; p=0.01) (McCarthy JCO 2017). In a study evaluating len maintenance MRD dynamics, pts negative for MRD at 2 years had no recorded progression events past the 2-year landmark after 19.8 months of median potential follow-up (Diamond Lancet Haematol 2021). Herein, we present early results from a phase II study examining the optimal duration of maintenance in sustained MRD negative pts.
Methods: This two-stage study design (n=50) evaluates MRD negative sustainability after ceasing maintenance therapy in eligible pts who have already demonstrated >3 years of durable MRD negative responses. Enrolled pts stop maintenance therapy and undergo active surveillance for three years with bloodwork and office visits every 3 months, bone marrow MRD testing multiparametric flow cytometry (single 10-color tube with limit of detection of at least 6x106 with at least 3 million cell acquisitions, meeting IMWG criteria) every 6 months, and annual PET-CTs. Endpoints include sustained MRD negative rate after 1 year (primary endpoint) and 3 years of cessation, re-treatment responses, microbiome and immune studies, health-related quality of life outcomes, and progression-free survival. Fifteen pts accrue in the first study stage, and if 8 or more remain MRD negative at the end of 1 year, study enrollment continues (n=35).
Results: From February 2020 to February 2022, a total of 21 pts (15 stage 1; 6 stage 2) enrolled onto study. Median follow-up was 12.2 months (0-25). Pts enrolled included 17(81%) male and 4(19%) female, 16(84%) stage I, 2(11%) stage II, 1(5%) stage III, and 2/21 (10%) high-risk cytogenetics [+t(4,14) and t(14,16); +1q21gain]. All pts were previously on len maintenance. For stage 1, 10/12 (83%) remained MRD negative at 12 months of stopping maintenance therapy. One patient converted from negative to positive MRD status at 6 months, demonstrating new FDG-avid bone lesions. A second patient converted at 12 months, opting to restart len maintenance again; follow-up MRD testing is pending. Study accrual is ongoing with enrollment onto second stage. Overall, 6-month MRD negative rate was 16/17 (94%). The 12-month landmark analysis from maintenance cessation demonstrated a PFS rate of 92.3% (95%CI: 56.6-98.9).
Conclusions: Initial first stage results demonstrate feasibility of stopping maintenance in MRD negative sustained pts (>3 years). To our knowledge, this is the first report of employing this strategy in a clinical trial and mature data from the full cohort will help establish guiding posts sustained MRD driven maintenance discontinuation.

P-047

ADVANCE multicenter clinical trial: MRD-driven therapy in newly diagnosed multiple myeloma patients

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Introduction: The use of modern combination therapy in newly diagnosed multiple myeloma patients delivers deep and durable treatment responses in large numbers of patients. Recently, the IFM 2009 and DFCI randomized studies for newly diagnosed patients have shown that MRD negativity 10^-6 translates into similar progression-free survival (PFS) and overall survival (OS) outcomes when comparing patients treated across treatment arms. Delayed transplant does not shorten OS. Here, patients are randomized between 8 cycles of carfilzomib-lenalidomide-dexamethasone with or without daratumumab (i.e. Dara-KRd versus KRd). High-dose melphalan (HDM) followed by autologous stem cell transplant (ASCT) is only offered to patients who remain MRD positive after 8 cycles. MRD negativity is the primary end-point. PFS, event-free survival (EFS), sustained MRD negativity, OS and correlative assays are part of the secondary endpoints. Unique features of this large study include the full integration of whole-genome sequencing, single cell sequencing, and MRD tracking.
Methods: A total of 308 newly diagnosed multiple myeloma patients will be randomized between Dara-KRd or KRd.Enrolled patients are encouraged to collect peripheral stem cells after 4-6 cycles of therapy. For patients who collect stem cells, afterwards they will continue with combination therapy (total of 8 cycles).After completion of cycle 8, patients will be worked up for MRD status (Adaptive ClonoSeq). HDM-ASCT is only offered to patients who are MRD positive after cycles 8. For patients who are MRD-negative, per study protocol, they transition to maintenance therapy with lenalidomide 10 mg daily days 1-21 on a 28 day cycle for a total of 2 years. Per protocol, sustained MRD status will be monitored annually while on maintenance. After 2 years, patient are encouraged to continue on maintenance outside the clinical trial. Patients will remain monitored for PFS, EFS, and OS.
Results: Over 20% of the patients have already been enrolled and we are opening up several sites across the US. at this time. The study is anticipated to open in Europe in the early fall of 2022. Early data confirm and expand our findings from the MANHATTAN trial (JAMA Onc, 2021). Detailed information on feasibility and early results will be presented at the meeting.
Conclusions: The large multicenter, randomized ADVANCE study is open for newly diagnosed multiple myeloma patients across the US. Using MRD testing after completed combination therapy, patients will only be offered HDM-ASCT if they remain MRD-positive after 8 cycles; else, they will keep the collected stem cells (delayed transplant) and move forward with maintenance therapy. The aim of this translational effort is to define the underlying biology of sustained MRD negativity in multiple myeloma patients.

P-048

The value of autologous hematopoietic stem cell transplantation in multiple myeloma patients with MRD negative after early induction therapy

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Introduction: Minimal residual disease (MRD) status has been proved to be a powerful prognostic indicator of multiple myeloma (MM) patients. With the application of new drugs, more and more MM patients can obtain MRD negative after early induction treatment. In this case, whether autologous hematopoietic stem cell transplantation (ASCT) is still valuable in improving the prognosis of MM patients is a question worthy of study.
Methods: 407 newly diagnosed MM patients suitable for transplantation (age≤65 years) were included in this retrospective study, of which 147 achieved early MRD negativity after induction treatment (4-6 courses), while the other 260 were MRD positive.High risk cytogenetic abnormalities (HRCA) included 17p deletion, 1q21 amplification, t(4; 14), t(14; 16), and t(14; 20). Patients were divided into the 0 HRCA group, 1 HRCA group, and 2 + HRCA group (≥ 2) according to the number of HRCA.
Results: 1.The prognosis of patients in MRD negative + ASCT group [median PFS 88.3 months, median OS 90.6 months] was significantly better than that of patients in MRD negative + non-ASCT group (median PFS 46.0 months, median OS 76.4 months), MRD positive + ASCT group (median PFS 42.8 months, median OS 78.8 months) and MRD positive + non-ASCT group (median PFS 22.7 months, median OS 52.3 months) ; 2.Among MRD negative patients, the PFS of ASCT group was significantly better than that of non-ASCT group in 1 HRCA group, 2 + HRCA group and R-ISS stage III patients, but not in 0 HRCA group, R-ISS stage I or II patients. In terms of OS, ASCT group was significantly better than non-ASCT group only in R-ISS stage III patients and 2 + HRCA group; 3.Among the patients with MRD negative, the duration of MRD negative in ASCT group was significantly longer than that in non-ASCT group (median time 58.1 months vs 33.5 months, P = 0.000); 89.1% (57 / 64) of patients in ASCT group had MRD negative duration ≥2 years, while only 49.1% (28 / 57) of patients in non-ASCT group (P = 0.000). Further analysis of different HRCA subgroups showed that ASCT mainly improved the rate of the MRD negative duration ≥2 years in patients with 1 HRCA group (90.6% vs 38.9%, P = 0.000) and 2 + HRCA group (88.2% vs 35.3%, P = 0.001), but not 0 HRCA group (86.7% vs 68.2%, P = 0.198); 4. The prognosis of patients with MRD negativity duration ≥2 years was significantly better than that of patients < 2 years; 5.Univariate and multivariate analysis of the factors affecting the negative duration of MRD showed that ASCT (HR = 0.30, 95% CI 0.16-0.56, P = 0.000) was an independent factor affecting the duration of negative MRD.
Conclusions: Our study showed that in the era of new drug treatment, it was still necessary to do ASCT for MM patients who achieved MRD negativity after early induction treatment, especially those with HRCA or in R-ISSⅢ.MRD negativity duration was a more important prognostic factor than negative MRD, while ASCT was an independent influencing factor in prolonging the MRD negativity duration.

P-049

Detection of multiple myeloma cell load by multiple-color flow cytometry as a useful approach for analyzing immune cell subsets in patients

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Introduction: The disturbance of the bone marrow immune microenvironment was an important mechanism of pathogenesis in multiple myeloma(MM). As important members of the bone marrow microenvironment, immune cells had been studied these years. In our study, we used the intracellular EuroFlow tube to look to identify immune cell subsets, which had never been practiced before.
Methods: Our retrospective study included the analyze of ninety-three newly diagnosed patients with MM and their stage of prognosis, clinical data, response to induce therapy data.
Results: We re-analysed our intracellular Euroflow MM tube containing CD38, CD138, CD56, CD19, CD27, CD45, cKappa, cLambda to look at immune cell subsets.The percentage of B cells and immature B cells were significantly lower in stage III patients than in stage I patients, while the trend was reversed in memory B cells for both the International Staging System and Revised International Staging System. The percentage of naive B cells were significantly lower in patients with severe anemia, while the percentage of memory B cells had reversed trend. The percentage of immature B cells were lower in patients with Cr≥2 mg/dL than in patients with Cr< 2 mg/dL. Similarly, both the percentage of immature B and plasmablast-like cells were increased in patients who achieved very good partial remission(VGPR) after four cycles of drug-based induction therapy. Patients with increased number of B cells and their subsets, specifically immature B and plasmablast-like cells, can be used to predict the response of patients with MM to induction treatment regimes. Additionally, the combination of seven immune subgroups had a better predictive value than any single immune subgroup.
Conclusions: Overall, these results suggested that the MM cell load evaluation by eight-color flow cytometry may be a useful approach for analyzing immune cell subsets and may

act as a potential index for determining the prognosis in patients with MM.

P-050

Detecting of myeloma cell-derived MPs by flow cytometry as a potential strategy to reflect minimal residual disease in MM patients.

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Introduction: Multiple myeloma (MM) is malignant tumor with abnormal proliferation of bone marrow plasma cells. MM-MRD monitoring is mainly through multicolourflow cytometry(Euro-Flow) and second-generation sequencing technology. Existing clinical tools used to determine treatment response and minimal residual disease (MRD) are affected by focal distribution of myeloma cell in bone marrow and the quantity of sample. In previous study, we demonstrated that the counts of Ps+CD138+MPs, Ps+BCMA+MPs, and Ps+CD319+MPs were potential biomarkers for monitoring myeloma cell load, detecting MM-MPs from the plasma as a potential way can overcome the shortage of directly detect of myeloma cell such as focal distribution and sample dilution. Here, we explore the role of detection of myeloma cell derived MPs by flow cytometry in MRD monitoring.
Methods: Bone marrow of MM patients were collected before and after transplantation.Microparticles were isolated by differential centrifugation and detected by flow cytometry (Cyto-FLEX). Mann-Whitney (U) test was conducted for the nonparametric data. MRD positive (Euro-Flow +) patients and MRD negative (Euro-Flow -) patients were compared, and ROC curves were used to identify cutoff points with optimal sensitivity and specificity concerning the counts and ratios of MPs.
Results: Compared with Euro-Flow negative patients, the counts of Ps+MPs, Ps+CD138+MPs, Ps+BCMA+MPs, and Ps+CD319+MPs from Euro-Flow positive patients were significantly increased; Based on the optimal cutoff points determined by ROC curve, 10 post-transplant patients were analyzed. Detecting MPs by flow cytometry to monitor MRD is consistent with Euro-Flow (patient 001, 002, 003, 005, 006, 008, 009, 010). Interestingly, patient 007achieved Euro-Flow (-) (< 0.001%) at 12 months, however, Ps+BCMA+MPs were always positive and Ps+CS1+MPs regained positivity subsequently; patient 004also achieved Euro-Flow (-) (< 0.001%) at 3 months, while the patient's Ps+BCMA+MPs remained positive, then at 6 months, the patient's Euro-Flow had regained positivity and all MPs had turned positive.
Conclusions: Our research showed that in addition to Euro-Flow, MPs counts can be used to monitor MM-MRD. MPs may keep positive in MRD- MM patients by Euro-Flow. In the future, we will continue following up patients who are negative for Euro-Flow but positive for MPs and explored whether detecting MPs can monitor a deeper level of remission than Euro-Flow technology.

P-051

Sustained bone marrow and imaging MRD negativity as indicators to discontinue lenalidomide maintenance after ASCT; preliminary results of a single-center prospective cohort study

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Introduction: Patients with newly diagnosed multiple myeloma (MM), who are eligible for autologous stem cell transplantation (ASCT), are usually treated with induction therapy followed by ASCT and lenalidomide maintenance until disease progression or unacceptable toxicity. Both bone marrow and imaging sustained minimal residual disease (MRD) negativity are significant prognostic factors for both PFS and OS, but yet, they are not used for treatment decisions. A notable proportion of patients on lenalidomide maintenance will remain progression-free in the long-term. In this context, it is important to define the optimal duration and the criteria to discontinue maintenance safely.
Methods: In this prospective cohort study, we included patients with newly diagnosed MM from January 1st, 2016 to December 31st, 2019, who received induction treatment and subsequently underwent ASCT followed by lenalidomide maintenance. MRD status was evaluated in patients who had achieved stringent complete remission (sCR) at 6, 12, 24, and 36 months after the initiation of maintenance. MRD samples were evaluated by next generation flow according to the EuroFlow guidelines. Patients who had at least 3 consecutive MRD negative results and had completed 36 months of maintenance, underwent a PET/CT scan. Those with negative PET/CT discontinued lenalidomide maintenance and MRD was performed every 6 months thereafter. In case of MRD conversion from negative to positive and/or relapse from sCR the patient restarted lenalidomide maintenance.
Results: Overall, 151 patients received induction with proteasome-inhibitor-based regimens (VCD or VRD) and underwent ASCT. During a median follow-up of 60.5 months (range 47-74 months), 44 (29.1%) patients had disease progression and 20 (13.2%) patients died. Out of 107 patients

who did not progress or die, 34 (31.7%) patients achieved sustained bone marrow MRD negativity and imaging MRD negativity at 3 years and thus they discontinued lenalidomide maintenance, according to study schedule. Their median age at MM diagnosis was 56.5 years (range 43-64). Twenty (59%) patients were males, whereas 19 (56%) had IgG, 9 (26%) had IgA and 6 (18%) had light-chain MM. Six months after discontinuation of lenalidomide maintenance, all evaluable patients (n=21) were found to be MRD negative, while 12 and 18 months post-lenalidomide discontinuation 82% of patients continued to be MRD negative. Two patients restarted treatment with lenalidomide monotherapy after converting from MRD negative to MRD positive at 12 months following the initial completion of maintenance. Both patients remain MRD positive and have no evidence of disease progression at 8 months after lenalidomide restart.
Conclusions: We conclude that sustained MRD negativity at 3 years post-ASCT and lenalidomide maintenance might help in the decision to stop maintenance treatment, although this has to be proven in prospective randomized clinical trials. Close follow-up with consecutive MRD testing can trace an early myeloma relapse.

P-052
Measurable residual disease (MRD) dynamics during maintenance with ixazomib vs placebo in 1280 newly diagnosed multiple myeloma (NDMM) patients: a pooled analysis of the TOURMALINE-MM3 and -MM4 trials

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Introduction: There are promising yet scarce data on the value of MRD assessment during continuous or fixed-duration maintenance. By contrast, there are minimal data on MRD status during observation. Paradoxically, maintenance and observation are the settings where MRD status is anticipated to help tailor treatment duration. We investigated the prognostic value of MRD dynamics over time in patients (pts) with NDMM receiving ixazomib or placebo maintenance.
Methods: Pts were randomized 3:2 to receive maintenance with ixazomib vs placebo for up to 2 years (26 cycles). Bone marrow aspirates were collected from all pts in complete response (CR; and/or very good partial response in TOURMALINE-MM3 only) at randomization, cycle 13, and end of treatment. MRD status, assessed by 8-color flow cytometry with a median limit of detection of 7.4x10-6, was available at randomization in 1280 pts. Pts with < CR who were missing MRD data were imputed as MRD+. Progression-free survival (PFS) was analyzed based on MRD dynamics over time, landmarked at 14 and 28 months.
Results: MRD status at randomization was an independent prognostic factor for PFS, with a median of 38.6 vs 15.6 months in MRD– vs MRD+ pts (hazard ratio [HR] 0.47). The prolonged PFS observed with MRD– vs MRD+ status was consistent in nearly all pt subgroups. Paired assessments of MRD status at randomization and during maintenance were evaluable in 1166 pts. The 14-month landmark analysis demonstrated prolonged PFS in pts converting from MRD+ to MRD– status (n=58) vs those with persistent MRD+ status (n=365), with 2-year PFS rates of 76.8% vs 27.6%. PFS was also prolonged in pts with sustained MRD– status (n=114) vs those converting from MRD– to MRD+ status (n=50), with 2-year PFS rates of 75.0% vs 34.2%. There was an increased risk of progression and/or death in pts who had converted from MRD– to MRD+ status vs those with sustained undetectable MRD (HR 3.31; p< 0.001), and in pts with persistent MRD+ vs those who had converted from MRD+ to MRD– status (HR 3.72; p< 0.001). Similar results were noted in the 28-month landmark analysis. Ixazomib maintenance improved PFS vs placebo in pts who were MRD+ at randomization (median 18.8 vs 11.6 months; HR 0.65; p< 0.001) and at the 14-month landmark (median 16.8 vs 10.6 months; HR 0.65; p=0.003); no difference was observed in pts who were MRD–.

Conclusions: This is the largest multiple myeloma dataset ever reported evaluating yearly MRD status during maintenance. Four main conclusions emerged from this study: 1) MRD status is dynamic, and its prognostic value increased considerably with periodic vs single assessment; 2) the favorable prognosis of undetectable MRD was similar if achieved before or during maintenance, and thus it can become a relevant endpoint in this setting; 3) loss of MRD– status vs sustained MRD– status markedly increases the risk of progression; and 4) treatment with ixazomib vs placebo improves the PFS in pts who were MRD+ at randomization or at the 14-month landmark in these studies.

P-053

A systematic review of measurable residual disease (MRD) assessment characteristics in myeloma trials from 2015-2020

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Introduction: Implementation of effective treatment combinations in multiple myeloma (MM) has led to increased response rates and improved survival over the last years. As survival of patients with newly diagnosed MM (NDMM) has improved, there is a need for prolonged follow-up to evaluate for progression free or overall survival benefit. Achievement of measurable residual disease (MRD) negativity is prognostic for progression free survival and has been suggested as a surrogate endpoint for drug approval. However, the landscape of MRD assessment in MM clinical trials has not been comprehensively assessed to date.
Methods: Here, we examined the use of MRD in 607 interventional MM trials from 2015 through 2020, utilizing data from clinicaltrials.gov. For studies that included MRD assessment in the database, an additional manual online search strategy was employed to identify published trials and publicly available trial protocols at time of writing.
Results: Of the 147 trials that contained MRD assessment (24.2% of all trials), 15 included MRD as part of the inclusion criteria, 36 (24.4%) as a primary endpoint, and 92 (62.6%) as a secondary endpoint. Nine trials (6.1%) employed MRD as a stratification tool to determine treatment. A total of 77 trials (52.4%) specified methodology of MRD assessment (i.e., flow cytometry versus sequencing). Among the 77 studies that did report method of MRD assessment, 29/77 (19.7%) used flow cytometry, and 37/77 (25.2%) NGS. A total of 36 trials (24.5%) specified sensitivity of MRD testing, which ranged from 1/104 to 1/106 cells. Of the 147 trials, 80 (54.4%) had reported results at the time of writing (54 abstracts and 26 peer-reviewed articles), of which 60 (75%) mentioned MRD assessment. For the studies that did not specify method/sensitivity on clinicaltrials.gov, published data provided clarification on the method (19/35, 54.2%) or sensitivity (23/54, 42.6%). Studies with MRD assessment were more likely to be Phase 2 (Ph2) (49.7% vs 31.1%, p< 0.001) or Ph3 (22.4% vs 7.0%, p< 001) and less likely to be Ph1 (12.9% vs 36.5%, p< 0.001). Studies that assessed MRD were more likely aimed at NDMM (32.7% vs 14.8%, p< 0.001) or to involve maintenance therapy (10.9% vs 5.2%, p=0.02) and were more likely randomized (37.4% vs 22.4%, p< 0.001). There was an upward trend in the proportion of trials utilizing MRD assessment from 13.0% in 2015 to 29.3% in 2020.
Conclusions: In conclusion, use of MRD as an endpoint of clinical trials in MM has increased between 2015 and 2020 and was present in 24.2% of studies overall. Recent trials have begun to incorporate MRD in decision making, with the prospect of treatment individualization. However, there was significant heterogeneity in MRD assessment, including methodology, assay sensitivity, and reporting of results. Although efforts have been made to standardize this, the current landscape of trials limits the use of MRD in clinic beyond prognostic assessment.

P-054

Neoplastic plasma cells in stem cell collection have no effect on the survival of multiple myeloma patients receiving autologous stem cell transplantation

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Introduction: Autologous stem-cell transplantation (ASCT) is considered as the standard of care for transplant-eligible multiple myeloma patients (TEMM), but no randomized trials have assessed the optimal number of induction cycles or the ideal depth of response required before ASCT. Whether it can lead to the presence of tumor cells in stem cell collection (SCC) without complete response (CR) before ASCT and impose negative impact on survival is being debated. Here we evaluated the effect of the minimal residual disease (MRD) of SCC on TEMM.
Methods: We analyzed clinical data of 90 MM patients undergoing ASCT between January 1, 2013 to June 1, 2021 in our hospital. MRD evaluation of both BM and SCC were carried out at the same time before ASCT. Response assessment was defined according to International Myeloma Working Group criteria. MRD was evaluated by multiparameter flow cytometry (MFC) with 10-5 sensitivity. Time from ASCT to disease progression was defined as

modified progression-free survival (mPFS) and time from ASCT to death as modified overall survival (mOS).
Results: Ninety patients met the inclusion criteria. The median age was 54 and 62.2% were males. 25 had high-risk cytogenetic abnormalities determined by FISH with the presence of at least one of t (4;14), t (14;16) or del (17p). Before ASCT, the percentages of MRD negativity in BM and SCC were 31.1% and 76.7%. By comparing the MRD-positivity status with different sensitivity and numeric levels of tumor cells, we found the percentage of patients with MRD-positivity in SCC was much less than that in BM, regardless of sensitivity ($P < 0.001$). The median follow-up was 26.8 months. The achievement of negative MRD in BM before ASCT was associated with longer mPFS (P=0.0094, 55.88m vs 34.17m) but not mOS (P=0.11, NR vs. 58.86m). Patients with different MRD status in SCC experienced the similar mPFS (P=0.937, 40.54m vs. 76.45m for negativity vs. positivity) and mOS (P=0.884, NR vs. 58.86m for negativity vs. positivity). Patients were divided into 3 groups according to MRD status, namely MRD negativity in BM and SCC (Group A, 32.3%), MRD positivity in BM and SCC (Group B, 23.3%) and MRD positivity in BM but negativity in SCC (Group C, 44.4%). Patients in Group A had better mPFS (P=0.047, median mPFS, 55.88m vs. 34.17m vs. 27.11m, for Group A, B, C), but mOS (P=0.53, median mOS, NR vs. 58.88m vs. 58.61m for Group A, B, C) showed no statistical difference. In patients achieving CR for best response, the presence of MRD negativity predicted longer survival compared with MRD positive CR and VGPR or less in mPFS ($P < 0.0001$, median mPFS, 55.88m vs. 24.74m vs. 27.10m) and mOS (P=0.0064, median mOS, NR vs. NR vs. 41.65m).
Conclusions: We discovered little association between MRD status in SCC before ASCT and survival prognosis in MM patients. It is reasonable to carry out ASCT when TEMM patients achieve PR. MRD negativity after ASCT can be a more valuable predictor of outcome compared with other prognostic factors for MM.

P-055
Monitoring the emergence of multiple myeloma high-risk subclones with whole-genome sequencing of circulating tumor cells

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Introduction: Multiple Myeloma (MM) develops from well-defined precursor stages, however, invasive bone marrow (BM) biopsy limits screening and monitoring strategies for patients with indolent disease. Circulating tumor cells (CTCs) are malignant cells that extravasate from the primary BM site to the peripheral blood (PB), and therefore amenable for repeatable enrichment, enumeration, and molecular characterization, for early detection, real time monitoring and assessment of treatment response and clonal evolution. Here, we present a novel technique, MinimuMM-seq, for Minimally Invasive Multiple Myeloma sequencing, which leverages advancements in tumor cell enrichment techniques, low-input sequencing, and tailored cancer genomics, for systematic genomic profiling of pathognomonic MM events from rare, highly pure CTCs.
Methods: Peripheral blood from 40 patients from the Dana-Farber Cancer Institute observational PCROWD study (IRB #14-174) was collected and processed on the CellSearch system (Menarini Silicon Biosystems) and enriched based on CD138+CD38+CD19-CD45- phenotype. After DNA library construction, whole-genome sequencing (WGS) data was processed on a cloud-based system for detection of copy number events, mutations, and translocations with the Cancer Genome Analysis pipeline from the Broad Institute. Tumor phylogeny was reconstructed with the PhylogicNDT algorithm in patients with matched CTC and BM sequencing (n=17), and serial CTCs derived from PB only (n=8).
Results: MinimuMM-seq yielded a median tumor purity of 98% (range, 45 to 100%) in CTCs. Our method was able to detect 100% of clinically reported BM biopsy events by fluorescence in situ hybridization (FISH), including translocations and copy number events, and could replace molecular cytogenetics for diagnostic yield and risk classification. A full agreement in MM pathognomonic events was found between the matched sequencing of BM and CTCs, with additional yield over FISH found in 15/17 (88%) of patients. Being unbiased, our method also enabled detection of driver mutations including in TP53 and RAS genes. In 8 patients with longitudinal sampling, we validated the stability of major clone, and describe shifting dynamics of subclones over time with emergence of potentially high-risk subclones bearing MM events over 33 months (e.g. del(13q)). Anecdotally, one SMM patient received early interventional treatment, and we describe selection of the new fittest clone bearing KRAS p.G12S mutation with our minimally invasive method before any resistance was clinically observed.
Conclusions: In this study we established an approach enabling WGS of CTCs to replace standard molecular cytogenetics. CTCs harbored the same MM abnormalities as BM plasma cells. Longitudinal sampling of CTCs was able to track clonal dynamics over time and detect emergence of high-risk genetic subclones. Our findings provide proof of concept that CTC detection and genomic profiling could be used clinically for monitoring and managing disease in MM.

P-057
Studying microRNAs from extracellular vesicles as potential biomarkers in liquid biopsies of multiple myeloma patients

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Introduction: Extracellular Vesicles(EVs) can be found in human biological fluids and carry cargo from their cell of origin,thus being a potential source of cancer biomarkers.The miRNAs packaged into EVs(EV-miRNAs) have been studied for their potential as biomarkers of drug resistance/response to treatment and as biomarkers of minimal residual disease(MRD) in Multiple Myeloma(MM).We aimed to quantify miRNAs from the cargo of EVs isolated from the peripheral blood(PB) and bone marrow(BM) of MM patients,at diagnosis and remission stages,to verify the potential of analysing EV-miRNAs as biomarkers in liquid biopsies of MM patients.
Methods: EVs were isolated by size-exclusion chromatography,concentrated by ultrafiltration,and characterized according to their size and concentration,morphology,protein concentration,and presence of EV-associated protein markers.Afterwards,miRNAs were isolated with the miRNeasy Serum/Plasma Advanced Kit,from 3 patient BM and PB diagnostic and remission samples.The TaqMan Advanced miRNA cDNA Synthesis Kit was used for cDNA synthesis. miRNAs levels were assessed with TaqMan Advanced miRNA Assays probes.Two miRNAs (miR-145-5p and miR-143-3p), previously found by us to be differentially expressed in the free form in PB and BM samples of MM patients,which was related to treatment response(unpublished results),were analysed.miR-185-5p,stably expressed among samples,was used for expression normalization.The Livak Method and the Mann-Whitney U test were used to determine statistical differences in the normalized relative expression of miR-145-5p and miR-143-3p among EVs from PB and BM samples at different disease stages.
Results: A statistically significant difference was found between the levels of both EV-miRNAs in the PB and BM samples at diagnosis,with higher levels being detected in the BM(3-fold higher for miR-145-5p and 15-fold higher for miR-143-3p).At remission,there was no statistically significant difference in the levels of these EV-miRNAs found in PB and BM patient samples.
Conclusions: Our preliminary work showed that it is possible to successfully isolate and quantify miRNAs from EVs isolated from PB and BM samples of MM patients,at both diagnosis and remission stages.The miR-145-5p and miR-143-3p have been previously associated with inhibition of proliferation,migration and invasion,by targeting different mRNAs,and can be associated to better treatment response in MM and gastric cancer.Our preliminary results indicate that at diagnosis there are statistically significantly higher levels of both EV-miRNAs in BM than in PB.Nonetheless,at remission this statistical difference in BM and PB EV-miRNAs levels was not verified,probably reflecting the effect of drug treatment.These preliminary results need to be validated in a larger number of samples but suggest that caution should be taken when interpreting the levels of EV-miRNAs on PB liquid biopsies from MM patients. ACKNOWLEDGEMENT:Authors acknowledge Celgene/BMS for providing funding to this work(Grant138800). *Authors equally contributed to this work.

P-058

Identifying microRNAs as potential biomarkers of drug resistance in multiple myeloma patients: proof-of-concept study

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Introduction: Over the last years, treatment of Multiple Myeloma(MM) presented significant improvement, with

better survival outcomes. Nonetheless, a small percentage of patients do not respond to initial therapy and are considered to have primary refractory MM. There are no specific biomarkers, and the current treatment algorithm fails to identify these patients. The microRNAs are key regulators of several cellular pathways, targeting several mRNAs, including some coding for proteins involved in drug response in cancer. Since microRNAs can be found in blood plasma, they are promising candidates as MM biomarkers. Our study aimed to identify circulating microRNAs in the plasma of MM patients, with potential use as non-invasive biomarkers of drug resistance.
Methods: This study included 14 newly diagnosed MM patients treated upfront with immunomodulators, proteasome inhibitors and steroids. Treatment response was assessed according to the International Multiple Myeloma Group recommendations. Peripheral blood(PB) and bone marrow(BM) samples were collected simultaneously and before treatment. The microRNAs were isolated with the miRCURY™ RNA Isolation Kit and were profiled by Next Generation Sequencing(NGS) using the Ion Total RNA-Seq kit v2 protocol. Results from NGS for the microRNAs found to be differentially expressed between PB and BM samples, and between samples from responders and refractory, were confirmed by quantitative real-time PCR.
Results: We identified 8 patients as drug refractory, and 6 as drug responders to the upfront therapy. By NGS, we found different expressions of microRNAs between PB and BM, and between responders and refractory patients. 4 microRNAs(miR-145-5p, miR-186-5p, miR-143-3p, and miR-214-3p) were found more expressed in BM, and one microRNA(miR-203a-3p) was found less expressed in BM compared to PB. Moreover, 2 microRNAs(miR-483-5p and miR-665) were more expressed in both PM and BM of refractory patients compared to responders. The same expression trend was obtained by quantitative real-time PCR.
Conclusions: Our work demonstrated that it is possible to isolate microRNAs from PB and BM of patients with MM. In addition, our proof-of-concept results suggest that the levels of specific circulating microRNAs may become promising biomarkers to be used for the early identification of patients with possible refractory disease, allowing to adjust their therapeutic strategy accordingly. Of the identified microRNAs, miR-483-5p was previously known to be upregulated in MM and associated with neoplastic plasma cell proliferation and escape from apoptosis(1). Likewise, miR-665 targets BLC2, MAPK3 and STAT3 mRNAs, and is known to be associated with resistance to immunomodulators and proteasome inhibitors(2). Future work will validate these results in a larger cohort of MM patients and investigate the role of these differentially expressed microRNAs in drug resistance. References:1)Qu X.et al.,Med Oncol.2014;31(10):219.2)Rastgoo N.et al., J Hematol Oncol.2017;10(1):121.

P-059
Chemotherapy-induced transcriptional reprogramming of multiple myeloma revealed by single-cell RNA sequencing

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Introduction: Multiple myeloma (MM) is a hematological malignancy with clonal expansion of malignant plasma cells (PCs) in the bone marrow. Despite substantial improvement in developing targeted therapeutics, MM remains an incurable malignancy, with most patients relapsing and dying from the disease. Drug-induced changes may have the potential to reveal important insights into the mechanisms in action of chemotherapeutics. Therefore, there is an urgent need to understand the molecular mechanisms underlying the drug response, disease heterogeneity and progression, and to identify more efficient targets for therapeutic treatment in MM.
Methods: We isolated mononuclear cells from the bone marrow (BM) or peripheral blood (PB) of 3 healthy donors and 10 newly diagnosis MM (NDMM) patients with paired samples before and after 2 cycles of bortezomib-cyclophosphamide-dexamethasone (VCD) treatment. Totally, 22 BM samples and 22 PB samples were collected and then subjected to single-cell RNA-sequencing (scRNA-seq) using the GemCode system (10x Genomics). A total of 25,231 PCs and 216,209 immune cells were captured and downstream analysis was performed majorly using Seurat R package.
Results: We observed multiple common malignant pathways in myeloma cells compared with normal PCs, and found substantial inter and intral-tumoral heterogeneity across MM driven by diverse signatures. We compared baseline and post-treated myeloma cells in BM, and found that exposure to VCD promoted transcriptional changes in tumor cells with decreased ER stress and IL6-STAT3 signaling, while increased NF-kB signaling and anti-oxidative stress. We observed that MM with inferior response upregulated myeloma stem cell-like signature and downregulated multiple genes associated with plasma cell identity and immune response, relating to drug resistant and prognosis.
Conclusions: Our findings reveal distinct transcriptional reprogramming during chemotherapy and key pathways that underlies drug sensitivity. Specifically, significant up-regulation of anti-oxidative stress after treatment, and manifestation of a stem cell-like phenotype in non-responder MM, suggest tumor-mediated escape mechanisms in early drug responding.

P-060
Pathogenic germline mutations in a large cohort of multiple myeloma

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Introduction: Multiple Myeloma (MM) is an incurable disease with no known associated germline high penetrant risk gene. The higher risk of MM among affected relatives suggests a genetic contribution to the etiology. To date, 24 common risk variants with low effects have been identified using genome-wide association studies, which account for 17% of heritability. However, a systematic analysis of the known rare alleles in cancer predisposition genes has not been undertaken so far in MM. We collaborated with six other academic centers across the United States to identify and select cases for analysis of genetic predisposition of MM.
Methods: We performed whole exome, next-generation sequencing of 2,387 germline myeloma cases. We called 1.5 million variants and performed standard quality control of the data. We analyzed 7,351 rare, coding variants in 90 clinically relevant or putative candidates for cancer predisposition. We then used the automated variant curator PathoMAN to annotate and assert pathogenicity of each variant. We contrasted our results with assertions of pathogenicity from ClinVar.
Results: Overall, we observed 109 pathogenic or likely pathogenic variants in these individuals. These included rare, singleton variants, and recurrent founder mutations. Across 31 germline cancer susceptibility genes we observed 201 high or moderate penetrant alleles. Overall, 8.4% of myeloma patients harbored a pathogenic variant in these known/putative cancer predisposition genes. Predominant group of pathogenic variants were observed within CHEK2 (19%), TP53 (8%), and ATM (5%). Our preliminary results suggest that known genes of cancer susceptibility also play a role in myeloma predisposition.
Conclusions: : In a large cohort of multicentric MM cases, we have identified a significant proportion of individuals who are carriers of known (solid) cancer predisposition. The study shows that these cancer predisposition genes are also relevant in a subset of MM cases. Further analyses of carriers versus non-carriers is ongoing in order to understand the differences in treatment and outcomes.

P-061
Differential expression profile and bioinformatic analysis of serum exosomal miRNA in multiple myeloma patients

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Introduction: Multiple Myeloma (MM) is a hematological malignancy characterized by the clonal expansion of malignant proliferation of plasma cells in the bone marrow. Moreover, the proliferation of MM cells highly dependent on the BM microenvironment. MicroRNA (MiRNAs) are short, noncoding RNAs that regulate gene expression at the posttranscriptional level. MiRNAs carried by exosomes plays pivotal roles in the crosstalk and signal transferring between malignant cells and non-malignant cell, which involved in the pathogenesis of MM. Here, we investigated the exosome miRNA profiling in peripheral blood serum of MM patients, and compared with healthy donors. Bioinformatics analysis was utilized to clarified the molecular pathways associated with exosome miRNAs via their target genes. Furthermore, a prognostic model based on exo-miRNAs was constructed in MM.
Methods: The serum samples including six newly diagnosed MM patients and four healthy donors were analyzed. Exosome in serum were isolated and miRNA profiling were investigated. Differential expression of miRNAs in exosomes was calculated between MM patients and HDs using the edgeR package. STRING and CytoHubba were applied to identify the hub miRNAs and core mRNAs. The exosomal miRNA-mRNA regulatory network was constructed. Functional enrichment of the core target gene was implemented using Metascape. Differential expression of hub miRNAs was verified in another 13 MM and 5 HD samples . Multivariate Cox analysis of hub miRNAs was utilized to construct a novel prognostic model based on the six hub miRNAs.
Results: In the present study, we found 71 differentially expressed exo-miRNAs between MM patients and healthy donors, and 2,906 target mRNAs by 71 exo-miRNAs were predicted. GO and KEGG analysis of target mRNAs showed that they were involved in biological processes including endoplasmic reticulum protein processing and ubiquitin-mediated protein degradation. TOP six hub exo-miRNAs were obtained according to the MCC score. The 106 critical differentially expressed target genes of the six top exo-miRNAs were identified, and the TOP 40 key genes were selected according to the MCC score. Among them, 25 genes were correlated with poor prognosis of MM patients. Pathway enrichment analysis of the TOP40 genes showed that enriched in the IGF1-Akt signaling pathway, Hippo signaling pathway, and MAPK cascade. Moreover, cytokine-related signaling pathways correlated to tumor immunity were enriched as well. Differential expression of hub exo-miRNAs was verified in another 13 NDMM and 5 HD samples. Multivariate Cox regression analysis of six hub microRNAs showed that the 6 exo-miRNAs-based signature could be utilized to construct a prognostic model.
Conclusions: In this study, 71 differentially expressed serum exo-miRNAs between MM patients and HD were clarified, and which were involved in the crosstalk and signal transfer

in the MM pathogenesis.. A novel 6 exo-miRNAs-based prognostic model was constructed to fruther stratify MM patients.

P-062
MAF translocations are enriched in high-risk NDMM patients with elevated levels of circulating tumor cells suggesting a genetic basis for the aggressive disease course

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Introduction: A subset of Multiple Myeloma (MM) patients responds poorly to treatment, highlighting the need to understand the pathobiology of high-risk MM. The correlation between aggressive disease and elevated levels of circulating tumor cells (CTCs) has been recognized. We recently identified a subset of high-risk newly diagnosed MM (NDMM) patients based on a transcriptomic classifier derived from patients with high levels of CTC, indicating that CTC levels are a relevant reflection of tumor cell biology. We hypothesized that comparing bone marrow plasma cells (BM PCs) of MM patients with high and low CTC levels will provide an opportunity to identify mechanistic drivers of aggressive disease.
Methods: Single cell transcriptomes from 111,045 PCs were generated of BM PCs of 22 NDMM patients and 5 paired peripheral blood PCs.
Results: Paired analysis of CTCs and BM PCs revealed large transcriptional overlap, with only 25 differentially expressed genes. These analyses confirm the previously described transcriptomic resemblance between PCs from both compartments and excludes the presence of circulating aggressive subclones in patients with high CTC levels. Next, we compared single cell transcriptomes from BM PCs from patients with high (>0.5%) and low (0.004-0.006%) percentages of CTCs. Based on cell cycle analyses an increase in cycling PCs (53% vs 32%, p=0.007) was associated with high CTC levels. Ki67 labeling of BM biopsies validated this finding. Interestingly, proliferation was increased across all plasma cell clusters, suggesting a common cell-intrinsic mechanism such as genetic background. To analyze whether the prevalence of genetic lesions associated with proliferation is increased in patients with high CTC levels, WGS was performed on the same 22 patients. This revealed an elevated mutation burden and a predilection for MAF translocations in 50% (4/8) of the patients with high CTC levels vs none in the patients with low CTC levels (0/14). We also observed increased transcription of cyclin D2 (CCND2), CCR1 and IntegrinB7 in patients with high CTC levels. These proliferation or tumor survival genes have been shown to be increased in patients with t14;16, a translocation also resulting in overexpression of MAF. To validate these findings in a larger patient cohort, clinical, genomic and CTC data were retrieved from the MMRF-CoMMpass database. Strikingly, 21% of patients with CTC levels above 0.3% showed MAF translocations vs only 3% of patients with CTC levels below 0.3% (p< 0.001), solidifying the correlation between MAF translocations and high levels of CTCs in NDMM patients with a high risk disease profile.
Conclusions: Single cell RNA sequencing and WGS of plasma cells from patients with high and low CTC levels identified a correlation between CTC levels and overrepresentation of MAF translocations in NDMM patients. This finding suggests that MAF target genes and downstream proliferation could be drivers of aggressive disease and might be used for future patient stratification.

P-063
The independent adverse prognostic significance of 1q21 gain in newly diagnosed multiple myeloma patients

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Introduction: 1q21 gain is a common karyotype abnormality in multiple myeloma, the positive rate of Chinese patients is higher, up to 40% - 60%. If 1q21 gain is included in poor prognostic factors, it will greatly increase the proportion of high-risk patients. So, the prognostic significance of 1q21 gain in newly diagnosed multiple myeloma patients (NDMM) is controversial. This study focused on analyzing the clinical characteristics, treatment response and prognostic significance of NDMM with 1q21 gain .
Methods: In a VRD registration study in our clinical center, 248 NDMM in the first affiliated hospital of Soochow university were retrospectively analyzed. According to the detection by FISH, 135 cases (54.4%) were with 1q21 gain. The difference of clinical characteristics, treatment response and prognosis between the total patient population and 1q gain subgroup were analyzed. The CD138 sorted samples of 153 patients were checked to go deeply into the involved gene changes by cytoscan.
Results: Compared with patients without 1q gain, patients with 1q gain (54.4%) were prone to anemia, hypoalbuminemia, renal insufficiency, high lactate dehydrogenase and higher proportion of R-ISS stage III. 1q21 gain is more likely to be combined with 13q14 deletion and t (4; 14) . The patients with 1q21 gain detected by cytoscan involving CKS1B gene had a higher proportion of complex karyotype and CNV abnormalities, accompanied with 1p32 deletion significantly, and were all middle and high-risk groups by PI definition (P< 0.0001). 1q21 gain patients had shorter PFS (P=0.0266) and shorter OS , P< 0.0001. 1q gain was an independent adverse factor affecting PFS and OS by multivariate analysis（PFS：HR＝2.207，95%CI 1.219～3.993，P＝0.009；OS：HR＝2.721，95%CI 1.138～6.507，

P＝0.024）. The PFS of 1q21 amplification（≥ 4 copies） was shorter than that of 1q21 gain（3 copies）(the median PFS was 24 months vs not reached, P = 0.0156), but the difference of OS between two groups was not clinically significant by now (the median OS was not reached, P=0.2808). The size of 1q21 gain clone including 5-19%, 20-49% and ≥50% subgroups, had no clinical significance in PFS and OS, but the prognosis of 1q21 gain in the main clone was significantly worse than that of patients in the subclone. ASCT can effectively improve the survival time of patients with 1q21 gain.
Conclusions: The patients with 1q21 gain have obvious end-organ injury and higher tumor burden. They are easy to be combined with a variety of cytogenetic abnormalities such as 1p32-, 13q14-, t (4;14), characterized by complex karyotypes. Among them, patients with 4 copies and more of 1q21 amplification had a worse PFS than patients with 3 copies , and the median PFS was only 24 months. 1q21 gain clone size didn't affect the prognosis, while the prognosis of 1q21 in main clone patients was significantly worse than that of subclone. 1q21 gain was an independent high-risk cytogenetic factor for the poor prognosis of newly diagnosed multiple myeloma.

P-064
Evaluation of single nucleotide variants of CDKN1A, TP53BP, and XRCC1 genes in multiple myeloma patients undergoing hematopoietic stem cells transplant and their association with treatment response

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Introduction: Multiple myeloma (MM) is a frequent hematological neoplasm, in which the use of high-dose melphalan (HDM) followed by hematopoietic stem cell transplantation (HSCT) improved the response and survival. The variability of responses to HDM is under investigation. However, there is little evidence of the effect of single nucleotide variants (SNV) in genes that code for proteins involved in DNA repair. Aims: To determine the association of SNV in CDKN1A (rs1801270 C >A), TP53BP1 (rs560191 G >C), and XRCC1 (rs25487 A >G) genes, with the response rate 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 Hospital de Clínicas "Dr. Manuel Quintela", Uruguay, who received HDM and HSCT as first-line consolidation therapy. Genomic DNA was extracted from blood samples using Quick-DNA™ Miniprep Kit (Zymo research). The regions containing each SNV were amplified by PCR and sequenced by Sanger methods. Sequences were analyzed by alignment using BioEdit software. We used SPSS v.26 for the statistical analysis. Descriptive statistics included quantitative and qualitative variables; represented by a median with interquartile range (IQR), and percentage, respectively.
Results: We included 17 patients with a median age of 57 years (IQR 12.5), 52.9% males, and 58.8% IgG. Regarding risk stratification 41.2% were ISS1, 35.3% ISS2, and 23.5% ISS3. The most frequent induction regimen was VCD at 47.1%, followed by CTD at 23.5%, and VTD at 17.6%. Maintenance therapy was used in 64.7% (81.8% receiving lenalidomide). The frequency of alleles observed for the variant rs25487 were GG 47.1% and GA 52.9%, for rs1801270 CA 47.1% and CC 47.1%, and for rs560191 CC 11.8%, GC 29.4%, and GG 58.8%. All patients achieved at least partial response at HSCT. After induction, the patients with the rs25487 GA genotype achieved a less proportion of ≥VGPR (66.7% vs 87.5% GG), whereas a higher rate of ≥VGPR was observed in patients with the SNV rs1801270 CA (87.5% vs 66.7% CC) and rs560191 CC/GC (80% vs 71.43% GG). After HSCT, the response was improved in patients carrying rs25487 GG (66.7% vs 42.9% GA), rs1801270 CC (85.7% vs 16.7% CA), and rs560191 CC/GC (71.43% vs 33.3% GG).
Conclusions: SNV in XRCC1, CDKN1A, and TP53BP may influence clinical outcomes in MM patients. The SNV genes involved in DNA single-strand and double-strand breaks repair, XRCC1 and TP53BP, respectively, may be associated with a higher proportion of improvement in response after HDM and HSCT, which is congruent with the melphalan mechanism of action. On the other hand, maintaining the reference allele in CDKN1A achieved an improvement in response after HSCT. However, as these are preliminary results, including a reduced number of patients, we cannot establish strong conclusionsFunding: This investigation was conducted with funding by the IMS, and Paula and Rodger Riney Foundation

P-065
Development of a mass cytometry-based toolkit to investigate myeloma therapeutic responses ex vivo

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Introduction: Cytometry time of flight mass spectrometry, CyTOF, is an established metal isotope-tagged, ligand-based proteomic technology platform that enables in-depth characterization of cellular populations and phenotypes at single-cell resolution. We have previously applied this technology to establish antibody panels that allow unprecedented deep phenotyping of the bone marrow immune microenvironment responses in the multiple myeloma (MM) phase 1b/2a CC220 (iberdomide) trial (NCT02773030) of heavily pre-treated RRMM patients. We reasoned that development of a myeloma cell-centred CyTOF panel, capturing cell surface and intracellular proteins, could (i) provide substantial additional information on myeloma cell therapy responses to novel CELMoDs and (ii) be applicable in mechanistic studies to understand resistance and response mechanisms in a wider context of myeloma research.
Methods: We designed and validated a CyTOF antibody panel including cell surface markers from the Euroflow panel to identify normal from malignant plasma cells, and checkpoint and MM surface markers TACI, FCRL5, CD137L, PD-L1, SLAMF7 and BCMA. We also included markers of intracellular response and signalling pathways comprising transcription factors (c-MYC, IKZF1, IKZF2, IKZF3, IRF4, TP53, FOXM1), proliferation and cell cycle (MKI67, CCND2, p16, p21, PLK1), and MM apoptosis and survival factors (ZFP91, HDAC6, CK1a, CASP9, MCL1, BCL-XL, BCL2, BCL6, BIRC5). Where information on antibody specificity was not available, we utilized a strategy of knockdown and heterologous overexpression of targets to identify suitable antibodies. Antibodies were custom labelled using the MaxPar metal isotope labelling kit (Fluidigm).
Results: We applied the CyTOF panel to different research scenarios; outcomes are as follows: (i) In the CC220 clinical trial setting, the panel provides information on MM clonality and shows degradation of Cereblon E3 ligase targets in MM cells, thus supporting the underlying mode of action and efficacy of 3rd generation CELMoDs against multi-refractory MM. (ii) Using isogenic MM cell lines sensitive and refractory to IMiD® agents and proteasome inhibitors, we show phenotypic differences between sensitive/refractory MM cells, e.g. loss vs. retention of Cereblon-mediated degradation targeting in IMiD-refractory cells. (iii) In target identification efforts (such as prolyl-tRNA synthetase, others) we demonstrate utility of the panel to assess and rationalise inhibitor effects.
Conclusions: The development of a mass cytometry panel to rapidly assess MM phentotypic responses shows utility in a broader MM research environment. We are developing a combined mass cytometry panel of MM, immune, stromal and bone markers for evaluation of spatial interactions in trephine biopsies. We are currently embedding these panels into a wider strategy including single-cell sequencing to derive a systems-based biomarker toolkit to characterise therapeutic MM responses.

P-066

Identification of novel driver SPANXD and preferential loss of arginine codons in multiple myeloma

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Introduction: Diverse mutations have been mapped in Multiple Myeloma (MM) genome, some of which aid in risk stratification/ prediction of clinical outcomes. Nonsynonymous (NS) mutations, in particular, may transform protein structure / function and turn them oncogenic or unresponsive to therapy. This study has focused on NS mutations, patterns of amino acid substitutions and their possible functional and clinical impact in MM.
Methods: Whole exome sequencing (using Nextera Exome library prep kit) was performed on malignant plasma cells (PCs) obtained from 109 PCPD patients including 71 MM patients. Mutational variants were called with Illumina Dragen pipeline. Nonsynonymous (NS) mutations and corresponding amino acid conversions were analyzed with dN/dS. Abcam's L-Arginine assay kit was used to measure circulating arginine levels in plasma
Results: A median tumor mutation burden of 1.5 with 15967 total NS mutations across 7874 genes (including 106 oncogenes, 148 tumor suppressor genes) was observed. The most common median substitution was C>T (43.%) followed by T>C (18 %), C>A(9%) and others. The mutational signatures linked with age (SBS5, SBS1, ID8) were most common (>80%) followed by defective DNA mismatch repair related SBS15 (22%) and APOBEC related SBS2/SBS13 (4%). Amino acid conversions due to NS mutations revealed a selective net loss of arginine specific codons (CGG(73%)> CGC(66%)> CGA(47%)> CGT(35%)>AGG (32%)>AGA (22%)). The circulating arginine levels in plasma of such patients were also significantly reduced from a median of 30 to 24 micromoles (p=0.03). Additional codonic net losses of alanine, proline while codonic net gains of cysteine, histidine were also observed. Kaplan Meier curve analyses showed a significant correlation between no loss of arginine with inferior PFS (p=0.012). Arginine is a key player in cell metabolism and supports growth and survival of malignant cells. If there is no loss of arginine, its continued abundance would tend to favor tumor progression and thus inferior outcomes. The dNS/dS analysis identified a novel potential driver SPANXD (Sperm Protein Associated with the Nucleus on the X chromosome-D). Ten missense mutations were observed recurrently across 4 sites in exon 2 and additional silent, intronic, splice and UTR3 mutations were also found in this gene. SPANXD is a cancer testis antigen and an attractive target for cancer immunotherapy. Somatic variations in this gene have been implicated to have a moderate effect in NCI-TCGA in solid tumors (prostate, kidney, oesophagus, skin, breast, etc) and warrants further evaluation in MM.

Conclusions: This is the first study to show a selective net loss of arginine codon usage in MM and its clinical impact on PFS. A targeted deprivation of Arginine in the tumor microenvironment is a potential therapeutic modality under trials in certain cancers but has not been deeply investigated in MM. The second novel finding of this study is identification of oncogene SPANXD as a potential driver of MM.

P-067

Systematic functional characterization for loss of function events cooperating with TP53 loss in high-risk 17p13(del) multiple myeloma

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Introduction: Del(17p), a high-risk subset of multiple myeloma (MM), remains a major clinical challenge, and is typically associated with double-hit lesions of TP53. Interestingly, deletion of chr17p is predominantly monoallelic and often involves a large part of the p-arm. TP53 is, thus, often co-deleted with several other genes whose biological consequences remain unknown. This study aims to dissect the biology of hemizygous del(17p) MM and identify other 17p-resident tumor suppressor genes (TSG).
Methods: We applied systematic in silico approach for the selection of candidate genes. We analysed public MM patients' datasets to identify the common region of deletion. We utilised the DepMap portal to exclude essential MM genes and performed survival analyses and copy number-expression level association study. Together with literature search, we shortlisted our candidates to final two. For in vitro assays, we performed CRISPR-based loss-of-function and overexpression gain-of-function studies to elucidate the functional role of the candidate genes in its cell autonomous state and in the context of standard-of-care therapeutics.
Results: While CoMMpass patients with double-hit TP53 had the shortest overall survival, those with hemizygous del(17p) without mutations on the remaining TP53 allele also displayed inferior outcome, underscoring the importance of the intact WT copy. Comparison of del(17p) events vs without, saw that at the genome-wide level, 98% of the top 100 differentially downregulated genes were residents of chr17p. Two of the top hits were SAT2 and ZBTB4, which we selected for further functional characterization. Both genes exhibit recurrent DNA copy number losses, that significantly correlated with their mRNA level in MM, compared with other cancers on CCLE, suggesting a putative preferential loss in MM. Transcript levels for both genes were closely associated with patients' survival in various independent patient datasets. Functionally, individual CRISPR-KO of SAT2 and ZBTB4 conferred growth advantage to the cells whereas overexpression abrogated the growth suppressive phenotype and enhanced apoptotic potential. In their responses to therapeutics, bortezomib washout assay and longitudinal lenalidomide exposure saw the SAT2-KO and ZBTB4-KO cells maintaining the growth advantage over their untreated control counterpart, highlighting their potential role in treatment resistance and relapse.
Conclusions: The inferior outcome conferred by hemizygous 17p loss suggests that inactivation of both TP53 alleles may not be sufficient to recapitulate the full biological effect of monoallelic del(17p) and that concomitant loss of other putative TSGs may play a role. In our study, SAT2 and ZBTB4 demonstrated potential roles in regulating growth and responses to therapeutics in MM. Our study unveiled the greatly underappreciated biological component of the high-risk del(17p) MM. Further studies involve the basis for the potential cooperating function of TP53 loss with SAT2/ZBTB4.

P-068

Relating subclonal mutational shifts with progression of multiple myeloma

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Introduction: Mutational landscapes of MM evolve continuously from pre-diagnosis to progression. The malignant plasma cells tend to evolve resistance and progress through branching clonal evolution. This study has investigated patterns of co-occurring mutations/ subclones and their correlations that may facilitate myelomagenesis.
Methods: The MMRF CoMMpass WES dataset available for 76 patients at multiple time points was processed sequentially through CNVkit, Quantum Clone and FishplotR for assessment of clonal evolution for every patient. The data was further analyzed for cellular prevalence, pairwise subclonal correlations and gene pathway enrichment.
Results: About 72% patients progressed through branching pattern of evolution where both clonal gains and losses were observed simultaneously. A few gene mutations (e.g., in BIRC3, ATR, ALK, TET2) were found exclusively at diagnosis while mutations in other genes (like JAK2, FLT4, KMT2A) were found only at progression. Other genes such TP53, NRAS, BRAF were found mutated at both diagnosis and progression. Predominant driver / actionable genes like NRAS, TP53, BRAF, MAGI3 underwent maximum clonal gains while others such as LAMA1, PTPRF had most clonal losses. Unique patterns of clonal gains or losses were observed in patient groups with different cytogenetic aberrations. The % clonality of some genes dropped with progression (e.g., LOXHD1) while it increased for others (MAGI3, TUSC3 etc.). Significant Pearson correlation was found between co-existing paired gene mutations/ subclones such as TP53+SYNE1 ($p=0.003$, $r= 0.365$), NRAS+MAGI3 ($p=0.023$, $r=0.283$) and KRAS+TP53 ($p=0.07$, $r= 0.228$). On the contrary, gain of other genes such

as FCGBP coincided with reciprocal loss of FAT3 (p=2.969E-10, r = 0.689). The topmost KEGG pathways that were perturbed at diagnosis included, Lysine degradation, ABC transporters, Adherens junction while those altered at progression included MAPK signaling, apoptosis etc. Hence, oncogenic dependencies corresponding to specific double hit gains/ losses of correlative or anticorrelative mutant gene pairs were identified that could impact progression.
Conclusions: Myelomagenesis proceeds predominantly through branching clonal evolution. The mutational profiles at diagnosis are different than at progression. Regular monitoring of druggable/ actionable gene targets of clinical relevance can aid early and personified treatment of patients. Multiple and simultaneous clonal shifts interact and drive clonal progression. Significant correlation exists between clonal gains or losses during progression. Double hits of clonal shifts or their mutual exclusivities within same or different subclones may synergize or antagonize oncogenic pathways and either promote or demote myelomatogenesis.

P-069
The observed genomic instability in myeloma is driven by functional co-operation between apurinic/apyrimidinic nuclease (APEX) and RAD51

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Introduction: Multiple myeloma (MM) is associated with a marked increase in genomic instability that arises early during oncogenesis, allowing the cancer cells to evolve toward greater proliferation and drug resistance. Homologous recombination (HR) contributes to genomic instability, and its key mediator is RAD51, but it is also affected by APEX1, an important nuclease in base excision repair. In fact, we've already shown that APEX1 binds to P73 at the RAD51 promoter to upregulate RAD51 expression. Therefore, we investigated whether there are more mechanisms by which APEX1 and RAD51 interact to induce genomic instability in MM.
Methods: RAD51-knockdown was mediated by lentivirus-based shRNAs and APEX1-overexpression by plasmid carrying APEX1 open reading frame. Homologous recombination was assessed using a strand exchange assay. Genomic instability was monitored using single nucleotide polymorphism arrays as well as by flow cytometry-based micronucleus assay. AP Sites Quantitation Kit (Cell Biolabs Inc.) was used to assess abasic sites.
Results: We observed that the overexpression of APEX1 in MM cells significantly increased the acquisition of genomic gains and losses over time and also increased the number of abasic sites, which are mutagenic and can lead to further increase in genomic instability. RAD51-knockdown in APEX1-overexpressing cells prevented the increase in genome instability, and surprisingly, also the increase in abasic sites. Interestingly, exposing MM cells to MMS, a chemical that induces abasic sites, led to more RAD51 foci. Treatment of MM cells with methoxyamine, a small molecule that binds to abasic sites and blocks their access to APEX1, inhibited MMS-induced RAD51 foci, suggesting that MMS-induced RAD51 foci formed on abasic sites and that RAD51 mediates their increase in numbers by blocking their access to APEX1, which would otherwise repair them. Furthermore, inhibitors of either RAD51 or APEX1 reduced HR activity, the number of abasic sites, and genomic instability in myeloma cells, as assessed by a micronuclei assay. The combination of these inhibitors had a stronger impact on stabilizing the MM genome. Transgenic suppression of APEX1 or RAD51 also induced apoptosis in MM cells, and the fraction of cells undergoing apoptosis was significantly increased following combined suppression of these genes. Small molecule inhibitors of APEX1 and RAD51 also synergistically inhibited MM cell viability and induced apoptosis. Consistently, we observed that APEX1 inhibition synergistically increases the efficacy of chemotherapeutic agents in MM cells.
Conclusions: We demonstrate that functional interaction between RAD51 and APEX1 contributes to the dysregulation of the HR and base excision repair pathways, drives genomic instability, and prevents apoptosis in myeloma cells. Combined inhibition of these genes could reduce evolution as well as the growth of MM cells.

P-070
A pleiotropy scan on multiple myeloma survival

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Introduction: The prognosis of multiple myeloma (MM) patients is very heterogeneous. Known factors like cytogenetic alterations and minimal residual disease do not explain all the observed prognostic heterogeneity. Germline genetic polymorphisms could play a role. Only two MM overall survival (OS) loci have been identified so far by genome-wide association studies (GWAS). This unsuccess might be partly explained by the stringent significance threshold used in GWAS ($p< 5x10-8$), which accounts for the many statistical tests being performed. Reducing the number of tests conducted will relax the required significance threshold, thereby increasing statistical power to detect associations with MM for each SNP. Recent GWASs have

identified thousands of loci robustly associated with human phenotypes, among which several pleiotropic ones, i.e. showing an effect on multiple traits. Based on the hypothesis that pleiotropic variants have a higher probability of association with other traits, we performed a scan to identify new loci associated with MM OS.
Methods: We used two discovery datasets (the InterLymph Consortium and the German GWAS) and a replication dataset (the International Multiple Myeloma rESEarch (IMMEnSE) consortium), with respectively 1277, 1030 and 1110 MM cases. The SNPs were selected using the GWAS Catalog (https://www.ebi.ac.uk/gwas/), that includes variants associated with at least one human phenotype in a GWAS at a significance level of p< 10-5. After filtering, we found 65,536 unique SNP-trait associations (p<5.0x10-8). In the first phase of the study we analyzed the selected variants in the InterLymph and German GWASs. Promising SNPs were genotyped in IMMEnSE. Survival analysis was performed with Cox proportional hazards regression, calculating hazard ratios (HR) and 95% confidence intervals (CI), using OS as endpoint. Results of the discovery and replication datasets were meta-analyzed.
Results: A total of 972 SNPs showed an association with MM OS (p< 0.05) in both discovery datasets. After filtering by linkage disequilibrium, we chose the 7 SNPs with lowest p-values for replication in IMMEnSE. None of the SNPs were significantly associated with MM OS in IMMEnSE. However, rs28613487 was significantly associated in the meta-analysis performed with the three datasets, with no heterogeneity between studies (HR=1.39, 95% C.I. = 1.22-1.57, p= 2.19x 10-7). This association remained statistically significant after correction for multiple testing. This SNP is located on chromosome 2q36.3 and was originally reported to be associated with body mass index.
Conclusions: The T-allele of rs28613487 showed a solid association with poor prognosis of MM in the meta-analysis and therefore could potentially represent a novel survival locus. To the best of our knowledge, with a total of 3417 cases, this is the largest study aimed at discovering the role of germline polymorphisms in MM prognosis

P-071
Exonuclease 1 co-operates with a pyrimidine synthetase to drive growth and genomic instability in multiple myeloma

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Introduction: Human EXO1 is a 5'–3' exonuclease with multiple roles in DNA repair and replication including DNA end resection, a key step in the initiation of homologous recombination (HR). Because HR mediates genomic instability in MM, we investigated EXO1 as a potential target
Methods: EXO1 expression in normal PBMC and MM cell lines was evaluated by Western blotting and activity monitored by a fluorescence-based assay. EXO1 knockdown was done using shRNA. Cell viability was done using CTG assay, DNA replication by EdU incorporation, and apoptosis by annexin-labeling. EXO1 protein complexes were identified using mass spectrometry. HR was assessed using a fluorescence based exchange assay. DNA breaks were estimated by using anti-H2AX antibody. Genomic instability was evaluated by micronucleus assay.
Results: We found that most MM cell lines (n=20) have elevated EXO1. In patient cohort (MMRF dataset), high expression of EXO1 correlated with poor overall and event free survival. EXO1 activity was elevated in all 8 MM cell lines tested. EXO1-knockdown in MM1S cells led to a time-dependent loss of EXO activity, resulting in >80% inhibition at day 9, and a loss of cell viability. Relative to control, the percentage of cell death in RPMI, MM1S, MM1R and U266 cells was ~95%, 85%, 60% and 40%, respectively. Apoptosis after treatment with two different shRNAs targeting EXO1 was 47.6% and 55.2% compared to 11.9% in control. Cells undergoing DNA replication in H929 cells after EXO1 knockdown was ~34% in control vs. 21% in knockdown cells, suggesting a role for EXO1 in MM cell replication. To understand the mechanisms of EXO1's impact on MM cell replication, we used mass spectrometry to identify proteins interacting with EXO1 in two different MM cell lines (MM1S and H929). One of the most prominent hits was CAD, which is involved in pyrimidine biosynthesis, and its binding was confirmed with co-immunoprecipitation. In two different non-cancerous cell types (HS5 and normal fibroblasts), we found that EXO1-overexpression increased the growth rate, whereas suppression of CAD reduced it. Importantly, suppressing CAD in EXO1-overexpressing cells completely reversed the EXO1-mediated increase in cell growth and inhibited DNA replication. The percentage of apoptotic HS5 cells was reduced ~2-fold following EXO1-overexpression, whereas it increased by ~5-fold following CAD suppression. Suppression of CAD in EXO1-overexpressing cells increased apoptosis by 3-fold. These data demonstrate that CAD is required for EXO1-dependent cell proliferation and survival. Furthermore, suppressing EXO1 in MM cells inhibited DNA end resection, DNA breaks, HR activity and genomic instability, as assessed by micronucleus assay, whereas overexpression of EXO1 in normal cells increased these processes, and CAD is required for all.
Conclusions: We postulate that EXO1 and CAD work in coordination to accomplish both DNA replication and repair. Both processes are vulnerable in myeloma, making this interaction therapeutically promising.

P-072
Single cell RNA sequencing reveals intrapatient multiple myeloma subpopulations with contrasting phenotypes and clinical behaviors

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Introduction: Multiple Myeloma (MM) is an incurable blood cancer due to enduring populations of residual cells that persist through treatment and inevitably develop drug resistance. The advent of single-cell technologies enabled increasingly granular evaluation of MM, with studies focusing on between-patient comparison. In this project, we followed subpopulations of MM cells across serial samples in a high-risk patient at diagnosis, first relapse and upon development of IMiD, proteasome inhibitor and monoclonal antibody refractory disease to interrogate the relationship between risk stratification, subclonal evolution and the development of multi-drug resistance.
Methods: We investigated the intra-patient heterogeneity of MM by single cell RNA sequencing (scRNAseq) of unsorted bone marrow aspirates from one patient at diagnosis, first relapse, and multi-drug-refractory time points. In parallel, we profiled ex vivo responses to the key clinically available anti-myeloma agents using myeloma drug sensitivity testing (My-DST, Walker et al. Blood Advances 2021). The gene expression profiles of the MM subpopulations were contextualized by applying their signatures to the Multiple Myeloma Research Foundation (MMRF) and GSE24080 databases.
Results: The study patient had R-ISS stage 3 disease, with t(8;14) and gain of chromosome 1q, and survived less than 2 years after diagnosis. Serial sample scRNAseq identified two subpopulations of MM. The larger population at diagnosis (MM1, 92% of MM cells), led to early relapse after induction treatment. The smaller population at diagnosis (MM2, 8%) was undetectable at first relapse, and recurred in the treatment-refractory sample. Prevalence of these subpopulations could be inferred through the patient's course by free kappa light chain (MM1) and M-protein (MM2) levels, as MM1 displayed a light chain- only phenotype with complete lack of IGH expression. In parallel, ex vivo drug sensitivity profiling with flow cytometry identified subsets of MM cells differentiated by CD46 (RNA FC = 1.41, p = 3.99x1023), showing relative IMiD resistance in MM1 at diagnosis, and triple-class drug resistance in MM2 at the refractory timepoint. Strikingly, MM1 overexpressed the osteolysis-driving gene LAMP5, and timepoints with light-chain only relapse corresponded exactly with spikes in the patient's serum calcium. Both MM1 and MM2 shared characteristic expression with the hyperdiploid 15++ MYC subtype in the MMRF dataset, while the MM1 subpopulation also shared expression with the 1q+ subtype.
Conclusions: Concurrent transcriptomic and phenotypic profiling of single cells identified unique MM subpopulations within a single patient, corresponding to distinct genotypic subclones. These subpopulations exhibited differential proliferative, osteolytic and drug resistance behaviors. These findings demonstrate the ramifications MM heterogeneity can have on clinical behavior and treatment outcomes in multiple myeloma.

P-073

Single-cell analysis of multiple myelomas refines bortezomib treatment responsiveness

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Introduction: Both the tumor and tumor microenvironment (TME) are crucial for pathogenesis and chemotherapy resistance in multiple myeloma (MM). Bortezomib, commonly used for MM treatment, works on both MM and TME cells, but innate and acquired resistance may develop.
Methods: By single-cell-RNA-sequencing (scRNA-seq), we investigated bone marrow aspirates of 18 treatment-naïve MM patients who later received bortezomib-based treatments.
Results: Twelve plasma cell populations (normal and malignant) and TME cells were identified. Suboptimal responders (SORs) exhibited higher copy number alteration burdens than optimal responders (ORs). Forty-four differentially expressed genes for SORs based on scRNA-seq data were further analyzed in an independent cohort of 90 treatment-naïve MMs, where 24 genes were validated. A combined model of three clinical variables (older age, low absolute lymphocyte count, and no autologous stem cell transplantation) and 24 genes were associated with bortezomib responsiveness and poor prognosis. In T cells, cytotoxic memory, proliferating, and dysfunctional subsets were significantly enriched in SORs. Moreover, we identified three monocyte subsets associated with bortezomib responsiveness and an MM-specific NK cell trajectory that ended with an MM-specific subset. The scRNA-seq predicted interaction of GAS6-MERTK, ALCAM-CD6, and BAG6-NCR gene networks. Of note, tumor cells from ORs and SORs were the most prominent sources of ALCAM on effector T cells and BAG6 on NK cells, respectively.
Conclusions: Our study identified cellular subsets, gene signatures, and interactions of tumor and TME for bortezomib responsiveness, indicating that single-cell markers in both tumor and TME besides clinical variables are essential for predicting treatment responsiveness in MM.

P-074

Exploring batch effect in single-cell data integration in a multi-center multiple myeloma immune atlas initiative

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Introduction: Multiple myeloma (MM) is a complex disease in which interactions between malignant plasma cells and the bone marrow microenvironment (BME) can greatly influence the prognosis. To characterize the complexities of the immune landscape in MM, we are building the Multiple Myeloma Immune Atlas, generating the single-cell RNA landscape of samples derived from bone marrow biopsies collected both at diagnosis and following therapy. Currently, we have processed 330 scRNA-seq samples from 236 patients; data was generated across four different medical centers and universities, including Emory University, Mount Sinai Medical Center, Mayo Clinic Rochester, and Washington University in St. Louis. To minimize variations between sites, a common sample processing protocol was developed and utilized by all centers performing single-cell profiling and analysis.
Methods: To investigate the batch effect among single-cell data generated at different centers, we assessed the clustering and embeddings of forty samples, ten per site. One sample from each site is a common reference from the same patient, while the remaining are from different patients who responded to RVd therapy. After preprocessing and normalization, the batch effect in cellular clusters was evaluated by calculating the adjusted rand index (ARI). The site-dependent ARI calculation ranges from zero, indicating minimum batch effect between cell types and processing site, to one, indicating significant batch effect. Embeddings and clusters were generated with Uniform Manifold Approximation and Projection and Louvain clustering.
Results: Clustering and embeddings with all cell types depicted minimal site-dependent clustering, with cells from lymphoid and myeloid lineages forming distinct clusters irrespective of the processing site. The BME clusters had a site-dependent ARI of 0.008, demonstrating that the variance between major cell compartments is much greater than the variance in processing sites. Interestingly, malignant plasma cells formed patient-specific clusters, highlighting the heterogeneity of MM. Further sub-clustering into more granular cell types detected a subtle batch effect between the processing sites. For example, T-cell subclusters had a site-dependent ARI of 0.1, that is variance between processing centers is influencing the clustering. Standard batch correction methods, such as Harmony, LIGER, and fastMNN, can correct for this batch effect, reducing the ARI for T-cell subclusters to 0.012, 0.005, and 0.04, respectively.
Conclusions: As part of the Multiple Myeloma Immune Atlas, we are building a standard scRNA-seq preprocessing and batch correction pipeline to handle the hundreds of bone marrow samples with more than 500000 cells. This subset of data shows that a standardized sample processing workflow has helped mitigate the variance between processing centers and suggests that with this approach, remaining batch effects in more granular clusters can be easily mitigated with standard batch correction methods.

P-075
CD200 expression in multiple myeloma is regulated by P53 and exerts its function as immune checkpoint on T cells via DOK2

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Introduction: CD200 is a membrane glycoprotein expressed in many hematological malignancies including multiple myeloma (MM). However, the mechanism of CD200 expression in cancer cells is largely elusive. CD200 and its cognate receptor CD200R are known to serve as immune regulators in myeloid-derived immune cells. CD200R is also expressed on T lymphocytes and is stipulated to mediate inhibitory signals, yet the mechanism of inhibition is unclear. In this study, we investigate the role of CD200 in immune escape by MM cells and seek to unravel the mechanism of inhibition in T lymphocytes.
Methods: Surface expression of CD200 on primary patient-derived MM cells and MM cell lines was assessed by flow

cytometry. Co-culture experiments of CD3/CD28-stimulated healthy donor T cells and CD200+/- MM cell lines were analyzed using luciferase assay or flow cytometry. To elucidate the downstream signaling of CD200R activation, CD3/CD28-stimulated T cells were co-cultured overnight with CD200+/- MM cell lines and re-isolated with CD3-positive isolation for Western blotting. To detect potential effector cascades involved, Western blotting and/or intra-cellular phospho-flow cytometry were performed. CD200 expression in MM cell lines upon Nutlin-3a treatment was quantified by real-time PCR (RT-PCR).
Results: CD200 surface expression was detected in more than 70% of patient-derived MM cells (n=97). In contrast, the MM cell lines tested (n=9) did not show any endogenous CD200 surface or cytoplasmic protein expression nor detectable CD200 mRNA levels. Hence, stable expression of CD200 on MM cells was obtained using a Sleeping Beauty transposon vector system. We observed up to 50% increase in MM cell survival upon CD200 expression in co-culture with primary T cells as assessed by both flow cytometry and luciferase-based cytotoxicity assay. CD200R signaling in myeloid-derived immune cells is known to inhibit the MAPK pathway by recruiting docking protein-2 (DOK2). In CD3/CD28-stimulated T cells, we observed an increase in phospho-DOK2 levels in presence of CD200 along with a reduction in phospho-levels of ERK1/2, STAT3 and ZAP70. Moreover, in TP53 wildtype MM cell lines, we observed an increase in CD200 mRNA levels by RT-PCR upon Nutlin-3a treatment while in patient-derived primary MM cells (n=103), a positive correlation between wildtype TP53 status and CD200 surface expression could be established.
Conclusions: Our study shows that the CD200/CD200R axis plays a functional immune inhibitory role in MM. CD200 expression on MM cell lines reduces primary CD3+ T cell-mediated cytotoxicity via a DOK2-mediated inhibitory signaling mechanism in T lymphocytes. Moreover, our data suggest that CD200 expression may be dependent on P53 in MM cells.

P-076
Network topology analysis reveals unique multiple myeloma genomic subtypes and potential new therapeutic targets

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Introduction: A range of genomic aberrations predicts prognosis in multiple myeloma (MM), including copy number variation (CNV), mutational processes, and structural variation. Recent studies have subtyped MM by genomic information, but no study has explored these abnormalities together with a global assessment of gene interactions. Network topology analysis integrates complex interactions to define patterns of biological behavior not captured by individual genomic events. We hypothesize that incorporating gene interaction networks will delineate biologically relevant MM subtypes and potential new therapeutic targets.
Methods: We overlaid RNA-Seq and CNV data from the MMRF CoMMpass dataset (IA19) on a gene interactome using a novel graph metric of network robustness — Ollivier-Ricci curvature (ORC). ORC considers both local and global connectivity in assessing the robustness of each pathway characterized by feedback loops. Positive ORC implies a gene is “hub-like,” whereas a negative indicates “bridge-like” behavior. The resulting ORC matrix was fed into hierarchical agglomerative clustering to identify subtypes based on the pattern of local curvature, with the optimal number of clusters determined by silhouette score. Clusters were characterized based on genetic composition, with Kaplan Meier analysis of progression free survival (PFS).
Results: RNA-Seq and CNV data were available for 659 patients. Gene interactions were determined by protein-protein interactions from the Human Protein Reference Database (HPRD), resulting in a network with 8,468 nodes and 33,695 edges. The ORC analysis using RNA-Seq data resulted in 6 clusters which differentiate PFS ($p=0.00161$, multivariate log-rank). Clusters predicting the best and worst PFS were associated with specific genomic features including CCND1 and MAF/MAFB translocations, respectively (each $p< 0.05$, Fisher’s exact test). The most robust connections were those involved in DNA-damage repair, encoding for histone acetyltransferases, NFKB regulation and CCND1. These include TP53-ATM, TP53-NFKBIA, TP53-EP300, TP53-CREBBP, CCND1-RB1 and CCND1-EP300. The most fragile connections include: IRF4-PRDM1, NRAS-PIK3CA, MAF-EP300 and MAF-CREBBP, potentially highlighting therapeutic vulnerabilities.
Conclusions: The analysis of CNV data on HPRD resulted in 8 clusters which differentiate PFS ($p=0.0082$, multivariate log-rank). Genomic features associated with the clusters included hyperdiploidy, CCND1 (longest PFS) and MAF-translocations, and APOBEC-activity (shortest PFS) (each $p< 0.05$, Fisher’s). The worst PFS cluster had a higher prevalence of chromothripsis ($p=< 0.0001$, Fisher’s), known to be a strong predictor for MM survival. Together, these results suggest that while “hub-like” nodes reflect redundancies in cancer cell signaling, “bridge-like” nodes may represent therapeutic vulnerabilities. Ongoing studies will explore changes in edge fragility under therapeutic pressure in MM, aiming to define dynamic risk categorization incorporating gene interactions.

P-077
Multiple myeloma genomic landscape explored by dimensional scaling technique highlights the presence of 1q&13+ patients with specific genomic, transcriptional and clinical features

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Introduction: The risk of Multiple Myeloma (MM) is hardly predictable, due to the complexity of interactions between factors that, at a different extent, might influence patients' clinical outcome. The up-front identification of early relapsing/refractory patients (pts) still represents an unmet clinical need. We employed descriptive evolutionary statistics and non-linear dimensionality reduction approaches to define biological meaningful MM pts' subgroups and to evaluate the clinical impact of specific genomic configurations, aiming at the definition of biology-based risk stratification models to be implemented in clinical practice.
Methods: Genomic landscape of 513 newly diagnosed (ND) MM pts was deeply explored by SNPs array and by FISH. Bioinformatics and biostatistics analyses were performed by R language. Results were validated on WGS and RNAseq data from 840 NDMM pts (CoMMpass dataset).
Results: By dimensional scaling techniques, we explored the relationships between all the genomic variables detected in NDMM and clustered pts according to their own genomic complexity, not just according to the presence of the most recurrent aberrations. Three main, partially overlapping pts' clusters, allocated along crossing axis were generated. The presence of either hyperdiploidy (HD) or t-IgH identified pts in opposite clusters; a third one, perpendicular to the HD-t-IgH axis, included pts carrying both 13q CN losses and 1q CN gains (named 1q&13+) suggesting a variance from the well-known HD-t-IgH stratification. By quantifying the alterations recurrence among pts' population and the complexity of the genomic carrying the tested alterations, we evaluated the probability of early onset of the different chromosomal aberrations and we showed that both 13q CN losses and 1q CN gains were the top earliest ones, along with t-IgH and odd-numbered trisomies. Gene expression profiles of 1q&13+ pts highlighted the differential expression of 301 genes, with the most significantly up and down regulated being CCND2 and CCND1, a pattern confirmed also by excluding all pts carrying t-IgH. 1q&13+ pts displayed well-known baseline high-risk features (e.g. ISS stage 3, Albumin< 3.5 g/dL, high CMMCs count) and their PFS and OS were significantly shorter than those of other pts (5-year PFS: 22% vs. 37% vs. 47%, p< 0.0001; OS: 50% vs. 74% vs. 78%, p< 0.001 for 1q&13+, 1q/13, 1q&13- pts, respectively), independently from the presence of either t(4;14)(p16;q32) or del(17p) (multivariate Cox analysis).
Conclusions: In conclusion, the use of dimensionality reduction techniques allowed to elaborate and model all the possible, unsupervised interactions between any MM chromosomal alterations, thus highlighting a previously unrecognized, independent 1q&13+ cluster, characterized by a peculiar expression profile and bad prognosis.
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P-078
Targeted sequencing in a diverse real-world cohort of multiple myeloma patients reveals pathogenic mutations of likely germline origin in BRCA2 and other DNA damage repair genes

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Introduction: Most individuals harboring a pathogenic germline variant (PGV) in a hereditary cancer gene (HCG) are unaware of their genetic predisposition & are not identified for preventive interventions despite their increased cancer risk. 5-15% of cancer patients carry PGV, & targeted sequencing (TS) of the tumor can lead to incidental discovery of unsuspected PGVs (PMID 26787237). We previously showed that 6% of MM patients carry moderate-to-high penetrance PGV in DNA damage repair (DDR) genes. The aim of this study is to assess the rate of detection of pathogenic mutations of likely germline origin in a diverse, real-world cohort of MM patients undergoing TS.
Methods: We retrospectively reviewed results of 1769 commercial NGS panels performed by a single genetic testing laboratory on bone marrow aspirates of 1213 MM patients treated at our institution since 2015 who were not enrolled in the MMRF CoMMpass study. Mutations were considered to be probable PGVs when all of the following criteria were met: 1) variant found in a curated panel of 106 well-established hereditary cancer genes, but excluding genes with high rate of somatic mutations in MM (e.g. TP53); 2) variant reported in ClinVar as pathogenic or likely-pathogenic (P/LP) by 2 or more CLIA-certified labs; 3) variant allele frequency (VAF) >30% in all available test reports for a given patient. We conducted a gene-level burden analysis of MM patients in this cohort against healthy gnomAD controls.
Results: 59% of patients were male. Median age at MM diagnosis was 61 (range 25-93). 58% were White, 19% Black, 19% Hispanic. 100 MM patients (8.2%) were found to have a heterozygous P/LP mutation meeting criteria to be classified as a probable PGV. 56 distinct variants were identified in 28 HCGs, and 46 (82%) involved DDR genes. Probable PGVs in BRCA2 were significantly enriched in the MM cohort as compared to gnomAD controls (OR=14, 95% CI 2.8-66, FDR p = 0.005). Probable PGVs in PALB2 & FANCI were 4-5 fold more common in the MM cohort, but the enrichment did not reach significance after adjusting for multiple comparisons. These

findings are consistent with those of our prior study, which identified BRCA2 as a potential susceptibility gene in MM, & also showed enrichment of PGVs in PALB2 & FANCI. After exclusion of founder variants, carriers of probable PGVs were more likely than non-carriers to be diagnosed before age 40 (11 vs 4%, p=0.07). There were no significant differences in ethnicity between carriers & non-carriers.
Conclusions: Targeted sequencing of bone marrow aspirate in MM patients incidentally detected P/LP variants of likely germline origin in HCGs in 8.2% of cases. As in our prior study, mutations in DDR genes were common, & BRCA2 variants were significantly enriched as compared to controls. In MM patients undergoing TS, detection of a mutation involving a HCG with a VAF >30% should prompt referral to genetic counseling for confirmatory testing, as PGV detection can have clear implications for patients & their families.

P-080
The mosaic microenvironment of myeloma bone marrow trephine mapped by deep learning

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Introduction: Bone marrow trephine biopsies contain rich information on the cellular, morphological, and spatial architecture of tumour and immune microenvironment that could help us understand diseases such as multiple myeloma. However, the high complexity of bone marrow tissue architecture and the coexistence of abundant and rare cell types pose challenges to the development of unbiased artificial intelligence-based analysis.
Methods: We used multi-panel multiplex immunohistochemistry staining of BLIMP1/CD4/CD8/FOXP3 markers to identify regulatory and effector T cells and tumour cells. The dataset includes 9 monoclonal gammopathies of undetermined significance (MGUS) and 10 paired newly diagnosed MM (NDMM) and post autologous stem cell transplantation (ASCT) samples. To study the spatial bone marrow trephine microenvironment, we developed a new multi-stage deep learning-based image analysis pipeline. Firstly, to dissect the spatial landscape of myeloma biopsy images into blood, bone, cellular tissue and fat regions, we developed a superpixel based method (MoSaicNet) which adapts to the complex bone marrow trephine tissue architectures. Secondly, we developed an attention-based cell abundance aware deep learning method for cell detection and classification on highly imbalanced pathological data (AwareNet). To avoid cell abundance bias, AwareNet assigns a higher attention score to rare cell types during model training. To train, validate and test AwareNet, we collected 8002 single cell annotations from 11 slides by an expert. To train, validate, and test MoSaicNet, we collected 260 regions segmentation from 19 samples. We analysed the spatial proximity/clustering of cells and heterogeneity of bone trephine structure and texture.
Results: MoSaicNet and AwareNet achieved an area under the curve >0.98 for classification on separately held test data. AwareNet outperformed state of the art methods in detecting both abundant and rare cell types. An auto-encoder based unsupervised clustering analysis revealed that bone superpixels from post ASCT samples were more similar to the bone superpixels from MGUS samples than those from NDMM samples (r=0.51, p = 0.026; r=0.04, p=0.86, respectively). Furthermore, after ASCT we observed a depletion of FOXP3+CD4+ regulatory T (p=0.004) and BLIMP1+ plasma (p=0.013) cells. There was a trend of an increase in BLIMP1+ cells density in NDMM compared to MGUS patients (p=0.08), however, MGUS patients show significantly fewer BLIMP1+ cells in proximity to CD8+ cells compared with NDMM patients (p=0.03).
Conclusions: Using a deep-learning based pipeline for spatial mapping allowed us to harness information on cellular and morphological heterogeneity of the myeloma bone marrow. Such information will complement our liquid based platforms, to expand our insights into the myeloma marrow microenvironment, and allow formulation of hypotheses for testing in larger cohorts of patients.

P-081
Obesity and sarcopenia are highly prevalent in newly diagnosed multiple myeloma patients and are associated with myeloma-specific characteristics

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Introduction: Environmental and host-intrinsic factors like age, ethnicity and obesity have been associated with an increased risk to develop multiple myeloma (MM). Recent studies suggested that MGUS progression to MM occurs earlier in obese individuals classified by the body mass index (BMI). However, the BMI ignores distribution patterns of adipose depots and their pathophysiologic consequences. Here, the increase of visceral fat contributes to a chronic systemic inflammation facilitating a loss of muscle mass. To gain a better insight into the relation between host factors and MM, we studied body composition (BC) of newly diagnosed (ND)MM patients and correlated these data with MM-specific characteristics.

Methods: In this single-center, retrospective analysis, we studied consecutive NDMM patients diagnosed at our department between 01/2010 and 01/2021. We collected clinical and laboratory data at initial diagnosis and integrated these with anthropometric and BC measurements generated from single computed tomography scans using CoreSlicer. BC analyses incorporated assessments of subcutaneous and visceral adipose tissue (SAT and VAT), waist circumference, waist-to-height ratio (WtHR) and skeletal and psoas muscle indices (SMI and PMI).
Results: A total of 244 patients (103 female, 141 male) were included in the analysis with a median age of 66 years (range 25-89). 61% of patients were stratified as transplant-eligible. Among the entire cohort, ISS was followingly distributed: ISS 1 34%, ISS 2 25%, ISS 3 25%, not available 16%. Cytogenetic analyses were available for 75% of patients with high-risk alterations found in 23%. According to BMI, 42% of patients were identified as normal weight, 37% as overweight and 17% fulfilled obesity criteria. In contrast, overweight/obesity occurred in up to 75% of patients applying waist circumference (mean 108.6 ± 13.6 cm) and WtHR (mean 0.63 ± 0.08) as more precise anthropometric measures of visceral adiposity. Accordingly, mean VAT and SAT values were high (VAT: 139.8 ± 88.5 cm^2; SAT: 200.2 ± 98.5 cm^2). Whereas VAT was higher in male than in female patients (p = < 0.001), female patients had more SAT compared to male patients (p = 0.03). Additionally, in 180 patients being eligible for muscle mass measurements, SMI was 34.3 ± 9.5 cm^2/m^2 and PMI was 6.5 ± 2.4 cm^2/m^2 resulting in sarcopenia rates of up to 90% based on published cut-offs. BC parameters did not differ between transplant-eligible and ineligible patients. However, patients with gain(1q) had a significantly increased waist circumference (p = 0.02) and a higher WtHR (p = 0.07). Moreover, increased SAT was associated with a lower ISS (ISS 1 vs 2/3: p = 0.03). SMI and PMI were higher in high-risk compared to standard-risk patients (p = 0.1).
Conclusions: We identified a high prevalence of obesity and sarcopenia in our NDMM patient cohort. Associations of disease stages and distinct genetic alterations with BC measures might reflect host-disease interactions and warrant further analyses.

P-082
Stromal cell - neutrophil interactions are driving a pro tumor environment in multiple myeloma

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Introduction: Multiple myeloma (MM) disease progression is influenced by signals from the bone marrow (BM) micro-environment. Recently, we showed that the MM BM contains inflammatory mesenchymal stromal cells (iMSC) that transcribe MM survival factors and myeloid cell modulators including chemokines that bind CXCR1 and 2. Neutrophils express high levels of CXCR1/2, are tumor-supportive in solid malignancies, and are the most abundant immune cells in the BM. This led us to hypothesize that iMSC and neutrophils collectively generate a myeloma-supportive BM micro-environment.
Methods: N/A
Results: To define alterations in the neutrophilic lineage of newly diagnosed MM patients, we subjected the entire BM granulocytic lineage to scRNA sequencing (n = 6 MM, 4 controls). While neutrophil differentiation was unaffected, activation status was altered in MM. Mature neutrophils in MM patients had elevated transcription of OSM, SLPI, CXCL8, TLR2 and IL1B, as well as of T cell modulatory factors PTGS2 (COX2), CD274 (PD-L1) and LGALS9 (Galectin-9). Flow cytometry of 5 MM patients and 3 controls confirmed the activated phenotype of mature neutrophils by increased expression of the active form of CD11b (74% vs. 17%, p = 0.03), loss of CD62L (62% vs. 95%, p = 0.03) and elevated expression of CXCR1 (mean fluorescent intensity [MFI] 7574 vs. 1831, p = 0.03) and CXCR2 (MFI 2284 vs. 813, p = 0.03). Interestingly, transcriptomic analysis showed that mature neutrophils are the main producers of plasma cell survival factor TNFSF13B (BAFF), and that transcription was increased in neutrophils of MM patients. To test if activation and BAFF production could be regulated by iMSC, we cultured naïve neutrophils with either non-inflammatory MSCs or IL1β-activated iMSC. In the presence of iMSC, neutrophils were activated as evidenced by upregulation of CD11c (fold change 27.3 on iMSC vs. 2.4 on MSC, p = 0.02), CD66b (2.7 vs. 1.1, p = 0.02), C3AR (3.7 vs. 1.8, p = 0.05), and the activated isoform of CD11b (47.3 vs. 2.3, p = 0.02). RNA-sequencing showed that in vitro, iMSC were able to induce a neutrophil transcriptome similar to that of activated mature neutrophils in MM. Importantly, only iMSC, and not non-inflammatory MSC, increased BAFF production by neutrophils (33pg/mL on iMSC vs. 16pg/mL on MSC and 14pg/mL without stroma), suggesting an iMSC-induced pro-tumor phenotype. scRNA sequencing of the BM granulocytic lineage after induction treatment consisting of carfilzomib, lenalidomide and dexamethasone with or without an anti-CD38 monoclonal antibody (n=5) demonstrated that mature neutrophils maintained an activated transcriptome including elevated levels of BAFF. This suggests that continued presence of BAFF during treatment could contribute to therapy resistance or disease recurrence.
Conclusions: These data reveal a stromal-neutrophil axis aimed at cultivating a pro-tumor micro-environment by increased production of plasma cell survival factor BAFF downstream of iMSC-derived signals.

P-084
Bone marrow of patients post ASCT, but not chemotherapy consolidation, contains expanded T cell receptor clonotypes that are present at diagnosis: results from the Phase 2 CARDAMON study

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Introduction: The benefit of high dose therapy and autologous stem cell transplantation (ASCT) lies in tumour reduction, and increasing depth of response. ASCT likely also augments host anti-tumour immunity, but this is less well understood. Immune reconstitution following ASCT is accompanied by increased T cell activation and differentiation, while expansion of T cell clones and early lymphocyte recovery associates with longer PFS. Every T cell has a unique genomically-encoded T cell receptor (TCR). When an activated T cell clonally expands to mount effector responses, this TCR becomes enriched within the TCR repertoire. Therefore, a clonal TCR repertoire dominated by a small number of expanded clones is indicative of clonal effector responses. We compared the TCR repertoire between patients receiving ASCT and those getting chemotherapy only, to understand the specific role of ASCT in T cell clonal expansion and dynamics.
Methods: We utilised BM samples from patients in the Cardamon (ClinicalTrials.gov NCT02315716) Phase 2 study, where patients 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 then post-ASCT or cons. Viably frozen cells were thawed and CD3+ cells selected for α and β-chain TCR sequencing using an RNA-based protocol. We statistically quantified repertoire clonality using Shannon and Renyi entropy. TCR viral reactivity was queried on the VDJdb. Similarity between TCRs was determined by amino acid sequence clustering.
Results: We acquired TCR repertoire data for 5 donors randomised to ASCT and 8 to cons. We observed a similar number of total TCRs between baseline and post-therapy in the two treatment arms. However, the number of expanded TCRs (defined as >0.003% total repertoire) was higher in the ASCT than cons arm (beta chain, ASCT: 24.2±13.5, cons: 14.7±11.5, P=.047) Furthermore, repertoire clonality increased significantly following ASCT(P=.008) but remained unchanged following cons (P=.54). Significantly more TCRs were shared between baseline and post-ASCT than between baseline and post-cons when analysed per patient (P=.03). TCRs present at baseline were expanded more frequently following ASCT compared to cons. Some TCRs expanded by ASCT rose from 0.002% of the baseline repertoire to >20% following ASCT. Expanded TCRs found post-ASCT were not annotated as reactive to common viruses. However, ASCT-expanded TCRs clustered by their sequence similarity, suggesting a shared reactivity to the same antigen.
Conclusions: Our results showed a greater degree of effector T cell clonal expansion in patients following ASCT than was seen on chemotherapy consolidation. A small number of structurally similar, but non-viral, TCRs expanded massively following ASCT, suggesting a reinvigoration of pre-existing tumour-specific effector response with immune reconstitution.

P-085
Resistance to immunogenic cell death as a novel mechanism of immune escape in high-risk multiple myeloma

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Introduction: Immune therapies using monoclonal antibodies and their derivatives, or T-cell directed therapies have shown promise in treating multiple myeloma (MM). However, immune dysfunction and exhaustion may limit their long-term effect. The first-line MM drug bortezomib (BTZ) induces a specific cell death modality in MM, called immunogenic cell death (ICD), which significantly accounts for the exceptional clinical benefit of BTZ. MM cells dying via ICD express calreticulin (CALR), which is an immunogenic "eat-me" signal that facilitates phagocytosis by dendritic cells (DC), T cell

priming and tumor clearance by endogenous T cells. Foundational to this work, we found that CALR exposure is an obligate step in the phagocytosis and the ICD process, since BTZ-induced ICD is impaired in CALRKO MM cells both in vitro and in vivo.
Methods: Therefore, we reasoned that genomic or transcriptomic alterations within MM cells that are correlated with clinical outcome may mediate resistance to ICD by specifically altering CALR exposure. We integrated genes that were differentially expressed in the IFM/DFCI dataset among patients with long (>5 years) vs short (< 1.5 years) survival with a list of proteins interacting with CALR after BTZ treatment, as assessed by Co-IP. We found that GABA Type A Receptor-Associated Protein (GABARAP) interacts with CALR after induction of ICD and is highly expressed in patients with longer survival.
Results: Interestingly, we found that in GABARAPKO cells, CALR is trapped in the endoplasmic reticulum and mitochondria. Indeed, we found a strong correlation between GABARAP protein levels and the intensity of CALR exposure after BTZ treatment in 10 cell lines. In addition, overexpression of GABARAP in GABARAPLOW cells restored CALR exposure. Moreover, GABARAPKO in 3 ICD-sensitive cell lines abrogated the induction of ICD by BTZ, and add-back experiments using pre-treatment with recombinant CALR or GABARAP overexpression in KO clones restored ICD. In vitro, CyTOF confirmed that treatment of GABARAPKO cells with BTZ failed to activate an efficient T cell response. In vivo, BTZ failed to induce ICD and tumor regression in immunocompetent mice bearing GABARAPKO tumors. The GABARAP gene locus is on chr17p13.1, a region deleted in high-risk (HR) MM patients that is associated with an unfavorable prognosis. We found that low GABARAP expression was correlated with shorter EFS (p=0.018), even after excluding MM patients with del17p. Thus, GABARAP is an independent predictor of clinical outcome.
Conclusions: In conclusion, our work identifies a unique mechanism of immune escape that may contribute to the poor clinical outcome observed in del17p HR MM patients. It further suggests that novel therapies to restore GABARAP may allow for the induction of ICD and improved patient outcome in MM.

P-086
Antitumor activity of activated marrow-infiltrating lymphocytes in patients with multiple myeloma

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Introduction: Adoptive immunotherapy is a promising treatment approach for multiple myeloma (MM), but a major limitation of adoptive immunotherapy is the availability of tumor specific and nonspecific T cells. We hypothesized that because the bone marrow (BM) is the tumor microenvironment for many hematologic malignancies such as MM, marrow infiltrating lymphocytes (MILs) could be harnessed to generate tumor-specific T cell therapy for these specific cancers. In MM, BM represents a potentially unique site for the isolation and expansion of tumor-specific T cells. MILs are present in all patients, can be obtained with a simple bedside procedure, and can be rapidly expanded in all patients makes this an attractive source for tumor-specific T cells. Here, we report an approach to generate ex vivo expanded MILs from MM patients based on anti-CD3/CD28 beads.
Methods: Anti-CD3/CD28 beads were used to expand MILs in the presence of IL-2, IL7 and IL15. Expansion rate, proportions of effector cells such as CD8, CD4 T cells, NK cells, memory T cells and functions of expanded MILs were determined over two weeks of culture.
Results: The study demonstrated that co-culturing of MIL with anti-CD3/CD28 beads in the presence of IL2, IL7, and IL15 resulted in remarkable expansion of MIL over 14 days culture period. In addition, expanded MILs showed increased proportions of CD8+ T cells, central memory T cells. Interestingly, eMILs showed a higher proportion of central memory T cells (>80%) while the proportions of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) are very low at days 14 or 21 of culture. Compared with expanded PBLs, eMILs demonstrated increased cytotoxicity towards target MM cells, particularly CD138+ primary MM cells from autologous patients. Increased activity of eMILs was further confirmed by CD107a degranulation, Incucyte cytotoxicity assay, and IFN-γ production. The collective observations are evidence of a potential treatment against multiple myeloma. However, the expression of inhibitory receptor (TIM3) is increased after MIL expansion (~40%) that is a limitation of eMIL, therefore we are currently investigating the combination of eMIL plus a checkpoint blockade against MM.
Conclusions: In conclusions, the complexity of MM suggests that MM patients require personalized therapies to achieve long term remission. In this study, we showed that, eMILs is a potential vaccine candidate against MM, MILs can easily be obtained from the BM and can be expanded vigorously. In comparison with PBL control, MILs demonstrate enhanced antigen specificity toward CD138+ MM cells. Therefore, MILs are a distinctive set of T cells that have been shaped by the unique BM microenvironment and may play a future role as a novel immunotherapy for hematologic malignancies.

P-087
Single-cell RNA sequencing reveals ZNF683 as a key regulator of NK cell exhaustion in multiple myeloma

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Introduction: Multiple myeloma (MM) remains incurable because most patients eventually relapse. As the first responders against malignant cells, NK cells play pivotal roles in MM immune surveillance. However, NK cells tend to become dysfunctional in MM microenvironment, the underlying molecular mechanisms need further elucidation. In the current study, we aim to uncover and validate molecularly novel insights into identifying regulators for NK cell exhaustion and provide potential therapeutic targets to improve NK cell response in MM.
Methods: We performed deep single-cell RNA sequencing on 30008 single NK cells isolated from bone marrow and peripheral blood of newly-diagnosed MM patients and healthy volunteers. Cell clusters were visualized using UMAP. For differentially expressed genes expression, we used model-based analysis of single-cell transcriptomics test (logFC≥0.25, min.pct=0.1) and only selected the genes with adjusting p value< 0.05. Based on the cluster-defining differentially expressed genes, we named and estimated functional states of each cluster via bioinformatics analyses. A variety of in vitro experiment, including luciferase reporter assay, lentiviral expression vector construction, NK cell transfection, flow cytometry, RT-qPCR, and cytotoxicity assay were employed to confirm the underlying regulators and molecular mechanisms for NK cell exhaustion.
Results: We identified 7 NK cell clusters. MM patients exhibited a remarkable increase in cluster 3 NK cells with "exhausted" transcriptomic profile, featuring as decreased expression of cytotoxicity markers (CD69, GNLY, GZMA) and activating receptor NCR1, as well as increased expression of inhibitory receptors (LAG3, KIR3DL2 and KLRG1). Moreover, we found MM-derived cluster 3 NK cells hardly expressed SH2D1B, which encodes a key adaptor protein transferring activation signals from SLAMF7 on NK cells. Transcription factor ZNF683 was further proven to be responsible for SH2D1B absence through directly binding to the promoter of SH2D1B. Finally, we demonstrated that ZNF683 transfection dysregulated NK cell cytotoxicity and promoted their acquisition of exhausted phenotypes.
Conclusions: Our research identified a cluster of ZNF683+ NK cells with exhaustive phenotypes and impaired cytotoxicity in MM patients. We further confirmed that ZNF683 overexpression significantly downregulated SH2D1B expression via directly binding to its promoter in NK cells, thus leading to decreased cytotoxicity and impaired immunosurveillance of NK cells.

P-088
Bone marrow mesenchymal stem cells regulate the function of NK cells via TIM-3/Gal-9 in multiple myeloma

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Introduction: Multiple myeloma (MM) is malignant tumor with abnormal proliferation of bone marrow plasma cells. MM cells are focally distributed in the bone marrow cavity and interact with other cells in their surroundings and the bone marrow stroma to form a complex pathogenesis. It is currently believed that genetic abnormalities are intrinsic to the development of MM. Furthermore, the changes of immune microenvironment are important extrinsic factors in the development and progression in MM patients. To explore the regulation effect of BMSCs on NK cells in MM patients, which will provide basis for further searching for new immunotherapy targets for MM.
Methods: Flow cytometry (FCM) was applied to detect the number and function of NK cells in the bone marrow. The expression of TIM-3 on bone marrow NK was also detected via FCM. Then, the vitro co-culture system of BMSCs and NK was induced and divided into 4 groups (A: NK cells; B: NK cells + TIM-3 inhibitor; C: NK cells co-cultured with BMSCs; D: NK cells co-cultured with BMSCs + TIM-3 inhibitor). The function of NK cells in the 4 groups was compared after co-culturing 6d.
Results: 1. The quantities of total NK cells were increased in NDMM compared with normal control [(46.27±1.99) %, (34.90±1.42) %] (p=0.0194) as well as CD56dimNK cells [(42.00±1.90) %, (31.35±1.69) %] (p=0.0244). For the function of NK cells, the expressions of CD107a, NKG2D, INF-γ and perforin in NK cells were significantly decreased in NDMM compared with normal control (p< 0.05). 2. The expression of TIM-3 of total NK cells was increased in NDMM [(71.58±1.62) %] compared with normal control [(63.93±3.42) %] (p=0.05) as well as CD56dimNK cells [(72.77±1.62) %, (65.39±3.45) %] (p=0.05). The expression of TIM-3 ligand Gal-9 (26.98±9.401%) was higher than Ps [(3.364±1.428)%], HMGB1 [(3.771±1.752)%], and CEACAM-1 [(3.717±2.622)%] on BMSCs (p< 0.0001). 3. The expression of CD107a on the surface of NK cells was significantly reduced after co-cultured with BMSCs (55.46±2.25 vs. 33.56±1.35%), while in TIM-3 inhibitor group, CD107a, NKG2D, INF-γ and perforin were restored in BMSCs and NK cells co-culture system.
Conclusions: The quantities of bone marrow NK cells were increased but the functions were significantly reduced in NDMM patients. The negative immune checkpoint TIM-3 on NK cells were increased in NDMM patients but decreased in CR patients. The ligand of TIM-3 Gal-9 was significantly increased than Ps, HMGB1, and CEACAM-1 on BMSCs. Mechanismly, BMSCs in MM patients can regulate NK cell immune depletion via TIM-3/Gal-9 and promote the development of MM.

P-089
Disordered metabolism mediates the immunosuppressive microenvironment in multiple myeloma

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Introduction: Immunotherapy is an effective strategy in various malignancy with encouraging results. However, the efficacy of immune checkpoints inhibitors on multiple myeloma (MM), a hematological malignancy, is unsatisfactory. Further understanding the immunosuppressive microenvironment in MM patients could help us to overcome the obstacle and develop more effective treatment options.
Methods: Here, utilizing single-cell RNA sequencing, we delineated the dynamic variation of immune cells in bone marrow (BM) of MM patients along with tumor burden.
Results: We found that immune cells were activated in MM patients with low-tumor burden (MM cell% ﹤ 30%) compared to health donors (HDs) and patients with high-tumo burden (MM cell%＞30%). There were more infiltrating effector immune cells in BM of low-tumor burden MM patients, including effector CD8 T cells (CD8-GNLY) and effector NK (NK-FCGR3A-CCL3). Moreover, conventional DC (cDC-CD1C-AREG) displayed a gene signature associated with the enhanced antigen presentation in low-tumor burden MM patients. Meanwhile, the immunosuppressive microenvironment in MM patients with high-tumor burden was identified, including dysfunctional effector CD8 T cells and NK as well as impaired cDC. The interaction among immune cells was obviously weakened in high-tumor burden group compared to that in low-tumor burden group. Our study proved that the immune response was dynamic along with the infiltration of MM cells. Further analysis showed that the PIM kinases played pivotal roles in the dysfunction of immune cells along with MM cells infiltration. Of note, we found that metabolic disorders were involved in the dysfunction of immune cells in MM. In particular, the impaired amino acid metabolism should be a crucial factor for the defective effector CD8 T cells, for example, the impaired “Arginine and proline metabolism” and “valine, leucine and isoleucine degration” in the defective CD8-GNLY from MM patients. Enhanced lipid metabolism was observed in dysfunctional NK-FCGR3A-CCL3 from high-tumor burden group, including “Sphingolipid metabolism” and “Ether lipid metabolism”. Meanwhile, cDC-CD1C-AREG in high-tumor burden group displayed enhanced “Histidine metabolism” and “pantothenate and CoA biosynthesis”. More and more researches report that PIM kinases are key regulators in numerous cellular metabolic processes. Considering this, we speculated that the abnormal expression of PIM kinases probably affect the function of immune cells via metabolism regulation in MM. Disordered metabolism caused by MM infiltration should be the chief culprit of defective immune response in MM patients. PIM kinases in dysfunctional immune cells could be novel potential targets for immune-based therapy to MM.
Conclusions: In summary, we delineate the immune microenvironment of MM patients with various degree tumor burden. Given the results of our study, redressing the disordered metabolism may be the key points to get promising effects by Immune-based therapies.

P-090
Immune biomarkers of survival and infection-related mortality in multiple myeloma (MM) patients treated with lenalidomide and dexamethasone (Rd)

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Introduction: Rd is a backbone of treatment in MM. The strong immunomodulatory effects of this regimen would suggest that immune profiling might complement conventional prognostic factors. However, immune signatures predictive of survival were not well defined in the past, and nowadays it is challenging to detach the effect of Rd from other backbone drugs in triplets or quadruplets.
Methods: The GEM-CLARIDEX trial was leveraged to identify immune biomarkers in 186 newly diagnosed transplant-ineligible MM patients treated with Rd (+/- clarithromycin) until disease progression. Immune profiling was performed in bone marrow aspirates at baseline, using multidimensional and computational flow cytometry together with lasso penalized Cox regression and 10-fold cross-validation, for a holistic and unbiased definition of prognostic immune signatures. Sixty-tree cell populations including 8 myeloid/erythroid and 55 lymphoid subsets, were analyzed.
Results: An immune signature associated with inferior survival was defined based on the increased frequency of adaptive cytotoxic CD314+ NK cells, and decreased percentages of circulating immunoregulatory CD314+ NK cells, Tregs with naïve and central memory (CM) phenotype, CD4+ CM CD127low PD1- and CD127+ PD1- CD25+ T cells, CD8+ PD1+ terminally differentiated T-cells, and B-cell precursors. Accordingly, patients with high (n=100) vs low (n=86) immune-risk showed inferior PFS (median 15m vs not reached; HR: 4.2, P< .001) and OS (median 31m vs not reached; HR: 5.2, P< .001). The immune signature was prognostic in the two arms of the study and was therefore independent of treatment with clarithromycin. Furthermore, in multivariate analyses including age, ISS, LDH and cytogenetic abnormalities by FISH, both the ISS (PFS_HR: 2.4, P=.026]; OS_HR: 2.9, P=.047) and the immune-risk signature (PFS_HR: 4.5, P< .001]; OS_HR: 5.3, P< .001) showed independent prognostic value. Being infections an important cause of morbidity and mortality in elderly MM patients as those included in this study, we next investigated if immune profiling at baseline could help predicting fatal infections (n=14/186). Interestingly, the combination of demographic (age ≥79y), clinical (hemoglobin ≤ 11.3 g/dL) and seven immune biomarkers showed the strongest association with fatal infections and an independent predictive value in a logistic regression with lasso regularization. Namely, increased percentages of CD8+ effector memory [EM] CD127low PD1+, CD4+CD8dim T cells and eosinophils, together with decreased frequencies of CD4+ and CD8+ naïve T cells, CD4+ EM CD127low PD1- and CD8+ CM CD127+ PD1- CD25+ T cells. The area under the curve (AUC) of the model was 0.99 with a 4-fold cross-validation showing mean AUC=0.98±0.02.
Conclusions: This study shows the clinical value of immune profiling at diagnosis and identifies immune cell populations predictive both of survival and of fatal infections in elderly MM patients treated with the backbone regimen Rd.

P-091

Thrombocytopenia with coagulation abnormality in multiple myeloma patients treated with proteasome inhibitor and/or immunomodulatory drugs

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Introduction: Thrombocytopenia is a poor prognostic factor, but thrombocytopenia affected survival time has not been discussed well. The purpose of this retrospective study was to investigate clinical significance of thrombocytopenia and thrombocytopenia related factors, including coagulation abnormality and myelosuppression, in the myeloma patients treated with novel agents.
Methods: We reviewed medical records of MM patients treated at the Jikei University Kashiwa Hospital between January 2000 and March 2021, and these patients were followed up until December 2021. Primary plasma cell leukemia was excluded. All laboratory data were collected at diagnosis. The cut-off value of thrombocytopenia was 130x103/μL . Coagulation abnormality was defined as high D-mimer or FDP level.
Results: 189 patients included in this study. The median age of patients was 72 years (range, 38–96 years). 157 and 73 patients were treated with proteasome inhibitor and immunomodulatory drug containing therapies, respectively. 48 patients received up-front autologous stem cell transplantation. The ratio of thrombocytopenia was 17.4%. The frequency of anemia, ISS stage 3, low PT level, and high APTT level were significantly higher in the patients with thrombocytopenia than those without thrombocytopenia. There was not a significant association between thrombocytopenia and the other factors including coagulation abnormality and megakaryocyte count. There was no significant relation between thrombocytopenia and treatment response; the overall response rate between the patients with and without thrombocytopenia were 69.7% and 78.2%, respectively (P = 0.364), and the very good partial response rate between the patients with and without thrombocytopenia were 36.4% and 41.2%, respectively (P = 0.698). In median follow-up period of 26.1 months, the 24 months-OS and PFS ratios in the thrombocytopenia group were significantly lower than those in the non-thrombocytopenia group (67.4% vs 80.7%; P = 0.024, and 29.2% and 57.0%; P = 0.001). Coagulation abnormality predicted short OS and PFS in not only all the patients but also the patients with thrombocytopenia. Therefore, we analyzed dividing into three groups. The OS and PFS in the thrombocytopenia with coagulation abnormality were significantly shorter (HR 2.336 and 3.723, P = 0.021 and < 0.001) although those in the thrombocytopenia without

coagulation abnormality were similar to those in the non-thrombocytopenia group (P = 0.565 and 0.883).
Conclusions: We considered that several molecules, which contributed to thrombocytopenia and coagulation abnormality, such as thrombopoietin, IL-6, TNF-alpha, lupus-anticoagulant, protein C, and protein S, were associated with progressive myeloma disease although we did not evaluate these cytokines unfortunately. We concluded that thrombocytopenia with coagulation abnormality could predict short OS and PFS in the myeloma patients treated with novel agents.

P-092
Impaired glutamine/glutamate metabolic axis into myeloma microenvironment affects osteoclast formation.

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Introduction: Multiple Myeloma (MM) is an hematological malignancy characterized by a severe osteoblasts and osteoclasts (OCLs) imbalance into the bone marrow (BM) microenviroment. Recently, we demonstrated that MM cells are Glutamine (Gln)-addicted and, in turn, Gln depletion impairs osteoblast differentiation. Consistently, the BM microenvironment of MM patients is characterized by lower levels of Gln and higher levels of Glutamate (Glu) as compared to patients with pre-malignant monoclonal gammopathies as Smoldering MM (SMM) and Monoclonal Gammopathy of Uncertain Significance (MGUS). Based on this evidence, we hypothesized that low Gln/high Glu levels may have a significant impact on OCL formation and thereby contribute to the development of osteolytic lesions.
Methods: BM CD14+ monocytes were isolated from a cohort of 29 patients with monoclonal gammopathies (3 MGUS, 14 SMM and 12 newly diagnosed MM (ND-MM)). Cells have been incubated in differentiating medium in the presence or absence of Glu and Gln. The samples were subsequently analyzed by real-time PCR and TRAP staining after 12-14 days. Amino acid uptake and amino acid content have been assessed under the same conditions by radiolabeled amino acids and liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), respectively.
Results: We show that the presence of Glu significantly increased the number of OCLs generated from CD14+ obtained from MGUS and SMM patients compared with cells differentiated in the absence of the amino acid. In these patients, Glu increased NF-κB and NFATc1 protein level. On the other hand, CD14+ obtained from MM patients have a lower response to Glu. Independently from the diagnosis, Gln and Glu deprivation completely blocks OCLs formation, while Glu supplementation partially reverts this effect. The analysis of intracellular amino acids (Gln, Glu, and α-ketoglutarate (2-OG)) indicated that Glu content increases after 8 days of differentiation while decreasing after 14 days pointing to a fast accumulation of Glu upon differentiation. The content of both Gln and 2-OG do not vary appreciably throughout the differentiation. Consistently, the activity of Glu transporter EAAT1, increases already after 3 days of incubation in differentiating medium without Glu, with a further increase in the presence of the amino acid. The expression of other Glu transporters did not change during differentiation.
Conclusions: In conclusion these data indicate that OCLs formation is characterized by increased activity of EAAT1 transporter and Glu content during the early phase of differentiation. A different sensitivity to Glu was observed in patients with MGUS and SMM as compared to MM due to the high Glu level found in MM bone niche that sustains OCLs formation by stimulating of NF-κB pathway thus contributing to the development of osteolytic bone lesions. Overall, our data suggest that glutamine-glutamate axis could be a possible target for MM-induced osteclastic bone destruction in MM patients.

P-093
Iberdomide induces activation and proliferation of innate and adaptive immune cell subsets in the tumor microenvironment of relapsed/refractory myeloma patients

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Introduction: Iberdomide is a potent cereblon E3 ligase modulator (CELMoD agent) with anti-tumor and immunomodulatory activities in preclinical multiple myeloma (MM) models. A phase 1/2 multicenter, dose-escalation study recently established efficacy and safety of iberdomide as monotherapy or in combination with other therapies in heavily pretreated patients with relapsed/refractory MM (RRMM).
Methods: We conducted deep immunophenotyping of the bone marrow (BM) tumor microenvironment of 93 MM patients treated with iberdomide (±dexamethasone) using mass cytometry (CyTOF) at baseline and on-treatment

(C2D15). Most treated patients (n=77, 83%) were triple-class refractory. We correlated findings to prior therapy, disease characteristics and clinical activity and found significant on-treatment increases of BM effector T and NK cells. Percentages are expressed as a fraction of bone marrow mononuclear cells (BMMC) unless otherwise specified.
Results: At C2D15, there was a significant expansion of NK cells (5.6% vs 13.1%, p< 0.001) and NKT cells (2.2% vs 4.3%, p< 0.001). While overall, T cells remained stable, they shifted towards an effector-memory phenotype (i.e. CD45RA-CCR7) at C2D15 compared to baseline (52.0% vs 67.0% of CD4+ T, p< 0.001 and 67.0% vs 84.2% of CD8+ T, p< 0.001). Within the NK cell population, expansion of both CD56hi cytokine-producing (2.8% vs 7.1%, p< 0.001) and CD16+ cytotoxic NK cells (1.6% vs 2.9%, p< 0.01) was seen. NKT cell increase was limited to expansion of CD8+ NKT cells (1.3% vs 3.3%, p< 0.001). Changes in co-stimulatory receptor and immune checkpoint expression in paired samples suggest functional activation: within the CD8+ T cell population, there was a significant increase of subsets expressing markers of a more activated phenotype: CD28 (p< 0.001), CD38 (p< 0.001), ICOS (p< 0.001), Granzyme B (p< 0.01) and HLA-DR (p< 0.001). In contrast, there was a significant decrease of CD8+ T cell subsets expressing markers associated with immune exhaustion or terminal differentiation and senescence, including TIGIT (p< 0.001), KLRG1 (p< 0.001), and CD57 (p< 0.001). CD8+ T cells co-expressing multiple inhibitory checkpoints (KLRG1+PD-1+TIGIT+) significantly decreased (p< 0.001). Specific to NK cells, there was a relative increase of NK cells expressing the co-stimulatory receptors NKG2D (p< 0.01) and CD226 (p< 0.001). Notably, changes were dose-dependent and independent of concomitant steroid dosing or prior refractoriness to lenalidomide/pomalidomide. Some changes were associated with response, suggesting that immune activation in the MM bone marrow niche may be a contributor to the antitumor efficacy of iberdomide.
Conclusions: The presented approach establishes a strategy to study treatment-induced changes in the tumor microenvironment. Our data demonstrate that iberdomide leads to strong and rapid immunomodulatory effects of innate and adaptive immunity. This data establishes rational combination strategies for iberdomide with other immune-enhancing therapies in RRMM.

P-094
The expression and prognostic significance of piRNA-823 in multiple myeloma

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Introduction: Until now, multiple myeloma (MM) is uncurable. It is necessary to further explore the molecular mechanism of MM progress in order to seek effective treatment strategies for MM patients. Researchers have found that piRNA is abnormally expressed in a variety of tumor cells and tissues, participating in the occurrence and development of tumor, and is expected to become a valuable biomarker in tumor diagnosis, treatment and prognosis evaluation . However, there are few studies on piRNA in MM.
Methods: The significant difference of piRNAs expression between MM patients and control group were screened by bioinformatics method; the expression level of piRNA was verified by qRT-PCR in 30 MM patients and 5 Control groups; The relationship between piRNA-823 and clinical indicators, transforming growth factor β induced gene (TGFBI) and DNA methyltransferases (DNMTs) were explored;
Results: 1.The expression of piRNA-823 in MM patients was significantly high by bioinformatics method, and was further verified in 30 MM patients and 5 Control groups, the expression level of piRNA-823 was significantly increased, which was significantly higher in relapsed/refractory MM (RRMM) group than that in the newly diagnosed MM group (NDMM) and Control group (p< 0.05); 2. The expression level of piRNA-823 was positively correlated with β 2-MG (p=0.041) compared with other clinical indicators of MM patients; 3. The expression level of piRNA-823 was negatively correlated with TGFBI mRNA in bone marrow (p< 0.01) and positively correlated with DNMT3A and DNMT3B (p< 0.05) in MM patients;
Conclusions: The expression of piRNA-823 in MM is heterogeneous, especially high in RRMM patients, which can be used as a good indicator of MM tumor burden; It has a negative correlation with TGFBI mRNA in bone marrow, and a positive correlation with DNMT3A and DNMT3B, which may inhibit TGFBI through methylation and promote the progression of MM. It has important prognostic significance in revealing the pathogenesis of MM, evaluating the prognosis, and even developing targeted drugs.

P-095
Exosomal miR-27b-3p suppresses CD28 expression in T cells and facilitates immune escape of multiple myeloma

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Introduction: Multiple myeloma (MM) is an incurable plasma cell malignancy. The crosstalk between immune cells and MM cell is an important determinant of MM progression, but the underlying mechanism has not been fully defined. Therefore, this study identified how biomarker miRNA interacting between MM cells and immune cells, and which target genes of the miRNA and the pathways involved in.

Methods: In this study, serum samples and their CD138+ cells of newly diagnosed MM patients (NDMM, n=8) and healthy donors (HD, n=2) were collected and total RNAs were isolated for small RNA sequencing. RT-qPCR was used to verify DemiRs in serum of MM patients. ROC and Kaplan-Meier analyses were conducted to evaluate the clinical significance of MM serum DemiRs. Exosomes of serum were isolated and characterized. Through in vivo and in vitro studies, the role of serum miRNAs in the progression of MM was clarified.
Results: Venn analysis was performed between the DemiRs in CD138+ cells and serum of MM patients, and 36 DemiRs were obtained. Subsequently, RT-qPCR validation was performed in a large cohort of MM serum samples (MM n=201, HD n=60). Compared with healthy controls, 5 down-regulated miRNAs were detected in MM serum, respectively ($P < 0.05$). ROC and Kaplan-Meier analysis showed that the expression levels of miR-27b-3p, miR-145-3p and miR-628-3p in serum of MM patients had better diagnostic efficiency and prognostic value. Of note, the low level of circulatory miR-27b-3p indicated the decreased proportion of CD3+ T cells, but the increase of CD3+CD28-CD57+ senescent T cells of MM. The expression level of miR-27b-3p in CD138+ cells and in MM serum derived exosomes was higher than that in HDs'. Subsequently, we constructed MM cell overexpressed (OE) miR-27b-3p. The expression level of miR-27b-3p in exosomes derived from the supernatant of MM cells OE miR-27b-3p was higher than that of the control, so the exosomes with high level of miR-27b-3p in MM serum were released by CD138+ cells of MM patients. Exosomes in serum were phagocytosed by CD3+T cells of MM patients. MiR-27b-3p down-regulated the expression level of CD28, which led to the senescence of CD3+T cells. In vivo experiments of mice, miR-27b-3p OE group had low proportion of CD3+T cells and high proportion of senescent T cells. Besides, miR-27b-3p could increase tumor load in mice. Therefore, it was found that miR-27b-3p could stabilize the expression level of c-MYC protein in MM cell lines by targeting FBXW7, thus promoting the proliferation of tumor cells. In GSE2658 and MMRF-Commpass MM databases, MM patients with low level of FBXW7 had poor prognosis.
Conclusions: In this study, three serum miRNAs (miR-27b-3p, miR-145-3p, and miR-628-3p) were identified as novel biomarkers of MM. MiR-27b-3p inhibits the function of T cells in the immune microenvironment of myeloma patients by exosomes, highlighting that myeloma cells promote the occurrence of immune escape in MM microenvironment by reprogramming bone marrow T cells.

P-096

MiR-27b-3p suppresses CD28 expression in T cells and facilitates immune escape of multiple myeloma

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Introduction: Multiple myeloma (MM) is an incurable plasma cell malignancy. The crosstalk between immune cells and MM cell is an important determinant of MM progression, but the underlying mechanism has not been fully defined. Our study aimed to identify and screen the profiling of miRNAs in MM patient serum and tumor cells to better understand the roles of miRNAs in MM pathogenesis and myeloma cells driving immune escape.
Methods: A pairwise miRNA profiling in serum and tumor cells was performed via small RNA-seq in NDMM patients and compared with HDs. RT-qPCR detection was performed for a large cohort including 201 NDMM patients and 60 HDs to further confirm the DEmiRs in patient serum. Exosome coculture experiments, confocal microscopy detection and in vivo experiments were utilized to investigate the function of miR-27b-3p encapsulated in exosomes. To upregulate the level of miRNAs, miR-27b-3p mimics was transfected to Jurkat and MM cell lines by using Lipofectamine 3000.
Results: (1). ROC and Kaplan-Meier analysis showed that the decreasing levels of miR-27b-3p, miR-145-3p and miR-628-3p in serum of MM patients presented diagnostic and prognostic efficiency. (2). The level of miR-27b-3p decreased in serum but significantly enriched in serum exosomes of MM patients. A large amount of miR-27b-3p in MM cells could be encapsulated in exosomes and secreted by MM cells into circulation. Confocal microscopy analysis showed that the PKH67-stained exosomes isolated from MM cells were transferred to CD3+ T cells after the coculture. More interesting, we found that the low level of circulatory miR-27b-3p in peripheral blood serum of MM highly correlated with the decreased proportion of CD3+ T cells, but the increase of CD3+CD28-CD57+ senescent T cells, especially after the coculture with serum exosomes from patient. (3). Deul luciferase assay confirmed that CD28 (the prominent costimulatory molecule on T cells) and FBXW7 (a component of E3 ubiquitin ligase) were target genes of miR-27b-3p in T and MM cells, respectively. In T cells, MiR-27b-3p down-regulated the expression level of CD28, which led to the senescence of CD3+T cells with decreasing level of cytokines IL-2 and IFN-γ. It was also found that miR-27b-3p could stabilize the expression of c-MYC protein in MM cell lines by targeting FBXW7, thus promoting the proliferation of MM cells. (4). The results in vivo further clarify the role of miR-27b-3p promoting T senescent phenotype and the proliferation of MM cells.
Conclusions: Circulatory serum miR-27b-3p decreased and act as an effective biomarker for MM diagnosis and prognosis evaluation. miR-27b-3p enriched in MM cells and secreted by exosome into circulation. High-level of miR-27b-3p promotes MM cell proliferation via targeting FBXW7/c-MYC axis in tumor cells. Moreover, miR-27b-3p encapsulated in exosomes communicated with surrounding cells and

promotes T cell senescence. High level of miR-27b-3p plays pivotal roles in MM pathogenesis.

P-097
A novel anti-BCMA lipid-based nanoparticle for multiple myeloma therapy

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Introduction: Multiple myeloma (MM) is an incurable haematological malignancy with a remarkable molecular heterogeneity that assumes a relapsing course with significant morbidity secondary to the disease pathology and its treatment. There has been a recent expansion in targeted therapies for MM, many of which exploit the B cell maturation antigen (BCMA) due to its plasma cell specificity. Such therapies showed remarkable results in clinical trials, but their benefits can be hampered by significant side effects and availability issues. Belantamab mafodotin, Teclistamab, and BCMA-targeting CART cells are prime examples of such therapies. We propose the design of an anti-BCMA targeted lipid nanoparticle that when internalised will deliver a payload of MMAF directly into the MM cells. This novel approach has the potential to eliminate off-target side effects and to be available off the shelf.
Methods: Liposomes were prepared using the lipid film hydration method followed by extrusion. Following MMAF encapsulation, BCMA antibodies were conjugated at the surface of liposomes. MM cells viability was assessed using the Alamar Blue assay. Flow cytometry was used to evaluate cellular uptake to confirm targeting specificity to myeloma cells by detecting DiI signal from fluorescently labelled liposomes.
Results: The binding specificity of free anti-BCMA antibody to myeloma cells was confirmed by testing a range of myeloma cell lines including KMS-12-BM, U266, and JJN3 in comparison to non-MM cell lines including HCT-116 and SW480. Following their synthesis, liposomes were stably and successfully encapsulated with a therapeutic dose of MMAF and conjugated to anti-BCMA antibodies. To confirm that the anti-BCMA antibody maintained its targeting specificity to the myeloma cells and to assess the added benefits of BCMA targeting, we tagged the liposomes with a fluorescent marker (DiI-Lp) and tracked their uptake into the cells with flow cytometry. A control of non-targeted liposomes was included. Our data indicated a significant increase in DiI-Lp-Ab uptake in myeloma cells (~44%) after only 1 h incubation compared to only 8% uptake of non-targeted DiI-Lp. Moreover, the conjugation of anti-BCMA antibody onto the surface of liposomes encapsulating MMAF resulted in a significant reduction in myeloma cells (KMS-12-BM) viability compared to non-targeted MMAF liposomes, thereby, confirming the added benefit of liposomal conjugation to BCMA antibody
Conclusions: The data from this research confirm, for the first time in MM, the feasibility of an off-the-shelf, anti-BCMA, tubulin toxin-carrying lipid nanoparticle as a potential future treatment for MM.

P-098
Serological proteome analysis identifying autoantibodies against tumor-associated antigen ENO1 as a potential prognostic biomarker in multiple myeloma

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Introduction: Most scientific efforts are commonly focused on the discovery of tumor-associated antigens (TAA) and relating anti-TAA autoantibodies, which can play protective role in cancer patients. As many studies show, such antibodies are becoming an important prognostic marker. The aim of this study was to check whether any natural autoreactive antibodies are present also in sera of multiple myeloma (MM) patients.
Methods: Fifteen samples of serum of MM patients and 15 samples of serum of healthy donors (age and sex matched) were screened for the presence of autoreactive IgG molecules against total proteins extracted from MM cell line, RPMI 8226. Serological proteome analysis (SERPA), a method enabling to detect thousands of proteins simultaneously in a single run, was applied for screening the immunoreactive molecules. The final identification of reactive proteins was performed by MALDI-MS and LC-MS/MS analysis.
Results: SERPA was used to identify TAAs from RPMI 8226 cell line in a discovery set. Sera from MM patients in complete remission showed repeatedly significant reactivity with only one protein in position (47 KDa and pI 6.99). Protein in this immunoreactive spot was identified by mass spectrometric analysis to be α-enolase (ENO1). Compared to healthy individuals and other MM patients, our preliminary data suggest that the presence and titer status of ENO1 autoantibody level is associated with complete remission.
Conclusions: It has already been proven that ENO1 is overexpressed in many types of cancer and is considered to be the main immunogenic targets involved in immune surveillance. This preliminary study has identified increased levels of specific anti-ENO1 antibodies in sera of MM patients in complete remission compared to patients who do not achieve it. Large-scale study monitoring the patients from diagnosis to maximal therapeutic response could help us to assess the effect of these autoantibodies and reveal whether

the anti-ENO1 antibodies can be a valuable prognostic marker for MM.

P-099
Novel targets detected by next generation sequencing among triple refractory patients can be clinically targetable

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Introduction: Herein, we aimed to analyze mutational profile of triple class refractory MM (RRMM) patients by Next Generation Sequencing (NGS) platform and in case of a targetable mutation, results of "off label" treatment with Trametinib, Evorolimus or Vemurafenib will be presented here.
Methods: A total of 28 consecutive triple class refractory MM and two newly diagnosed patients between November 2018-May 2022 were included in the analysis. Isolated plasma cells or marrow/ plasmacytoma smears were subjected to QIAseq targeted DNA panel (12)- Human myeloid neoplasm panel covering all exons and exon-intron junctions of 141 target genes on İllumina Miseq platform (USA).
Results: Patient characteristics are: Female/male: 12/18; age: median 57 (range, 39-87) prior lines of treatment: median 4 (range; 1-13) extramedullary disease (EMD)(+/-): 12/18. NGS results were as follows: 59 mutations in 26 genes were detected. Among these recurrent genomic abnormalities, concomitant missense protein coding alterations were detected in all patients. Mutations of RAS/MAPK pathway genes were the most frequently detected ones. The hotspots of mutation in KRAS, NRAS and BRAF were codon 61; codons 61 and 13 as well as codon 600 respectively. In addition, we detected novel myeloproliferative and myelodysplasia associated mutations previously not described in MM. A diverse range of recurrent gains and losses were detected in our cohort. Two patients at diagnosis also carried mutations in KRAS. Comparison of mutations between w/wo EMD (n=12/18) was. NRAS/KRAS (6/12 vs 10/18), BRAF (1/12 vs 2/18) and TP53 (6/12 vs 2/18) in favor of p53 mutations among patients with EMD. Treatments: Based on these results seven patients were able to obtain off-label approval for treatment with Everolimus (Evo) (for PTEN) (Patient 1 & 11) or Trametinib (Tra) (for KRAS) (Patient 3, 5,6 & 9) in combination with Pomalidomide (PomDex) w/wo Daratumumab. One patient with BRAF mutation was given vemurafenib monotherapy. Responses are summarized as follows: Patient-1 had extensive extramedullary disease (EMD) in the skin, which responded completely to Dara-EvoPomDex combination with a VGPR duration of only two months. Patients-3, 9 and 11 could not survive enough to observe a benefit of Tra-or EvoPomDex. Patient-5, plasma cell leukemia, received Tra-PomDex for three months with a deepest response of VGPR lost after allogeneic hematopoietic stem cell transplantation. Patient-6, also presenting with EMD, was treated with TraPomDex as the seventh treatment line which was well tolerated with a transient VGPR, lost during interruption secondary to an infectious episode. Currently only patient-20 who also has EMD is on treatment and has responded to four months of vemurafenib with VGPR.
Conclusions: Detection of clonal mutations in our experience has shown higher incidence of p53 mutations among EMD and has led us to design novel treatment options achieving transient ≥VGPR responses.

P-100
Allosteric HSP70 inhibitors perturb mitochondrial proteostasis and overcome proteasome inhibitor resistance in multiple myeloma

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Introduction: Even in the era of novel immunotherapeutics in myeloma, proteasome inhibitor (PI) resistance remains a central challenge in this disease. PI resistance is thought to lead to large-scale remodeling of the malignant plasma cell proteome, and exploiting this proteomic remodeling may reveal new vulnerabilities for treatment of relapsed/refractory disease.
Methods: Genetic dependencies in proteostasis were evaluated using data in the DepMap Avana CRISPR screen data (Q1 2019). "JG" class allosteric compounds were synthesized and characterized as previously described. Cell line screens for drug sensitivity were performed in technical quadruplicate with viability measured by CellTiterGlo. Mass spectrometry experiments were performed using a Thermo Q-Exactive Plus mass spectrometer. In vivo experiments were performed using NSG mice intravenously implanted with luciferase-labeled RPMI-8226 cells. Patient survival analysis was performed using MMRF CoMMpass database (release IA14).
Results: To identify pathways mediating resistance, we first mapped proteasome-associated genetic co-dependencies using the DepMap CRISPR viability screen database. We identified heat shock protein 70 (HSP70) chaperones as potential targets, consistent with proposed mechanisms of myeloma cells overcoming PI-induced stress. We therefore explored allosteric HSP70 inhibitors (JG compounds) as myeloma therapeutics. 14 of 15 tested JG compounds exhibited increased efficacy against acquired and intrinsic PI-resistant myeloma models, unlike HSP90 inhibition. In vivo studies suggested efficacy of the lead compound JG342 versus a disseminated myeloma model. To further investigate the mechanism of increased potency vs. PI-resistant disease, shotgun and pulsed-SILAC mass spectrometry across several

myeloma cell line models demonstrated that JGs unexpectedly impact myeloma proteostasis by destabilizing the 55S mitoribosome. Further analysis of mitochondrial dynamics confirm specific localization of JG compounds to mitochondria and selective impacts on PI-resistant disease. Taken together, our data suggest JGs have the most pronounced anti-myeloma effect not through inhibiting cytosolic HSP70s but instead, surprisingly, through mitochondrial-localized HSP70, HSPA9/mortalin. Analysis of myeloma patient data in the CoMMpass database further supports effects of global proteostasis capacity, and particularly HSPA9 expression, as a central determinant of PI response.
Conclusions: Our results characterize myeloma proteostasis networks under therapeutic pressure, motivate further investigation of HSPA9 as a specific vulnerability in PI-resistant disease, and suggest "JG" compounds as a promising class of myeloma therapeutics.

P-101
Long noncoding RNA LINC01410 interacts with the minichromosome maintenance (MCM) complex to promote tumor cell growth in multiple myeloma

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Introduction: The human genome contains thousands of loci that produce long non-protein coding RNAs (lncRNAs) that play critical roles in tumorigenesis and healthy cell function. We have recently described the lncRNA landscape in newly diagnosed multiple myeloma (MM) patients, identified their role as independent risk predictors for clinical outcome, and validated the functional contribution of specific lncRNAs to MM cell growth and viability. Although these examples suggest the significance of lncRNAs in myeloma pathobiology, the vast majority of lncRNA genes have not been functionally tested.
Methods: To identify lncRNAs that promote MM cell growth, we performed a large-scale cell viability screen of lncRNAs using CRISPR interference (CRISPRi) to inhibit gene expression. To find lncRNA targets, we first interrogated our large RNA-seq dataset from 360 newly diagnosed MM patients and identified 913 lncRNA transcripts expressed in primary MM cells. We designed the CRISPRi library to target the transcription start site of these 913 lncRNA genes, each with 7 sgRNAs. We screened 3 MM cell lines (H929, KMS12BM, KMS11) and identified 32 lncRNA loci that modified cell growth upon CRISPRi targeting, with 7 lncRNAs impacting all three cell lines tested. We then evaluated the differential expression of these lncRNAs in primary MM cells as compared to normal plasma cells.
Results: We observed that LINC01410 was significantly overexpressed in MM patients compared to normal PC, especially in MM patients with t(4;14) translocations, and was an independent risk predictor that highly correlated with EFS and OS in newly diagnosed MM patients. We next knocked down LINC01410 using gapmeR antisense oligonucleotides (ASO) in a panel of MM cell lines and observed time-dependent inhibition of MM cell viability, including in the t(4;14) cell lines. As LINC01410 appears to localize to both the cytosol and nucleus, we also utilized siRNAs to specifically target the cytosolic isoform and observed a robust reduction of cell growth, suggesting that both cellular localizations are important for the activity of LINC01410. Transcriptomic analysis indicated a set of genes modulated in response to LINC01410 depletion, with an enrichment in genes involved in cell cycle and DNA replication. An RNA-protein pull down (RPPD) assay identified three out of six minichromosome maintenance (MCM) protein complex subunits (MCM4, MCM5, MCM7) as relevant protein interactors of LINC01410, highlighting a potential role of LINC01410 in the modulation of the DNA replication machinery. The functional impact of modulating LINC01410 on MCM proteins is under investigation and will be presented.
Conclusions: In conclusion, we report the identification of a novel lncRNA LINC01410 that supports MM cell growth via control of the cell cycle/DNA replication axis. Promising developments in the field of lncRNA inhibitors may allow forthcoming clinical applications.

P-102
Novel anti-CD84 humanized monoclonal antibody enhances anti-tumor immunity in multiple myeloma

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Introduction: In recent years, monoclonal antibodies (mAbs) have become important weapons in the arsenal of anti-myeloma drugs. We previously showed that targeting CD84 with antagonist anti-CD84 mAb (B4) reduced immune checkpoints (ICs) on myeloma cells, immunosuppressive myeloid cells, and T cells, increased T cell activity, and reduced MM progression.
Methods: In this study, we demonstrate the efficacy of our first-generation humanized B4 mAb with respect to binding, reduction of ICs, and induction of antibody-dependent cell-mediated cytotoxicity (ADCC) and macrophage-mediated programmed cell removal (PrCR) in MM.
Results: The first-generation humanized B4 mAb constructs (HB4-1 to HB4-10) were developed by working with CrownBio Science. The back-to-mouse mutations in the light and/or heavy chain(s) of the constructs improved the antigen affinity, except for HB4-4, HB4-5, and HB4-9. We detected a significant reduction of PD-L1 levels in CD14+ cells following

the treatment with HB4-1 (n=4, p< 0.001), HB4-3 (n=3, p< 0.001), and HB4-6 (n=4, p< 0.0001) from the specimens of healthy donors (HDs) and MM patients. We also confirmed the specificity of the selected HB4 constructs on the generated CD84-HEK293T stable cell line, and HB4-6 showed strong binding to the CD84-HEK293T stable cells. Next, the cells from the bone marrow (BM) aspirates of MM patients and HDs were treated with either HB4-6 or control hIgG1 antibody and examined using mass cytometry (CyTOF). We noted that HB4-6 increased the total T- and NK cell numbers and slightly reduced classical monocytes compared with the control hIgG1 antibody. HB4-6 significantly reduced PD-L1 expression on CD14+ cells derived from BMs of MM patients who received multiple line therapies. Similarly, the single-cell RNA sequencing showed HB4-6 reduced multiple ICs, including PDL1, PD1, and CTLA4 mRNA levels in the BM aspirates of MM patients. The capacity of HB4-6 to induce macrophage-mediated PrCR of MM cells was tested using human or mouse macrophages (mϕ) as effector cells and MM.1S/GFP+ target cells. HB4-6 induced mϕ-mediated phagocytosis by increasing GFP positive mϕ (n=3, p< 0.001). The ability of HB4-6 to lyse MM cells by ADCC was examined using Cr51 assay. HB4-6, but not isotype control hIgG1, triggered ADCC against CD84-expressing cell lines cultured with T-, NK cells, and PBMC from different donors. To further explore the therapeutic potential of HB4-6 on the anti-tumor immunity in MM, HB4-6 was tested in vivo with the lowest dose (1mg/kg) using MM.1S/Luc+ xenograft model in the mice. The results show that HB4-6 treatment significantly reduced MM progression by the induced anti-tumor activity in the mice compared with the control group (n=4, p< 0.05) in the low dose setting with once a week, intravenous administration, a total of four doses.
Conclusions: Our data suggest that targeting CD84 with the novel humanized B4 mAb, HB4-6, represents promising results to enhance anti-myeloma immunity and allow to advance a novel therapeutic approach for MM.

P-103
ADAR1-dsRNA metabolism in myeloma cells with 1q amplification: a novel therapeutic target

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Introduction: Amplification of chromosome 1q (Amp1q) has been drawn attention because of the high-frequent detection in high-risk multiple myeloma (MM). ADAR1, whose gene resides in chromosome 1q21, edits adenosine to inosine (A to I) in double strand RNAs (dsRNAs) to eventually elicit DNA mutation and miRNA generation. Recent study has revealed that dsRNA transcription is induced by inhibition of DNA methyltransferase DNMT1, resulting in cancer cell death (Nature 2020). We have reported the therapeutic impact of targeting class I histone deacetylases (HDACs), especially HDAC1 and HDAC3 with targeting DNMT1 in MM (Leukemia 2017). We here aimed to clarify the therapeutic impact of targeting the ADAR1-dsRNA metabolism on MM cells with Amp1q.
Methods: dsRNAs were detected by flow cytometry and fluorescent immunohistochemistry. Cytotoxic activity and apoptosis were evaluated by CCK-8 assay and Annexin V – PI assay, respectively. Gene suppression was conducted using lentiviral shRNA systems. We transplanted RPMI 8226-Luc cells in the right tibia of C.B-17 SCID mice, and the tumor were detected using IVIS imaging system.
Results: ADAR1 expression was found to be higher in MM cells acquiring Amp1q, especially more than 4 copies of 1q (GSE4581). We detected ADAR1 expression in accordance with CD138 positive cells in the primary bone marrow samples in immunohistochemistry. ADAR1 knockdown induced MM cell apoptosis and suppressed tumor engraftment and growth in vivo, suggesting anti-MM potential by perturbation of A-to-I dsRNA edition. We then examined the cytotoxic effects of anti-MM agents such as carfilzomib, pomalidomide, and HDAC inhibitors in RPMI 8226 cells with ADAR1 knockdown. Class I HDAC inhibitor entinostat (MS-275) cooperatively induced cell death in the MM cells. MS-275 induced dsRNA accumulation with downregulation of DNMT1 in MM cells. To delineate the roles of difference between HDAC1 and HDAC3, we carried out RNA-seq in HDAC1 or HDAC3-knockdown RPMI 8226 cells. The gene set enrichment analysis revealed that HDAC1 knockdown but not HDAC3, significantly upregulated genes related to dsRNA-binding and/or type I interferon (IFN) production, i.e. IFN-stimulated genes (ISGs) such as IRF7 and EIF2AK2, suggesting a role of NuRD complex containing HDAC1 in ISG repression. Because ISGs are upregulated by type I IFN, we next the cytotoxic effect of type I IFN in MM cells. Interestingly, IFN-a/b alone did not induce MM cell death but was able to enhance it by ADAR1 knockdown; however, MS-275 did not induce further cytotoxic effect of type I IFN in MM cells, indicating utilization of the same targets of ISGs with between HDAC1 inhibition and type I IFN-stimulation in targeting ADAR1-dsRNA metabolic axis in MM cells.

Conclusions: dsRNA overloading with ADAR1 inhibition may become a unique strategy targeting MM cells with Amp1q. Further study is warranted on the roles of ADAR1 for dsRNA-editing and development of novel immunotherapies targeting dsRNA accumulation in high-risk MM.

P-104
Multi-omics data integration reveals molecular targets of carfilzomib resistance in multiple myeloma

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Introduction: Multiple myeloma (MM) is a heterogeneous malignancy with frequent clonal evolution during the course of the disease adding to the genetic complexity. Furthermore, prolonged exposure to specific treatments often results in loss of sensitivity and outgrowth of drug resistant clones. This phenomenon applies to all conventional therapies including proteasome inhibitors. In order to evaluate the mechanisms leading to carfilzomib (CFZ) resistance, we aimed to identify significantly deregulated genes and proteins in MM cell lines, which we rendered resistant to CFZ. In addition, we compared the in vitro data with gene expression data of CFZ-sensitive or resistant patients of the Multiple Myeloma Research Foundation (MMRF) CoMMpass study.
Methods: MM cell lines were continuously exposed to increasing doses of CFZ, leading to the outgrowth of CFZ-resistant clones. Resistant cell lines and their sensitive parental cell lines were subjected to RNA-sequencing and proteomic profiling. The obtained results were analyzed for differential expression by contrasting CFZ-sensitive cell lines to their resistant variants. This was followed by comparing the cell lines' protein expression data to identify gene/protein candidates associated with CFZ resistance. To further prioritize the top candidates, we integrated the findings with the outcomes of survival analyses of CFZ-exposed and resistant patients of the CoMMpass data base. Protein expression was analyzed by western blotting. Cell viability was determined by WST-8 proliferation assay and apoptosis (Annexin V, 7AAD) was analyzed by flow cytometry.
Results: The computational analyses identified 526 genes as significantly deregulated (±2 fold) in CFZ-resistant cell lines as compared to their sensitive counterparts. Integrating the gene expression and protein expression data revealed a total of 509 deregulated genes/proteins associated with CFZ resistance being consistent in direction, of which 237 genes were significantly upregulated and 272 were downregulated. These data were compared with results obtained by gene expression and gene set enrichment analysis of patients that were sensitive or resistant to a CFZ-based first line therapy of the CoMMpass study. As a result of this comparison six genes/proteins, namely ABCB1 (MDR1), WEE1, STRIP1, PACSIN1, RICTOR (upregulated) and GATM (downregulated), were identified and associated with resistance both in vivo and in vitro. These targets were experimentally validated at the protein level, via western blotting. Drug combination screening and shRNA-mediated perturbations are currently being performed to further elucidate their impact on resistance.
Conclusions: Our integrative data analysis identified the significant deregulation of six genes in CFZ-resistant MM cell models and patients. GATM, PACSIN1 and STRIP1 have not been reported previously in this context and thus seem to represent promising novel targets for treatment strategies aiming to overcome CFZ resistance in MM.

P-105
HDAC6 inhibitors enhance proteasome-dependent antigen presentation to promote T-cell-mediated tumor killing

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Introduction: Proteasomes are a central component of a cascade of proteolytic processing steps required to generate antigenic peptides presented at the cell surface to cytotoxic T lymphocytes (CTLs) by MHC class I molecules. Importantly, cancer cells downregulate the generation and presentation of antigenic peptides as a means to escape host anti-tumor immunity. Moreover, proteasomes may not generate certain antigenic peptides with adequate efficiency which limits the susceptibility of cancer cells to antigen-presenting cells. Here, we hypothesized that the proteasome-mediated generation of antigenic peptides could be pharmacologically enhanced to increase the presentation of tumor antigens as a means to enhance CTL-mediated tumor lysis.
Methods: We performed a cell-based, high-throughput screen (HTS) using ~3,400 FDA-approved drugs and bioactive molecules to identify those that increased proteasomal peptide-hydrolyzing activity. We then determined whether "hits" identified in the HTS also increased presentation of a specific MHC class I antigen (SIINFEKL which is derived from chicken ovalbumin). We engineered a T-cell that specifically expresses a T-cell receptor (TCR) that recognizes SIINFEKL. Tumor cells were pre-treated with hits identified in the HTS, most notably the histone deacetylase (HDAC6) inhibitors Tubastatin A and ACY-1215, and then incubated with the engineered T-cells to determine the effect of pharmacologics on T-cell-mediated tumor lysis.

Results: Results of the cell-based HTS indicated that the HDAC6 inhibitors Tubastatin A and ACY-1215 were among the most potent agents to increase proteasome activity. We then studied the lymphoma cell line EG.7-ova which constitutively expresses the chicken ovalbumin gene. Proteasomal degradation of ovalbumin generates a peptide, SIINFEKL, that is presented at the tumor surface complexed with MHC class I molecules. Treatment of EG.7-ova cells with HDAC6 inhibitors enhanced presentation of the SIINFEKL:MHC class I complex up to 3-fold. B3Z CTLs are T cells that engineered to express a TCR that specifically-recognizes SIINFEKL. When EG.7-ova cells were pre-treated with HDAC6 inhibitors and co-cultured with SIINFEKL-restricted B3Z cells, tumor lysis was increased up to 3-fold. Western blotting showed that treatment of MM cells with HDAC6 inhibitors increased immunoproteasome levels and activity.
Conclusions: While the majority of current immunotherapeutics are designed to activate T cells that express native or chimeric-antigen receptors, here, here we demonstrate that pharmacologic modulation of proteasomes can potently stimulate presentation of tumor antigens and represents an actionable approach to trigger anti-tumor immunity. Taken together, our results endorse a paradigm-shifting approach to exploit pharmacologics that enhance proteasomal generation of tumor antigens as an anti-myeloma strategy.

P-106
Overcoming IMiDs-resistance in multiple myeloma by targeting MAP4K2

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Introduction: MM is characterized by clonal evolution with a rising number of mutations. Over 43% of newly diagnosed MM patients carry RAS mutations associated with a poorer prognosis. Unfortunately, so far there is no treatment targeting RAS mutations in MM. Recently we have shown that MAP4K2 knockdown in K- or N-RAS mutated MM cells induces MM cell growth inhibition, associated with the downregulation of critical transcriptional factors including IKZF1/3, BCL-6, and c-MYC proteins (Li et al. Blood 2021). Immunomodulatory drugs such as lenalidomide, pomalidomide, and iberdomide are very effective backbone treatments by binding to cereblon (CRBN), and subsequently inducing IKZF1/3 protein degradation that leads to MM cell growth inhibition. Interestingly, our data showed that MAP4K2 knockdown or inhibition also decreases the IKZF1 level, indicating that IKZF1 is under the regulation of MAP4K2.
Methods: To further validate MAP4K2 inhibition as a novel strategy to overcome IMiDs-resistance, we generated lenalidomide-resistant human myeloma cell lines. In this model, MM1S-LENRES cells showed significantly decreased expression of CRBN protein compared to the parent cells resulting in abrogated CRBN-mediated down-regulation of IKZF1, c-MYC, IKZF3, and IRF4. Moreover, we evaluated the combined effects of Iberdomide which has a higher affinity to CRBN with MAP4K2-silencing in MM. Tet-on sh-MAP4K2 lentivirus was introduced into RASMut MM cells to establish the inducible MAP4K2 knockdown cells upon doxycycline treatment. To address the combination effects, Tet-on sh-MAP4K2 RASMut was activated by doxycycline, and MM cells were treated with different dosages of iberdomide.
Results: As expected, MM1S-LENRES cells were resistant to lenalidomide induced growth inhibition in the cell proliferation assay. In contrast, MAP4K2 inhibition using TL4-12 potently induced IKZF1, c-MYC, and IRF4 downregulation as well as cell proliferation inhibition, demonstrating that MAP4K2 regulates IKZF1 and cell growth independently of CRBN. These results indicate that MAP4K2 is a novel therapeutic target to overcome IMiDs-resistance MM. We found that MAP4K2 silencing strongly increased iberdomide-induced apoptosis (iberdomide alone vs. with MAP4K2 KD: 32% vs 92). Similar, in western blot assays, MAP4K2 silencing combined with Iberdomide significantly enhanced the downregulation of IKZF1, c-MYC, and IRF4 compared to the iberdomide treatment alone. These data suggest that the combination of iberdomide and MAP4K2 inhibition has synergetic anti-MM effects.
Conclusions: Taken together, our findings demonstrate that MAP4K2 is a novel therapeutic target to bypass IMiDs resistance in RAS mutated MM. The combination of MAP4K2 inhibition with Iberdomide results in synergetic anti-cancer effects in MM, therefore could be a potential novel therapeutic regimen for patients with relapsed/refractory multiple myeloma.

P-107
Anti-tumor activity of covalent menin inhibitor, BMF-219, in high-grade B-cell lymphoma and multiple myeloma preclinical models

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Introduction: Menin is a scaffold protein that interacts with various transcriptional regulators and partner proteins to promote tumorigenesis in a context-dependent manner. Menin drives oncogenic signaling by regulating expression of genes such as HOXA9 and MEIS1 and is also known to play a key role in MYC-mediated transcriptional activities. BMF-219 is a highly selective, potent, orally bioavailable, small molecule covalent inhibitor of menin. We previously reported the ability of BMF-219 to modulate MYC expression and exhibit high potency against Double HIT Lymphoma (DHL) DLBCL (Diffuse Large B Cell Lymphoma) preclinical models.
Methods: In the current study we demonstrate the anti-tumor activity of BMF-219 in multiple myeloma (MM), and

Double/Triple Hit Lymphoma (DHL/THL) and Double Expressor Lymphoma (DEL) high-grade B-cell lymphomas (HGBCL) preclinical models harboring various mutational backgrounds. Additionally, we provide mechanistic evidence for direct inhibition of menin protein, in cell line models representing MM, DHL and DEL.
Results: BMF-219 exhibited high potency in THL and DEL cell lines (IC50 = 0.27 μM and 0.37 μM, respectively), achieving >90% growth inhibition as single agent. BMF-219 was multi-fold more potent and exerted dramatically greater growth inhibition compared to clinical reversible menin inhibitors in all DLBCL cell lines tested, including an expanded panel of DHL cell lines. In ex vivo studies, an R-CHOP refractory THL patient sample and an R-EPOCH refractory MYC-amplified DLBCL patient sample were highly sensitive to BMF-219 treatment (IC50 = 0.15 μM and 0.2 μM, respectively) and demonstrated complete growth inhibition at 1 μM exposure. In contrast, two clinical reversible menin inhibitors demonstrated much lower potency (IC50 = ~1 μM to >10 μM). MM cell lines harboring mutations in TP53, KRAS and NRAS were all sensitive to BMF-219 with growth inhibiton IC50 values in the range of 0.25 μM to 0.5 μM and achieved 100% inhibition at 1 μM. Notably, BMF-219 demonstrated single-agent efficacy (IC50 = 0.1 μM to 0.3 μM) against a panel of newly diagnosed and R/R ex vivo MM samples, including a p53-deleted clinical profile. Mechanistically, BMF-219 induced a reduction in menin protein levels, the direct target of this covalent inhibitor. The dose-dependent reduction in menin protein across the collection of MM and DLBCL cell lines with varying cytogenetic and mutational backgrounds will be discussed. Analysis of additional proteins modulated by BMF-219 in these cell line models will also be addressed.
Conclusions: Collectively, our data demonstrate the novel and robust anti-tumor activity of BMF-219 in HGBCL and MM preclinical models that represent categories of high unmet need. BMF-219 exhibits multi-fold higher potency and complete growth inhibition in these preclinical models compared to clinical reversible menin inhibitors, demonstrating its unique anti-tumor potential in these cancers.

P-108
An antisense platform for the pre-clinical development of novel LncRNA inhibitors in multiple myeloma

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Introduction: Our recent studies indicate that long non-protein coding RNAs (lncRNAs) play fundamental roles in the growth of multiple myeloma (MM). These RNA molecules provide essential chromatin scaffolds for protein interactions contributing to the epigenetic and transcriptional reprogramming of tumor cells. Therefore, inhibiting specific lncRNAs could be an avenue for novel and more effective treatments.
Methods: To this end, we developed an antisense oligonucleotide (ASO)-based platform to optimize the design and chemistry of clinically applicable inhibitors to specified lncRNAs. Our platform is based on ASOs with a phosphorothioate backbone, 2'-O-Methoxyethyl (2'-MOE) sugar moiety, and chemically modified nucleobases (e.g., methyl-C), which ensure ASO stability while promoting antisense activity. ASOs are configured either as 2'-MOE / DNA "gapmeRs" to trigger RNase H-mediated degradation of their lncRNAs or as fully 2'-MOE "blockmeRs" to block the interaction of lncRNAs with other molecules. To design both a gapmeR and a blockmeR to knock down a specific lncRNA, we use three steps. In step 1, 22-mer ASOs are used to identify the most accessible lncRNA stretches by tiling the entire lncRNA sequence. In step 2, the selected sequences are fine-tuned to become up to twenty shorter ASOs (16- to 20-mer) that are tested for enhanced knockdown activity. In step 3, ASOs are lipid-conjugated to either cholesterol, tocopherol, or palmitic acid to facilitate their intracellular trafficking and endosomal release.
Results: Here, we used this platform to target RROL, a lncRNA that forms an essential chromatin scaffold to transcribe genes key for myeloma cell growth. From >80 ASOs, we identified two 18-mer tocopherol-conjugated molecules (gapmeR G2-15b-T and blockmeR B9-19-T) with strong knock-down activity. Both ASOs showed potent anti-proliferative effects against MM cell lines (n=10) and CD138+ cells from 3 MM patients, while sparing non-malignant cell lines (n=5) and PBMCs from 3 healthy donors. We next assessed in vivo anti-tumor activity in three models: an AMO1-based plasmacytoma xenograft model in immunocompromised NOD SCID mice, an aggressive model of diffused myeloma, and a clinically relevant PDX-NSG mouse model using tail-vein injection of CD138+ MM cells obtained from an advanced-stage patient. In all three models, both compounds inhibited tumor growth by 52–84%. In the aggressive model, treatment with G2-15b-T resulted in tumor clearance in 2 out of 8 mice (25%) and prolonged survival. In the tail-vein model, we observed a regression of tumor growth with G2-15b-T, whose effects were comparable to bortezomib. We also observed no overt toxicity in the mice. Toxicity and safety studies in rats and non-human primates are ongoing and will be presented.
Conclusions: Overall, this study validates a powerful process to develop inhibitors to target the tumor-promoting lncRNAs, such as RROL, to develop the next generation of therapeutics in MM and other cancers.

P-109
ER-phagic control of lipid metabolism supports multiple myeloma cell survival

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Introduction: Autophagy is a highly conserved lysosomal strategy recycling supramolecular structures. We previously demonstrated distinctive autophagic activity in plasma cell (PC) ontogeny, and proved it indispensable for long-lived bone marrow PCs, responsible for immune serological memory, and their malignant counterpart, the age-onset cancer, multiple myeloma (MM). We also defined the endoplasmic reticulum (ER) as a major target of selective autophagy in normal and malignant PCs, but the role of ER-phagy in PCs is unknown. We investigated the mechanisms and functional significance of ER-phagy in search for new vulnerabilities against myeloma.
Methods: To dissect and characterize ER-phagy in MM, we adopted molecular and cell biology approaches, including the assessment of bioenergetics and organelle dynamics via SeaHorse, electron microscopy (EM), EM cytochemistry, proteomics, and ImageStream assays upon targeted genetic and pharmacologic inhibition in human MM cell lines.
Results: In professional secretory cells, ER-phagy has been shown to cooperate with the proteasome for secretory protein quality control. In contrast, by pulse-chase radiometabolic assays we found that degradation of immunoglobulins, the main PC secretory client proteins, is entirely accounted for by the proteasome. We thus postulated an alternative function whereby ER-phagy may recycle the ER biomass into energetic equivalents. Imaging studies revealed abundant lipid droplets (LD) in MM cells, whose number and size dropped upon pharmacologic or genetic inhibition of autophagy or the lysosomal acid lipase, implicating constitutive autophago-lysosomal lipid recycling in LD replenishment in MM cells. Attesting to a key energetic role, pharmacologic and genetic inhibition of mitochondrial fatty acid import increased LD number and size at the expense of mitochondrial respiration, cellular ATP, and proliferation. We then investigated recently recognized tissue-specific ER membrane inbuilt autophagy receptors and identified the ER-resident protein CCPG1 as highly expressed and mediating vital constitutive ER-phagy in PCs, as its ablation significantly increased the ER proteome and ER size, reduced LD and ATP cellular content, arrested cell growth, and compromised survival of MM cells.
Conclusions: Despite the unrivaled secretory proteosynthetic activity of PCs, ER-phagy does not mediate quality control in MM, but maintains LDs, which in turn fuel mitochondria to sustain bioenergetics. We infer an unexpected level of ER plasticity in PCs, which exploit constitutive ER biogenesis as a default source of fatty acids as energy equivalents via an autophago-lysosomal recycling route.
P-110

Activity and tolerability of lenalidomide (LLD) is enhanced following low-dose continuous percutaneous delivery compared to once daily dosing in an NCIH929 MM Xenograft model in SCID mice

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Introduction: The daily administration of lenalidomide (LLD) is well established in the treatment of MM. LLD has a short half-live, which leads to high peak to trough fluctuations leading to excessive or sub-therapeutic exposure with daily dosing while toxicity is associated with its high exposure (AUC). Continuous drug delivery is an ideal method to eliminate peak to trough variations and may improve tolerability and efficacy.
Methods: The study employed an implantable osmotic pump (iPrecio) which can deliver a continuous s.c. infusion of LLD. An H929 MM xenograft was implanted in SCID mice and allowed to reach a tumor volume (TV) of > 100 mm3 prior to any treatment. Six groups of N=10 animals were evaluated which included: Grp1 i.p. vehicle injected controls; Grp2 LLD 25 mg/kg i.p. once daily; Grp3 LLD 6 ug/hr sc; Grp4 LLD 2 ug/hr sc; Grp5 LLD 1 ug/hr sc; and, Grp6 LLD 0.5 ug/hr sc. Grps 3-6 received LLD by a continuous infusion while Grps 1-2 where dosed once a day Treatment was administered daily over 29-days. The maximum dose of 6 ug/h as the MTD based on a separate tolerability study in healthy mice. TV was assessed by caliper measures and treatment failure was considered a TV of > 2000 mm3. LLD pharmacokinetics were measured using a sparse technique. CBCs were also obtained in a sparse fashion. A separate toxicology study was performed in healthy male and female mice treated with continuous LLD at 6 ug/h and 2 ug/h compared to control vehicle over 29 days.
Results: Changes in body weight were acceptable in all treatment groups. Animals in Grp 3 had a PR (60%) or CR (40%) while no animals in Grp 2 achieved a decrease in tumor volume. No animals in any other group had a PR or better. The time to 100% treatment failure was 53 days in Grp 2, 71 days in Grp 4, and >100 days in Grp3. In Grp 3, 2 animals remained tumor free at 100 days and were euthanized. The daily exposure (AUC) and dose (ug/day) in Grp3 was ~29% of that observed with a standard i.p. dose. Results from the toxicology study demonstrated no treatment-related histopathologic changes. There was no significant difference in any hematology parameters (e.g., WBC, ANC, platelets) compared to the vehicle controls at day 29.
Conclusions: To our knowledge, these data represent the first demonstration that dosing of LLD can be altered to improve the efficacy and tolerability of treatment. A percutaneous delivery of just 29% of the standard i.p. LLD dose was superior in disease control and can produced objective responses in this model. Tolerability in terms of body weight, histopathology, and hematology suggest no aberrant effects from continuous delivery. These data suggest percutaneous

administration of continuous low-doses of LLD may improve the tolerability and efficacy compared to once daily dosing.

P-111
Targeting the mitochondrial protease ClpP unveils novel vulnerabilities in multiple myeloma

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Introduction: Mitochondria are enticing potential targets against cancer, owing to their role as signaling hubs orchestrating key homeostatic functions. Of special interest is ClpP, a major protease of the mitochondrial matrix, recently found essential for leukemic cell viability via maintenance of oxidative phosphorylation (OXPHOS) activity. Prompted by its distinctive expression in multiple myeloma (MM) cells, we investigated the role of ClpP in maintaining mitochondrial and cellular homeostasis in malignant plasma cells (PC) in search for new potential anti-myeloma targets.
Methods: We used public and proprietary RNA-seq datasets of normal and malignant PCs and MM cell lines to analyze the expression of ClpP and its correlation with other transcriptional features. We genetically manipulated ClpP expression in MM cell lines, by both stable and inducible shRNA-mediated knockdown (KD) and CRISPR/Cas9 knockout (KO), and assessed their sequelae by combining electron microscopy, Seahorse and ATP assays, transcriptomics, proteomics, and metabolomics.
Results: ClpP mRNA was significantly higher in bone marrow-purified malignant than normal PCs, and MM cells were the highest ClpP-expressing human cancer cell lines. Attesting to a crucial role in myeloma, both acute KD and chronic KO led to apoptosis and reduced proliferation. Intriguingly, toxicity in MM proved independent of the currently acknowledged ClpP-controlled mitochondrial functions, i.e., mito-ribosome assembly and OXPHOS maintenance. Indeed, not only did Seahorse demonstrate no effect of ClpP KD on OXPHOS activity, but toxicity of ClpP ablation extended to glycolytic cell lines, thus unveiling an unprecedented energy-independent vulnerability. To unbiasedly define the role of ClpP in MM, we undertook a threefold orthogonal approach employing RNA-seq, proteomics, and metabolomics upon ClpP KD. We observed a transcriptional and protein downregulation in the enzymes of the polyamine pathway, coupled with correspondingly reduced abundance of active polyamines, including spermidine, recently found essential for several cellular homeostatic functions, including pro-survival autophagy in activated B cells. In parallel, unbiased Gene Set Enrichment Analysis (GSEA) of RNA-seq data identified activation of interferon-responsive pathways following ClpP KD. In line with recent evidence of activation of cGAS-STING by mitochondrial DNA leakage in CLPP KO fibroblasts, we were able to confirm transcriptional up-regulation of interferon-stimulated genes in MM cells upon ClpP KD, hinting at mitochondria and ClpP as possible targets to manipulate MM immunogenicity.
Conclusions: Overall, our data strongly suggest that ClpP is essential to MM cells due to a novel non-bioenergetic function through an unprecedented role of mitochondrial homeostasis in regulating polyamine biosynthesis. Our data also hint at ClpP as a novel target to stimulate anti-tumoral immunity via cGAS-STING activation in MM.

P-112
Anti-BCMA therapy in multiple myeloma: a single-center experience

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Introduction: Triple-class refractory multiple myeloma (MM) represents an unmet medical need, because there is not a standard of care and overall survival (OS) is not superior to 9 months. BCMA has appeared as an interesting immune target to treat MM, targetable both by bispecific monoclonal antibodies (BiAbs) and CAR-T, however no head-to-head comparative studies are available.The aims of the present study were to indirectly compare the time to access to the therapy and hospitalization, toxicity and efficacy of BCMA BiAbs antibodies and CAR-T.
Methods: An observational retrospective study was designed including MM patients treated with BCMA CAR-T or BCMA BiAbs antibodies in clinical trials at the Hospital of Salamanca (October 2018 – April 2022).
Results: Forty-nine patients treated with BCMA therapy were included. Twenty-seven (55.1%) received CAR-T and 22 (44.9%) BiAbs. Twenty-eight (57.1%) were male and the median age was 60 years (36-77). The median prior lines was 3 (1-10) and 39 (79.6%) were triple exposed and 28 (57.1%) triple refractory. Patients who received BiAbs were treated earlier (12 vs. 56 days; $p < 0.001$) and were hospitalized for less time (13 vs. 21 days; $p = 0.018$). Overall response rate was superior in CAR-T patients (100% vs. 52.4%; $p < 0.001$) as well as percentage of CR (70.4% vs. 47.6%; $p = 0.110$). Incidence of CRS was higher in the CAR-T group than the biespecifics group (92.6% vs. 68.2%; $p = 0.028$) and the percentage of grade 4 neutropenia (92.6% vs. 22.7%; $p < 0.001$) and thrombocytopenia (70.4% vs. 9.1%; $p < 0.001$). No differences in neurotoxicity were observed. Infections were

more frequent in the bispecifics group (especially between the first- and third-month treatment initiation, 55.6% vs. 14.8%; p = 0.004), including COVID-19 infection (50.0% vs. 29.6%; p = 0.002). In addition, patients who received CAR-T readmitted less than BiAbs (51.9% vs. 81.8%; p = 0.028). With a median follow up of 14.3 months (1.1-41.8), PFS was superior in patients treated with CAR-T (18.9 vs. 6.1 months; p = 0.045) as well as OS (not reached vs. 25.5 months; p = 0.016).
Conclusions: The time to access to therapy and hospitalization was shorter in patients treated with BiAbs antibodies. The incidence of CRS and cytopenia were higher in the CAR-T group, but mid-term and COVID-19 infections were more frequent in patients treated with BiAbs. Although these are indirect comparisons, response, PFS and OS were statistically superior in patients treated with CAR-T than bispecific monoclonal antibodies.

P-113
Infectious toxicities in patients treated with bispecific antibodies in multiple myeloma

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Introduction: Bispecific antibodies (BsAbs) are a novel immunotherapeutic approach designed to bind antigens on malignant plasma cells and cytotoxic immune effector cells. Teclistamab and Elranatamab target BCMA, and Talquetamab targets GPRC5D.The increasing numbers of trials of BsAbs has highlighted their toxicity profile; but the risks for infection associated remain unclear. The objective of our study is to describe the infectious complications in patients with multiple myeloma (MM) treated with BsAbs.
Methods: Single-center retrospective study in which 14 adult patients with MM treated with at least 1 cycle with Teclistamab (57,1%), Elranatamab (14,3 %) or Talquetamab (28,6%) have been included with a median follow-up of 24,78 months (range 4- 44,9 m). Safety data for each patient were collected from time of BsAbs initiation until discontinuation of drug, or death. All patients received prophylaxis with acyclovir and cotrimoxazole; 2/14 with immunoglobulins intravenous. The safety profile of BsAbs was assessed by estimating the incident of infection, type of microorganism involved and the need for hospital admission.
Results: The median of previous lines was 4 (2-10). At the start of treatment, the median IgG and lymphocyte numbers were 1150 and 370,5 mg/dL , respectively.The characteristics of the patients are summarized in Table 1. Of the 14 patients, 7 (50%) have any infection and 5/14 (35,7 %) required hospital admission (HA). The most frequent cause of infection was bacterial (35,7 %). 3/14 patients had SARS-COV2 infection, 2 of whom died. The most frequent causes of death were COVID (2/14) and myeloma relapse (2/14). 1/14 (7,14%) patient presented CMV viremia. The summary of side effects is in table 2.

Table 1. Characteristics of the patients.

Characteristic	N (%)
Age, median years (range)	61, 65 (50,03-79,15)
Sex (Male/Female)	8 (57,1 %) / 6 (42,9 %)
Number of previous lines (range)	4 (2-10)
Teclistamab Elranatamab Talquetamab	8/14 (37,1 %) 2/14 (14,3 %) 4/14 (28,6%)
Acyclovir Cotrimoxazol propaxishys	14/14 (100%)
Inmunoglobulins intravenous prophylaxis	10/14 (71,4%)
Median of lymphocytes (range)	1150 (200-2100)
Median IgG mg/L (range)	370,5 (67-2337)

Table 2. Adverse events.

Adverse Event summary	N (%)
Any grade	14/14 (100 %)
Grade 3/4	8/14 (57,1 %)
CRS 2/4	1/14 (7,14 %)
ICANS 2/4	0/14 (0 %)
Hematological grade 3/4	8/14 (57,1 %)
Neutropenia grade	8/14 (57,1%)
Thrombocytopenia	5/14 (35,7 %)
Anemia grade	2/14 (14,3 %)
Lymphopenia	14/14 (100%)
Hypogammaglobulinemia	14/14 (100 %)
Infection	7/14 (50%)
Bacterial	5/14 (35,7%)
Viral no COVID	4/14 (28,6&¡%)
COVID	3/14 (21,4%)
CMV	1/14 (7,14%)
Fungal	0/14 (0%)
Delays in treatment	5/14 (35,7%)
HA	5/14 (35,7 %)
Death from infection	2/14 (14,3 %)

Conclusions: In our center, the rate of infections is similar to what has been published on these drugs. In a population with a high number of prior lines, BsAbs are safe. The high mortality from COVID is striking. The main limitation of our study is the number of patients.

P-114

Real-world experience with belantamab mafodotin therapy for relapsed/refractory multiple myeloma: a multi-center retrospective study

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Introduction: Despite the advances in management of multiple myeloma (MM), outcome remains poor for patients who are refractory to drugs from 3 therapeutic classes: proteasome inhibitors, immunomodulators and anti-CD 38 monoclonal antibodies. Belantamab mafodotin (GSK2857916) is a first-in-class anti-BCMA immunoconjugate, showed promising anti-myeloma activity in phase 1 and phase 2 trials, and recently approved for the treatment of advanced RRMM in the US and Europe.
Methods: This was a retrospective, multi-site study, conducted in 12 hospitals throughout Israel. All consecutive RRMM patients aged 18 years or older who received more than a single dose of belantamab mafodotin as monotherapy or in combination with corticosteroids under GSK expanded access compassionate care, from May 1st 2019 through March 1st 2021, were included.
Results: One-hundred and six patients included in the study cohort. The overall response rate (ORR) was 45.5% (46/101). Rates of complete response, very good partial response and partial response (PR) were 4.0%, 13.9% and 27.7% respectively. By univariate analysis, no significant association was found between age, sex, triple/penta refractoriness, international staging system and revised inetrnational staging system score, high-risk cytogenetics and extramedullary disease to ORR. The median follow-up was 11.9 (95% confidence interval [CI] 10.0-13.8) months. Median progression-free survival (PFS) was 4.7 (95% CI 3.5-5.9) months for the entire cohort and 8.8 (95%CI 6.6-10.9) months for responders. Median duration of response (DOR) was 8.1 (95% CI 5.7-10.5) months. The median overall survival (OS) was 14.5 (95% CI 9.5-19.6) months. Patients achieving PR or better had a statistically significant longer OS (NR for responders vs. 7.1 for non-responders). At twelve-months the OS was 81.9±6.3% vs 35.0±7.5% in responders vs non-responders (p=0.000016). Safety: Ocular toxicity: Sixty-five patients (68.4%) experienced keratopathy (40% grade 3/4). Blurred vision was reported in 36.8% (6.3% grade 3/4). Four patients (3.8%) discontinued treatment due to ocular toxicity. Non-ocular toxicity: Thrombocytopenia occurred in 27.4% (grade ≥3: 17.9%; one major bleeding) of the patients, anemia in 11.3% (grade ≥3: 3.8%) and neutropenia in 7.5% (grade ≥3 4.7%). Other frequent (≥5%) adverse events were infection (11.3%, grade ≥3: 3.8%) and hypersensitivity/ infusion reaction (7.5%; grade ≥3: 2.8%). Two patients in the entire cohort (1.9%) died of adverse events considered to be related to belantamab mafodotin administration by their treating physicians (both of them infections: pneumonia and sepsis).
Conclusions: This study presents favorable outcomes in patients with advanced RRMM treated with belantamab mafodotin in a real-world setting. Response rate, duration of response and toxicity profile appear to be comparable to those observed in prospective trial setting. These findings support the role of belantamab mafodotin as valuable treatment option for heavily-pre-treated RRMM patients.

P-115

Unc-51 Like Kinase 3 protein (ULK3)-mediated autophagy is responsible for multiple myeloma resistance to chemotherapy

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Introduction: Multiple myeloma (MM) is an incurable disease. Classical chemotherapeutics including bortezomib, melphalan, lenalidomide and thalidomide have greatly enhanced survival times. Unfortunately, patients typically relapse and become refractory with an average survival of 5-6 years post-diagnosis. Our emerging studies demonstrate a novel role for ULK3 in regulating autophagy in MM, a key program that sustains cell survival under times of stress and has been implicated as a major mechanism of proteasome inhibitor (PI) resistance. MM is known to be highly dependent on autophagy and, currently, specific ULK3 inhibitors are lacking. We posit that by targeting this marker in chemotherapy resistant MM patients, we can circumvent alternative metabolic routes and re-sensitize to standard of care pro-apoptotic therapy.
Methods: We performed RNASeq analysis of CD138+ MM cells derived from patients across the disease stages spectrum (n=815) to confirm the role of ULK3 in disease progression and resistance to chemotherapy. We developed

novel inhibitors SG3014/MA9060 that target multiple kinases including ULK3 (EC50 90nM) as well as BRD4. BRD4 is a known driver of MYC and its expression is increased in refractory MM. The BRD4 inhibitor, JQ1, effectively impairs the tumorigenic potential of MM but resistance has also been noted. We determined the efficacy of MA9060 for the treatment of CD138+ MM isolated from naïve and refractory patients using a novel ex vivo high throughput platform developed at Moffitt.
Results: ULK3 is highly associated with MM stage of the disease. Refractory MM patients have increased autophagy activity with significantly higher expression of ULK3 in refractory patients and in drug resistant cell lines (immunoblotting U266 vs U266-PSR; RPMI-8226 vs RPMI-8226-B25; ABNL vs V10 resistant cells). Genetic ablation of ULK3 by siRNA in U266 and 8226 cell lines results in rapid cessation of the downstream autophagy proteins (ULK1, ATG13, pATG13) and MM cell death within 72h of transduction. Increased concentrations of autophagy inhibitors MA9060/SG3014 progressively decreased CMYC and ULK3 levels, as measured by immunoblotting in U266 cells. In vivo preclinical model of U266Luc tail vein injection (1x10^6) proved our drugs are highly effective in reducing tumor dissemination and extending overall survival (CTRL untreated n=65 days vs MA9060 n=110). Importantly, we noted no overt toxicity and protected effect against myeloma-induced bone disease. This novel class of drug works synergistically with PI (Bortezomib/Carfilzomib) and can re-sensitize PI resistant disease to these effective therapies. We also show by EMMA ex vivo platform that MA9060 is highly effective for the treatment of CD138+ MM cells isolated from patients with refractory disease.
Conclusions: ULK3 represents a novel target for treatment of MM refractory disease. Our dual inhibitors can increase overall survival in vivo and ex vivo, therefore we expect to quickly translate our novel molecules to the clinic.

P-116
S-adenosylmethionine biosynthesis is a targetable metabolic vulnerability in multiple myeloma

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Introduction: Multiple Myeloma (MM) is the second most prevalent hematological malignancy and is incurable due to the inevitable development of drug resistance. Epigenetic modifications induced by metabolic changes play a major role in MM drug resistance. The methionine adenosyltransferase 2α (MAT2A) is a metabolic enzyme that affects DNA and histone methylation, as it is the primary producer of the methyl donor S-adenosylmethionine (SAM). Several studies reported MAT2A deregulation in different solid cancers, showing that silencing of MAT2A resulted in cancer cell death and reduced proliferation. However, its' role in MM is still not clear. Therefore, our study was to clarify the potential role of MAT2A in MM, exploring new therapeutic avenues to overcome drug resistance.
Methods: The expression of MAT2A in MM patients was analyzed using Genomicscape. The human MM cell lines ANBL6, JJN3 and OPM2 were used to perform in vitro experiments. MAT2A was inhibited by siMAT2A or the specific small molecular inhibitor FIDAS-5. The effects of MAT2A inhibition on cell viability, apoptosis, cell cycle progression and proliferation were determined by CellTiter Glo® Luminescent Cell Viability Assay, Annexin V/7AAD staining, propidium iodide staining and BrdU incorporation, respectively. Downstream pathways and protein synthesis were evaluated using Western Blot and SUnSET method. MAT2A function was also investigated in vivo by using the 5TGM1 murine model.
Results: MAT2A was found to be highly expressed in patient-derived myeloma cells compared to normal BMPC, correlating with an inferior OS. Direct inhibition of MAT2A, using either siMAT2A or FIDAS-5, impaired the cell viability of JJN3, ANBL6 and OPM2. Mechanistically, we found that FIDAS-5 reduced protein levels of p-mTOR, p-p70, and p-4EBP1 in JJN3 and OPM2, whereas, by knocking down MAT2A, we found a decrease in p-p70, p-S6 and p-4EBP1 levels in ANBL6 and OPM2. These changes suggested a decrease in protein synthesis, which we confirmed in the corresponding cell lines. Furthermore, our results showed that upon MAT2A depletion, proliferation of JJN3 and OPM2 cells was reduced due to a significant accumulation in the G0/G1 and G2-phase. Furthermore, FIDAS-5 was found to induce apoptosis in the three cell lines, by inducing cleavage of PARP, caspase 3, and MCL-1. In vivo, FIDAS-5 was able to reduce the tumor burden in the BM from 54.9% to 26.3%, and the M spike levels from 5.3 g/l to 2.3 g/l in the blood. On protein level, consistent with in vitro results, FIDAS-5 significantly reduced the expression of p-mTOR and p-4EBP1. Finally, we found that both FIDAS-5 and siMAT2A could significantly increase the anti-myeloma effect of the bortezomib in all three cell lines.
Conclusions: In summary, MAT2A inhibition reduced MM cell proliferation and survival by inhibiting m-TOR mediated protein synthesis. Our findings suggest that the MAT2A inhibitor FIDAS-5 could be a novel compound in bortezomib-based combination therapies for MM.

P-117
High throughput metabolism related drug screening identifies hypoxia inducible factor-1 alpha as a promising therapeutic target in proteasome inhibitor resistant multiple myeloma

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Introduction: Multiple myeloma (MM) remains incurable despite many treatments now being available. Proteasome inhibitors (PIs) are highly effective therapies in MM and form a backbone of many treatment regimens but while patients usually respond well initially, the PIs efficacy typically declines with each relapse as the MM develops resistance. Metabolic variations are a well-known feature of cancer but little research has been done into the metabolic adaptations that occur with the development of PI resistant MM. Here we investigate these metabolic adaptations in more detail and perform high throughput compound screening to assess for vulnerabilities.
Methods: AMO1-S (PI sensitive, parental), AMO1-BTZ (bortezomib resistant) and AMO1-CFZ (carfilzomib resistant) cell lines were assessed for metabolic differences on a Seahorse XFe96 extracellular flux analyser to identify variations in oxygen consumption rates (OCR), extracellular acidification rates (ECAR) and ATP production. High throughput compound screening was performed on the cell lines using 817 anti-cancer metabolism related compounds (MedChemExpress) with and without the addition of either bortezomib or carfilzomib. RNA sequencing data from patients with newly diagnosed MM and with subsequent relapse following treatment with a PI were analysed from the CoMMpass dataset (NCT01454297). Cell line RNA sequencing data from bortezomib resistant and sensitive versions of AMO1, L363 and RPMI-8226 were also grouped and analysed.
Results: Extracellular flux analysis revealed that PI resistant AMO1 cell lines had greater OCR, ECAR and ATP production rates than AMO1-S, indicating an overall increase in metabolic activity within these cells. The high throughput screen identified 40 compounds that induced significant cell death (Z-score>2) in either AMO1-BTZ or AMO1-CFZ but that were not significantly effective in AMO1-S. The most common target associated with these compounds was hypoxia-inducible factor 1-alpha (HIF-1α). In the PI resistant cell lines, 5 out the 7 compounds targeting HIF-1α showed a synergistic effect with either bortezomib or carfilzomib suggesting that they at least partially reduce PI resistance. RNA sequencing data from the CoMMpass dataset identified increased expression of the HIF1A gene at relapse compared to diagnosis, with log fold change 0.734 (p=0.0107). Cell line differential gene expression analysis also indicated overexpression of HIF1A in the bortezomib resistant group with log fold change 0.702 (p=0.0186).
Conclusions: HIF-1α appears to be a promising therapeutic target in MM with particular relevance in PI resistance as shown though both multi-omic analysis and compound screening. Future work will involve validating relevant compounds across additional PI resistant cell lines and patient samples under normoxic and hypoxic conditions.

Three distinct destines of malignant plasma cells based on single-cell transcriptomes and evolutionary trajectories

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Introduction: Multiple myeloma (MM) is an incurable and highly heterogeneous plasma cell-derived hematological malignancy. Nowadays, neoplastic plasma cells (PCs) from monoclonal gammopathy of undetermined significance (MGUS) or MM can be distinguished from normal PCs but not from each other. Risk stratification system capturing the heterogeneity of PCs still remains a challenge.
Methods: Four MGUS patients, six newly diagnosed MM (NDMM) and five relapsed/refractory MM (RRMM) patients at the department of hematology of Zhongshan hospital, Fudan University, were included in this study. Collection of bone marrow mononuclear cells (BMMC), preparation of single-cell suspensions and 10× Genomics scRNA-seq, data preprocessing, copy number karyotyping of aneuploid tumors (CopyKAT) analysis, single-cell copy number variations (CNV) analysis, differentially expressed genes (DEGs), gene set enrichment analysis (GSEA), pseudo-time and GeneSwitches analysis, identification of transcription factors (TFs), metabolism analysis, intercellular ligand-receptor analysis and survival analysis, cell line and cell culture, stable transfection cell line generation, quantitative real-time polymerase chain reaction (qRT-PCR) and western blot (WB), cell proliferation analysis, statistics analysis were all performed.
Results: A total of 97,793 cells, including 8,541 cells from MGUS, 40,749 cells from NDMM, and 48,503 cells from RRMM, with an average of 1,594 genes per cell, were obtained for further analysis. A special sample, which was collected from a RRMM patient relapsing following anti-CD38 antibodies, that contained highly homogeneous were analyzed separately. PCs from this sample lost expression of CD38, CD138, IGHG1 and MZB1, which presented the potential “escape mechanism” from immunotherapy. The other malignant PCs clustered into three distinct states with completely different inner and outer conditions. State-1 contained PCs from 82.7% MGUS cells and part of NDMM or RRMM, suggesting these particular MM PCs exhibited an expression pattern similar to that of MGUS PCs. State-2 and State-3 included PCs from 86.5% NDMM and 85.6% RRMM, respectively. By combining survival data from MMRF CoMMpass and GSE24080 databases, DERL3, GABARAP and LGALS1 were identified as three significant biomarkers in predicting the fates of malignant PCs. To verify the above results of bioinformatics analysis, the function of the three genes and related pathways were validated by CCK8 assays and WB in H929 and 8226 cell lines.
Conclusions: Accordingly, this study’s results may provide insight into the analysis of MGUS-NDMM-RRMM, which can guide personalized clinical care decisions and support the development of novel treatment modalities for a significant proportion of PCD patients.

P-119

CDK7 is a proximal regulator of cellular functions impacting MYC-driven pathways and eliciting unique metabolic vulnerabilities in multiple myeloma

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Introduction: CDK7 is a high-value therapeutic target due to its role in regulating transcription and the cell cycle—two pathways commonly altered in cancer cells, including multiple myeloma. We confirmed that CDK7 inhibition, both chemical and genetic, disrupts both cell cycle CDKs and Pol2 activity, causing reduced MM cell proliferation and potent activation of the E2F1-dominant repressor Rb. Inhibition of CDK7 in MM cells expressing the T121 fragment of the SV40 large T antigen to inactivate Rb proteins restored E2F1 chromatin binding but only partially rescued cell proliferation. These results suggest that CDK7i impinge on oncogenic E2F-driven transcription by stabilizing cell cycle deregulation and that CDK7 controls additional pathways relevant to MM biology.
Methods: CDK7 inhibition was achieved with 1. Selective covalent inhibitor YKl-5-124;2. Protein degradation dTAG system; 3. Inducible KD/KO system. The transcriptional and proteomic networks were evaluated by RNA-Seq and Mass spectrometry data analysis. Metabolic changes were evaluated by EACR and OCR assessment using Seahorse analyzer. In vivo results were evaluated by human myeloma models.
Results: Global transcriptional profiling in MM cells after CDK7i showed that MYC-induced gene expression programs and MYC-associated biological modules (e.g., glycolysis) were significantly downregulated. Concordantly, CDK7 gene expression was associated with high levels of MYC-associated gene expression programs in patient derived MM cell RNA-seq data; and inactivation of c-MYC by tetracycline (Tet) in Burkitt's lymphoma P493 cells, which bear a Tet-repressible c-Myc construct, significantly inhibited the susceptibility to CDK7 chemical inhibition. The essential role of CDK7 in sustaining MYC activity in MM cells was confirmed in vivo in a genetically engineered mouse model of MYC-dependent MM where aged, de novo mice treated with the CDK7 inhibitor YKL-5-124 display tumor regression associated with decreased levels of monotypic serum immunoglobulins. In addition to potentiating MYC-driven transcription, we also observed that CDK7 participates in the proteasomal degradation of c-Myc; as CDK7 inhibition caused a rapid decrease in MYC protein abundance and it controlled the expression of E3 ligases, which regulate MYC stability. Importantly, by regulating the cellular levels of c-MYC, CDK7 controls the expression of key components of the glycolytic cascade in MM cells, and its inhibition thereby impairs aerobic glycolysis, causing increased levels of reactive oxygen species, DNA damage, and tumor cell apoptosis in vitro as well as in vivo in several human myeloma models.
Conclusions: In conclusion, CDK7 represents a proximal regulator of the cell cycle, transcription, and metabolism in MM, and its chemical inhibition (YKL-5-124) elicits a strong therapeutic response in MM cells, while sparing normal cells, representing an attractive and therapeutically actionable molecular vulnerability in MM.

P-120

Indirubin-3'-monoxime acts as proteasome inhibitor: therapeutic application in multiple myeloma

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Introduction: Deregulation of the ubiquitin-proteasome system (UPS) is linked to pathogenesis and drug resistance of multiple myeloma (MM). Proteasome inhibitor has provided significant therapeutic advances in the treatment of MM, however resistance and dosage dependent side effects remain a clinical challenge. Our research efforts to investigate the anti-MM activity and explore the possible mechanisms of a novel agent, indirubin-3'-monoxime (I3MO) mediating.
Methods: Anti-MM cytotoxicity of I3MO was analysis in MM cell lines and primary patient cells. The zebrafish PDX model of MM and murine xenograft model were utilized to confirm the in vivo anti-myeloma activity of I3MO. RNA-seq was performed to investigate the downstream signal pathway of I3MO treatment. Molecular docking and biotin-based pull-down assay were utilized to identify the target of I3MO.

PSME3 and PSME4 functions in cell proliferation and drug resistance were investigated as well.
Results: Our data demonstrated the conspicuous anti-myeloma activity of I3MO both in drug sensitive and bortezomib-resistance myeloma cells via in vivo and in vitro study. The combination of I3MO and bortezomib enhanced MM cell sensitivity to bortezomib-induced apoptosis. I3MO induced the cell cycle arrest and suppressed the NF-κB signal in myeloma cells. Strikingly, I3MO acts as an alternative proteasome inhibitor and directly binds to the proteasome activators PA28γ and PA200. I3MO treatment notably down-regulates the expressions of PSME3 (PA28γ) and PSME4 (PA200) which plays a pivotal role in its anti-myeloma activity. Knockdown PSME3 or PSME4 causes the increased protein load and decreased proteasome activity to sensitize MM cells to proteasome inhibitor-mediated growth arrest. GEO data analysis showed that PSME3 and PSME4 were over-expressed in relapsed /refractory patient and associated with the shortened overall survival of patients. Thus, PSME3 and PSME4 would be potential targets in rescue drug-resistance of MM cell.
Conclusions: Taken together, our studies demonstrate that I3MO is an effective agent in myeloma treatment which has the potential efficiency to eradicate drug-resistant cells when applied in conjunction with other effective treatments. I3MO acts as an alternative proteasome inhibitor and a promising therapeutic strategy for multiple myeloma by binding to proteasome activators PA28γ and PA200. PSME3 and PSME4 are drug resistance associated genes which was overexpressed in relapsed patients and correlated with an inferior outcome in myeloma patients.

P-121
Representation of multiple myeloma patients in the cancer genome atlas and clinical trials

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Introduction: Outcomes for patients with multiple myeloma (MM) demonstrate disparities. African-Americans have higher risk of developing MM, earlier age at diagnosis, and higher mortality compared to Whites. It is important to ensure that demographic factors are considered in the investigation of disease biology, course and treatment, so investigators can identify any associations between outcomes and demographics. Equitable representation should be promoted in biological databases like The Cancer Genome Atlas (TCGA) and clinical trials (CT).
Methods: MM incidence was obtained from North American Association of Central Cancer Registries (NAACCR) 2014-2018 USA data for R&E, sex and age. In this analysis, race and ethnicity (R&E) includes White, Black, Asian, and Hispanic, as TCGA MM cases were limited to these groups. TCGA MM cases include patients from USA, Canada, Italy, and Spain. On clinicaltrials.gov, completed MM CT limited to these countries were included. Representation was calculated as [demographic cases in TCGA divided by total TCGA cases] divided by [demographic cases in NAACCR divided by total NAACCR cases]. Two-proportion z-tests were used to analyze differences within TCGA groups, representation in TCGA and CT, and disparities compared to NAACCR. To explore implications of TCGA data, genes with differences in mutation frequency between patient groups were identified.
Results: Race was not reported in 20% of TCGA cases (n=1065), 4% of CT (n=36766), and 3% of NAACCR (n=26843). In TCGA, women with MM are underrepresented compared to men across all R&E ($p< 0.05$). White patients are overrepresented compared to other R&E, with Asian patients least represented. Patients age < 50 represent < 25% in TCGA across all R&E. In the 171 included CT, 2.5% of participants were Asian, 13% Black, 81% White, and 5.6% Hispanic. Asian, Black, and Hispanic patients were underrepresented in both TCGA and CT cases compared to their distribution in NAACCR ($p< 0.05$). Gene analysis was limited to Black and White patients due to insufficient numbers of other races. Black patients in TCGA had 8 genes with higher mutational frequency compared to Whites ($p< 0.05$), including those of oncogenic potential such as BCL7A and BCL11B. White patients had 3 such genes: TP53, KALRN, and IGLV3-25. If TCGA accurately represented patients, the current mutation frequencies would reveal 2 more such genes in Black patients and 2 more in White patients. Kaplan-Meier curves between Black and White patients in TCGA show a survival disparity (log-rank test $p=0.02$).
Conclusions: Substantial disparities in Black race, Hispanic ethnicity, women, and age representation exist for MM cases in TCGA and CT. The comparison between TCGA and CT offers new insight on these demographic disparities. Demographic representation in public databases is important as its absence can lead to disproportionate data. Equitable demographic representation should be pursued to diminish disparities in public databases representing patients with MM.

P-122
Racial differences in spinal cord compression related hospitalizations in patients with multiple myeloma: a population based study

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Introduction: Non-Hispanic Black Americans and Hispanic Americans with multiple myeloma (MM) face multiple health-related disparities. Spinal cord compression (SCC) is a medical emergency and can occur in approximately 5 percent of MM patients. Racial differences in the rates of SCC not previously reported.

Methods: We conducted this 12-year retrospective analysis of inpatient hospitalizations from 2008 to 2019 using the Nationwide Inpatient Sample (NIS) data. The study sample included the occurrence of MM in the discharge records of adults (18+ years). The outcome for the study was spinal cord compression. International classification of diseases ninth and tenth edition (ICD-09 and ICD-10, respectively) were used to identify MM and SCC diagnoses. The analysis for this study was generated using R version 3·5· 1. All the hospitalizations were weighted to account for the complex sampling design of the NIS, which allowed for the generation of national estimates. To identify and describe temporal changes in the rates of SCC in MM-related hospitalizations during the 12-year study period, joinpoint regression was utilized. Each joinpoint indicated a change in the trend, and an average annual percent change (AAPC) and 95% confidence interval (CI) were estimated to characterize how the rate of the outcome (SCC in MM cases) changed during the entire study duration.
Results: Of 368,188,112 hospitalizations, 1,247,364 (0.34%) were related to MM. Of MM hospitalizations, 56,902 (4.6%) were associated with SCC diagnosis. MM hospitalizations were more common in non-Hispanic Black Americans (5 per 1000 hospitalization) compared to non-Hispanic Whites (3.3 per 1000 hospitalizations) and Hispanics (2.6 per 1000 hospitalizations). SCC related hospitalizations in patients admitted with MM were more common in non-Hispanic Whites (4.9 per 100 MM hospitalizations) compared to non-Hispanic Blacks and Hispanics (4.2 and 4 per 100 MM hospitalizations, respectively). AAPC was higher in non-Hispanic Blacks when compared to both Hispanics and non-Hispanic Whites (10.5, 9.6 and 7.9, respectively- $p < 0.01$). Despite the higher AAPC in non-Hispanic Blacks and Hispanics, non-Hispanic Whites continued to have the highest rate of SCC in MM hospitalizations. Multi-variable adjusted survey logistic regression for patient's sex, age, income quartile, primary payer, and comorbidities showed lower odds ratio (OR) of SCC in non-Hispanic Blacks (OR 0.83 (95% CI: 0.78-0.88) and Hispanics (OR 0.83 (95% CI: 0.76-0.91) when compared to non-Hispanic Whites.
Conclusions: The rates of SCC in patients with MM are overall increasing and is lower in non-Hispanic Blacks and Hispanics when compared to non-Hispanic Whites.

P-123
Global quantitative lipidomic profiling of bone marrow (BM) plasma between patients with multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS)

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Introduction: Alterations of lipid metabolism within malignant cells support their growth and proliferation while simultaneously dampening the immune response by the surrounding microenvironment. In this study, we evaluated the quantitative differences across the spectrum of lipid species present in the BM plasma of a prospective set of MM and MGUS patients in order to elucidate potential metabolic pathways that may serve as future therapeutic targets.
Methods: BM plasma samples were prospectively extracted from the BM aspirates of 25 MM and MGUS patients each who were enrolled in the study. Lipids extracted from the samples underwent liquid chromatography (LC) separation and subsequent mass spectrometry (MS) analysis. A total of 991 individual lipid species belonging to classes of neutral lipids (cholesteryl esters (CEs), triacylglycerols, diacylglycerols, monoacylglycerols, and free fatty acids (FFAs), phospholipids (phosphatidylcholines (PCs), phosphatidylethanolamines (PCs), phosphatidylinositols (PIs), lysophosphatidylcholines (LPCs), lysophosphatidylethanolamines (LPEs)) and sphingolipids (sphingomyelin, ceramides, hexosylceramides, lactosylceramides, dihydroceramides) were quantified using isotopically labeled internal standards. Quantitative differences among the different lipid species between the two groups were compared statistically using SPSS (IBM Corp. V 22.0).
Results: There were 101 individual lipid species whose concentrations were statistically different (of which 97 were lower and 4 were higher in MM) in the BM plasma between MM and MGUS patients. Among total lipid classes, MM patients had lower but statistically insignificant concentrations of CE, PC, and PI concentrations in their BM plasma compared to MGUS patients. Statistically significant alterations involved individual lipid species within PEs and very long-chain chain FFAs (VLCFAs) classes. Specifically, the concentrations of monounsaturated VLCFAs such as FFA(22:1) and FFA(24:1) were increased in MM compared to MGUS ($p=0.02$ for both) and were both positively associated with BM clonal plasma cell levels. In contrast, concentrations of specific PEs in the form of plasmalogens such as PE(P-16:0/18:1) ($p = 0.003$) and ethers like PE(O-18:0/16:0) ($p = 0.003$), and PE(O-18:0/16:1) ($p = 0.005$) were significantly lower in MM compared to MGUS patients and negatively associated with BM clonal plasma cell levels.
Conclusions: Rather than global alterations in entire lipid classes, MM patients have alterations in the levels of individual lipid species in their BM microenvironment (i.e., BM plasma) compared to MGUS patients that are correlated to the clonal plasma cell burden. Future studies evaluating the biological significance of these differences are required to determine if they can be exploited for diagnostic and therapeutic purposes.

P-124
High protein concentration in CSF is a hallmark in multiple myeloma with CNS involvement

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Introduction: Central Nervous System (CNS) involvement in multiple myeloma (MM) is a rare presentation of extramedullary disease (≈1%), and has a very poor prognosis with a reported overall survival (OS) of a few months.
Methods: We present a retrospective cohort of 36 cases diagnosed with multiple myeloma and clinical suspicion of CNS involvement at the Instituto Nacional de Enfermedades Neoplasicas in Peru from 2012 to 2022. 15 of 36 cases met the criteria of CNS infiltration: plasma cell in CSF detected by (1) cytology or/and (2) flow cytometry; (3) radiology confirmation. We described the clinical features of confirmed cases and compared them with the cohort without CNS infiltration.
Results: CNS involvement was confirmed in 15 cases, 3 cases diagnosed by cytology findings, 6 cases by flow cytometry, and 6 by imagining confirmation. The median age at diagnosis of MM was 52 years old [range 30-75]. The median interval between diagnosis CNS-MM was 19.5 months, 4 cases were detected at the time of diagnosis and 11 cases at progression. Eastern Cooperative Oncology Group performance status was ≥2 in 66.7% of patients. Clinical presentation was characterized by encephalopathy (40%) and headache (20%), less frequent focal deficit (13.4%), and seizures (6.7%). Nine patients had IgG, three had IgA, six had Kappa light chain, and 9 Lambda light chain. Plasmacytoma at diagnosis was present in 80% of patients. CSF findings were increased protein (median, 1333 mg/dL, range 42-3543) and 26% reveal pleocytosis. Imaging findings were intracranial leptomeningeal involvement in 6 cases and 1 case reported periventricular enhancement. Treatment received before CNS MM involvement was 86% IMIDs, 60% proteasome inhibitors, and 20% autologous SCT, 2 patients did not receive any treatment due to poor status performance at diagnosis. The median overall survival (OS) was 52 days after CNS-MM diagnosis and only 2 longer survivors, who received intrathecal chemotherapy, were reported with an OS of 46.9 and 25.2 months. Also, we compared clinical features between suspicious and confirmed cases of CNS-MM, CSF protein and the presence of plasmacytoma at diagnosis was statistically significant between those groups, $p< 0.001$ and $p=0.002$ respectively. We used receiver operating characteristic (ROC) analysis to determine the optimal cut-off value for CSF protein to diagnose CNS-MM, 1054 mg/dL, with a calculated AUC of 0.838.
Conclusions: Our Peruvian cohort of 15 confirmed cases of CNS-MM has a dismal median overall survival. Higher CSF protein levels and plasmocytoma at diagnosis are distinguished characteristics of these patients. When flow cytometry or high-resolution images are not available, as in developing countries' institutions, CSF protein can be useful to determine myeloma infiltration in CNS.

P-125

Multiple myeloma in Reunion Island: a descriptive and pronostic study on newly diagnosed patients between 2015 and 2019

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Introduction: Multiple myeloma is the 2nd most frequent blood malignancy in the world, with different incidence between regions. The incidence of plasma cells dyscrasia (MM, MGUS) is increased in black individuals. Survival data according to patient ethnicity can be contradictory. The french Indian Ocean territory (Reunion Island and Mayotte) represents a young population of more than one million inhabitants with varied ethnic origins. Few data are described concerning such a population.
Methods: This is a cohort study of newly diagnosed multiple myeloma cases in Reunion Island between January 1, 2015 and December 31, 2019. The primary objective was to describe the characteristics of patients with MM. The secondary objectives were to assess the incidence of MM and the prognosis of patients treated in Reunion Island (PFS, TTNT and OS). A descriptive study of the characteristics of patients from the Indian Ocean outside Reunion Island is also carried out.
Results: Over our study period, 229 patients were included in the Reunion Island patient cohort. The median age at diagnosis is 69 years. The M/F sex ratio is unfavorable to women (ratio 0.96). The worldwide age-adjusted incidence is 3.3 cases/100,000 person-years. The prognosis of patients treated in Reunion remains unfavorable compared to the population of metropolitan France, with a median PFS of 20.5 months (95% CI [18.0-26.4]) and OS at 5 years estimated at 52% (95% CI [42-64]).
Conclusions: The Reunionese population has a lower incidence rate of MM than the population of metropolitan France. We report a subgroup of young patients with an unfavorable diagnosis among the Reunionese population.

P-126
Thrombosis in multiple myeloma – risk estimation by induction regimen and association with overall survival

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Introduction: Lenalidomide-containing (R) triplet and quadruplet regimens are the standard of care for multiple myeloma (MM) induction therapy and have been shown to increase the risk of thrombosis, even with routine thromboprophylaxis. The association between venous thromboembolism (VTE) and survival in the novel multi-drug era is not yet delineated.The study objective is to evaluate the incidence of VTE during the first year of MM diagnosis, its association with the type of induction regimen, and its impact on overall survival for patients treated with lenalidomide-containing triplet or quadruplet regimens.
Methods: We studied newly diagnosed MM (NDMM) patients from 2008-2018 who received a triplet or quadruplet lenalidomide-based induction regimen at our institution. Baseline disease characteristics and the type of induction regimen were collected. VTE definition included DVT, PE, or a stroke within a year of diagnosis. Survival analyses were performed using the Kaplan-Meier method. Cox proportional hazards models were used for univariate and multivariable analyses, adjusted for high-risk fish abnormalities, sex, age, receipt of upfront transplant, and R-ISS stage. A two-sided p-value < 0.05 was considered statistically significant.
Results: A total of 672 patients were identified. VTE was diagnosed in 85 patients (12.7%). Of these, 57 had a DVT, 24 had PE with or without DVT, and 4 patients had a stroke. In a comparison of different treatment regimens, carfilzomib-Rd (KRd) had the highest risk of VTE at induction (22.1%, 19/86), followed by bortezomib-Rd (10%, 53/530), quadruplets (11.1%, 5/45), and 0/11 (0%) treated with other lenalidomide containing regimens. The difference in VTE risk between KRd and the other regimens was statistically significant (OR=2.6, p< 0.01). Eight patients developed a VTE before being exposed to any treatment. OS was significantly lower among patients that developed a VTE (67.7 vs. 145 months, p< 0.01). The association of VTE with reduced survival that was demonstrated in univariate analysis (HR=2.3, 95% CI=1.6-3.3) was maintained in the multivariable analysis adjusted for commonly used prognostic factors (HR= 2.5, CI=1.77-3.7).
Conclusions: This study evaluated the impact of VTE during the first year of MM diagnosis on OS in the novel treatment era. The incidence of VTE at induction was found to be 12.7%, with KRd carrying a significantly higher risk compared to other regimens. VTE seems to be an independent prognostic factor of shorter OS, perhaps signifying more aggressive disease biology. We conclude that VTE is an important aspect of MM management and effective thromboprophylaxis is especially relevant in the novel treatment era.

P-127
Evaluation of the Mayo Additive Staging System in patients with newly diagnosed multiple myeloma, a real-world analysis

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Introduction: Recently, Mayo Clinic introduced a new simple stage system called the Mayo Additive Staging System (MASS) for patients with newly diagnosed multiple myeloma（ NDMM）， which was based on the number of high-risk abnormalities: high-risk IgH translocations, 1q gain/amplification, chromosome17 abnormalities, ISS-Ⅲ, and elevated LDH. Patients with 0, 1, or ≥2 HR abnormalities were defined as stage Ⅰ, Ⅱ, or Ⅲ, respectively. This staging model had not been validated in real- world clinical application.
Methods: we retrospectively screened and analyzed cytogenetic and laboratory test results of 589 consecutive patients with NDMM, who were treated between from January 2010 to January 2022 in a single center.
Results: Among all the patients, 544 had simultaneous information available for disease stratifying, 90(16.5%) had no high-risk factors (MASS-Ⅰ), 193(35.5%) had 1 high-risk factor (MASS-Ⅱ) and 261(48%) had ≥2 high-risk factors (MASS Ⅲ). The median progress free survival (PFS) was 48, 28 and 20 months in the 3 groups, respectively (P < 0.001). The overall survival (OS)in the 3 groups was 137, 73 and 39 months (P < 0.001). In subgroup analysis, patients with different MASS stages had different survival outcomes according to age and renal function grouping. However, statistically different survival was not found between MASS groups in patients receiving autologous stem cell transplantation (ASCT).
Conclusions: In conclusion, our findings suggested that MASS system is a reliable risk stratification tool for patients with NDMM, performing well in real-world clinical practice.

P-128
Value of bone marrow examination in determining response to therapy in patients with multiple myeloma in the context of mass spectrometry based M protein assessment

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Introduction: Detection of the monoclonal protein is central to the monitoring of patients undergoing therapy for multiple myeloma (MM). Currently, definition of complete response includes a requirement for < 5% plasma cells (PCs) on bone marrow examination (BME) in addition to serum and or urine immunofixation (IFE), and prior studies have shown added

value of BME in terms of disease progression. However, BME is uncomfortable, and a high level of non-compliance is observed. In this study, we assessed if BME without MRD assessment provided added value to conventional response assessment if mass spectrometry-based assay (MALDI-TOF/Mass-Fix) is used in place of traditional immunofixation.
Methods: In this retrospective study, we included all consecutive patients with new diagnosed multiple myeloma who had a serum Mass-Fix assay with a concomitant bone marrow examination after initiation of therapy. Only patients with one line of treatment and achieving at least very good partial response (VGPR) were included. Patients with nonsecretory disease or light-chain myeloma were excluded. The minimal residual disease (MRD) was measured by flow cytometry (with a threshold of 1 tumor cell/10-5 white blood cells).
Results: Between May 2017 and May 2022, 402 patients fulfilled the study criteria; 153 patients had a negative and 249 patients had a positive Mass-Fix assay. Both groups had similar distribution of sex, ISS stage III, and high-risk cytogenetic. Among patients with negative Mass-Fix, 100% had < 5% of PCs on BME (153/153), while 92% among those with a positive Mass-Fix had < 5% of PCs (229/249) on BME. Conversely, among those with ≥5% of PC, 100% (20/20) had positive MASS-FIX. In addition, 41% of patients achieving negative Mass-Fix had absence of PCs (< 1%) by morphology on BME. Among patients achieving Mass-Fix negativity, 85% achieved absence of PCs by minimal residual disease (MRD) assessment by flow. Only 39% of patients with 0% PCs by morphology achieved MRD negativity. Patients with negative Mass-Fix with < 1% of PCs by morphology had a similar 2-year PFS compared with patients with negative Mass-Fix and ≥1% of PCs on BME (84.6% vs. 83.8% p=0.989). However, patients with negative Mass-Fix and negative MRD had a better 2-year PFS than patients with negative Mass-Fix and positive MRD (86.5% vs. 77.2%, p=0.02).
Conclusions: In summary, bone marrow examination did not add to traditional complete response (CR) assessment in patients who were Mass Fix negative. Moreover, patients with negative Mass-Fix and ≥1% PCs by morphology does not seems to have a better outcome, thus greatly limiting the usefulness of this invasive procedure except in the context of MRD assessment. These results suggest that a marrow should only be performed if MRD assessment is being planned in patients with negative Mass-Fix.

P-129
Simultaneous versus consecutive assessment of disease markers for defining progressive disease in multiple myeloma

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Introduction: Disease progression in multiple myeloma (MM) is an important endpoint for assessment of treatment efficacy. Currently, the IMWG progressive disease (PD) criteria are defined as an increase in serum M-spike, urine M-spike, bone marrow plasma cells (PC) and/or in difference between involved and uninvolved free light chains (dFLC). These assessments must be confirmed by at least one repeated investigation, with exception of marrow. However, this can be cumbersome in routine clinical practice and can make clinical trial endpoints non-assessable when values are missing. Herein, we hypothesized that if two markers meet criteria of progression at the same time, then a repeat of either for confirmation will not be necessary.
Methods: We retrospectively studied all consecutive patients with MM enrolled in clinical trials at Mayo Clinic. Patients with confirmed and unconfirmed progressive disease were included in this study. Unconfirmed PD was defined as not meeting PD threshold at the second and third consecutive assessment. Progressive disease was defined per IMWG criteria: (1) >25% in serum M-spike or (the absolute increase must be >0.5g/dL), (2) >25% in urine M -spike (the absolute increase must be >200mg/24hr), (3) >10% in absolute increase of plasma cell on marrow examination or (4) > 25% in the dFLC (the absolute increase must be >10 mg/dL).
Results: We identified 609 episodes of confirmed (n=583) or unconfirmed (n=26) PD for inclusion in our study. In patients with two consecutive measurements of any one parameter as per IMWG criteria, 76% progressed with serum M-spike, 12% with urinary M-spike, and 25% with free light chain. In addition, 54% of patients in PD had an increase of 25% or more in quantitative immunoglobulins at 2 consecutive assessments. In patients meeting the serum M-spike progression threshold at the first assessment, 39% also met the dFLC criteria, 12% marrow criteria, and 51% quantitative immunoglobulin criteria, at the same time. In patients meeting the dFLC criteria, 15% met the urine M-spike, and 11% the marrow threshold at the same time. More specifically, using only three groups: (1) serum M-spike/ immunoglobulin, (2) serum M-spike/dFLC, (3) urine M-spike/dFLC, more than than 80% of the patients are reaching the PD threshold at the first assessment. In addition, among those meeting threshold at the same time for two variables considering all markers combination available (serum M-Spike, urine M-spike, dFLC, immunoglobulin and/or bone marrow examination), 86% had subsequent confirmation of PD.
Conclusions: In summary, we demonstrate that meeting progression thresholds in two markers: (1) serum M-spike/quantitative immunoglobulin, (2) serum M-spike/dFLC, or (3) urine M-spike/dFLC is a valuable tool to predict nearly 90% of patients with progressive disease. Indeed, patients with MM having two positive markers meeting PD criteria at

the same time, then repeating either one may not be necessary.

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Brazilian ineligible multiple myeloma patients: real world data from a prospective multicenter platform

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Introduction: Introduction: The Brazilian Multiple Myeloma Group (GBRAM) developed an electronic database platform with the intention of prospectively registering the multiple myeloma (MM) cases diagnosed at Brazilian healthcare system and analyze the disease characteristics, treatments patterns and the outcomes.
Methods: Methods: This is a prospective, multicenter data-based platform. MM patients diagnosed after January 1, 2018 have been included. The eligibility criteria were: intent-to-treat (ITT) MM patients, aged over 18 years and under care in any healthcare system (private and public). All clinical and laboratory data, prognostic profiling, treatment patterns and responses, adverse events and survival were compiled. The data were analyzed with the NCSS® 2020 software. This project is registered in the Brazilian study platform (CAAE-05340918.3.1001.8098).
Results: Results: From a total of 1,600 patients included from whom 1,296 were analyzed and 508 were transplant ineligible patients (TIMM). A hundred and forty eight (29.1%) patients were treated in the private sector and 360 (70.8%) in the public sector. The median age at diagnose was 74 (37-96) years and 258 (50.8%) patients were female. Two hundred and four (40.1%) of the patients were nonwhite. According to the ECOG at diagnose: 0 = 80 (20.6%), 1 = 111 (28.6%), 2 = 84(21.6%), 3 = 73 (18.8%), 4 = 40 (10.3%). Private versus public ECOGs 3 and 4- represented 17.6% and 34.5%, respectively. The ISS 1, 2, and 3 were 80 (16.5%), 141 (29.1%) and 221 (45.6%), respectively, and 43 (8.9%) not available (NA). The patient's treatment in the public sector were mainling based on thalidomide and alchilators 195 (61.7%) and on proteasome inhibitor (PI) 101 (31.9%). On the other hand, the induction chemotherapy treatment in the private sector were based on PI 76 (55%) and on an anti-CD38 53 (38.4%). After a median follow- up of 17.4 months a total of 115 deaths occurred, 49 (42.6%) of them secondary to progression disease. The median overall survival was 40.6 months in th public system and not reached in the private.
Conclusions: Discussion and Conclusion: This prospective register enrolled patients diagnosed since January 2018 and is of a nationwide scope. In addition to identifying the epidemiological characteristics of Brazilian patients with multiple myeloma, our registry demonstrates the paterns of treatment in public and private institutions. The high percentage of ECOG 3-4 level was observed in the public when compared to the private sector. In this analysis we observed an inferior median overall survival of 40.6m for TIMM in the public sector, and not reached in the private sector. The limited access to new agents, due to delayed approval or incorporation, contributes to this discrepancy and further discussion on policy and pricing for these agents is imperative.

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Changes in the parameters of oxidative stress in blood of patients over 50 years old with multiple myeloma after participation in a 6-week health training cycle

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Introduction: Oxidative stress is defined as an imbalance between pro- and antioxidants and plays an important role at both in initiation and progression of cancer. The level of oxidative stress is affected by physical activity. Prior studies

have compared the biochemical oxidative stress markers and low antioxidant enzyme activity between patients with multiple myeloma (MM) and healthy control subjects. This study investigated the effect of a cycle of Nordic walking health training on oxidative stress-related blood parameters in MM patients.
Methods: Twenty-six MM patients older than 50 years old in remission were enrolled in the study and divided into 2 groups: an health training group(NW, n=13, mean age: 64.7±5.4 years) and a control group (CG, n=13, age: 63.7±4.8 years). The NW group participated in 18 Nordic walking training sessions consisting of 3 times a week for 6 weeks. In the NW group, Exercise intensity was monitored by heart rate monitor (60-70% of estimated HRmax, moderate intensity). Both the NW and CG had venous blood collected at 2 time points: at baseline and after 6 weeks (at the end of the training cycle). Selected parameters of oxidative stress (lipid peroxidation marker: malonylodialdehyde (MDA) and antioxidant plasma capacity ImAnOX) and antioxidative defence system (activity of antioxidant enzymes in red blood cells: catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR) and serum concentration of uric acid (UA)) were analysed. At baseline a diet analysis was also performed.
Results: A significant decrease in serum MDA concentration was observed in NW group (from 8.53±0.99 µmol/l to 7.51±1.23 µmol/l, p=0.004). There was a trend for a decrease in ImAnOX and UA concentrations. In the NW group, an increase in antioxidant enzymes activity was observed, however, only the changes in CAT activity were significant (from 156.97±35.67 U/g Hb to 170.77±33.08 U/g Hb, p=0.037). There were no significant changes in any of the studied parameters in the control group. The results of the diet analysis did not differ from the norms for the Polish population and did not show significant differences in antioxidant intake between CG and NW groups.
Conclusions: The participation of patients in NW training had a positive effect on the markers of oxidative stress. A significant decrease in MDA serum concentration was observed after 6 weeks which shows the reduction of oxidative stress level in serum. An increase in antioxidant enzymes activity shows an improvement in antioxidant defence and is related to adaptation to exercise. However, the non-enzymatic antioxidant system was not affected by the NW training.

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Clinical characteristics and infection-related outcomes in patients with lymphoid malignancies with or without secondary immunodeficiencies: results from a retrospective multi-database study

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Introduction: Current guidelines do not provide an adequate framework for clinicians to identify patients with lymphoid malignancies at highest risk of developing secondary immunodeficiencies (SID). This study aimed to understand the demographics, clinical characteristics and burden of infection in patients with lymphoid malignancies and SID, compared with those in patients without SID.
Methods: In this observational, retrospective cohort study, data were extracted from the Optum-Humedica (H-DB) and Guardian Research Network (G-DB) databases for the period Oct 1, 2015 to Mar 10, 2020. This period included a 6-month pre-index period (PIP) and 12-month follow-up after patient identification. Patients aged ≥18 years were included if they had a confirmed diagnosis of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), multiple myeloma (MM) or non-Hodgkin lymphoma (NHL; H-DB only) in the PIP. Eligible patients in each database were stratified into two cohorts: those with SID (SID cohorts) and those without SID (no-SID cohorts). Patients with SID or primary immunodeficiencies in the PIP were excluded. The SID index date was defined as the first occurrence of an ICD-10 hypogammaglobulinemia code or a record of low (< 5.0 g/L) serum IgG levels. The primary outcome was severe bacterial infection over 12-month follow-up. Secondary outcomes included overall survival (Kaplan–Meier analysis).
Results: In total, this study included 2,221 patients with SID (H-DB/G-DB: n=1,959/262 [25.6%/33.6% CLL or SLL, 44.4%/66.4% MM, 30.0%/0% NHL]) and 19,141 patients without SID (H-DB/G-DB: n=17,598/1,543 [22.3%/50.2% CLL or SLL, 21.4%/49.8% MM, 56.3%/0% NHL]). Patients were more likely to be younger and White/Caucasian in the SID cohorts than the no-SID cohorts. At 12-month follow-up, more patients with SID had experienced ≥1 infection (H-DB/G-DB: 63.4%/62.2%) than those without SID (H-DB/G-DB: 29.4%/32.9%); p< 0.001 for both databases). Bacterial infections were the most frequently reported type of infection in both databases and both cohorts. More patients with SID experienced ≥1 severe bacterial infection (H-DB/G-DB: 34.5%/30.5%) than those without SID (H-DB/G-DB: 9.7%/10.2%); p< 0.001 for both databases). The mean (standard deviation) number of severe bacterial infections was 7.6 (9.9; H-DB) and 2.9 (2.7; G-DB) for the SID cohorts versus 5.2 (6.8; H-DB) and 2.4 (2.2; G-DB) for the no-SID cohorts. Overall survival at 24 months was lower for patients with SID (H-DB/G-DB: 76.3%/77.3% of patients alive) than for those without SID (86.9%/87.8%).
Conclusions: With comparable results in two large databases, this study confirms that patients with lymphoid malignancies and SID face a significantly higher burden of infectious complications and have shorter overall survival than those without SID. Abstract previously presented at the European

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Myeloma-induced bone pain: lessons learnt from a localized, immunocompetent mouse model

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Introduction: Pain and fatigue are the main complaints of multiple myeloma (MM) patients, severely impairing their quality of life. As novel treatment avenues continue to expand the overall survival of MM patients, identifying the mechanisms of myeloma-induced bone pain and potential treatment targets has become a crucial step towards improved patient care.
Methods: Male KaLwRij mice were transplanted with 50,000 5TGM1 myeloma cells transfected with green fluorescent protein (GFP) in the femoral bone marrow. Myeloma-bearing and control mice were assessed over time for pain-like behaviours and euthanized on post-surgical day 24, upon the onset of nociception. Lumbar dorsal root ganglia (DRG) were isolated and bulk RNA was sequenced for identification of differentially expressed genes (DEG). In a separate experiment, myeloma-bearing and control mice were euthanized on post-surgical day 24 by transcardial perfusion upon confirmation of a pain-like phenotype, and lumbar DRGs and femurs were collected. Sectioned DRGs were stained for markers of blood vessels (CD34), neuronal profiles (tyrosine hydroxylase, TH), nerve injury (Activating Transcription Factor 3, ATF3) and MM cells (GFP). To investigate alterations in peripheral bone innervation, nerve markers for sensory fibers (calcitonin gene-related protein, CGRP) and for axonal growth (growth associated protein 43, GAP-43), were quantified in ipsilateral femurs.
Results: Myeloma-bearing mice developed splenomegaly and increased serum paraprotein at euthanasia, confirming disease development. Bioinformatic analyses of sequenced DRGs showed a total of 766 DEG, including GFP expression. Transcriptomic dysregulation in DRGs from MM mice was independent of tumor burden and pain scores, but correlated with percentage GFP reads, indicating MM metastases to the nervous system. Immunohistological staining of GFP+ cells in the DRGs of myeloma-bearing mice confirmed these results. Myeloma cell-infiltrated DRGs displayed a significant decrease in density and length of CD31+ blood vessels, and significantly increased ATF3+ neuronal profiles compared with controls, suggesting that myeloma metastasis to the DRG induces both blood vessel damage and neuronal damage. As ATF3 is a known indicator of nerve damage in neuropathic pain models, we next evaluated innervation in the myeloma-bearing femurs. Immunostaining of myeloma-bearing bones showed complete bone marrow denervation but significant nerve sprouting in the periosteum compared with sham (increased GAP43+ and CGRP+ nerve fibre densities).
Conclusions: We present the first evidence of myeloma metastasis to the DRG. Moreover, our results suggest that MM induces periosteal nerve sprouting, which has been associated with nociception in other models of cancer-induced bone pain. Further research is needed to clarify the role of MM cell infiltration in the DRG and altered bone innervation in myeloma-induced bone pain, and whether they can be targeted for improved analgesia in this patient population.

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Clinical characteristics and long-term outcomes of patients with POEMS syndrome: a large academic center's experience

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Introduction: POEMS syndrome is a rare paraneoplastic syndrome caused by an abnormal plasma cell clone. Prospective data regarding therapy outcomes are scarce and treatment is based on small case series and single institution experiences. We report herein our institution's experience over a 10-year time period.
Methods: We conducted a retrospective analysis of the clinical features and therapy outcomes of 29 patients (pts) with POEMS syndrome treated at our institution from 2010 to 2020. Kaplan-Meier method was used to estimate the progression free (PFS) and overall survival (OS).
Results: The median age of our pts was 67 years; 72% were male. 16 (55%) and 10 (34.5%) pts had IgG and IgA heavy chain isotypes respectively, with 25 (86%) pts having involved lambda light chain. Median % of bone marrow plasma cells was 5 (range 0-20). At diagnosis, 18 (62%) pts had peripheral edema, 8 (28%) organomegaly, 11 (38%) endocrinopathy, 18 (62%) skin changes, 8 (28%) thrombocytosis, 6 (21%) deep venous thrombosis and 2 (7%) papilledema. Elevated VEGF level was noted in 55% of our cohort, with a median of 216 pg/ml. The median number of treatment (Tx) lines was 1 (range 1-5). Frontline Tx included immunomodulatory drug (IMiD)-based, proteasome inhibitor (PI)-based and Cyclophosphamide (Cy)-only therapies at 23 (80%), 2 (6.6%), and 2 (6.6%) pts respectively, whereas 2 (6.6%) pts received only radiation (RT) therapy. Eleven (38%) pts were non-evaluable (NE) for hematologic response, whereas 12 (41%) achieved ≥VGPR (of these 9, 1 and 2 pts were treated with IMid, PI, and RT-only regimens, respectively). In terms of VEGF response, 14 (48%) pts were NE, 12 (42%) achieved CR (11 received IMiD-based Tx, 1 RT-only) and 3 (10%) improvement. Clinically, 27 (93%) pts demonstrated improvement. Consolidation with autologous hematopoietic cell transplant (AHCT) after 1 line of Tx was used in 5 (17%) pts; of those 4 achieved ≥VGPR. Daratumumab was used as monotherapy in 7 (24%) pts with relapsed disease as 3rd or 4th line. Of them, 1 achieved VGPR, 2 Partial response, and 3 were NE; clinically 71% had improvement. VEGF response was NE in 5/7 pts, 1 had improvement and 1 no response. The median PFS of 1st line Tx for the entire cohort and the subset of pts who received IMiD-based therapy was 63 (95% CI, 32, not reached [NR]) and 63 (95% CI, 31, NR) months respectively. The median OS for the entire cohort was NR. Only 4 pts died; cause of death was unrelated to POEMS. All pts who underwent AHCT are alive.
Conclusions: Our cohort treatment outcomes are similar to what has been published. IMiD-based therapy is very effective in the upfront setting. AHCT also leads to excellent response rates translating into long survival. Daratumumab appears to be increasingly utilized, mainly in the relapsed setting and has shown marked activity. A prospective study is currently enrolling to assess the latter's safety and efficacy in combination with lenalidomide in POEMS syndrome.

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Global myeloma trial participation and drug access in the era of novel therapies

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Introduction: The globalization of clinical trials has accelerated recent advances in multiple myeloma (MM). However, it is unclear whether trial enrollment locations are reflective of the global burden of MM and whether access to novel therapies is timely and equitable for countries that participate in those trials.
Methods: To assess this, we characterized the countries where MM trials that led to United States Food and Drug Administration (FDA) approvals were conducted. Then, we determined how often and quickly these drug regimens received approval for use in their participating trial countries based on country income level and geographic region. To identify pivotal trials, a systematic review was conducted to identify all MM clinical trials that met their primary endpoint, enrolled patients outside the US, and resulted in FDA approval from 2005-2019.
Results: A total of 18 pivotal MM clinical trials were identified. High-income countries enrolled patients in 100% (18/18) of the trials identified while upper-middle and lower-middle-income countries were represented in 61% (11/18) and 28% (5/18) of trials respectively. No patients from low-income countries were enrolled in these trials. One trial enrolled patients in Sub-Saharan Africa and no trials enrolled patients in South Asia or the Caribbean. For drugs/regimens that were approved in their participating countries, the median time from FDA approval to approval was 10.9 months. There were no drugs approved in lower-middle-income trial countries.
Conclusions: MM trials leading to FDA approval are generally conducted in countries that are high-income and located in Europe or Central Asia. However, in the lower-income countries where trials are run, these agents remain unavailable for use. The underrepresentation of low-income, South Asian, Caribbean, and Sub-Saharan African countries in MM clinical trials continue to exacerbate disparities.

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COVID – 19 vaccine uptake in patients with multiple myeloma and AL amyloidosis: a cross-sectional observational study from India

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Introduction: Patients with multiple myeloma (MM) and immunoglobulin light chain amyloidosis (AL amyloidosis) are prone to immune impairment and infections. COVID-19 related mortality is also increased, emphasising protection given by vaccination. Two vaccines widely used in India are Covishield [ChAdOx1 nCoV-19; Oxford–AstraZeneca] manufactured by Serum Institute of India, and Covaxin [BBV152] by Bharat Biotech. Vaccine acceptance rates in LMICs are comparable, if not higher, than in developed nations. We report the outcome of active counselling for COVID-19 vaccination in patients with MM and AL amyloidosis and the reasons for hesitancy in those who were unvaccinated
Methods: Institutional Ethics committee clearance was obtained. This was a cross-sectional observational study carried out in a tertiary care cancer hospital in South India. At diagnosis or follow-up, patients with MM and AL amyloidosis who visited the hospital between January 1 to June 30, 2021, were enquired about their COVID-19 vaccination details. The vaccination details were confirmed and verified on the Indian government's purpose-built platform (https://www.cowin.gov.in).
Results: Out of 195 patients, 178 (91%) were included in the study; 17 were lost to follow-up; MM – 176 (99%), AL amyloidosis- 2 (1%). Patients were actively counselled for COVID-19 vaccination during OPD visits or hospital admission. In subsequent hospital visits, the reasons behind vaccine hesitancy were identified. Baseline characteristics: Age: 30-85 years [median: 58]; males 101 (57%). The most widely used treatment regimen at the time of vaccination was thalidomide or lenalidomide maintenance in 81 (46%) cases. At the time of vaccination, 61 (34%) were on induction chemotherapy. Of the 178 patients, 15 (8%) developed COVID-19 infection during the study duration; out of the 15 patients, 7 did not receive a single dose of vaccine before infection. 2 out of 3 patients who died due to COVID-related causes were unvaccinated. At least a single dose of either vaccine was received in 154 (86%) patients, and both doses were administered in 119 (67%). Vaccine-related mild side-effects were reported in 4 (2%) patients; no vaccine-related thrombotic events or hospitalisations due to adverse events noted. Among the 24 (13%) patients who were not vaccinated, 9 reported a poor general health condition, 8 reported lack of advice from doctors as the reason for hesitancy, 2 did not take the vaccine owing to fear of side-effects, and 2 did not receive the vaccine due to unavailability of a vaccine delivery center nearby. 3 patients did not give any specific reason for not taking the vaccine. Our study reported a higher vaccine uptake rate compared to previous studies assessing acceptance of COVID-19 vaccine in patients with hematological malignancy. Around 70% took both the doses of COVID-19 vaccine.
Conclusions: Vaccine hesitancy among high-risk patients can be reduced with targeted counselling and reassurance by health personnel.

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Clinical profile and outcome of invasive aspergillosis in patients with myeloma: a single centre expereince from North India

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Introduction: Though, the advent of effective chemotherapy, newer antimicrobials and better supportive care has improved the survival of patients with hematological malignancies; invasive aspergillosis(IA) remain a major cause of mortality in a country like India posing a serious challenge for haemato-oncologists. An important consequence of IA is that apart from the high morbidity and mortality; it requires a long duration of treatment that leads to a significant delay in the therapy of the underlying hematological malignancy. primary treatment of AL which in turn is associated with poor outcome. The use of novel therapies and steroids in the therapy of Multiple Myeloma has made this set of patients to be a vulnerable group for IA though patients with acute leukemia remain the most common amidst hematological malignancies to have IA.
Methods: We retrospectively analysed 222 patients treated for multiple myeloma in our centre between December 2018 and March 2022. The clinical data and outcome of patients with myeloma who were admitted in our centre for pulmonary infections were analysed for possible risk factors, therapy received and outcome.
Results: 222 patients were treated for multiple myeloma in our centre with median age of 54 years (32-82). 24 patients were diagnosed with Invasive Pulmonary Aspergillosis (IPA). Among these, 4.16% had proven IA, 75% had probable IA and 20.83% had possible IA. Almost 80% of these patients were receiving their second or higher lines of therapy . Aspergillus attributable mortality at 6 weeks was 20.83% and was exclusively seen patients in their second or further lines of therapy. It was also noted that all five patients who succumbed to the illness had baseline Galactomannan Index(GMI) of more than 3 and required atleast 2 lines of antifungals for therapy. All except 4 patients were neutropenic at the time of presentation and were oxygen dependent.
Conclusions: Though not much recognised, patients with multiple myeloma form a significant group with high susceptibility and increased mortality from Invasive Aspergillosis. Serum GMI is one of the most useful tools in diagnosing IA. The data from our centre emphasizes that the

outcome of these patients are especially poor if they receiving second or more lines of therapy due to prolonged use of steroids and immunosuppressive therapy. High baseline galactomannan and its kinetics are soft signs of need for more aggressive therapy and consideration for more than one line of antifungals. More clinical studies may be warranted at the use of mold active prophylaxis especially in relapsed cases with neutropenia as these patients have poor outcome and high mortality.

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Pim-2 kinase regulate the expression of TIGIT and function of NK cells from multiple myeloma patients

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Introduction: Multiple myeloma (MM) is a malignant hematologic disease in which large numbers of abnormal plasma cells in the bone marrow proliferate and produce monoclonal globulin, bringing about clinical manifestations such as multiple osteolytic damage, hypercalcemia, anemia, and kidney damage. Pim-2 kinase is a serine/threonine protein kinase that participates in the development of multiple myeloma and myeloma bone disease by regulating the proliferation, differentiation and cell cycle of myeloma cells and osteoblasts. NK cells are in a functionally suppressed state in multiple myeloma, and this is one of the important mechanisms by which immune escape occurs in multiple myeloma. Previous studies have confirmed the importance of pim2 in the expansion of MM tumor cells and the production of bone destruction, while we have explored the role of Pim-2 kinase on immune cells in MM patients to provide a preliminary basis for the clinical use of small molecule inhibitors using Pim-2 kinase as a therapeutic target in MM.
Methods: Flow cytometry and qRT-PCR(Quantitative real time polymerase chain reaction) were performed to detect intracellular pim-2 kinase expression in MM patients and normal control bone marrow NK cells. Bone marrow single nucleated cells from MM patients were sorted and cultured in vitro, using SMI-16 as a pim2 kinase inhibitor. Flow cytometry was performed to detect changes in the expression of NK cell function-related molecules (CD107a, TNF, IFN-γ) and NK cell surface immunodetection sites BTLA, VISTA, LAG-3, CD226, Tim-3, CD96, PD-1, and TIGIT in both groups. Statistical analysis was performed by SPSS.
Results: The proportion of NK cells was higher in MM patients compared to normal controls (21.89±12.82 vs 15.17±7.15, $p< 0.05$). Intracellular Pim-2 kinase expression was significantly higher in bone marrow NK cells of MM patients compared to normal controls [52.15(17.94, 76.36) vs 14.57(8.15, 29.57), $p< 0.05$]; MM Pim-2 kinase mRNA levels were significantly higher in NK cells of patients compared to normal controls [2.67(1.22, 5.90) vs 1.01(0.77, 1.88), $p< 0.05$]. The addition of Pim-2 kinase inhibitor (SMI-16a) resulted in a significant increase in NK cell functional molecules CD107a, IFN-γ, elevated TNF expression; significantly lower TIGIT expression on the surface of NK cells [28.14(9.26, 38.89) vs 49.55(27.00, 66.14), p=0.0010]. However, the expression of PD-1, CD96, BTLA, LAG-3, CD226, PD-1, and VISTA did not change significantly.
Conclusions: Our study demonstrates that pim-2 kinase participates in the regulation of the immune microenvironment in MM patients by regulating the function of NK cells in the bone marrow and the immune checkpoint TIGIT, refining a new target of pim2 kinase for the clinical treatment of MM patients. The specific mechanism needs to be further discovered.

P-140

Outreach and satellite transplant clinics increase multiple myeloma (MM) transplant referrals and specifically transplant referrals of African American patients

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Introduction: Racial disparities exist between White and African Americans (AA) with multiple myeloma (MM) resulting in an inferior outcome among AA. The disparities are due to socioeconomic barriers that limit access to timely, appropriate and high quality medical care. A Veterans Administration study showed that with equal access, AA have superior survival compared to Whites. Autologous hematopoietic stem cell transplant (AHST) is a standard treatment modality in MM and improves survival but only 20% of AA receive AHST compared to 39% of Whites. This could be due to lack of resources and family support to travel to a distant transplant center (TC) to receive the procedure. Despite this compelling data, there are no programs to our knowledge to increase AHST availability to AA.
Methods: At our TC, we embarked on a program of outreach beginning July 2017 to market our TC with the intention of increasing transplant volumes. This included personally visiting community practices in our catchment area and meeting physicians and staff to create awareness of our services, make available our mobile numbers, familiarize them with an efficient referral process and establishing a meticulous line of communication. Beginning in early 2019, we also started satellite clinics (SC) in two large community practices; practice A 65 miles and practice B 89 miles from our TC. A transplant attending physician traveled to each of these SC once a month where patients were evaluated and those requiring a transplant were brought to the TC to undergo the procedure. Most of the pre-transplant work up to include labs, organ function evaluation, scans and bone marrow exams were conducted at the SC to limit travel and make it easier for patients and families. In this analysis, we only included patients with MM who received an AHST.

Results: Before outreach and SC, between 2013 and June 2017, we performed 81 MM AHST comprised of 39 White (48%), 41 AA (51%), and 1 other. After outreach and SC, from July 2017 to April 2022, we did 219 AHST with 92 White (42%), 123 AA (56%), and 4 other. Before outreach and SC, there were 4 AHST patients from practice A and 0 from practice B. From July 2017 to April 2022 (post-outreach and SC), there were 36; 29 from practice A and 7 from B. The median age was 65.6 years, 16 male (44%), and 28 AA (78%) and 22% White. The median distance from the patients' home to practice A and B was 14.8 and 41.3 miles and 81.5 and 93.6 miles to the TC, respectively.
Conclusions: We conclude that outreach and personal communication with the practices in the community increases transplant referrals. Additionally, setting up SC and seeing patients in the SC will not only increase AHST referrals but also increase referrals of minority patients, specifically AA. We think this could be due to making it more convenient for AA patients to be seen locally and closer to home. We strongly believe that this is one way of decreasing disparities and making AHST more accessible to minority populations.

P-141
Prognostic impact of CD3/CD34 ratio in apheresis collection in multiple myeloma patients undergoing autologous stem cell transplant

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Introduction: The use of immunotherapeutic agents in multiple myeloma (MM) has shown improvements in clinical outcomes, emphasizing the role the host immune system plays in disease control. Efforts aimed at identifying biomarkers of immune surveillance in MM have identified prognostic value in the peripheral absolute lymphocyte (ALC) and absolute monocyte (AMC) counts at various stages of disease and following autologous stem cell transplant (ASCT), with lower ALC and AMC serving as a surrogate for immune dysregulation and correlating with inferior progression free (PFS) and overall survival (OS). With ASCT remaining the standard of care in the treatment of MM, we sought to examine whether CD3 content relative to CD34 yield in the apheresis product during stem cell collection could be used as a biomarker for immune competence and whether it influences outcomes.
Methods: A retrospective study was conducted on 1797 MM patients who underwent stem cell (CD34) collection with available CD3 data and subsequent ASCT at our institution. We recorded the total absolute CD3 and CD34 cell count upon completion of mobilization, with a lower CD3/CD34 ratio serving as a surrogate for immune dysregulation. We used CD3/CD34 ratio instead of the absolute CD3 count given variation in the CD34 goals. Patients were dichotomized based on whether their CD3/CD34 ratio values were above or below the first quartile. A Kaplan-Meier model was used to compare median PFS and OS between groups.
Results: The median length of follow-up from date of ASCT for the entire cohort (N=1797) was 65 months (range: 0.26-157 months) and the median time from stem cell collection to ASCT was 9 days (range: 3-3143 days). The most common mobilizing regimen was Neupogen and plerixafor (N=610, 34%) and 1323 (74%) patients received ASCT in the first line setting. The median absolute total CD3 count was 4.3 x 10^8/kg (range: 0.1-21.9). The median absolute total CD34 count was 8.9 x 10^6/kg (range: 0.2-37.0) and median CD3/CD34 ratio was 49.0 (range: 1.0-1500). The 1st quartile CD3/CD34 ratio was 31.0, which served as the cutoff used to dichotomize groups. The median PFS among patients with a CD3/CD34 ratio 70 years, ASCT in first line setting, MRDNeg, and novel triplet induction as follows: PFS HR: 1.28 (95% CI: 1.04-1.58; p=0.02); OS 1.52 (95% CI: 1.1-2.0; p=0.003).
Conclusions: Our study demonstrates that patients who have lower CD3 content in their apheresis product relative to the CD34 yield have inferior PFS and OS following ASCT. These findings reveal a possible role for using CD3/CD34 ratios in the autograft product as a surrogate marker for immune competence and in predicting clinical outcomes.
P-142
Validation of new diagnostic criteria of primary plasma cell leukemia: a study of the Korean Multiple Myeloma Working Party (KMMWP-2003 study)

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Introduction: Recently, the International Myeloma Working Group revised the diagnostic criterion of primary PCL to 5% or more circulating plasma cells (CPC) in peripheral blood

smears. Therefore, this study validated the new criteria for the diagnosis of PCL.
Methods: We analyzed the medical record of 1,357 patients from 8 hospitals in South Korea. Patients who received conventional chemotherapy only as initial therapy were excluded.
Results: The median age of the all patients was 64 years, and 187 patients had circulating plasma cells at initial diagnosis. Most patients had less than 5% CPC, and 79 had more than 5% CPC. In this study, we evaluated the overall survival (OS) by the percentages of CPC; 0, 1-4%, 5-9%, 10-15%, 15-19%, and ≥ 20%. The OS of patients ≥ 5%, and ≥ 20% CPC were similar, and patients with more than 5% CPC had significantly inferior progression-free survival (PFS) and OS than those with less than 5% (median PFS; 13.1 months vs 21.5 months, P< 0.00, median OS; 21.5 months vs. 60.9 months, P < 0.001). Primary PCL diagnosed using new criteria showed higher white blood cell counts, total calcium, serum creatinine, and lower platelet counts and was frequently accompanied by organomegaly and extramedullary disease at initial diagnosis. On the univariate and multivariate analyses, achievement of complete response and extramedullary disease were significantly associated with PFS and OS in patients with PCL.
Conclusions: In conclusion, revised diagnostic criterion for PCL to 5% or more circulating plasma cells in peripheral blood smears is appropriate and more clinical studies are needed to determine the clinical and molecular features of primary PCL.

P-143
SLIM CRAB criteria revisited: a meta-analysis of studies on 'biomarker defined early multiple myeloma'

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Introduction: The IMWG updated the criteria for the diagnosis and treatment initiation in pts with multiple myeloma (MM) in 2014 (Rajkumar V. et al). The most important innovation was the inclusion of pts with smoldering MM (SMM) meeting specific criteria (≥60% BMPCs, FLC ratio ≥100, and >1 MRI defined focal lesion) in the definition of MM, which up to this publication was confined to pts with one or more CRAB criteria. The main argument for including these biomarker-defined pts in the definition of MM was the anticipated risk of rapid progression to CRAB positive MM and possible detrimental complications by delaying therapy. As this definition was based on data published until 2014, we conducted a meta-analysis of all relevant published studies until May 2022.
Methods: We did a comprehensive literature research and retrieved 3, 6, and 3 studies that included survival curves for time to progression (TTP) for SMM pts with ≥60% BMPCs, or a FLC ratio ≥100, or >1 focal lesion, respectively. As individual pt data for meta-analysis were not available, we applied the algorithm described by Guyot P et al., 2012, and digitized (using WebPlotDigitizer) the published survival curves of pts enrolled in these studies. This approach yields an excellent proxy for individual pt level data used for the original publications. We then meta-analyzed the data and constructed time to progression (TTP) curves for the combined data for each of the three biomarker-defined MM groups.
Results: Pts with ≥60% BMPCs: The combined analysis of the data published by Rajkumar-V et al., 2011 and Kastritis-E et al., 2013 yielded a median TTP of 9.1 mos. By adding the data from 243 pts published by Wu-V et al., 2018, our calculations revealed a median TTP of 15.5 mos. Pts with a FLC ratio ≥100: The combined analysis of the two studies (Larson JT et al., 2013 and Kastritis E et al., 2013) that were available before the consensus publication showed a median TTP of 15.3 mos. By including the extracted patient level data from four studies published after 2014 (Wu V et al., Blood Advances. 2018, Sørrig R et al., Eu J Haematol. 2016, Henriot B, et al. 2019, Akhlaghi T et al, 2022) in the meta-analysis, the median TTP of pts with a FLC ratio of ≥100 was 21.4 mos. Pts with >1 MRI defined focal lesions: Three studies were available for the IMWG update publication (Hillengass J et al., 2010, Merz M et al., 2014, Kastritis et al., 2014). Meta-analysis of their data revealed a median TTP of 15.1 mos. No further relevant studies were published after 2014.
Conclusions: Our meta-analysis revealed a median TTP of 15.5 mos, 21.4 mos, and 15.1 mos in biomarker-defined MM pts with ≥ 60% BMPC, FLC ratio ≥ 100, and > 1 focal lesion, respectively. This is markedly longer for the first two conditions than initially anticipated, indicating that initiation of therapy in SLIM CRAB positive pts should be carefully considered and not solely based on the diagnostic term 'SLIM CRAB positive MM'.

P-144
Treating multiple myeloma in a resource-limited setting: real-world outcomes

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Introduction: Over 70% of the Brazilian population (> 150 million people) do not have access to private health care. Alkylating agents, thalidomide, and autologous stem cell transplantation (ASCT) are the mainstay of newly diagnosed multiple myeloma (NDMM) treatment in the public health care system. Therefore, real-life data from resource-limited countries are scarce and essential to optimize the incorporation of new technologies into this scenario.
Methods: Describe characteristics of patients with NDMM, access to therapy, and outcomes, including overall survival (OS) and progression-free survival (PFS). Retrospective chart

study including all patients with NDMM treated at Hospital das Clinicas de São Paulo Complex between 2009 and 2019. **Results:** A total of 816 patients with NDMM were included. Mean age was 63 years and 55% were male. At the diagnosis, 91% of patients had bone lesions, 56% anemia, 41% hypercalcemia, and 26% presented with impaired renal function. Regarding the clinical stage, 88% were Durie Salmon III clinical stage, and 46% were ISS III stage. Median follow-up time was 5 years. A triplet regimen (cyclophosphamide, dexamethasone, and thalidomide) was the most prescribed in the frontline (446/792, 56%), followed by alkylating agent + dexamethasone regimens (281/792, 27%). Only three patients (0.4%) in this cohort received bortezomib upfront. 379 (46%) were referred to ASCT for consolidation, and 257 (25%) proceeded with it in the first-line treatment. 36% of the patients received three or more lines of therapy. Patients who underwent ASCT had fewer comorbidities by Charlson's index, lower ECOG at diagnosis, and fewer ISS stage III patients (31%) ($p< 0.001$ for all). Only 16% of the patients over 60 years underwent ASCT. Median time from diagnosis to transplant was ten months. Early mortality (≤ 120 days after diagnosis) was 9.7%, mainly due to infection. For the whole cohort, the overall response rate (ORR) after the first induction was 408/647 (63%), and 144 (22%) had disease progression. PFS and OS were 1.7 years (95% CI 1.6-1.9) and 3.7 years (95% CI 3.4-4.2), respectively. Median OS for patients that received ASCT was 5.9 (95%CI 5.1-7.8) years. **Conclusions:** This real-world cohort demonstrated that the available therapy in a resource-limited setting is far from the current gold standard for NDMM. Alkylating-based therapy results in suboptimal response rates, while the ASCT procedure is not timely available for all patients. In addition, poor clinical status and advanced disease may impact the choice of not using triplet regimens upfront. Early diagnosis, incorporating proteasome inhibitors and newer agents into the frontline, and ASCT availability are the major initiatives to decrease the disparity between rich and developing countries.

P-145
The clinical significance of a “MGUS” tumor board

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Introduction: Our large academic medical center consists of both a main campus and several regional sites that all offer hematology/oncology services where monoclonal gammopathy cases are referred for consultation. Cases initially suspected to have monoclonal gammopathy of undetermined significance (MGUS) are commonly managed by advanced practice providers (APPs) at our institute.

Methods: Due to the concern for varying experience managing MGUS, differences in diagnostic practice and limited guidance we developed a novel concept to have a tumor board to review MGUS cases. This is ran by two of our main campus myeloma focused hematologists and our myeloma dedicated APRN-PhD. We meet twice a month to review cases.
Results: Over the past 9 months we reviewed 64 cases providing recommendations for further work up. Of these, 16 cases (25%) were found to have a clinically significant monoclonal protein necessitating referral to a physician at main campus. The breakdown of these cases are detailed below in table 1. Nine patients (14%) were started on treatment, the other 7 (11%) remained on observation. Another aspect of the tumor board is to provide education regarding clinically significant scenarios that involve monoclonal proteins. This tumor board offers CME credit for both APPs and physicians.

Table 1:

Diagnosis	#Patients (%), total n=64	Location of Patient Care
Low-Risk MGUS	36 (56.2%)	Remained with APP
Paraproteinemia	12 (18.8)	
High-Risk MGUS	3 (4.7%)	Referred to physician on main campus
Low-Risk sMM	1 (1.6%)	
High-Risk sMM	1 (1.6%)	
Active Myeloma	2 (3.1%)	
Cryoglobulinemia—monoclonal	2 (3.1%)	
WM/LPL	4 (6.3%)	
WM with anti-MAG Neuropathy	1 (1.6%)	
MZL	1 (1.6%)	
TTR amyloidosis	1 (1.6%)	

Conclusions: There were higher than expected percent of patients with clinically significant monoclonal proteins. Our data shows that it is essential for there to be some standardization for reviewing and working up “MGUS” referrals. This is especially important at large centers with multiple locations. We recommend a tumor board style review as it allows for discussion and education of MGUS cases which prove to be far more complex in many cases.

P-146
Screening technique for M-proteins in acetonitrile precipitates of serum using MALDI-TOF mass spectrometry: a comparison with serum immunofixation electrophoresis and serum free light chain assay

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Introduction: Several studies have demonstrated the analytical sensitivity of MALDI-TOF mass spectrometry by immunoenrichment for the screening, detection and follow-up of M-protein. We have previously reported the results of a novel methodology for the detection of serum M-protein by a direct reagent-based extraction process using acetonitrile (ACN) precipitation by MALDI-TOF mass spectrometry (MS).
Methods: Institutional Ethics committee approval was obtained for the study. The work was carried out in accordance with the Declaration of Helsinki after obtaining written informed consent. Serum samples from patients with MGUS, smoldering multiple myeloma (SMM), multiple myeloma (MM), plasmacytoma or immunoglobulin light chain amyloidosis (AL amyloidosis) underwent ACN precipitation. MALDI-TOF MS measurements were obtained for intact proteins using alpha-cyano-4-hydroxycinnamic acid as a matrix. The images obtained were overlaid on apparently healthy donor serum samples to confirm the presence of M-protein. A sample was considered positive for M-protein if there was a sharp or broad peak within the κ or λ mass/charge (m/z) range: κ m/z- [M+2H]2+: 11550-12300 Da; [M+H]+: 23100-24600 Da), and λ m/z- [M+2H]2+: 11100-11500 Da; [M+H]+: 22200-23100 Da. Images were acquired at a m/z range of 10000-29000 Da. Corresponding serum protein electrophoresis (PEL), serum immunofixation electrophoresis (IFE) and serum free light chain (sFLC) assay by nephelometry were performed for all the samples.
Results: One hundred and seventy-three serum samples were included for analysis (MM-158; plasmacytoma- 7; MGUS- 4; Waldenström macroglobulinemia- 2, SMM- 1; AL amyloidosis-1). Out of 158 patients with MM, 87 (55%) were newly diagnosed, and 71 (45%) were patient follow-up samples on treatment. [M+2H]2+charge state images were chosen for further analysis due to superior visual sensitivity. An M-protein was identified in 114 (66%) by PEL, 153 (88%) by IFE, 137 (79%) by sFLC and 156 (90%) by MALDI-TOF MS. Among patient samples that were PEL+/IFE+, PEL-/IFE+ and PEL-/IFE-, MALDI-TOF MS identified the M-protein in 111/113 (98%), 36/40 (90%) and 9/19 (47%), respectively. Concordances rates for light chain analysis (κ, λ or absent): IFE with MALDI-TOF MS- 148 (86%); sFLC with MALDI-TOF MS- 134 (77%); IFE, sFLC and MALDI-TOF MS- 128 (74%). In comparison with IFE, sFLC or the combination, MALDI-TOF MS identified a discordant light chain, i.e. κ called λ or vice-versa, in 9 samples (5%); this ranged from 11504 to 11660 m/z in the [M+2H]2 charged state. This could be due to an overlap observed in the κ and λ m/z ranges. This study demonstrates the feasibility of qualitatively identifying M-protein without the need for nanobody-based immunoenrichment using agarose or sepharose beads, making the technique less expensive.
Conclusions: We report the results of a low-cost technique by ACN precipitation and MALDI-TOF MS for the screening, identification and follow-up of M-protein.

P-147
Renal transplant in light chain deposition disease – salvation or highway to hell? A case presentation

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Introduction: We present a rare case of a patient with light chain deposition disease (LCDD) who underwent kidney transplant in remission phase of LCDD.
Methods: Case presentation: A 47-year old man presented with refractory hypertension, edema, renal failure and proteinuria (over 9g/24h). Kidney biopsy revealed LCDD with no amyloid deposits. Laboratory findings included high serum levels of free light chains (FLC; kappa 2215mg/L, lambda 33mg/L, K/L 67,12), 30% infiltration by clonal plasma cells in bone marrow biopsy, with no further attributes of multiple myeloma (MM) – normal calcium levels, blood count and no osteolytic involvement on radiography and magnetic resonance imaging. The patient underwent 2 cycles of bortezomib and dexamethasone with normalization of FLC levels, due to the rapid onset of painful peripheral neuropathy he continued with 7 cycles of cyclophosphamide and dexamethasone with the achievement of complete hematological response. Creatinine levels decreased but did not normalize (~180umol/L). Stem cell transplant was not indicated due to poorly controlled hypertension and patient´s wish. Three years later, renal functions deteriorated while LCDD was still in remission and the patient started hemodialysis. The patient requested kidney transplant as regular hemodialysis was affecting his activities of daily living. With long lasting complete response of LCDD and no signs of active malignancy, he was put on waiting list, and underwent kidney transplant in 2018 followed by immunosuppressive support. One year after the kidney transplant, creatinine levels normalized but serum levels of FLC kappa increased, fulfilling the criteria of relapse. Bone marrow examination confirmed plasma cell increase (12%), PET/CT was without activity or lytic involvement. As the patient was asymptomatic, we started therapy with MP regimen (melphalan and prednisone) which appeared sufficient and delivered remission after 9 cycles. Six months later the patient presented with overall deterioration, hypercalcemia, multiple lytic involvement and bone marrow infiltration by plasma cells. We initiated therapy with daratumumab, lenalidomide and dexamethasone (DRD), which was, however, ineffective, the patient progressed and finally died. The renal functions, paradoxically further improved and remained normal (creatinine 80umol/L) despite the aggressive course of multiple myeloma.
Results: -

Conclusions: Organ transplant and immunosuppressive therapy is not recommended for patients with MM. In sustained remission of LCDD, however, some authors suggest kidney transplant as a feasible approach to restore renal functions. Our case confirms significant improvement of renal functions, however, immunosuppressive therapy very likely induced the evolution of a very aggressive form of multiple myeloma. We therefore urgue a very careful approach if organ transplant and immunosupressive therapy is considered even in patients with non-malignant plasma cell dyscrasias. Supported by IGA_LF_2022_001.

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Second booster BNT162b2 restores SARS-CoV-2 humoral response in patients with multiple myeloma, except for those under treatment with anti-BCMA agents

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Introduction: COVID19 vaccination leads to a less intense humoral response in patients with multiple myeloma (MM) compared with healthy individuals, whereas the SARS-CoV-2-specific immunity fades over time. Booster doses have been implemented in order to maintain an adequate antibody response. The purpose of this study was to explore the kinetics of SARS-CoV-2 neutralizing antibodies (NAbs) in patients with MM after vaccination with the BNT162b2 mRNA vaccine (Pfizer-BioNTech), focusing on their response before and after the fourth vaccination.
Methods: NAbs were measured at baseline (before the first vaccination), before the second dose, one (M1P2D), three and six months after the second dose, before the third dose, one (M1P3D) and three months (M3P3D) after the third dose, before the fourth dose (B4D), and one month after the fourth vaccination (M1P4D). The second booster shot was provided at 6 months following the first booster vaccination. The Institutional Ethics Committee approved the study. NAbs measurements were performed with GenScript's cPassTM SARS-CoV-2 NAbs detection Kit (GenScript, Inc.; Piscataway, NJ, USA). Statistical analysis was performed with SPSS (v.26) and all comparisons were made at the 5% significance level.
Results: Overall, 189 patients with a median age of 67 years were included, whereas 108 (57.1%) were men. Among them 43 (23%) patients were receiving anti-CD38-based treatment, 9 (5%) were under anti-BCMA-based therapy and 137 (72%) were receiving other combinations. At baseline, no difference in NAbs was found among the three treatment groups. 28 (15%) patients were found positive for SARS-CoV-2 after receiving the third dose and before the fourth vaccination. No significant differences were found in terms of NAbs titer, age, or gender between patients with a history of COVID19 and those without. Overall, the median level of NAbs titer at M3P3D were 93.77% (standard error ±2.28), but declined to 80.0% (±2.54) at B4D. However, the median NAbs titer increased to 96.1% (±2.48) at M1P4D. The differences in NAbs between the subsequent timepoints were statistically significant ($p<0.001$). Interestingly, patients under anti-BCMA therapy had significantly lower NAbs compared to those under anti-CD38 or other treatment at all three timepoints (p-values<0.001). Gender, age, ISS, and RISS were not found to exert a statistically significant effect on NAbs levels at M3P3D, B4D, or M1P4D. Furthermore, the NAbs levels one month after the second, third, and fourth vaccination were also compared for the whole study population. Statistical analyses showed the NAbs titers at M1P4D (mean 76.4%±4.14) did not differ significantly ($p=0.062$) with those at M1P3D (mean 80.55±3.61), but were significantly higher compared to those at M1P2D (mean 61.02%±3.52).
Conclusions: In conclusion, booster vaccination with the BNT162b2 results in substantially improved humoral response against SARS-CoV-2 in patients with MM. Anti-BCMA treatment remains an adverse predictive factor for NAbs response.

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Prevalence of type 1 Gaucher disease in patients with multiple myeloma: interim analysis of a prospective, multicentre, observational study

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Introduction: Type I Gaucher disease (GD1) is an autosomal recessive lysosomal storage disease, caused by deficiency of the enzyme glucocerebrosidase, that degrades glycosphingolipids. In GD1, aberrant macrophage activation and immune dysregulation are associated with increased cancer risk. The International Collaborative Gaucher Group (ICGG) Registry comprising 2,742 eligible patients [Rosenbloom BE et al, 2005] found there was a 5.9-fold (95% CI 2.8–10.8) increased risk of Multiple Myeloma (MM) in patients with GD1. However, this risk was likely underestimated in this study because the younger age distribution of the study population and incomplete ascertainment because the ICGG is an observational registry to track responses to treatment. So, we thought it was useful to prospectively investigate the prevalence of GD1 in a large population of patients affected by MM.
Methods: This is an observational, prospective, cross-sectional, multicentre study. The primary objective was to determine the prevalence of Dried Blood Spots (DBS) test positivity in a large prospective MM population. Patients with DBS test positivity were then purposed for genetic test to confirm the diagnosis GD1. The DBS test will be centralized at the Istituto per la Ricerca e l'Innovazione Biomedica CNR-Palermo. Considering that no effective prevalence data of GD1 in patients with MM are available, the sample size has been determined considering clinically relevant a prevalence > 0.5% for defining as "high risk" the selected population. To test this hypothesis (alpha 5%, beta 5% errors), we will enrol approximately 1000 patients.
Results: Three-hundred and forty five patients have been enrolled, so far. Median age was 67 years (range 37-90 years) and 56% of patients were male. No patients was of Jew ethnicity, one was Asian and one was black, Caucasian the remaining. Fifty-five percent had newly diagnosed MM while 45% had relapsed-refractory MM. Monoclonal component was IgG in 56%, IgA in 24%, light chain in 10%. Median Ferritin was 325 ng/ml (range 17-1236 ng/ml) and median Alkaline Phosphatase was 83 U/L (range 29-355 U/L). Among 4 patients identified with low glucocerebrosidase enzyme activity by DBS screening (< 4 nM/h/ml), 3 had heterozygous mutation in GBA gene (enzymatic activity 2.7, 3.4 and 3.9 nM/h/ml) whereas one was double heterozygous (enzymatic activity 2.0 nM/h/ml). This patient had Lyso Gb1 high level (14.6 ng/ml) and than he started eliglustat for GD1 in conjunction with therapy for MM. Considering only this patient as DBS positive the prevalence was 1/349 (0.28%), so far.
Conclusions: Despite the trial enrolment is just in the first third of the whole planned sample size, our preliminary data showed an interesting prevalence of DBS test positivity. Data updates are needed to define the real incidence of DBS test positivity in MM and the relationship of GD1 and plasma cell disorders. Acknowledgment. This study is supported by Sanofi Genzyme

P-150
Identification of misclassified multiple myeloma patient risk subgroups with a novel biological disease stratifier

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Introduction: The outcome of high-risk MM patients classified by ISS, R-ISS or adverse risk cytogenetics is not uniform and patients show heterogeneous survival. Recent insights into the pathogenesis of MM highlighted APOBEC cytidine deaminase enzyme as well as inflammation are involved in MM progression. We hypothesized that inclusion of these molecular features into risk stratification could potentially resolve the challenge of identifying unrecognized patient subgroups, who have been previously misclassified by current risk stratifiers.
Methods: The Multiple Myeloma Research Foundation CoMMpass study genomics dataset, combining mRNA Seq and clinical data from more than 700 MM patients, allowed us to define an accurate weighted OS/PFS risk score (Editor-Inflammation (EI) score) based on mRNA expression of APOBEC2, APOBEC3B, IL11, TGFB1, TGFB3, as well as ß2-microglobulin and LDH serum levels. The novel EI-score applied to different ISS, R-ISS and cytogenetic risk subgroups to see whether EI-score can identify misclassified patient subgroups by current MM risk stratifiers.
Results: The EI-score identifies patient subsets who classified in ISS/ R-ISS stage II/III with good prognosis and patients classified in ISS/ R-ISS stage I/II with poor prognosis. The EI-score also identified subgroups of MM patients with adverse risk cytogenetics [carried either del(17p)/ gain(1q)/ t(4;14)] but with favorable outcomes. For example, the EI-score was able to subclassify del(17p) MM patients into three main risk subgroups: a very good prognosis group (0% additional TP53mut) with 5-year OS of 100%, an intermediate group (30% TP53mut) with 5-year OS rate of 75%, and a very poor prognosis group (40% TP53mut) with 5-year OS of 0% (2-year

OS: 40%). Furthermore, we found that patients that carried del(17p) and a high EI-score, display an enrichment of APOBEC-induced genomic mutations compared to intermediate and low EI-score patients supporting the hypothesis that del(17p) along with high APOBEC expression levels activate the APOBEC mutation program and thus create an optimal environment for tumor progression. These findings support the necessity of a prognostic score that more accurately reflects MM disease biology.
Conclusions: Although MM is considered as an incurable disease, an improved risk stratification could help to identify previously unrecognized low- and high-risk patient subgroups that are over- or undertreated and lead to improved outcomes. Our EI-score is a simple score that is based on recent insights into MM biology and accurately identifies high-risk and low-risk newly diagnosed MM patients as well as misclassified MM patients in different cytogenetic and ISS risk subgroups.

P-151
Primary plasma cell leukemia in Latin America: demographic, clinical, and prognostic characteristics. A study of GELAMM group

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Introduction: Primary plasma cell leukemia (pPCL) is an infrequent and aggressive plasma cell disorder. The use of novel agents, along with autologous stem cell transplantation (ASCT), has improved survival outcome in pPCL. However, the prognosis is still very poor, and the optimal treatment remains to be established. There are scarce data on this disorder in Latin America (LA). The aim of this study was to describe demographic, clinical, and prognostic characteristics of pPCL in LA.
Methods: A retrospective, multicentric, international observational study was performed. Patients from 9 countries of LA with a diagnosis of pPCL between 2012 and 2020 were included. pPCL was defined as 20% or more plasma cells in peripheral blood at diagnosis, or an absolute number of PCs >2000/mm3. Demographic and clinical data were collected from clinical records. Survival curves were estimated using the Kaplan–Meier method. Uni- and multivariable Cox proportional hazards models were used to assess risk factors.
Results: Seventy two patients were included. Median age was 57 years, 53% were male and 55% had performance status (ECOG) ≥2. Anemia was present in 79%, hypercalcemia in 45%, renal failure in 39%, thrombocytopenia in 57% and bone lesions in 80%. High LDH was observed in 71% and hypoalbuminemia in 57%. Extramedullary disease was reported in 29% of patients, 2 of them with CNS involvement. The involved paraprotein was IgG in 36% and light chain in 45% (55% Kappa). Six patients died before receiving any specific treatment. Most patients (83%) were classified as eligible for ASCT and received at least 1 cycle of treatment. Treatment was based on thalidomide in 15% (group 1), proteosome inhibitors (IP)-based triplets in 38% (group 2), chemotherapy plus IMIDs and/or IP in 29% (group 3) and other in 18% (group 4). The most used regimens were CyBorD in 26%, VTD-PACE in 20% and CTD in 14%. Seventeen (24%) patients died during induction with a mortality rate at 3 months of 30% (CI95% 20-42) without significant differences between treatment groups. The complete response rate (CR) or better was 0% in group 1, 24% in group 2, 28% in group 3 and 17% in group 4. ASCT was performed in 15 patients (21%), including 7 with tandem modality. Three patients received allogeneic transplant. Twenty-one patients received maintenance therapy. Median overall survival (OS) was 18 months (CI95% 9-28), 5 years OS was 20% (CI95% 8-38). Median OS for patients that achieved CR or better was not reached in this study, with a 2-year OS of 80% (CI95% 41-95) versus 28% (CI95%14-44%). In the multivariate analysis, frontline therapy group 2 and 3, and maintenance were independent factors of better OS.
Conclusions: As reported internationally, patients with pPCL were young, and had aggressive clinical features. We observed more bone lesions than classically described. Frontline therapies were heterogeneous. Reasons for 75% of potential candidates not being transplanted merit further analysis. OS is still very poor.

P-152
Prevalence of monoclonal gammopathies in adult Uruguayan population

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Introduction: Multiple myeloma is an incurable disease. Late diagnosis is associated with end-organ failure, inferior quality of life and survival, and increased costs for healthcare institutions. Early detection of MM through follow-up of preclinical entities (MGUS and SMM) has shown 13-14% fewer major complications and improved overall survival, compared to patients with MM without a previous diagnosis of MGUS. To date, there is no data on the prevalence of monoclonal gammopathies in the adult population in our country, and most MM patients (87%) are diagnosed in an advanced stage. Aim: To assess the prevalence of monoclonal plasma cell disorders in adult population in Uruguay, and describe the clinical features and cause-specific survival.
Methods: This prospective, single-cohort, descriptive study was initiated in October 2021, and the end of recruitment is planned for October 2022. We included patients with age ≥40 years and excluded patients with a previously known plasma cell disorder. Medical history was obtained in all participants. All blood samples were processed in the central laboratory at our institution. CAPILLARYS 2 Flex Piercing is used for Protein and Immunotyping analyses, Hydrasys 2 for immunofixation, and Freelite (The Binding Site) for serum-free light chain assay. When a monoclonal component (MC) was found, the patient was referred to the hematology department to complete the evaluation. This study was approved by the Hospital de Clinicas Ethics committee.
Results: We report the data for the first 6 months of recruitment. 1016 consecutive patients were included; the median age was 61 years (IQR 19), and 59.3% were females. MC was reported in 39 patients (3.83%); the median age was 71 years (IQR 17), and 64.1% were females. Patients without MC had a median age of 60 years (IQR 18) ($p< 0.01$). Median value of the MC was 0.5 g/dl, (IQR 0.4; 0.1-1.2 g/dl). Subtype of immunoglobulins were IgG-kappa in 53.8%, IgG-lambda in 28.2%, IgA-lambda in 7.7%, IgA-kappa in 5.1%, IgM-kappa 5.1%. The median value of FLC kappa, lambda, and ratio (rFLC) were 31 mg/L (IQR 48), 20 mg/L (IQR 17), 1.36 (IQR 1.44) respectively. An abnormal rFLC was found in 34.2% (13/39). One patient was diagnosed with a low-risk IgG-k smoldering myeloma and the rest are MGUS. The proportion of patients with MC did not differ statistically between genders ($p=0.53$). Of the symptoms investigated in the initial questionnaire, only weight loss was significantly higher in patients with a positive SPEP (23.08% vs 8.09% in negative SPEP, $p< 0.01$). Age >60 years was associated with a 2.6 increase in the detection of MC (95% CI 1.28-5.29 $p< 0.01$).
Conclusions: In this preliminary analysis the prevalence of MC was 3.8%, consistent with the internationally reported data. The risk of having a monoclonal gammopathy increases with age. The next steps are to expand the study to the rest of the country and to compare the performances of the SEBIA FLC assay with Freelite results.

P-153

Impact of t(11;14) in multiple myeloma on response to treatment and survival

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Introduction: Cytogenetic abnormalities detected by FISH (fluorescent in situ hybridization) in Multiple Myeloma (MM) allow differentiating groups with different biological characteristics, response to treatment and prognosis. The t(11;14) is the most frequently detected (15-20%) and its impact on prognosis in the era of new treatments is not well established.
Methods: An observational retrospective study was designed including 1111 patients diagnosed of MM in Hospital of Salamanca and Leon (1984-2018). Patients without t(11;14) study by FISH were excluded. Patients were classified in 3 groups: 1) t(11;14) group; 2) high-risk (HR) group (included patients with t(4;14), t(14;16), del17p and t(11;14) with del17p); and 3) standard risk (SR) group (patients that were not included in groups above). SR and HR patients were pooled in the non-t(11;14) group. Proteosome inhibitors, immunomodulators and anti-CD38 monoclonal antibodies were named novel agents.
Results: A total of 600 patients were included. One-hundred and five patients harbored t(11;14) (17.5%). Ninety-eight (16.3%) belonged to the t(11;14) group, 104 (17.3%) to the HR and 398 (66.3%) to the SR group. Three-hundred and fifty (58.3%) were male and the median age was 66 years (28-96). The median prior lines of therapy was 2 (0-14) and 356 (62.7%) received new drugs. With a median of follow up of 55.9 moths (0-364.1), no differences were observed in OS between the t(11;14) and the SR group (75.8 vs. 93.4 months; $p = 0.222$), but was better than the HR group (48.7 months; $p = 0.0023$). MM t(11;14) treated with new drugs had not better ORR nor percentage of CR (89.6% and 31.3%, respectively) than who received conventional therapy (80.0% and 32.5%, respectively) ($p = 0.207$ and 0.900). No differences were observed in patients with t(11;14) treated with new drugs in comparison with conventional therapy in PFS (39.5 vs. 29.9 months; $p = 0.461$) nor OS (93.2 vs. 75.8 months; $p = 0.171$). The non-t(11;14) group treated with novel agents presented superior ORR (89.0% vs. 77.6%; $p = 0.001$), percentage or CR (43.8% vs. 31.7%; $p = 0.011$), and OS (91.1 vs. 67.1 months; $p = 0.033$). Within patient of good prognosis

ISS-1, the t(11;14) group presented worse OS than non-t(11;14) group (63.0 vs. 117.7 months; p = 0.006). In the univariant study of the t(11;14) group, patients with oligosecretory disease (≤ 1 g/dL of paraprotein) had trend to inferior OS than non-oligosecretory disease (32.0 vs. 86.6 months; p = 0.052)
Conclusions: Patients with t(11;14) in our cohort did not benefit from the introduction of novel agents in terms of quality of response and survival. The t(11;14) and the SR group had similar prognosis, but superior than the HR group. However, in patients with good prognosis (ISS-1), the presence of t(11;14) was associated with worse OS.

P-154
Incidence and prognosis of renal failure in multiple myeloma: 50-years experience from an academic institution

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Introduction: Approximately 20% of patients with multiple myeloma (MM) have renal failure (RF) at the time of diagnosis and 5% require hemodialysis (HD). The presence of RF is associated with a shorter overall survival (OS), although the introduction of new drugs has improved the prognosis of these patients.
Methods: a series of 1377 patients (51% men, median age 64 years) with MM diagnosed at our institution between 1970 and 2020 were retrospectively analyzed. Two time periods were defined (1970-1999: N=567; 2000-2020: N=810) based on the availability of new drugs. At diagnosis, serum creatinine was ≤2mg/dl in 82%, 10% had moderate RF (serum creatinine >2-4mg/dl) and 8% had severe RF (serum creatinine >4mg/dl).
Results: overall, 243 patients (17%) presented RF (10% moderate, 8% severe). The incidence of severe RF decreased significantly in the second period (11% vs 5%, p=0.0001). Moderate RF was reversible in 52% of patients while 6% of them required HD, which could be discontinued in 44% of cases. Severe RF was reversible in 25% of patients (17% in period 1 vs. 37% in period 2, p=0.01). 62% of the patients with severe RF required HD, which could be discontinued in 59% of the patients in period 2 vs. 11% in period 1 (p=0.0001). Early mortality decreased significantly from the year 2000 in all patient subgroups, particularly in those with severe RF (patients with creatinine≤ 2mg/dl: 6.1% vs 3%, p=0.009; moderate RF 24.9 % vs 11.9%, p=0.05; severe IR: 32.3% vs 13%, p=0.01). Patients with RF have a shorter OS, although their prognosis, particularly in patients with severe RF, has improved in recent years. Thus, the OS was 34 vs. 22 vs. 8 months (p< 0.0001) in period 1 and 67 vs. 33 vs. 38 months in period 2 (p< 0.0001) for patients without RF, moderate RF and severe RF, respectively. First-line treatment based on new drugs has significantly improved the OS of patients with severe RF compared with conventional chemotherapy (81 vs 39 months, p=0.007), while in patients with moderate RF the benefit has been scarce (39 vs 30 months, p=0.692).
Conclusions: RF in MM is associated with a higher early mortality and shorter OS. The prognosis of patients with severe RF has improved significantly in recent years with a higher rate of reversibility, a higher proportion of patients who discontinue HD, a decrease in early mortality, and a significant prolongation of OS that might be attributed to the introduction of new drugs. In contrast, the outcome improvement in patients with moderate RF has been scant, despite the introduction of new drugs.

P-155
Paraskeletal and extramedullary plasmacytomas in multiple myeloma at diagnosis and at first relapse: 49-years experience from an academic institution

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Introduction: the presence of plasmacytomas in multiple myeloma (MM) is considered an adverse prognostic factor. We can differenciate two types of plasmacytomas according to their origin: 1) paraskeletal (PPs), consisting of soft-tissue masses arising from focal bone lesions and 2) extramedullary (EMPs) resulting from hematogenous spread. In this context, the aim of our study was to analyze the incidence and outcome of patients with MM and plasmacytomas diagnosed at our institution in a long period of time focusing on the two types of plasmacytomas: PPs and EMPs
Methods: a series of 1304 patients with MM diagnosed at our institution between 1970-2018 were retrospectively analized. Two time periods were defined (1970-1999 and 2000-2018) according to the availability of novel agents.
Results: overall, 256 of 1304 patients (19.6%) had plasmacytomas at diagnosis (paraskeletal: 17.6%, extramedullary: 1.9%). Patients with plasmacytomas had lower serum M-protein and less advanced ISS stage than those without. At first relapse, 192 out of 967 patients (19.8%) developed plasmacytomas (PPs 14.6%, EMPs 5.1%). The only factor associated with plasmacytomas at relapse was the presence of plasmacytomas at diagnosis (46% vs. 13%, p< 0.00001) with no impact with exposure to novel drugs or previous autologous stem-cell transplantation (ASCT). The median overall survival (OS) was 45, 44 and 20 months for patients without plasmacytomas, PPs and EMPs,

respectively (p=0.013). Patients with PPs who underwent ASCT had similar OS than those without plasmacytomas (98 vs. 113 months) and significantly longer than those with EMPs (98 vs. 47 months, p=0.006). In patients non-eligible for ASCT the presence of PPs or EMPs was associated with shorter OS compared with patients without plasmacytomas (32 vs. 24 vs. 6 months, p=0.009). In the relapse setting, a significant survival improvement was observed beyond the year 2000, but still with significant differences among patients without plasmacytomas, PPs and EMPs (37 vs. 22 vs. 16 months, p=0.003). Importantly, rescue therapy with combinations of proteasome-inhibitors (PI) plus immunomodulatory drugs (IMiDs) resulted in a prolonged OS of 73 vs not reached vs 90 months (p=0.414) in patients without plasmacytomas, PPs and EMPs, respectively.
Conclusions: the incidence of PPs is similar at diagnosis and at relapse while EMPs are more frequent at relapse than at diagnosis. The only factor associated with plasmacytomas at relapse is the presence of plasmacytomas at diagnosis. Patients with plasmacytomas have low tumor burden (lower ISS and serum M-protein size) than those without plasmacytomas. Patients with PPs at diagosis undergoing ASCT have similar survival than those without plasmacytomas while patients with EMPs had poor outcome.At first relapse, rescue therapy with PI+IMiDs is associated with prolonged OS (over 6 years) even in patients with EMPs.

P-156
Evaluation of SAVED and IMPEDE-VTE scoring systems for venous thromboembolism prophylaxis in patients with multiple myeloma

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Introduction: Patients newly diagnosed with Multiple Myeloma (MM) who are on immunomodulatory drug (IMiD)-containing therapy have a substantial risk of developing venous thromboembolism. Current risk stratification models (RSM) such as SAVED, IMPEDE-VTE, and IMWG claim high predictive value of these scores for VTE prophylaxis, however, the risk of breakthrough VTE in MM patients remains. The objective of this study is to apply and compare the performance of the SAVED and IMPEDE-VTE RSM to patients newly diagnosed with MM on active treatment at our institution and to identify risk factors for VTE.
Methods: We performed a retrospective review of patients newly diagnosed with MM concurrently on IMiD therapy between 1/1/10-8/1/21 with at least 1 year of follow up. The IMPEDE-VTE, SAVED, and IMWG scoring system variables and additional factors identified through literature review were included. The scores were evaluated for their ability to stratify patients who are at high risk of developing VTE. Multiple logistic regression was performed to identify additional risk factors such as comorbidities, biomarkers, and myeloma characteristics. Receiver-operator curves were generated for each scoring system for both up to 180 days, and for the duration the patient was on an IMiD plus steroid combination.
Results: Out of 60 subjects, 23% developed VTE while on IMiD plus steroid therapy, 71% of which were within the first 6 months. Only the IMPEDE RSM (p=0.035, AUC= 0.6901) was significant for capturing any VTE event. Sensitivity, specificity, positive predictive value, and positive likelihood ratio for this RSM were 85%, 50%, 34%, and 1.7, respectively. The other models did not significantly identify patients at risk for VTE within 180 days of treatment initiation or by the total duration of IMiD plus steroid treatment. Surgery within 90 days (p< 0.0001), prior VTE (p< 0.0001), pelvic/hip fracture (p=0.0007), and aspirin use prior to myeloma (p=0.033) were significantly associated with a higher risk of VTE (43% of patients on aspirin prior to myeloma therapy). Other variables such as biologic sex, cycles of combination therapy, cytogenetics, free light chain ratio, M protein, clonal plasma cell bone marrow involvement, other comorbidities, or R-ISS prognostic score did not significantly contribute to VTE risk.
Conclusions: In patients on IMiD and steroid therapy, both the SAVED and IMPEDE RSMs performed poorly as risk stratification tools for VTE prophylaxis. Regression analysis supports surgery within 90 days, prior VTE, and pelvic/hip fracture as factors for VTE development. Aspirin use prior to the start of antineoplastic treatment was suggestive of higher risk of VTE development indicating aspirin may not be enough, whereas its use after treatment initiation may be a surrogate protective factor against VTE development. Limitations of the study include a retrospective nature and small sample size.

P-157
Carfilzomib (CFZ) resistance is associated with significant deregulation of the BH3 family proteins in multiple myeloma (MM)

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Introduction: Despite the exceptional success of PIs (proteasome inhibitors) in MM treatment, most patients become PI resistant. Deregulation of the BCL2 protein (BH3) family, which orchestrates the apoptosis pathway, potentially causes drug resistance in tumor cells. Previous studies indicated a substantial role of the intrinsic apoptotic pathway in PI resistance and in response to PI. Here, we aim to analyze the interplay between BH3 protein family members in PI

resistant vs. sensitive cell lines to decipher the survival strategies of PI resistance.
Methods: MM cell lines were exposed to increasing doses of CFZ, leading to the outgrowth of clones with acquired CFZ resistance. Protein expression was analyzed by western blotting. Cell viability was determined by WST-8 proliferation assay. Apoptosis (Annexin V, 7AAD) and BH3 profiling was analyzed by flow cytometry.
Results: All 7 CFZ resistant MM cell lines developed cross resistances to the MCL-1 inhibitors S63845 and AZD-5991. Decreased sensitivity to the BCL-2 inhibitor venetoclax and to the BCL-xL inhibitor A1331852 was observed in resistant KMS12PE cells. These effects are partially linked to MDR1 upregulation in CFZ resistant cells and are reversed by MDR-1 inhibition. Moreover, a slight increase in sensitivity to venetoclax or A1331852 was observed in resistant OPM-2 or NCI-H929 and U266 cells, respectively. In untreated conditions BH3 profiling indicates changes in BH3 protein dependencies in 3/7 CFZ resistant cell lines: Resistant KMS12PE cells depend less on MCL-1; resistant OPM-2 cells show an increased sensitivity towards peptides binding to BCL-xL / A1 and resistant AMO-1 cells are less dependent on BCL-w and to some extent to BCL-2 and BCL-xL. Considerable differences in BH3 protein dependencies were detected in CFZ sensitive vs. resistant cell lines exposed to CFZ. CFZ treated resistant cells exhibit a decreased dependency towards anti-apoptotic proteins in a cell line dependent manner. CFZ treated resistant AMO-1 cells appear to have a higher MCL-1 dependency. Protein expression analysis of CFZ sensitive vs. resistant cell lines indicate alterations of BH3 proteins in untreated conditions and under CFZ exposure. Notably, CFZ treatment upregulated BCL-xL in 5 and BAK in 7 out of 7 CFZ resistant cells. Exposure to ixazomib (IXA) upregulated BCL-xL and BAK in CFZ resistant cell lines.
Conclusions: Our data show significant deregulation of BH3 proteins in CFZ resistant cell lines highlighting the importance of the apoptosis signaling pathway in PI resistance. Consistent deregulation of BCL-xL and BAK throughout CFZ and IXA exposed CFZ resistant cell lines suggests that this might not be a CFZ specific effect. BH3 profiling indicates a change in dependency on anti-apoptotic BH3 proteins in CFZ resistant vs. sensitive MM cell lines in untreated and CFZ treated conditions in a cell line dependent manner.

P-158
End-of-life treatment and treatment costs of multiple myeloma patients in a real-world setting: a retrospective analysis of 104 patients from diagnosis to death

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Introduction: Novel treatment options have improved overall survival (OS) of patients with multiple myeloma (MM) and life time expectancy is expected to further lengthen given continuous drug development. Notwithstanding being within this privileged situation, the increase in costs puts health care funding and access to drugs under pressure. Therefore, cost-effectiveness, providing insight in the relation between input (scarce resources) and outcomes (i.e. health benefits for patients), is increasingly important in treatment decisions. Specifically, the end of life (EOL) phase often comes at high cost, while the contribution to OS and quality of life might be minimal. Despite its importance, data on EOL treatment-associated costs in MM are scarce. Therefore, we investigated this in a real-world cohort of MM patients.
Methods: We identified all MM patients who received (a part of) their treatments in Amsterdam University Medical Center, the Netherlands, and who died between January 1st 2017 and July 1st 2019. All anti-MM treatments from diagnosis to death, including dose adjustments and start- and stop dates were extracted from health records. We calculated treatment costs using the Dutch Z-index (indicating drug costs), of August 2020 and converted this to USD using the exchange rate on April 1st 2022 of the IMF.
Results: Data were available of 104 patients, of whom 70 male (67.3%), diagnosed between 2001 and 2019. Median age at diagnosis was 63 years (range: 40-83), 64 (61.5%) underwent a stem cell transplantation. Median OS was 56.6 months (95%CI: 46.2-67.0). The median number of lines of therapy was 3 (range 1-16). In first line, median time to next treatment (TTNT) was 19.2 months. With each subsequent line, TTNT and numbers of patients decreased to a median of 3.16 months in 8th line (n=17). 78 patients died of MM, 18 patients due to other causes. Median last day of MM therapy administration was 20 days before death (range 0-3087 days), most often being pomalidomide (29.5%), lenalidomide (26.3%) or bortezomib (10.5%). Mean total treatment costs (without study treatment) from diagnosis to death were $175,941 (range: $3,567- $702,303). Mean costs of treatments in the last 3 months before death were $18,837 (10.7% of total costs) (n=82; 79%). Mean total costs during the last 30 days were $5,540 (3.15%) (n=66; 63%), $2,760 (1.6%) in the last 14 days (n=48; 46%) and $1,479 (0.8%) in the last 7 days (n=32; 31%).
Conclusions: We here show that almost 50% of patients received anti-MM therapy during the 14 days preceding death, which was even 63% in the last month before death. Associated treatment costs were considerable, especially in light of limited survival benefit. The identification of factors

predicting efficacy and clinical benefit of continuing EOL therapy, warrant further investigation.

P-159
Effectiveness of anti-SARS-CoV-2 vaccine “booster” dose in patients with multiple myeloma

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Introduction: COVID-19 showed poor outcome in patients with multiple myeloma (MM) before starting vaccination campaign; in particular, fatality rates reported in non-vaccinated MM patients ranged from 27% to 57%. Recent data also indicate lower immune response in MM patients after receiving anti-SARS-CoV-2 vaccines than in the general population. However, data about clinical effectiveness of a third, “booster” dose of vaccine in this subset of high risk hematological patients is limited. The aim of this study was to evaluate the outcome of SARS-CoV-2 breakthrough infection in MM patients after three doses of anti SARS-Cov-2 vaccine.
Methods: We performed a retrospective analysis of 39 consecutive patients with active MM who experienced SARS-CoV-2 infection between December, 2021, and May, 2022. All patients had received three doses of anti-SARS-Cov2 miRNA vaccines and 3 of them had also received a “fourth” dose. A case of “reinfection” was documented. SARS-CoV-2 infections were diagnosed by RT-PCR or by antigen rapid test on nasopharyngeal swabs. We collected data about sex, age, ongoing treatment, symptoms, hospitalization, mortality, and additional use of antiviral drugs or monoclonal antibodies for the treatment of COVID-19.
Results: The median age of the whole group was 67.5 (range: 39-84) years. Twenty-five patients (64.1%) were male. The most frequent isotype was IgG (59%), followed by IgA (23.1%), light chain (12.8%) and non-secreting subtype (5.1%). Median number of days between the last dose of vaccine and infection was 109 (range: 11-191). About disease status at SARS-CoV-2 breakthrough infection, 18 cases (46.1%) were newly diagnosed/first line MM, 15 (38.5%) were first relapses, 6 (15.4%) were further relapsed MM. Thirty-six patients (92.3%) were under treatments including dexamethasone (92.3%), proteosome inhibitors (20.5%), IMiDs (82%), anti-CD38 monoclonal antibodies (43.6%) or other therapies (7.7%). Three patients, in complete response after ASCT, were in follow-up, without active therapy. One patient was infected 156 days after CAR-T treatment. Infection was symptomatic in 25 patients (64.1%) and the most common symptoms were fever, cough, muscle pain, headache, fatigue. Overall, 3 patients (7.7%) were hospitalized: among them, 1 (2.6%) was admitted to an intensive care unit due to respiratory distress. One patient (2.6%) died. Eight patients (20.5%) received antiviral drugs: 5 molnupivar, 1 redemsivir, 1 PF-07321332/ritonavir + sotrovimab, 1 sotrovimab.
Conclusions: Our data indicate that SARS-CoV-2 infection in “triple vaccinated” MM patients is quite frequent, but also that the clinical outcome of COVID-19 appears to be significantly improved by a “booster” dose of vaccine with respect to pre-vaccination era in this high risk population. The role of new antiviral agents and monoclonal antibodies currently used to reduce the risk of progression of COVID-19 to severe disease warrants to be further investigated in larger series.

P-160
Disparities in multiple myeloma between hispanics and non-hispanics – real world outcomes

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Introduction: Multiple myeloma (MM) is the second most common hematological malignancy in the United States (US), constituting 1.8% of all new cases (SEER database). It is a heterogeneous disease and has shown to be influenced by sociodemographic factors, with poor survival in non-Hispanic (NH) Blacks and Whites (Pulte et al. 2014). Yet, clinical characteristics and outcomes of MM are not well understood in Hispanics - one of the fastest-growing populations in the US.
Methods: We used the Texas Cancer Registry to evaluate the differences between Hispanic and NH MM patients diagnosed between 1996 to 2016. Socio-demographic characteristics including ethnicity, gender, age, and comorbidities at diagnosis, and primary payer (Medicaid, Medicare, private insurance, or self-pay) were evaluated. Ethnicity was identified as Hispanic and non-Hispanic, while the race was described as Whites, Blacks, and American Indians. Descriptive statistical analysis was performed using SAS statistical software. Hazard ratios (HR) for death and corresponding 95% confidence intervals (CI) were estimated using the cox proportional hazard model.
Results: We found 5115 Hispanic and 22426 NH MM patients satisfying the inclusion criteria. Hispanics were diagnosed with MM at a younger age compared to NH (mean (CI) - 65.2 (12.4) vs 68.0 (11.8), P< 0.001). Hispanic ethnicity was associated with poor survival after controlling for age at

diagnosis, gender, race, and treatment (HR death 1.19, p=0.001). Additionally, increasing age at diagnosis correlated with higher mortality (HR 1.88 in 51-65 years old (yo), HR 2.65 in 66-79 yo, and HR 4.30 in 80+ yo, p=0.001), while females (HR 0.85, p=0.001) and transplant recipients (HR 0.5, p=0.001) had better survival on multivariate cox regression analysis. Blacks (HR 1.17) and American Indians (HR 1.13) did worse when compared with Whites, however, the difference was not statistically significant; this could be due to low numbers in the analyzed population. Moreover, patients with private insurance had better outcomes than uninsured or Medicare insured (HR 0.85, p=0.049) when controlled for other covariates.
Conclusions: To our knowledge, this is the largest analysis reporting outcomes of MM in Hispanics in the US. While the study is limited by its retrospective nature, the recognition that outcomes in MM patients are impacted by ethnicity is important. This could be related to our findings of earlier age at diagnosis in Hispanics and higher survival in patients with private insurance relative to other payors. Altogether, these data highlight the need for improved access to equitable healthcare and clinical trials for Hispanics.

P-161
Oral antivirals ritonavir-nirmatrelvir and molnupiravir are highly effective in patients with multiple myeloma and COVID-19; a single-center, prospective study

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Introduction: Patients with multiple myeloma (MM) and COVID-19 have often severe clinical course and high mortality rates (~25%), due to the concomitant disease and treatment-related immunosuppression. Beyond supportive care, antiviral drugs, including molnupiravir and the ritonavir-boosted nirmatrelvir, have been licensed for the treatment of high-risk COVID-19. Although available evidence supports the use of antivirals in patients with SARS-CoV-2 to prevent severe disease, relevant data on MM patients is scarce. This prospective study investigates the effect of the aforementioned antiviral agents on COVID-19 severity and mortality in patients with MM.
Methods: Consecutive patients with MM and COVID-19 were prospectively enrolled in the study, which started in February 2022. All patients had a positive PCR test for SARS-CoV-2. The patients received either ritonavir-nirmatrelvir or molnupiravir, according to the national guidelines. Treatment with antivirals was initiated during the first five days from COVID-19 symptom onset in patients without need for supplemental oxygen. All patients were at high risk for severe COVID-19 disease due to the underlying MM. Baseline demographic and clinical characteristics, as well as levels of neutralizing antibodies (NAbs) were collected and compared. The effect of different treatments on COVID-19 severity and mortality were examined.
Results: A total of 64 MM patients infected with SARS-CoV-2 were included; 34 (53%) received ritonavir-nirmatrelvir and 30 (47%) molnupiravir. There was no difference in median age (65±10 vs 62±10 years, p=0.387), gender (44% vs 50% females, p=0.638), body weight (79±14 vs. 75±16 kg, p=0.255), or any other baseline medical condition (p >0.05 for all comparisons), between the ritonavir-nirmatrelvir and the molnupiravir group, respectively. All patients were fully vaccinated (three doses of mRNA vaccines) against COVID-19. Moreover, NAbs titers before the infection were similar [median (IQR) 82% (28.5-95.5) vs 78.5% (20.5-95.25), respectively, p=0.544]. Regarding COVID-19 severity, the two groups did not differ significantly in terms of patients with severe symptoms requiring hospitalization [2.9% vs 6.7%, for ritonavir-nirmatrelvir vs molnupiravir, respectively, relative risk (RR) 0.44, 95%CI 0.04-4.63], need for tocilizumab (2.9% vs 6.7%, respectively, p=0.48) or corticosteroids (2.9% vs 6.7%, respectively, p=0.48). The outcome was also similar when comparing patients with severe/moderate COVID-19 between the two groups (11.8% vs 10.0%, RR 1.18, 95%CI 0.29-4.84, respectively). Finally, mortality was similar for the two groups, reaching 2.9% for patients on ritonavir-nirmatrelvir and 3.3% for those on molnupiravir (RR 0.88, 95%CI 0.06-13.50).
Conclusions: In conclusion, ritonavir-nirmatrelvir and molnupiravir are highly effective in preventing severe disease in MM patients with COVID-19 and we suggest that all myeloma patients who are affected by SARS-CoV-2 should start antiviral treatment within five days of diagnosis.

P-162
Validation of the second revision of the international staging system in a real-world myeloma population: a myeloma and related diseases registry study

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Introduction: The R2-ISS risk algorithm is a revision to the R-ISS scoring system to improve risk stratification of newly diagnosed multiple myeloma patients (1). However, the R2-ISS was derived from a clinical trial myeloma population,

which is subject to strict eligibility criteria and whose treatment by definition deviates from current standards of care. Validation of the R2-ISS score with a "real-world" myeloma population is needed prior to widespread adoption.
Methods: R2ISS scoring was retrospectively applied to 1,013 newly diagnosed multiple myeloma patients in the Myeloma Related Diseases Registry (MRDR) diagnosed between January 2012 and February 2022. The Kaplan-Meier method was used to calculate PFS and OS, with groups compared using the log-rank test.
Results: The median follow-up was 33 months; median age was 65.3 years. The majority of pts were transplant-eligible (54.8%). 6.8% of the pts received immunomodulatory drugs (IMiDs) only, 73.5% proteasome inhibitors (PIs) only, 18.8% both drug classes during their first-line treatment. There was a significant difference in OS between R2-ISS I versus III (HR3.7 (95%CI 2.1-6.4), p< 0.001) and I versus IV (HR5.7 (95%CI 2.8-11.5), p< 0.001), but not group I versus II (HR1.6 (95%CI 0.88-2.92), p=0.121). Similarly, there was a significant difference in PFS between R2-ISS I versus III (HR2.11 (95%CI 1.5-2.9), p< 0.001) and R2-ISS I versus IV (HR3.93 (95%CI 2.52-6.11), p< 0.001), but not I versus II (HR1.17 (95%CI 0.82-1.66), p=0.394). Of the patient cohort, 688 (67.9%) were categorised as R-ISS stage II. R-ISS II patients were distributed across all four R2-ISS risk groups when re-categorised, highlighting the heterogenous nature of the R-ISS II patient group: risk groups: 1.0% in group I, 48.0% in group II, 47.9% in group III, and 3.2% in group IV. There were statistically significant differences in PFS and OS between R2-ISS II versus III (PFS HR1.66 (95%CI 1.29-2.13), p< 0.001; OS HR1.88 (95%CI 1.30-2.72), p=0.001) and the II versus IV (PFS HR2.59 (95%CI 1.45-4.62), p=0.001; OS HR3.02 (95%CI 1.36-6.71), p=0.007).
Conclusions: The R2-ISS was largely able to risk stratify our real-world patient cohort but with no clear distinction between R2-ISS groups I and II in this population. The R2-ISS would provide a robust framework for high-risk-stratified front-line clinical trials.

P-163
Mortality in patients with multiple myeloma: the mylord study from the french national health data system (SNDS)

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Introduction: Multiple myeloma (MM) is an incurable hematological cancer. However, there is an increase in overall survival of patients thanks to therapeutic innovations in recent decades, with some patients achieving long-term remission. Between 1998 and 2018, the standardized 5-year net survival of MM patients has increased from 42% to 63% in France, and in 2017, global standardized mortality rates were 2.0 per 100,000 person-years for men and 1.2 per 100,000 person-years for women. The MYLORD study focused on mortality of MM patients France, estimating their excess mortality compared to the general population, based on data from the national health data system (SNDS, "Système National des Données de Santé") which contains the healthcare consumption of 66 million French people.
Methods: MYLORD is a retrospective observational cohort study of MM patients identified between 2014 and 2019 from the SNDS via a published algorithm and adapted to consider recent developments in the management of MM. To allow international comparison, mortality rates were standardized using the average age distribution in the world population. The standardized mortality ratio (SMR - ratio: mortality rate of the MYLORD study population divided by that of the general population) was estimated by indirect age standardization using national mortality data from the National Institute of Statistics and Economic Studies (INSEE).
Results: 40,747 prevalent MM patients were identified between 2014 and 2019. The median age of patients initiating first-line therapy without transplant (L1NT) in 2019 was 73 years, whereas the median age among patients initiating L1 with transplant (L1T) was 62 years. The standardized mortality rate for the MYLORD study population was estimated at 2.36 (2.27-2.44) per 100,000 person-years in 2019, 2.94 (2.79-3.09) for men, and 1.89 (1.78-1.99) for women. This rate was 0.60 (0.54-0.66) for those under 65 years of age, 9.88 (8.77-10.99) for patients 65-69 years of age, 19.15 (17.49-20.80) for patients 70-74 years of age, 28.07 (25.57-30.57) for patients 75-80 years of age, and 43.03 (40.70-45.37) for those over 80 years of age in 2019. This rate is higher in L1NT patients (1.83 (1.76-1.91)) than in L1T patients (0.52 (0.47-0.57)). With an SMR of 4.12 (3.98-4.26), the excess mortality of MM patients is 4 times higher compared to the general population. In L1T patients, the estimated SMR was 6.83 (6.22-7.43), and in L1NT patients it was 3.49 (3.36-3.62).
Conclusions: There is a significant excess mortality in patients treated for MM compared with the general population, especially in the L1T group. The transplanted patients have an excess mortality approximately twice higher than non-transplanted patients, a difference due to the younger age of the L1T group. Despite the intensive autograft strategies in young patients, this analysis highlights the even greater need for transplant patients to have the best treatment options to continue improving their survival.

P-164
Daratumumab, carfilzomib, pomalidomide and elotuzumab for the treatment of poems syndrome: the Mayo Clinic experience

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Introduction: POEMS (Polyneuropathy, Organomegaly, Endocrinopathies, Monoclonal protein, Skin changes) syndrome is a rare paraneoplastic syndrome, and therapies are directed against plasma cells that produce the proteins that cause this syndrome. Novel therapies are widely used in multiple myeloma aiming for plasma cell eradication. However, data on their use in POEMS syndrome are lacking.
Methods: We identified all POEMS patients seen at Mayo Clinic Rochester, Minnesota using a prospectively maintained database of patients seen at our center between June 1979 and May 2021. Of these patients, we identified all the patients that were treated with a "novel" agent, defined as daratumumab, carfilzomib, pomalidomide, or elotuzumab. The primary endpoints were response to therapy (hematological, PET, VEGF, and clinical, which will be referred to as response H, P, V, C, respectively), and time to next therapy (TTNT), defined as time from institution of regimen of interest to next therapy. The secondary outcome was safety.
Results: The median age at POEMS diagnosis was 57 years (range 39-79) and 15 patients (93%) were men. The median time from diagnosis to novel agent's first dose administration was 50 months (IQR 23-122) and the median lines of therapy prior to novel agent was 2 (range 1-4). Twelve patients (75%) underwent prior autologous stem cell transplantation, and 5 patients had prior lenalidomide. The median age at novel agent administration was 63 years (IQR 51-70) and 4 patients (24%) were 70 years or older. The patients were treated with a doublet including dexamethasone (N=5) (31%) or in various combinations with other agents: DRd (N=6), DC(V)d (N=3), KRd (N=3), KPd (N=1), DP(V)d (N=5), and EloRd (N=1). The outcomes with novel agent therapies were favorable. Among patients treated with daratumumab based therapies (N=17), 9 patients achieved CR/VGPRH, 7 patients achieved CRV , and 5 patients achieved CRP. Among patients treated with carfilzomib-based therapies (N=6), 3 patients achieved CR/VGPRH, and one achieved PRH. At a median follow-up of 38 months since starting of the novel agent (IQR 24-57), 15 of the patients (94%) are still alive, and the median TTNT was not reached. None of the patients discontinued therapy due to adverse events and no deaths occurred on therapy. Novel therapies were safe with 7 events of hospitalization due to pneumonia (4 in daratumumab-based therapies and 3 on carfilzomib based therapies), and 4 patients were hospitalized due to volume overload (all received dexamethasone with therapy). Three patients experienced infusion-related reactions (IRR) to the first dose of IV daratumumab.
Conclusions: The response rate was high and the responses were deep. Novel agent therapies were safe, and no death case occurred on therapy. Future studies are needed to clarify the optimal sequence of novel agents and the best combination.

P-165
The clinical characteristics and prognosis of patients with primary plasma cell leukemia (pPCL) according to the new IMWG definition criteria

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Introduction: Recently, IMWG recommended CPCs ≥ 5% by peripheral blood (PB) smear as the new diagnostic criteria for pPCL. Nevertheless, as the definition has been revised, these former results seem to be partial and biased owing to their few cases with limited proportion in the new-defined pPCL cohort. On the other hand, those patients who were diagnosed as pPCL with more than 20% CPCs had received more active and intensive therapy. It is noted that many patients who were classified in multiple myeloma before with 5-19% CPCs had always been treated with conventional regimens, which could possibly induce the failure of induction treatment.
Methods: We retrospectively analyzed 2266 patients with plasma cell disorders who received treatment in our hospital from 2000 to 2019, and found 158 pPCL patients with 5% or more circulating plasma cells. In order to confirm the value of new criteria again, we conducted the comparisons for baseline characteristics based on different CPCs.
Results: Among 2266 patients registered in our MM database during 2000-2019, we found 67 pPCL patients with more than 20% CPCs. Then, according to the new definition (CPCs≥5%), we recognized another 91 new-defined pPCL patients who were diagnosed with MM before. We found that patients with CPCs≥20% are slighter younger(median age 54 vs 59 years, P=0.033) than others, but other laboratory results and clinical characteristics did not show statistic difference between two groups($P > 0.05$). We found that patients with 5-19% CPCs showed same poor prognosis as those with more than 20% CPCs (PFS: 16.0 months vs 20.0 months, P=0.26; OS: 30.0 months vs 31.0 months P=0.89). We also found that cytopenias and adverse prognostic biomarkers were more common in pPCL compared with MM ($P< 0.05$,). Overall, the median PFS and OS of 130/139(93.5%) pPCL patients were 16.9 months and 30.0 months respectively, both significantly shorter than the control NDMM patients($P< 0.001$). We found that those patients with t (11;14) displayed longer survival tendency (PFS: 33.1 months vs 20.5 months, OS: 73.4 months vs 31.5 months, respectively), even without the statistical

significance (P=0.27, P=0.18). On the other hand, the presence of hypodiploidy and elevated serum LDH were found to be prognostic for worse PFS, whereas age＞60 and elevated LDH were the independent predictors for worse OS. **Conclusions:** In conclusion, we have reverified the revised diagnostic criteria of pPCL based on the same clinical characteristic and ominous prognosis between patients with 5-19% and ≥20% circulating tumor cells. Then, we identified a double higher prevalence (7%) for primary plasma cell leukemia than before. Moreover, we firstly demonstrated that the new-defined pPCL remains aggressive features characterized with the frequent occurrences of cytopenias, renal dysfunction, elevated LDH, EMD-E, and high-risk cytogenetics. And the elevated level of serum LDH may play a more important role in the prognosis of pPCL than cytogenetic abnormalities.

P-166
Free light chain escape: should we monitor free light chains more closely?

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Introduction: Free light chain escape (FLE) is a rare phenomenon seen in 3% of multiple myeloma patients. It is characterized by rise of involved free light chain levels without involved heavy chain component. It often accompanies extramedullary disease progression or rapid renal impairment. Here we present four case with FLE.
Methods: Patient data has been obtained from patient files.
Results: Case A: 52-year-old female patient is referred after pathologic fracture due to plasmacytoma. IgGλ myeloma R-ISS stage III is diagnosed and treatment is started immediately with weekly bortezomib+cyclophosphamide+dexamethasone (VCD). In the last day of the first course it was observed that her general condition deteriorated; anemia, hypercalcemia, and a slightly higher creatinine level is detected. At the same time, free λ light chain escape is observed. She received carfilzomib and underwent autologous stem cell transplant (SCT) but relapsed and died in 7 months after SCT. Case B: A 46-year-old male patient was evaluated in June 2010 with complaints of low back pain and fatigue and and was diagnosed IgAλ MM R-ISS: I. The patient has a history of two autologous SCTs (in 2011 and 2018). After his second transplant he was started on lenalidomide maintenance with VGPR. He presented with back pain in July 2020. Magnetic resonance imaging revealed a mass lesion with significant compression of the spinal cord and FLE is observed. He underwent allogeneic SCT. Case C: 56-year-old female patient is referred with mild anemia and hypercalcemia and diagnosed with IgGκ multiple myeloma R-ISS: II. She underwent autologous SCT after VCD. Relapsed after 8 months and received carfilzomib+lenalidomide+dexamethasone(CarLenDex) with no response and she progressed with many cervical lymph nodes and left pleural effusion. FLE has been detected simultaneously. She died after several months. Case D: 60 year-old patient has been diagnosed with IgGλ ISS: 2 myeloma. He underwent 2 autologous SCTs in 2013 and 2019. del17p and 1q Gain has been observed after his second relapse. He received CarLenDex and PomDex sequentially with short durations of response (PR). FLE was detected under PomDex treatment and he presented with worsening anemia and acute kidney injury one month later.
Conclusions: Our cases show that in during the treatment of myeloma, a clone that may be selected which can lead to light chain escape and disease progression. This progression is usually sudden and requires close monitoring of serum free light chain levels to detect. Also light chain escape can accompany extramedullary/extraosseous disease progression or rapid renal impairment. Serum free light chain follow-up during treatment could be useful in identifying this phenomenon even when FLC ratio seems stable for a while. We suggest monitoring free light chain levels in addition to heavy chain levels during treatment and follow-up of myeloma patients.

P-167
Comparison of frontline treatment regimens in Waldenström Macroglobulinemia – a multi-centre Asian cohort

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Introduction: Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma associated with monoclonal IgM. It is a rare malignancy with an incidence of 2-4 million per million per year. Rituximab is the cornerstone of frontline therapy of WM, and combination therapy has been found to be superior to monotherapy. Comparative data to inform optimal therapy of WM is sparse, particularly in Asia. We evaluated four regimens as frontline therapy – a) Rituximab-bendamustine (R-Benda) b) Dexamethasone, rituximab, cyclophosphamide (DRC) c) Bortezomib, dexamethasone, rituximab (BDR) d) Ibrutinib.
Methods: A retrospective cohort study was performed on patients with WM seen at Singapore General Hospital and National University Hospital between 2010 to 2020. 63 patients with symptomatic previously untreated WM were identified. These patients received one of aforementioned regimens. Primary outcomes were overall response rate (ORR), major response rate (MRR), progression free survival (PFS), time to next therapy (TTNT), time to best response (TTBR). Probabilities of time to progression, death, best response, and next therapy were estimated using the Kaplan-

Meier method and compared between groups using the log-rank test. Univariable analyses were performed using the Cox proproportional hazards regression method.
Results: 24 (38.1%) patients received R-Benda, 23 (36.5%) received DRC, 5 (7.9%) received BDR and 11 (17.5%) received ibrutinib. Median time from diagnosis to frontline therapy was 21 days (IQR 11-40 days). Median follow-up was 5.07 years (IQR 3.54-6.44 years). We did not observe significant differences in ORR and MRR between the treatment arms. ORR for R-Benda, BDR and Ibrutinib was 100% and 85% for DRC. MRR for R-Benda, BDR, DRC and ibrutinib were 91.7%, 69.6%, 100% and 72.7% respectively. OS was also similar across the four cohorts. In our cohort, patients who received DRC or BDR had shorter PFS (HR 3.91, 95% CI 1.09-14.01, P=0.037) and shorter TTNT (HR 3.65, 95% CI 1.14-11.63, P=0.029) compared with patients who received R-Benda or ibrutinib. The poorer response to BDR in our cohort could possibly be associated with significantly higher incidence of renal impairment at diagnosis in the BDR treatment group (40% vs 0-21% in the other treatment groups, p = 0.049). 29 out of 35 patients who were tested for MYD88 harboured the mutation (83%). Primary outcomes were unaffected by patients' MYD88 signature within the chemoimmunotherapy treatment groups.
Conclusions: Fixed-duration R-Benda and indefinite BTK inhibitor-based regimens provide improved PFS and TTNT compared to DRC or BDR in treatment-naïve WM. Our study which reports similar results as current literature can help to inform clinicians about the benefits and limitations of choosing one regimen over the other.

P-168
A multicenter prospective study for validation of the Korean Simple Geriatric Assessment Tool in elderly patients with multiple myeloma

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Introduction: Frailty is a multidimensional state of diminished reserve (energy, physical ability, cognition, and health) which gives rise to vulnerability to cancer treatment. The purpose of this study was to prospectively validate the Korean Cancer Study Group Geriatric Score (KG)-7, a novel geriatric screening tool, in older patients with multiple myeloma planned to undergo first-line chemotherapy.
Methods: The study included 100 newly diagnosed MM patients aged 70 years or older. Participants answered the KG-7 questionnaire before undergoing IMWG frailty score and first-line bortezomib- and/or lenalidomide- based chemotherapy.
Results: The median age was 77 years and 50.5% of patients were older than 75 years. Fifteen patients (15.8%) had an ADL score ≤ 4, 24 (25.3%) an IADL score ≤ 5, and 19 (20.0%) a CCI ≥ 2. Based on the 5 cut-off value of KG-7 for abnormal geriatric assessment, a lower proportion of patients in the unfit group had grade 3–5 hematologic toxic effects (41.2%) compared with the fit group (63.6%; relative risk = 0.4; 95% confidence interval [CI] = 0·64-0·86; P = 0.029]). There was no statistically significant difference between the two groups in non-hematological toxicity. There was no significant difference between the two groups (fit versus unfit) in PFS (hazard ratio [HR] = 1.50; 95% CI = 0.61-3.68; P = 0.382) and PFS (HR = 1.31; 95% CI 0.37-4.69, P = 0.679), which was attributed to the short FU period of 11.6 months.
Conclusions: This analysis is an interim analysis, and additional analysis is needed on the relationship between KG-7 score at diagnosis and dose adjustment during chemotherapy to reducing serious toxic effects. Geriatric assessment with management should be integrated into the clinical care of older patients with multiple myeloma and ageing-related conditions.

P-169
Bendamustine rituximab primary therapy for Waldenström Macroglobulinemia: an international, multicenter collaborative study

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Introduction: The promising results of Bendamustine rituximab (BR) in a subset analysis of patients with Waldenström macroglobulinemia (WM) of the Study group indolent Lymphomas (StiL) trial, with a median progression-free survival (PFS) of 69.5 months in the frontline setting, served as the basis for widespread adoption of BR. The impact of the more recently identified somatic mutations within the MYD88 and CXCR4 genes on the outcomes with BR is unclear, which we aim to address through this international, multicenter collaborative effort.
Methods: Records of patients (pts) with newly diagnosed active WM who received BR between January 2012 and July 2021, in the US and Europe, were reviewed. The MYD88L265P and CXCR4WHIM mutation status were captured, if available. All time-to-event analyses were performed from the frontline therapy initiation, using the Kaplan-Meier method.
Results: Among 248 pts treated with BR, 208 pts received BR induction without rituximab maintenance, and were included in the primary analysis. The median follow-up was 4 (95% CI: 3.6-4.6) years. The estimated median PFS was 5.9 years [95% CI: 5.3-not reached (NR)]. The estimated 5-year overall survival (OS) was 90%. Among 174 pts evaluable for response, the overall response rate (ORR) and major response rate (MRR) were 95% and 93%, respectively, per the modified IWWM-6 criteria based on serum IgM alone. Pts with progression of disease (POD) within 24 months of BR therapy (11%) had an inferior OS compared to those without POD within 24 months, the reference group [5-year OS, 75 % versus (vs) 94%, p=0.03]. Among 131 (63%) pts with a known MYD88L265P status, 88% (n=116) had MYD88L265P genotype. The 4-year PFS was 71% for both pts with MYD88L265P and MYD88WT genotypes (p=0.44). The very good partial response or better (≥VGPR) rates were also comparable between the 2 groups (41% for MYD88L265P and 50% for MYD88WT genotypes, p=0.55). Among 42 (20%) pts with a known CXCR4WHIM mutation status, 28% harbored CXCR4WHIM mutation. The ≥VGPR rate for pts with CXCR4WHIM genotype was numerically lower; 33% vs 57% for those with CXCR4WT genotype, p=0.3. A trend towards shorter PFS among pts with CXCR4WHIM genotype [estimated median PFS for 3.9 years (95% CI: 0.8-NR) vs 5.5 years (95% CI 5.3-NR) for pts with CXCR4WT genotype, (p=0.05) was observed. After 1:1 matching for age for the 40 (16%) pts who had received rituximab maintenance following BR, the 4-year PFS for the rituximab maintenance group was 89% vs 73% for pts who did not receive rituximab maintenance (p=0.09); OS was comparable (5-year OS 85% for both groups, p=0.99).
Conclusions: Fixed duration BR is a highly effective primary therapy for WM, irrespective of the pts' MYD88L265P mutation status. Progression of disease within 2 years (POD-24) of initiation of BR is associated with inferior OS. Our preliminary analysis, suggesting that CXCR4WHIM mutation confers resistance to BR, warrants confirmation in prospective studies.

P-170
Evaluating serum free light chain ratio as a biomarker for multiple myeloma

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Introduction: In 2014, the definition of multiple myeloma (MM) was updated to include serum free light chain ratio (FLCr) ≥100 as a myeloma defining biomarker, based on retrospective data indicating a 2-year progression rate of 80% and a median time to progression (TTP) of 12 months associated with this marker. However, more recent studies have reported lower 2-year progression rates, 30-44%, and a longer median TTP of 40 months in patients with FLCr ≥100. Because of the disparity in risk prediction by FLCr across studies, we aimed to assess the risk of progression in patients with smoldering MM (SMM) and FLCr ≥100.
Methods: We performed a retrospective analysis of patients with SMM diagnosed between 2002-2019. Diagnosis of SMM and progression to MM requiring therapy or AL amyloidosis was defined according to the International Myeloma Working Group (IMWG) criteria at the time of diagnosis. Only patients with available FLCs at diagnosis of SMM were included in the study and only patients with an involved FLC level >100 mg/L were included in the FLCr ≥100 group. Chi-square test was used to compare categorical values and Mann-Whitney U test to compare continuous variables between the < 100 and ≥100 FLCr group. Kaplan-Meier method was used to determine TTP and generate survival curves, with log-rank tests for comparison between groups.
Results: A total of 466 patients were included in the study, of which 65 patients (14%) had a FLCr ≥100. Light chain MM was more prevalent in the FLCr ≥100 group (14% vs 2.8% among patients with FLCr < 100, p< 0.001). Patients with FLCr ≥100 had overall higher Mayo-2018 risk, where 14% had 3 risk factors compared to 4% in patients with FLCr < 100, 39% 2 risk factors compared to 19%, and 48% 1 risk factor compared to 29% (p< 0.001). In the FLCr ≥100 group, the median TTP was 32 months compared to 108 months in patients with

FLCr < 100, (p< 0.001). At 2 years, 38% of patients with FLCr ≥100 had progressed. To identify patients in the FLCr ≥100 group with a higher risk of progression, we stratified the patients based on number of Mayo-2018 risk factors. Patients with 2 risk factors in addition to FLCr (BMPC >20% and M-spike >2g/dL) had a median TTP of 17 months and 2-year progression rate of 89%, compared to a median TTP of 31 months and 59 months, and 2-year progression rate of 45% and 24%, in patients with 1 and no additional risk factors, respectively (p=0.0024).
Conclusions: To conclude, we found that FLCr ≥100 is not an independent risk factor of imminent progression from SMM to active MM. On the contrary, patients with FLC ≥100 were a heterogenous group with varying disease risk, where those with both BMPC >20% and M-spike >2g/dL indeed progressed within 2 years, while those with no other risk factors had a median TTP of 5 years before progressing. These findings suggest that patients with FLCr ≥100 as the sole myeloma defining event and otherwise low-intermediate risk disease may be considered for observation rather than early treatment.

P-171
African American patients with smoldering multiple myeloma may have a lower risk of progression compared to white patients

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Introduction: The incidence of multiple myeloma (MM) and its precursor stages is two to threefold higher in African Americans (AAs) compared to whites when adjusted for socioeconomic status, age, and sex. However, there is limited information on whether racial background affects the risk of progression from smoldering MM (SMM) to MM.
Methods: Patients with SMM presenting to our institution between the years 2000 and 2019 and who identified as either AA or white were included in the study. Baseline patient and disease characteristics were collected at the time of diagnosis including laboratory, imaging, and pathology reports. Differences in distributions of continuous and discrete characteristics were assessed by Kruskal-Wallis and chi-square tests. Time to progression (TTP) was assessed using the Kaplan-Meier method with log-rank test for comparisons. Univariate and multivariate Cox proportional hazard models were used to estimate effects of risk factors on TTP with hazard ratios (HR) and 95% confidence intervals (CI).
Results: A total of 576 patients were included (70 were AA, 12%). Median follow-up time was 3 years in AAs and 4 years in whites. Differences in baseline characteristics between AAs and whites included median age (60 years in AAs [IQR 51-67] vs 64 years in whites [IQR 56-72], p = 0.01), median hemoglobin level (12.3g/dL in AA [IQR 11.8-13] vs 12.8g/dL in whites [IQR 11.8-13.9], p = 0.02), and immunoparesis including 1 or 2 uninvolved immunoglobulins (31% and 10% in AAs vs 56% and 27% in whites, p = 0.002). There was no difference in bone marrow plasma cell percentage (BMPC), M-spike, free light chain ratio, or Mayo-2018 SMM risk score. AA race was associated with a significantly decreased risk of progression in the univariate model (HR 0.57, CI 0.34-0.94). In the multivariate model adjusting for age, sex, and variables associated with an increased risk of progression in the univariate model (BMPC, M-spike, free light chain ratio, immunoparesis and low albumin), AA race remained associated with a decreased risk of progression (HR 0.39, CI 0.16-0.95). Overall, AA patients with SMM had a significantly (p = 0.027) longer median TTP (9.7 vs 6.2 years), and a lower 2-year (12.6% vs 20.1%) and 5-year (34% vs 44.6%) progression rate than whites. Because AA patients were younger at diagnosis, we stratified patients by age group, < 65 vs ≥65 years. In patients < 65 years, there was no difference in progression rate. In patients aged ≥65 years, AA patients continued to have a longer TTP than whites (9.8 vs 5.2 years, p = 0.02).
Conclusions: In our retrospective single institution experience, AA patients with SMM had a lower risk of progression to MM compared to whites. Both groups had similar Mayo-2018 risk scores, however, AA patients had a lower degree of immunoparesis at baseline. Future studies are needed to better understand if these differences are explained by differences in disease biology including genomic mechanisms, immune microenvironment, and systemic immune response.

P-172
Pre-malignant plasma cells exhibit senescence features and may drive multiple myeloma tumorigenesis through LINE1-mediated genomic instability

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Introduction: Multiple Myeloma (MM) is preceded by monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM). Despite having similar oncogenes and chromosomal abnormalities to MM, MGUS and SMM are considered benign. Since oncogenic stress induces senescence growth arrest to prevent tumor formation, we hypothesized that MGUS and SMM PCs may be in a senescent-like state; further, senescence mechanisms driving genomic instability may contribute to MM tumorigenesis.
Methods: We performed differential expression analysis of a published human PC gene array dataset (GSE5900). We also evaluated the KaLwRij MGUS mouse model compared to the related C57BL6 strain. 10-month-old female KaLwRij mice were treated with placebo or senolytic combination therapy (dasatinib + quercetin, D+Q) and evaluated for B cell and PC number and gene expression. Aged KaLwRij PCs were compared to C57BL6 PCs by single cell RNA-sequencing. Immune staining and whole transcriptome RNA-sequencing was performed on PCs isolated from normal, MGUS, and SMM patients.
Results: MGUS (N=44) and SMM (N=12) PCs exhibited significant increases in the senescence marker CDKN1A (LogFC=1.59, 1.44) versus normal (N=22) and both MGUS and SMM PCs showed gene set enrichment (FDR< 0.05, q< 0.25) for senescence pathways. Placebo KaLwRij mice (N=6) exhibited significantly increased PCs and reduced B cells compared to age matched C57BL6 (N=5). D+Q treatment (N=7) significantly reduced PCs compared to placebo, while restoring B cell number and functional gene expression. Single cell (sc) RNA-seq and gene set enrichment analysis (GSEA) of 24-mo-old KaLwRij PCs (N=3) revealed a PC subset enriched for senescence with increased Trp53 (p< 0.001). PCs isolated from D+Q KaLwRij mice exhibited a trend for reduced Trp53 (p=0.12) supporting that senescent PCs are targeted by D+Q. Of interest, KaLwRij PC scGSEA showed senescence-enriched PCs can exhibit inflammatory or interferon (IFN) senescence-associated secretory phenotypes (SASP). The IFN SASP is characteristic of late senescence and is driven by the accumulation of transposable elements and activation of cytosolic DNA sensing pathways. Using the human PC gene array dataset, we found enrichment of the IFN SASP in SMM (FDR< 0.05, q< 0.25) but not MGUS PCs. Further, RNA-seq showed SMM, but not MGUS PCs, had increased expression of LINE1 retrotransposon L1HS (LogFC=1.06, FDR< 0.05, N=4). Immunostaining confirmed increased cytosolic ssDNA and RNA:DNA in MGUS and SMM PCs, with increased mean and max intensity in SMM compared to MGUS PCs, consistent with cytosolic DNA-mediated activation of the IFN SASP.
Conclusions: Altogether, these data demonstrate that MGUS and SMM PCs exhibit senescence features and mechanisms that may contribute to MM tumorigenesis, and pharmacological ablation of senescent cells may prevent disease progression.

P-173

Prognostic utility of the evolving biomarker-based progression model (e-model) for smoldering multiple myeloma (SMM) in a diverse population

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Introduction: SMM is a clinically heterogeneous condition. The e-model has been used to prognosticate risk of progression by factoring in dynamic changes in M-protein and hemoglobin. This model was built and tested with data mainly from white (W) patients seen at Mayo Clinic in Rochester, MN. To replicate the prognostic utility of the e-model in a diverse patient population, we pursued a retrospective analysis of W and Black (B) pts with SMM diagnosed at Levine Cancer Institute, US (LCI) and W pts diagnosed at Karolinska University Hospital, Sweden (KUH).
Methods: A total of 127 pts from LCI (84 W, 43 B) and 121 pts (all W) from KUH diagnosed with SMM between 12/2002 and 3/2020 were included. SMM was defined by bone marrow plasma cells (BMPC) ≥ 10% and/or serum M-protein ≥ 3 g/dL (or ≥ 500 mg/24 h in urine), and no CRAB features. We excluded those with BMPC ≥ 60%, or with > 1 focal lesion (if MRI was performed). Patients with serum FLC ratio ≥ 100 and involved FLC level > 10 mg/dL were not excluded if they had been followed up without progression for >2yr. TTP was evaluated with cumulative incidence methods, with death as a competing risk event and compared between groups with Gray's tests. A multivariable model for TTP was determined with entry/elimination criteria of p = 0.10
Results: Median follow-up was 4.8 yr (range 0.2 – 17.3). Median age at diagnosis was 68yr (B 65, W 69) with 53.2% female. Most pts were W (82.7%), had IgG (75.4%) subtype, and serum M-protein < 3 g/dL (84.3%). The median TTP for the whole cohort was 6.1yr, with 2yr progression rate of 19.9%. According to the Mayo 20/2/20 risk criteria, 41.3% had low risk (LR), 35.7% intermediate risk (IR), and 23.0% high-risk (HR) SMM, with corresponding 2yr progression rates of 9.0%, 26.5%, and 30.3%, respectively. After applying the e-model, 33.9% had LR, 41.3% IR, and 24.8% HR SMM, with corresponding 2yr progression rates of 11.4%, 18.0%, and 37.2%, respectively. Interestingly, the distribution of Mayo 20/2/20 risk groups differed between W vs. B (LR 36.5% vs. 65.8%, IR 39.6% vs. 15.8%), whereas no difference was noted in risk distribution for W vs. B using the e-model. However, for patients deemed HR by the e-model, the 4yr progression rate was higher in W: 69.4% vs. B: 35.1% (not statistically significant). Similarly, for IR SMM, the 4yr progression rate was 35% vs. 14.2%; and for LR SMM, 4yr progression rate was 20% vs. 11.4%, respectively. Age, BMPC

at diagnosis, M-protein, eMP, FLC ratio, and b2m were significant factors in a multivariable model.
Conclusions: Our analysis validates the e-model using a heterogeneous population from two myeloma centers across the Atlantic. The number of B pts is small and further studies are warranted to evaluate the e-model in this population.

P-174
Validation of Mayo Clinic 2018 and IMWG 2020 prognostic risk score for smoldering multiple myeloma (SMM), real world data; single center experience

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Introduction: Due to SMM disease heterogeneity, it is sometimes difficult to detect patients requiring closer observation and eventually early treatment. We therefore investigated the ability of the Mayo 2018 and IMWG 2020 risk stratification models to detect SMM patients at risk to evolve into MM.
Methods: We retrospectively studied 153 patients diagnosed with SMM diagnosed from 1997 to 2021. Patients' medical records were retrieved after patients' informed consent was obtained and relevant findings were collected at diagnosis. Time from diagnosis to MM progression was defined as TTE (time to evolution). Statistical analysis was performed using SPSS v. 26 software.
Results: According to the Mayo 2018 score, 46% of patients were low risk, 42% were intermediate risk and 12% were high risk. IMWG score was additionally applied, by incorporating the cytogenetic findings, however, it failed to produce statistically significant results, since very few patients presented genetic abnormalities. Patients' median follow up was 77 months (range, 4-267). 43% were men and 57% were women, with a median age of 71 years. The involved immunoglobulin type was IgG in 73%, IgA in 24%, biclonal in 2% and 1% light chain only. 63% of patients were staged ISS-1, 16% ISS-2 and 21% ISS-3. Out of 153 patients, 106 (57 low-risk, 39 intermediate-risk,10 high-risk) remained stable, whereas 47 (3 low-risk, 25 intermediate-risk, 9 high-risk), progressed to symptomatic MM. The median TTE was 22 months, with 34 months for low-risk, 22 months for intermediate-risk and 7 months for high-risk patients. Separated analysis for each risk factor included in the stratification model showed increased risk of progression for patients with BMINF ≥20% (p< 0.0001) and serum M protein ≥20g/L (p =0.007), while FLCR ≥20 was not statistically significant (p =0.479). Further analysis revealed that immunoparesis and low immunoglobulin IgM alone (< 40mg/dL) constituted prognostic markers (p=0.001, p=0.002, respectively). Applied Mayo 2018 risk score, effectively separated our patients (p=0.008). It however failed to predict progression risk within the first 24-month follow-up (p= 0.091) in our cohort, and less than 50% of high-risk patients evolved during this time period. The same was observed for immunoparesis.
Conclusions: As the goal of predicting progression in SMM is to discriminate patients at very increased risk of evolution to symptomatic MM within two years and in such case to eventually treat them, additional prognostication is needed. Mayo Clinic investigators suggested the dynamic score assessment and the IMW group, the addition of genetic variable. Microenvironmental factors should also be investigated.Authors: A. Gkiokas *, A-I Gkioka** equal contribution

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Assessment of renal outcome following therapy in monoclonal immunoglobulin deposition disease: a retrospective study of 34 patients highlighting the need for consensus criteria

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Introduction: Monoclonal immunoglobulin deposition disease (MIDD) is a rare condition predominantly affecting the kidneys. Although hematologic response to treatment is reliably assessed by International Myeloma Working Group (IMWG) consensus criteria, uniform criteria for assessing renal response (RR) are lacking. In this retrospective study of 34 patients (pts) with MIDD, we report our experience of treatment outcomes focusing on renal outcomes
Methods: We assessed hematologic responses according to the IMWG uniform response criteria. RR criteria used were the IMWG RR criteria based on eGFR for pts with decreased eGFR < 50mL/min/1.73 m2 with or without significant proteinuria (>1 g/24 h) or amyloid response criteria for pts with significant proteinuria with or without preserved eGFR, at presentation. Categorical pts characteristics were summarized by frequency (%) and continuous characteristics by median and interquartile range. Time to best RR (time from start of Rx to best response) and renal survival (time from start of Rx to hemodialysis) were evaluated by Kaplan-Meier method. Associations between pts characteristics and time to response outcome were assessed by log-rank. The effects of baseline characteristics on RR were estimated by univariate Cox proportional hazard model.

Results: Baseline Hematologic, renal and treatment characteristics will be presented for 34 pts. With most pts treated with bortezomib and autologous stem cell transplantation (ASCT), 26 of 28 (94%) achieved very good partial hematologic response or better.We demonstrate that both IMWG (based on eGFR) and amyloid (based on proteinuria) criteria are needed to capture RR: Among 28 pts whose RR could be assessed, initial renal presentations included proteinuria with preserved eGFR (n=6, 21%), proteinuria and decreased eGFR (n=9, 32%), and decreased eGFR without proteinuria (n=13, 46%). Using both criteria, which were concordant in pts with both decreased eGFR and proteinuria, 22 of 28 pts (79%) had a RR, including 2 of 7 discontinuing dialysis. All 6 pts (100%) with isolated proteinuria and 7 of 13 (54%) with isolated decreased eGFR achieved RR, suggesting that isolated proteinuria may be an early and reversible manifestation of MIDD.Baseline eGFR was predictive of RR ($p< 0.02$ by quartile), while hematologic response (CR vs. non-CR) was not, probably due to high hematologic response rates. With a median-follow up of 110 months (95% CI: 71-NR), the median overall survival was 136 months (95% CI: 79–NR) and median RS had not been reached.
Conclusions: We have used a systematic approach to assess RR in MIDD, a field that remains mired in uncertainty in the literature. We show that IMWG and amyloid response criteria are both essential to adequately assess the RR in MIDD. We also show that the RR rate is high and durable in this disease with bortezomib-based treatment and ASCT. This study will help inform the development of consensus renal response criteria that are needed in MIDD.

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Outcomes in risk-stratified patients with smoldering multiple myeloma: a retrospective analysis of real-world data from the Czech Registry of Monoclonal Gammopathies

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Introduction: Smoldering multiple myeloma (SMM) is an asymptomatic precursor to active MM. The Mayo clinic have developed criteria (20-2-20) to identify patients with SMM at high risk of progression to symptomatic MM.(1) The aim of this study was to report clinical characteristics and outcomes of Mayo 20-2-20 risk-stratified patients with SMM using data from the Czech Registry of Monoclonal Gammopathies (RMG).
Methods: Patients were included who presented with ≥1 of the following: serum M protein ≥30 g/L, urinary M protein ≥500 mg/24 h, and ≥10% of bone marrow plasma cells (BMPCs) plus the absence of MM-defining end-organ damage or light chain amyloidosis. Patients who were potentially incorrectly identified as SMM were excluded using an appropriate algorithm. The Mayo 20-2-20 criteria(1) define high-risk SMM as ≥2 of the following: free light chain ratio >20 and 2 g/dL, and clonal BMPCs >20% to < 60%. Key outcomes were overall survival (OS) and time to progression (TTP) from first SMM diagnosis to active MM. Kaplan-Meier methodology was used to estimate OS, the Fine-Gray method to estimate TTP, and a Cox proportional hazards model to calculate hazard ratios (HR).
Results: Data were collected from 18 Czech hematological centers. Of the 498 patients included in this study, 174 (34.9%) met the criteria for high-risk SMM and 324 (65.1%) for non-high-risk SMM. Baseline demographics were generally consistent between high-risk and non-high-risk cohorts including median age (67 vs 65 years) and sex (female: 55.2% vs 51.9%). At SMM diagnosis, most patients in both cohorts had International Staging System stage 1 or 2 (high risk, 91.4%; non-high risk, 91.7%) and an Eastern Cooperative Oncology Group performance status of 0 or 1 (high risk, 94.8%; non-high risk, 94.1%). During the follow-up period (median follow-up was approximately 65 months in both groups), more patients in the high-risk group progressed from SMM to active MM than in the non-high-risk group (HR, 2.7 [95% confidence interval, 2.08–3.42], $P < 0.001$). Median TTP from SMM to active MM was significantly shorter in high-risk patients (14.9 months vs 74.8 months, $P < 0.001$). Median OS was significantly shorter in high-risk than non-high-risk patients (93.2 months vs 131.1 months, $P = 0.012$). The monthly OS rate was similar between cohorts (< 5% difference) until 36 months, after which it was lower in the

high-risk group than in the non-high-risk group (70.5% vs 80.9% at 60 months; 43.2% vs 54.7% at 120 months).
Conclusions: These analyses using real-world data from the RMG add to the growing body of evidence that patients with high-risk vs non-high-risk SMM have significantly worse outcomes, including OS, and could benefit from early interventional therapy. 1. Lakshman A, Rajkumar SV, Buadi FK, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J. 2018;8:59.

P-178
A pilot plant based dietary intervention in MGUS and SMM is feasible and associated with reduction in insulin and leptin levels

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Introduction: Trial in Progress. Obesity, low adiponectin, high insulinemic foods and diets lacking plant-based foods are risk factors for plasma cell disorders, thus providing a rationale for studying dietary interventions in MGUS/SMM to reduce risk of progression. We therefore initiated a pilot dietary intervention study (NUTRIVENTION) of a whole food, plant-based diet (WFPBD) in MGUS/SMM patients (pts) with BMI ≥25 (NCT04920084). The primary objective is to determine the feasibility of a WFPBD, as measured by weight loss and adherence at 12 weeks. We present interim results on weight loss, adherence, and metabolic markers (insulin, IGF1 and leptin).
Methods: Pts received WFPBD meals for 12 weeks and health coaching for 24 weeks from Plantable. Detailed education (via a phone app from Plantable) for snacks and breakfast were given (no calorie restriction). Adherence was assessed through food logs and 72-hour recalls (analyzed via ASA24 Dietary Assessment Tool) conducted by a research dietitian every 2 weeks for the 12-week intervention. Adherence was calculated as the percentage of kcal that were whole unprocessed plant foods out of total kcal consumed. Plasma leptin, insulin and total IGF1 levels were measured at baseline and 12 weeks via ELISA immunoassays.
Results: To date, 19 of 20 pts have enrolled and 10 have completed 12-weeks. One additional pt dropped out on day 11 and was replaced but included in adherence analysis. Baseline demographics for 19 pts include 47% male, 42% Blacks/Hispanics/Mixed, 53% MGUS, 74% obese and 26% prediabetic/diabetic. The first 10 pts had preintervention unprocessed plant food adherence mean of 23% (range 3-52%) and 12-week mean of 92% (77-100%). They had a mean BMI of 38.3 kg/m2 (28-51 kg/m2) at baseline and a mean 7% (3-13%) BMI reduction to 35.8 kg/m2 (25-49 kg/m2) at 12 weeks. Five of 10 pts had LDL cholesterol >100 mg/dL at baseline with 20 mg/dL (6-32 mg/dL) mean reduction at 12 weeks. Two diabetic and 1 prediabetic pt had improved glycemic control (reduction in A1c or medications). One pt on medications no longer required oral hypoglycemics and insulin. Pts had an average 4% reduction in M spike at 12 weeks with 20% reduction in 2 pts (-12-20%). Preliminary data for the first 9 pts that completed the intervention showed mean decrease in insulin 1.73 mU/L (IQR: -1.18, 4.12) or 22% and leptin 3610 pg/mL (IQR: -599, 12686) or 11% at 12 weeks. IGF1 remained unchanged -0.18 ng/mL (IQR: -70, 40).
Conclusions: A WFPBD is feasible given adherence and BMI reduction with decreased insulin and leptin levels. Because increased insulin and leptin are associated with myeloma cell growth and proliferation, reduction in these biomarkers may mitigate long-term risk of progression and provide mechanistic insights into plant based dietary and weight loss interventions. We will present data on adiponectin, microbiome, and metabolome at the meeting. The study is funded by the Allen Foundation, Riney Foundation, NCI K12 and ASH CRTI award.
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Comorbidities associated with monoclonal gammopathy of undetermined significance, its subtypes, and risk factors

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Introduction: Monoclonal Gammopathy of Undetermined Significance (MGUS) is recognized as a precursor to multiple myeloma, with the risk of progression being about 1-2% every year. Although MGUS is typically asymptomatic, these individuals may initially present with clinical symptoms, that thus lead to a workup and diagnosis of MGUS. Research has shown that MGUS patients have a shorter life expectancy due to an increased risk of death from causes such as bacterial infections, heart, liver, and kidney diseases. The goal of this retrospective, single center cohort study was to determine the correlation between various comorbidities, patient characteristics, and attributes of MGUS, such as immunoglobulin type, plasma cell percentage, and risk level.
Methods: The medical records of 265 patients (135 males/130 females; median age 66, ranging from 30 to 91) with a confirmed MGUS diagnosis were retrospectively studied at a single institution. Patients were diagnosed

between 2003 and 2021. Demographic data was collected, as well as baseline clinical labs. MGUS types were categorized according to heavy chains (IgA, IgG, IgM) and light chains (kappa or lambda) expressed. Plasma cell percentage levels were defined as a median of 5, with patients characterized below or at and above the median. Risk factors for MGUS were non-IgG subtype, M protein > 1.5 g/dL, and abnormal free light chain ratio. If all factors were met, the patient was categorized as having high-risk MGUS. If no factors were identified, the patient was categorized as low-risk, all other patients were considered to have intermediate-risk. Patient charts were reviewed to determine the presence of all the comorbidities that are described by The Hematopoietic Cell Transplant Comorbidity Index, as well as other common comorbidities not included in the index. The association between comorbidities, type of MGUS, plasma cell percentage, and risk level were evaluated using Fisher's Exact test.

Results: IgG kappa subtype was associated with a higher rate of diabetes (p=0.037) and IgM kappa with or without monoclonal gammopathy of neurological significance (MGNS) had a higher rate of rheumatologic conditions (p=0.026). Additionally, there was a statistically significant difference with plasma cell percentage, arrhythmia (p=0.008), and cerebrovascular incidents (p=0.029), with these conditions being associated with a less than median plasma cell percentage. There was also a higher rate of chronic infection in patients with high-risk MGUS (p=0.044).

Conclusions: Previous studies have described the correlation between MGUS and certain comorbidities. Our results demonstrate that specific characteristics of MGUS (immunoglobulin type, plasma cell percentage, and risk level) may play a significant pathophysiologic role in these comorbidities. Further research into the identification and meaning of the involved mechanisms may help to lower disease burden, individualize surveillance, and improve overall survival in patients diagnosed with MGUS.

P-180

18F-FDG PET/CT can be used to predict progression in smoldering multiple myeloma patients

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Introduction: There is a need to refine smoldering multiple myeloma (SMM) risk stratification, to identify high-risk patients that may benefit from early intervention. In SMM, prior work has shown that focal lesions on 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) with FDG uptake and without osteolysis are associated with an increased risk of progression to active myeloma. In SMM patients with post-diagnosis PET/CTs, an increased mean standardized uptake value (SUV) at L4 has been shown to increase the progression risk. We aimed to validate these findings in an independent SMM cohort.

Methods: We retrospectively studied SMM patients diagnosed between January 2000-2020. We included patients with available 18F-FDG PET/CT images within 3 months of SMM diagnosis, or between diagnosis and treatment for MM. PET/CT scans conducted within 3 months of progression to MM or last follow-up were excluded. PET/CT scans were evaluated by two independent reviewers. Focal lesions were defined as FDG-avid lesions without underlying osteolysis on CT. The mean SUV of L4 and the liver were determined using MIM software (MIM Software Inc., Cleveland, OH, USA). Kaplan Meier survival analysis was used to assess the time to progression (TTP), which was calculated from the date of PET/CT imaging acquisition. Cox proportional hazards models were used to estimate hazard ratios.

Results: Baseline PET/CT scans were available for 159 SMM patients, and 138 patients had a PET/CT scan after diagnosis and prior to MM progression. On review of baseline PET/CT scans, 5 (3.1%) patients had a focal lesion (n=1 with 5 focal lesions, n=1 with 2 focal lesions, n=3 with 1 focal lesion). The median TTP was 0.9 years versus not reached in patients with versus without a baseline focal lesion, respectively. The TTP to symptomatic MM was significantly higher in SMM patients with a focal lesion on baseline PET/CT imaging versus those without (HR 12.7, 95% CI 4.2-38.3, p< 0.001). The increased progression risk associated with focal lesions remained significant when adjusting for baseline Mayo 2018 SMM risk score, sex, PET/CT location (images acquired at Mayo Clinic vs. an external institution) and age at SMM diagnosis (HR 6.1, 95% CI 1.9-20.3, p=0.003). Among the 138 patients with a PET/CT scan post-diagnosis, the median L4 SUVmean was 1.9 (IQR 1.6-2.2). Progression risk was higher in patients with an L4 SUVmean above versus below the liver SUVmean even after adjusting for sex, hemoglobin level, serum MCP, and age at the time of PET/CT imaging (HR 4.3, 95% CI 1.8-10.3, p< 0.001).

Conclusions: We validated findings that focal lesions without osteolysis on baseline 18F-FDG PET/CT imaging and an SUVmean higher at L4 than the liver on a post-diagnosis PET/CT scan are associated with an increased progression risk in SMM. Incorporating these markers into SMM risk stratification models may improve prognostication.

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Assessing the association between body mass index at diagnosis and the risk of progression in patients with monoclonal gammopathy of undetermined significance

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition with a risk of approximately 1%/year for progression to multiple myeloma (MM), a lymphoproliferative disorder, or systemic light chain (AL) amyloidosis. Obesity has emerged as a potential modifiable risk factor that is associated with an increased progression risk. We assessed whether body mass index (BMI) at MGUS diagnosis was associated with risk of progression independent of established clinical risk factors in a cohort of patients with clinically detected MGUS.
Methods: This single-center retrospective cohort study included MGUS patients diagnosed between January 2000 to January 2020 with a BMI available within 30 days of diagnosis. Patients progressing within 1 year of diagnosis were excluded. The strength of the association of BMI with progression to MM, a lymphoproliferative disorder, or AL amyloidosis was expressed as a subdistribution hazard ratio (sHR) estimated by Cox proportional hazards regression, accounting for death as a competing risk and adjusting for known clinical risk factors (baseline monoclonal protein (MCP) isotype and size, sex, and age at MGUS diagnosis). We adjusted additional models for height, which has been independently associated with disease progression in other cancers. Lastly, we examined risk of progression only to MM as a secondary outcome.
Results: We included 12,564 MGUS patients (n=3,525 normal BMI [18.5-24.9 kg/m2], n=4,599 overweight BMI [25-29.9 kg/m2], n=4440 obese BMI [≥30 kg/m2]), of whom 236 progressed (160 to MM, 48 to a lymphoproliferative disorder, 28 to AL amyloidosis). An elevated baseline free light chain ratio, MCP size >15 g/L, and non-IgG MCP isotype were all associated with an increased progression risk, as expected. In the simplest models, an overweight or obese BMI was similarly associated with an 80% increase in the risk of progression compared to a normal BMI (overweight v. normal BMI sHR =1.79, 95% CI=1.30-2.57, p=0.001; obese v. normal BMI sHR 1.80, 95% CI 1.30-2.60, p=0.002). These associations persisted in multivariable analyses (overweight v. normal BMI sHR=1.84, 95% CI=1.27-2.67, p=0.001; obese v. normal BMI sHR=1.69, 95% CI=1.16-2.47, p=0.007) after additional adjustment for height (overweight v. normal BMI sHR =1.84, 95% CI=1.27-2.66, p=0.001; obese v. normal BMI sHR 1.71, 95% CI 1.17-2.50, p=0.006) and in analyses focused only on progression to MM (overweight v. normal BMI sHR =2.18, 95% CI=1.36-3.50, p=0.001; obese v. normal BMI sHR 1.96, 95% CI 1.21-3.16, p=0.006).
Conclusions: This is the largest cohort study to date to show that in patients with clinically detected MGUS, accounting for death as a competing risk, a BMI above 24.9 mg/m2 at MGUS diagnosis is associated with an increased risk of progression independent of established clinical risk factors. Further work is needed to assess whether BMI reduction can mitigate progression risk in MGUS patients.

P-182
Mosaic chromosomal alterations increase risk of incident monoclonal gammopathy of undetermined significance and multiple myeloma

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Introduction: Mosaic chromosomal alterations (mCAs) are somatic structural alterations including chromosomal gains, losses, and copy neutral loss of heterozygosity. They increase in frequency with age and are found in the peripheral blood of 1-3% of healthy individuals over the age of 70. Previous research has found a strong association between mCAs and the incident diagnosis of chronic lymphocytic leukemia. MCAs are also an early event in myelomagenesis and are found in the plasma cells of 65% of patients with monoclonal gammopathy of undetermined significance (MGUS) and nearly 100% of patients with multiple myeloma. The mCAs found in multiple myeloma are currently believed to originate from somatic hypermutation and class switch recombination in the germinal center.
Methods: We analyzed the data of 89,783 BioVU participants whose DNA extracted from peripheral blood was sequenced using the Illumina Mega-ex Array. Individuals under the age of 18, individuals with less than 6 months of follow up from sample collection, and individuals with a diagnosis of hematologic malignancy before or within 6 months of sample collection were excluded. Hematologic malignancy diagnoses were determined by the presence of corresponding ICD codes in the patient's deidentified medical records. Diagnoses of MGUS and multiple myeloma were verified by manual chart review. MCAs >2Mb were identified by the validated MoChA algorithm (Loh Nature 2018). The association between mCAs and incident diagnosis of MGUS or multiple myeloma was assessed using a Cox proportional hazards model.
Results: 62,541 individuals were included in the analysis. Mean (SD) age was 50 (17) and 58% of individuals were female. We detected mCAs in the autosomes of 0.5% of individuals. The frequency increased with age, from 0.2% under age 50 to 1.6% over the age of 70. After a median follow up 6.5 years, 3.1% of individuals with mCAs were diagnosed with MGUS or multiple myeloma compared to 0.6% of individuals without mCAs. After controlling for age at sampling, sex, self-reported race and ethnicity, smoking status, and principal components 1-10, mCAs were positively associated with incident diagnosis of MGUS or multiple myeloma (hazard ratio: 2.920 [1.373-6.231], p=0.005). The fraction of white blood cells (WBCs) containing mCAs in individuals who were later diagnosed with MGUS or multiple myeloma ranged from 13.5% to 48.8% (mean: 29.2%).
Conclusions: Patients with mCAs in their peripheral blood have a 2.92x increased risk of being diagnosed with MGUS or

multiple myeloma. The fraction of WBCs containing mCAs in individuals who were later diagnosed with MGUS or multiple myeloma are larger than the fraction of post-germinal center B cells found among WBCs (0.5-3%) in healthy adults. This provides indirect evidence that predisposing mCAs in peripheral blood occur before the germinal center during myelomagenesis.

P-183
Outcomes in respiratory tract infections in hospitalized multiple myeloma patients with asthma and chronic obstructive pulmonary disease

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Introduction: Respiratory tract infections are common in multiple myeloma (MM) due to compromised immunity resulting from the disease pathology and expected therapeutic side effects. Pre-existing respiratory diseases like asthma and Chronic Obstructive Pulmonary Disease (COPD) predispose patients to Upper Respiratory Tract Infection (URI) and Lower Respiratory Tract Infection (LRI). URI includes sinusitis, pharyngitis, tonsillitis, epiglottitis, and laryngitis. LRI includes tracheitis, bronchitis, and pneumonia.
Methods: We analyzed the National Inpatient Sample database from 2016 to 2019 using IBM SPSS 28.0 to compare outcomes in MM patients with asthma and Chronic Obstructive Lung Disease (COPD). The results reported are statistically weighted. Cases and Diagnoses were identified using the International Classification of Disease, 10th Revision codes. Chi-square tests and T-tests were utilized as appropriate. Inpatient deaths, length of stay (LOS), and total hospitalization charges (TOTCHG) are reported.
Results: A total of 477,065 MM cases were identified. Overall, 65,055 (13.6%) cases had COPD and 27,890 (5.8%) cases had asthma. 13,985 (2.9%) cases had URI and 101,340 (21.2%) cases had LRI. Compared to non-asthmatic cases, asthmatic cases had higher URI (2.9% vs 4%, P< 0.001) and LRI (21% vs. 25.1%, P< 0.001). Compared to non-COPD cases, COPD cases had higher URI (2.9% vs 3.2%, P< 0.001), and higher LRI (19.3% vs 33.6%, P< 0.001). Compared to non-asthmatic cases, asthmatic cases had lower in-hospital deaths (5% vs 2.8%, P< 0.001). Compared to non-COPD cases, COPD cases had higher in-hospital deaths (4.8% vs 5.4%, P< 0.001). URI was associated with lower in-hospital deaths (4.9% vs 3.5%, P< 0.001), but higher LOS (7.11 vs 7.34 days, P< 0.001) and higher TOTCHG ($81,335 vs $84,910, P< 0.001). LRI was associated with higher in-hospital deaths (3.4% vs 10%, P< 0.001), higher LOS (6.77 vs 8.39 days, P< 0.001), and higher TOTCHG ($77,134 vs $97,413, P< 0.001). In asthmatic cases, LRI was associated with higher in-hospital deaths (1.9% vs 5.4%, P< 0.001). In COPD cases, LRI was associated with higher in-hospital deaths (3.7% vs 8.6%, P< 0.001).
Conclusions: Asthma and COPD in MM patients are associated with increased respiratory tract infections. Respiratory tract infections are associated with increased in-hospital deaths, LOS, and hospitalization charges. Prevention strategies like adequate management to avoid exacerbations, smoking cessation, and appropriate vaccination are advisable in patients with asthma and COPD. Early recognition and timely treatment of infections could help mitigate the mortality and morbidity in such patients. Further research in this direction is needed.

P-184
Pegfilgrastim versus filgrastim in the supportive care of heavily pretreated multiple myeloma in treatment with pomalidomide-dexamethasone

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Introduction: Pegfilgrastim is a pegylated long-acting recombinant form of G-CSF that extends the half-life and allows for once-per-cycle dosing, requiring less frequent dosing than nonpegylated G-CSF. The objective of this study was to compare the efficacy and safety of pegfilgrastim in patients affected by heavily pretreated MM, treated with pomalidomide-dexamethasone, in order to determine whether a single subcutaneous injection of pegfilgrastim is as effective as daily injections of standard filgrastim, in terms of haematological toxicity, febrile neutropenic episodes, antibiotic usage and hospedalization duration.
Methods: 57 patients (31 M and 26 F) were enrolled, median age at diagnosis 69 years (r. 52-84), and median age at start of treatment 76 years (r.56-90) treated with several lines of treatments (median 7, r. 2-12), every refractory to all the drugs previously received, received Pomalidomide-Dexamethasone (P 4 mg for 21 days, D 40 mg days 1,8,15,22, pegfilgrastim day +8) every 28 days, until progression.
Results: During neutropenia after first cycle, Filgrastim (5 µgr/kg/day for 3 days) was given if neutrophils count was < 1500 x 10^9 cells/L. Median number of filgrastim administrations was 4.6 (r. 3-6); nadir neutropenia was registered after a median of 10.4 days (r. 7-14); median of nadir neutrophil count was 1.13 x 10^9 cells/L (r.0.3 – 1.5), with maximum duration of 14 days. From the second course, all patients switched to prophylaxis with pegfilgrastim (6 mg), injected subcutaneously with a single administration on day +3 independently from the neutrophil count at that time. During pegfilgrastim, neutropenia was never longer than 8 days, with a consequent reduction of neutropenia-related infections. Median nadir neutrophil count, evaluated for every patients for at least three courses of therapy (r. 3-6) registered at day +11, was 1.28 (r.0.9-2.2). Only 4 patients needed a supplement of 3 administrations of filgrastim.

Pegfilgrastim was well tolerated in all patients: main side effects in our patients were mild fever and bone pain (21.2%).
Conclusions: In patients affected by heavily pretreated MM treated with pomalidomide-dexamethasone, pegfilgrastim seems to reduce the incidence of severe neutropenia and infections and may increase the possibility to maintain the scheduled time of treatment.

P-185
Domestic opportunity in heavily pretreated multiple myeloma not eligible to hospital-based treatment: role of pomalidomide-dexamethasone

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Introduction: Many patients affected by heavily pre-treated Multiple Myeloma could be not eligible to hospital-based treatment: in this context domestic opportunities should be considered. Pomalidomide is a new generation IMID, with a very good compliance, thanks to oral administration, which can be used also in heavily pretreated patients, in a domestic setting. In this retrospective observational trial, It has been evaluated efficacy and tolerance of pomalidomide plus dexamethasone (PD) as salvage regimen in heavily pretreated patients with relapsed and refractory MM (rrMM), whose prognosis is particularly severe.
Methods: 57 patients (31 M/26 F), with rrMM, median age at diagnosis 69 years (r. 52-86), and median age at start of treatment 76 years (r.56-90) treated with several lines of treatments (median 7, r. 2-11), every refractory to all the drugs previously received (also Bortezomib, Thalidomide and Lenalidomide), received Pomalidomide-Dexamethasone (Pomalidomide 4 mg for 21 days, Dexamethasone 40 mg days 1,8,15,22, pegfilgrastim day +8) every 28 days, until progression. ISS was equally distributed, and cytogenetic at relapse was evaluable in 14 patients. All the patients had previously been treated with schedule containing bortezomib and IMIDs. 63% (36/57) had undergone at least to a single ASCT. All patients were relapsed and refractory to last therapies received before PD.
Results: Pomalidomide was well tolerated, with grade 3-4 transfusion-dependent anemia in 58% (33/57) of patients, 44% (23/57) grade 3-4 neutropenia (pegfilgrastim in primary prophylaxis was given, no hospitalization was required, no septic shocks were observed), 40% (23/57) grade 3-4 thrombocytopenia without hemorrhagic events and transfusion-dependence. No severe extra-hematologic toxicity was observed. According to IMWG, ORR1 (≥PR) was 47.3% (27/57: 5 CR, 11 VGPR, 7 PR, 4 MR), but, considering that we are evaluating a cohort of heavily pretreated patients, with poor prognosis, another parameter should be considered, ORR2 (≥SD), considering stable disease as a successful result in progressive MM. ORR2 was 77.1% (17 SD). These can be considered as impressive result in this subset of patients. Oral treatment gives a really good compliance, in frail and unfit patients, and response, when present, is always really fast (median time to response: 2 months (r.1-6)), median OS from diagnosis was 94 months (range 21-234), median OS from start of pomalidomide was 9 months (range 1-25). Nine patients have surprisingly achieved a notable response (3 VGPR, 4 PR, 2 MR) after failure of novel agents (i.e. Carfilzomib, Daratumumab and Pomalidomide).
Conclusions: Pomalidomide-dexamethasone has shown significant efficacy and a very good compliance, thanks to oral administration, in a particularly severe setting of heavily pretreated patients, relapsed and refractory to all available therapeutic resources, also after failure of novel agents.

P-186
The impact of a 6-week cycle of Nordic walking health training on the functional fitness of women with multiple myeloma

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Introduction: Many patients with multiple myeloma (MM) experience a deterioration in motor fitness, which affects their quality of life. Since overall survival has significantly improved due to the increasing efficacy of MM treatment, it is important to improve functional aspects of patients everyday life. The aim of this study was to assess the impact of a 6-week training cycle on the motor skills of females with MM.
Methods: Fifteen females with MM in the remission who had no contraindications for moderate intensity physical activity were enrolled in the study. Participants were divided into 2 groups: a group performing Nordic walking training 3 times a week (NW, n = 9, mean age 62.6 years, BMI = 29.9 ± 4.0), and a control group (CG, n = 6, mean age 62.8 years, BMI = 25.4 ± 6.0). Anthropometric measurements (selected skinfolds and body circumferences), body composition estimation with use of bioimpedance method, and the Fullerton functional test (senior fitness test, SFT) were performed at the initiation of the training intervention and after 6 weeks in all subjects. Patients from NW group also subjectively assessed for changes in their fitness after participating in the project.
Results: The NW group showed a significant improvement in 3 out of 6 motor tasks in SFT. In the "Chair Stand Test", the examined women performed an average of 1.9 more repetitions during the 30 seconds of the test ($p = 0.003$), which indicated an improvement in lower body strength. The strength of the upper body, assessed in the "Arm Curl Test", also improved significantly in the NW group: patients performed an average of 1.6 more repetitions ($p = 0.011$). An improvement was also observed in terms of balance (the "8-

Foot Up and Go Test"), where subjects improved the task completion time by an average of 0.8 seconds (p = 0.006). There were no statistically significant changes in the flexibility of the lower ("Chair Sit and Reach Test") and upper ("Back Scratch Test") body and aerobic capacity ("Step in Place Test"). The subjective assessment of the improvement in motor fitness were consistent with the objective results. No statistically significant changes were observed in the results of anthropometric measurements and body composition, but their direction was favourable. No statistically significant changes were observed in any of the anthropometric measurements in CG.
Conclusions: The applied training cycle significantly improved strength and balance, which is beneficial for the daily functioning of patients. These results were reflected in the subjective assessment of the effects of training which confirms the positive impact of participation in applied training on patients' everyday life. The lack of changes in the remaining parts of the SFT, as well as in measured anthropometric parameters and body composition, could indicate that the training cycle time was too short or that the intensity of training sessions was too low to demonstrate beneficial changes.

P-187
Retrospective review of chronic pain causes and management in multiple myeloma patients

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Introduction: The survival of patients with multiple myeloma has improved dramatically since the introduction of proteasome inhibitors such as bortezomib, which can have the adverse effect of peripheral neuropathy. This study retrospectively examines the incidence and causes of chronic pain in myeloma patients as well as the modalities and duration of treatments used for pain control.
Methods: Rush University Medical Center multiple myeloma patients who were diagnosed and treated between 2000-2019 were included. Outcome measures were abstracted from the medical record and included: classes of pain medication used, duration of treatment, prevalence of peripheral neuropathy symptoms, grade of neuropathy, and use of adjunct treatment modalities. Descriptive statistical models including Chi-square and Fisher's exact test were used for categorical variable analysis.
Results: In all, 134 patients were included, of which 75.4% (N=101) patients received at least one cycle of bortezomib. 42.5% (N=57) patients were seen in palliative clinic. 72.9% (N=97) reported bone pain symptoms. A total of 73.7% (N=98) patients experienced peripheral neuropathy symptoms. Of those with neuropathy, 60.2% (N=59) experienced grade 1 neuropathy, 31.6% (N=31) experienced grade 2, and 8.2% (N=8) experienced grade 3. 86.1% (N=87) of patients who received bortezomib reported neuropathy, as compared to 34.4% (N=11) of patients who did not have bortezomib therapy (OR 11.8, p< 0.0001). 66.4% (N=67) patients who received bortezomib took anticonvulsants as compared to 31.3% (N=10) of those who did not receive bortezomib (OR 4.3, p< 0.0005). Patients were on anticonvulsant therapy for a mean of 32.6 months (SD=26.7) with no significant difference in the bortezomib group. 79.7% (N=106) patients took opioid medications. Norco was the most commonly used opioid (N=55) and average duration of use was 36.6 months (SD=34). 18.8% (N=25) took antidepressant medications such as TCAs or SNRIs for pain, and all of these patients received bortezomib therapy (p=0.0003). 36.6% (N=45) of patients received radiation and 16.5% (N=22) underwent kyphoplasty. 70.7% (N=94) patients attended at least one physical therapy session. There was no statistically significant difference in radiation or kyphoplasty utilization between patients who had received bortezomib and those who had not, but there was a significant difference in physical therapy (OR 4.9, p< 0.0001).
Conclusions: Patients who received bortezomib as part of their myeloma treatment were more likely to experience peripheral neuropathy and required anticonvulsant therapy more frequently. It is important to better understand and define the health burden of chronic pain, the severity of adverse effects, and use of pain medications in patients with multiple myeloma.

P-188
Moving from research priorities to clinical research: implementing the results of a priority setting partnership on multiple myeloma

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Introduction: As people live longer with multiple myeloma (MM), new questions are being asked about the diagnosis, treatment, and management of this disease. However, when it comes to answering these questions, research evidence is often lacking. At the same time, given the slow uptake of study results, researchers continue to struggle to close the "knowledge-to-practice" gap. To address these challenges, researchers need to focus on the needs of the myeloma community. To this end, our study identified the Top 10

research priorities shared by three key groups: people living with MM, caregivers, and clinicians.
Methods: To elicit and prioritize unanswered questions about MM, our project followed the robust and transparent approach developed by the James Lind Alliance. A national steering group oversaw the project to ensure relevance of results, and people living with MM, caregivers, and clinicians all had equal representation on this committee. An iterative process was used to develop the Top 10 list, including two national surveys, a literature review, and a final consensus-building workshop (https://www.jla.nihr.ac.uk/priority-setting-partnerships/myeloma/top-10-priorities.htm). The project is now in its knowledge translation phase where the aim is to move from research priorities to clinical research. The goal of this presentation is to describe our approach thus far and demonstrate how the International Myeloma Society and its members can help ensure that research on MM is meaningful to those affected by the disease.
Results: At the outset, we used a traditional knowledge translation approach. Seeking to raise awareness of the shared priorities and to foster research and systematic reviews on these concerns, we reached out to clinicians and researchers via peer-reviewed publications and dissemination at local and national conferences. Elsewhere, we highlighted the benefits of engaging patients and caregivers as full-fledged research partners and shared recommendations on how best to do so. To promote uptake, our approach also included partnering with a national charitable organization, one that is using our findings to accomplish its primary mission of improving the daily lives of those within the MM community. Initiatives include the creation of educational materials to address frequently asked questions and the funding of priority-related research projects. The organization recently launched a new research grant that will award at least $100,000 in funding for priority-related research this year alone.
Conclusions: Clinical and scientific experts on MM, as well as research funders, all have a pivotal role to play when it comes to acknowledging the experiences and needs of those impacted by MM and investigating their priority concerns. A focus on stakeholder-identified priorities is crucial as it will facilitate the uptake of meaningful research into practice and improve the quality of life of people living with MM and their caregivers.

P-189
Updated trial in progress: understanding treatment experience of individuals receiving isatuximab using both patient-reported outcomes and wearable data

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Introduction: The experience of patients being treated for relapsed/refractory multiple myeloma (RRMM) is complex and multifaceted. An ongoing multicenter trial is exploring the patient experience during treatment for RRMM with isatuximab using multimodal data sources collected from both patient-reported outcomes (PRO) assessments and wearable devices. This study is designed to provide a richer understanding of the real-world experience of treatment with isatuximab for RRMM in the era of CD38-directed monoclonal antibody therapy coupled with the COVID-19 pandemic. This trial-in-progress abstract presents updates on the status of this study, including enrollment and a demographic profile of participants to date.
Methods: Fifty adults with RRMM receiving isatuximab will be enrolled across 2 sites: the University of Texas MD Anderson Cancer Center and University of Washington (new since this trial's original presentation). The sample size is consistent with the exploratory aims of the study. Consented participants are enrolled in a 3-month digital health coaching program through which PROs, specifically the Patient's Qualitative Assessment of Treatment-Real World (PQAT-RW), Patient Global Impression of Change/Severity (PGIC/S), FACT-G (Item GP5-side effect bother), EORTC-QLQ-C30, QLQ-MY20, and EQ5D, are collected. Clinical data, including treatment history, healthcare utilization, and co-morbidities, as well as demographic data will be collected via the electronic health record from each clinical site. In addition, physical activity data collected from all participants through a wrist-worn activity tracker, and qualitative data will be collected from a purposefully selected cohort of participants in an individual interview focused on treatment experience with isatuximab and overall quality of life.
Results: As of submission, this protocol is open and enrolling at The University of Texas MD Anderson Cancer Center (NCT05053607). Patient accrual at the second site (University of Washington) is expected to begin in October 2022. Demographic data from enrolled participants will be presented.
Conclusions: Outcomes from this study, for which enrollment is anticipated to continue through early 2023, are anticipated to provide insight into diverse PROs, including both validated measures of quality of life and symptom burden, as well as physical activity and qualitative data. Results are anticipated to enhance the literature and implications for clinical practice for individuals receiving treatment with isatuximab for RRMM in the real-world setting.

P-190
Bone remineralization of lytic lesions in newly diagnosed multiple myeloma (NDMM) patients treated with carfilzomib, lenalidomide, dexamethasone +/- daratumumab induction regimen

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Introduction: The impact of carfilzomib-based induction therapy on lytic bone lesions is not well-described. Herein, we examined the effect of carfilzomib-based induction on bone remineralization and identified potential mediators of bone healing. We evaluated for changes in radiologic parameters on serial scans of NDMM patients (pts) treated with high dose carfilzomib- lenalidomide-dexamethasone (KRd) and daratumumab and KRd (Dara-KRd).
Methods: Thirty-nine pts treated at MSK from 10/2016 to 11/2019 with ≥1 lytic lesion measuring ≥0.5cm on pretreatment PET/CT were included in this analysis. Changes in the target lesion from baseline to first follow-up (f/u) scan ≥6 months (mos) after was assessed by 1 radiologist. The primary endpoint was the incidence of bone remineralization defined as the presence of a sclerotic CT change within the lesion or decrease in the lytic component using the largest diameter compared to baseline. Extent of remineralization was defined as the percent change in the size of a lesion on f/u scan from baseline and categorized into quartiles: < 25, 25-50, 51-75, and 76-100%. Discrete pt characteristics were summarized by frequency (percentage) and continuous characteristics were summarized by median (IQR). Associations between binary variables were assessed by Fisher's exact test.
Results: Characteristics of the 12 KRd and 27 Dara-KRd treated NDMM pts are in table 1. Common locations for target lesions were ilium/sacrum (16), vertebrae (12), rib/sternum (6). Remineralization was observed in 41% of pts (16/39), and 23% (9/39) achieved ≥25% of bone remineralization (2 KRd and 7 Dara-KRd pts). Median time from baseline to f/u scan was 12 mos (IQR10–13) in the KRd group and 9 mos (8.5–10) in the Dara-KRd group. There was no difference in rates of remineralization between KRd and Dara-KRd (OR 1.60, 95%CI 0.32–9.00, P=0.73). There was no association observed with age, gender, cytogenetic risk, best overall response, and MRD negativity and the presence of bone remineralization likely due to the small sample size. There was a trend toward higher rates of remineralization in pts on antiresorptive agents during induction (13/25, 52% vs 3/14, 21%, P=0.09).

Table 1. Pt characteristics

	KRd(N=12)	Dara-KRd(N=27)
Age, median-yrs(IQR)	61(52-68)	59(51-65)
Sex: F/M,%	33/67	67/33
Cytogenetic risk: High*/Standard,%	33/67	41/59
Best response (%)		
≥CR	5(42)	11(41)
VGPR	5(42)	14(52)
PR	2(17)	1(4)
MRD neg (flow)	6(50)	20(74)
Antiresorptive therapy with induction(%)	9(75)	16(59)

*gain1q, t(4;14), t(14;16), t(14;20), del(17p)

Conclusions: This analysis demonstrates that bone remineralization occurs in a considerable proportion of NDMM pts treated with carfilzomib-based regimens. Longer f/u and serial scans may show increased rates of remineralization with continued therapy. In addition, antiresorptive therapy may improve remineralization rates in these pts, further supporting studies in bone anabolic agents targeting sclerostin or other pathways that may enhance bone healing and decrease SRE risk.

P-191
The prevalence and outcomes of frail older adults in clinical trials in multiple myeloma: a systematic review

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Introduction: Multiple myeloma (MM) is an incurable blood cancer that primarily affects older adults. To understand the heterogeneity in this older population, several frailty tools,

including the International Myeloma Working Group (IMWG) frailty index and the simplified frailty score, have been developed. Uptake of these measures across clinical has been variable, leading to a gap in knowledge about the proportion of enrolled trial participants considered as frail and a direct observation of treatment-related effects and outcomes among this high-risk population. The objective of this systematic review was to: 1) examine the inclusion and prevalence of frailty in therapeutic MM trials 2) evaluate outcomes among frail older adults in MM clinical trials.
Methods: We searched the following databases from inception to April 5, 2022: Ovid MEDLINE, Ovid Embase, Scopus, Web of Science, Cochrane Library, and clinicaltrial.gov using keywords: “multiple myeloma”, “frailty” and/or “geriatric assessment”. We included studies that: (1) evaluated combination MM therapies (2) within a clinical trial setting and (3) reported on frailty. We included studies where tools used to measure frailty assessed ≥2 aging-associated domains.
Results: We identified 41 individual therapeutic MM trials for inclusion. This included 22 randomized controlled trials [RCTs] (15 in NDMM and 7 in R/R) and 19 non-randomized trials (10 in NDMM and 9 in R/R). Most trials incorporating frailty were published in the last 5 years (83%) and were conducted in Europe (49%). The most commonly used tools were the IMWG frailty index (37%) and the simplified frailty score (37%). Frailty assessment was conducted as a subgroup analysis (planned or post-hoc) in 66% of studies, used for study eligibility criteria in 20%, or to guide dose modifications in 12% of studies. The UK FiTNEss study, an ongoing phase III RCT, was the only study which used frailty to guide fitness assessment into its primary trial design. Additionally, only one prior study (VBDD-VERRUM) evaluated how frailty changed longitudinally over time in R/R MM with the UK FiTNEss study currently evaluating longitudinal changes in the NDMM setting. Frailty prevalence ranged from 17% to 74%. Frailty was dichotomized (frail, non-frail) in 31% of the studies and divided into three categories (frail, unfit, fit) in 69% of the studies. With regards to efficacy, 4 RCTs reported a statistically significant improvement in PFS for the experimental vs control arm among the frail subgroup: MAIA, ALCYONE, FIRST, ENDEAVOR.
Conclusions: Frailty assessments are increasingly being incorporated into therapeutic MM trials using the IMWG frailty index and the simplified frailty tool. While most commonly considered in subgroup analysis, frailty assessment incorporation in primary study design and outcomes will be a key step in personalizing treatment and improving outcomes for older adults with MM.

P-192
Patient reported outcome & family reported outcome and the most correlated clinical measures over one year of follow-Up

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Introduction: Survival in Multiple Myeloma (MM) has been improved over the last decades thanks to new treatments and medications. Therefore, MM can be considered a chronic disease, in the elder age. Since MM affects a variety of aspects of the patient and caregiver's life, it’s important to consider the patient and caregiver's experience and the disease's multifactorial influences. Our main goal is to examine the relationship between Patient Reported Outcome (PROM) & Family Reported Outcome (FROM) and specific clinical & lab parameters.
Methods: This is a quantitative, prospective, observational study of MM patients. The participants completed questionnaires of PROM (EORTC-QLQ-C30/MY20, and TSQM-9) and FROM (FROM-16 Questionnaire) at intervals of 3 months for one year. Besides, we monitored specific clinical parameters (e.g., R-ISS staging, ECOG performance status, CRAB, M-Protein, Disease Evaluation). The required sample size was calculated using Win-Pepi software, using 5% significance and 80% power. For a correlation of 0.4 between PROM/FROM and clinical parameters, the sample size required is 47 patients.
Results: This study included 57 patients. The statistical analysis included 12 domains of PROM and 3 domains of FROM. On the other hand, this study included 13 clinical parameters and lab results. The results demonstrated that the total PROM score (physical function, role function, social function, emotional function, cognitive function, fatigue, pain, nausea & vomiting, dyspnea, insomnia, appetite loss, constipation, and diarrhea) and Quality of Life, negatively correlated with Charlson Comorbidity Index, R-ISS staging, Kappa/Lambda Ratio (K/L Ratio), and ECOG (i.e., the higher these clinical domains, the worse the PROM score). The total PROM score and quality of life positively correlated with disease evaluation, at least at one follow-up point. In addition, the results showed that a better patient report regarding his disease symptoms, side effects of treatment, future perspective, and body image correlated with better clinical parameters results, especially in disease evaluation, ECOG, and K/L Ratio. In the treatment satisfaction questionnaire- a better convenience reported by the patient correlated with a better disease evaluation, ECOG, K/L Ratio, and Hemoglobin results. The results demonstrated that a high emotional, personal & social effect on the caregiver (FROM), correlated with higher R-ISS stage, ECOG, K/L Ratio, and worse disease evaluation. This research demonstrated that the domains of PROM/FROM- appetite loss, effectiveness, global satisfaction, and total caregiver effect, improved from baseline to at least one follow-up point at Wilcoxon's test.
Conclusions: This study validates the relation between PROM/FROM tools and the different clinical parameters

among MM patients and enables the clinical team to refer to a specific clinical parameter according to PROM/FROM. Finally, it's important to complete repeated PROM/ FROM over time due to a variety of disease related events.

P-193

Quantitative analysis of free light chains in multiple myeloma patients using volumetric absorptive microsampling

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Introduction: The aim of this study is to evaluate a self-administered, capillary blood sampling technique utilising volumetric absorptive microsampling (VAMS) for monitoring free light chains (FLC) in multiple myeloma (MM) patients. MM is a relapsing-remitting cancer with unpredictable relapse patterns. Blood test monitoring is crucial and requires frequent visits to the hospital; the measurement of FLC, a prognostic biomarker found in blood, can provide a rapid indication of MM disease progression and therapeutic response.
Methods: The VAMS FLC method was developed by adapting the Binding Site FLC serum assay on the SPA+ and is currently undergoing analytical and clinical validation in line with ISO15189:2012 standards. Method comparison studies were carried out between paired VAMS and serum FLC concentrations in 71 patients using Passing-Bablok regression. Twenty patients were longitudinally monitored to observe changes in the form of decreasing FLC (response to treatment), increasing FLC (relapse) and stable FLC (remission). Additionally, a questionnaire was administered to gain insight into patient experience with VAMS.
Results: VAMS and serum results had good correlation for κ-FLC ($y = 9.425+0.8477x$, $r2 = 0.877$) and λ-FLC ($y = 2.662+1.103x$, $r2 = 0.992$). Intra- and inter-assay precision are within an acceptable range for κ FLC and λ FLC (intra-assay, CV ≤10%; inter-assay, CV ≤ 15%). Linearity for κ and λ FLC VAMS method has been confirmed over a measuring range of 12-260 mg/L and 6.5-221mg/L, respectively. Trends of increasing, decreasing and stable FLC are in-line for both VAMS and serum results. There was no significant difference in perception of pain between phlebotomy and VAMS (P=0.5502); however, 63% of patients preferred VAMS; 4% preferred phlebotomy; and 32% had no preference.
Conclusions: This is the first study demonstrating the quantification of FLC from capillary blood. Validation is ongoing as paired samples are being collected to longitudinally examine intra- and inter-individual capillary FLC variation. The data thus far suggest that VAMS is a promising tool for remote FLC monitoring, especially for patients who require frequent monitoring and/or who are immune-compromised and vulnerable during travel or at a clinical setting.

P-194

Plinabulin after autologous hematopoietic cell transplant to decrease duration of neutropenia and improve quality of life peri-transplant

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Introduction: High dose melphalan with autologous hematopoietic stem cell transplantation (AHCT) remains standard of care for patients with multiple myeloma (MM), but is associated with a period of myelosuppression and obligate neutropenia. Symptom burden during AHCT peaks at the time of white blood cell nadir. Plinabulin, a small molecule differentiated tubulin-binding agent, is a synthetic analog of a substance found in Aspergillus species with tumor-inhibiting and immune-enhancing effects. In preclinical studies, plinabulin prevented chemotherapy induced neutropenia (CIN) via a mechanism of action different from that of G-CSF analogues, and it is currently in phase 3 clinical trials for solid tumors evaluating efficacy for CIN and anti-tumor activity.
Methods: In this pilot trial (NCT05130827, a single dose of 40mg of intravenous plinabulin was given on day of stem cell infusion (Day 0) in conjunction with pegfilgrastim on Day +1 after high dose melphalan and AHCT with the primary objective to reduce the period of absolute neutropenia in patients with MM. Secondary objectives include the safety, tolerability, and toxicity profile of plinabulin in combination with pegfilgrastim, neutrophil and platelet engraftment rate, disease response, progression free and overall survival, patient reported outcome (PRO) assessment of symptom burden, and plinabulin pharmacokinetic profiling. Exploratory objectives include transfusion requirements, phenotypic characterization of neutrophil population through day 30, and analysis of cytokine levels early post AHCT.
Results: To date, 10/15 patients have been enrolled and received plinabulin on Day 0 between January and May 2022, with a median age of 64 (range 58-74) and 40% female. Initially, patients were monitored in the hospital, but 3 patients received the AHCT and plinabulin outpatient without significant issues. Patients received melphalan 140 (n=3) or 200mg/m2 (n=7). Median CD34+ cells/kg infused was 4 x 10^6 (range 2.7 – 6.5). Half of the patients had hypertension immediately after the plinabulin infusion, which is a known toxicity and resolved within a few hours. Median WBC on Day 0, 1, and 2 was 7.6 (3.6 – 9.8), 5 (3.2 – 13.6), and 18.7 (5.1-59.1), respectively. Of the 8 patients who have engrafted to date, median time to ANC >0.5 was 11 days (range 10-16) with median days from AHCT to ANC < 0.5 of 5 days (range 5-6). The median number of days of ANC < 0.1 and < 0.5 were 2 (range 1-3) and 5 days (range 4-9), respectively. For the 5

patients who had a fever, the median time to fever was 8 days from AHCT (range 8-12), and all were peri-engraftment. Median length of stay was 17 days (range 15-21). No patients have progressed or died. PROMIS-29 PRO data was collected and will be analyzed.
Conclusions: To date, plinabulin appears well tolerated, and patients have not had non-engraftment related neutropenic fevers. Enrollment is ongoing, and full trial results will be presented.

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Lenalidomide, bortezomib, and dexamethasone (RVd) as first-line (1L) therapy in patients who are non-transplanted: results from the Connect® MM registry

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Introduction: RVd is standard of care in newly diagnosed multiple myeloma (NDMM); however, use in 1L among non-transplanted (NT-1L) patients (pts) has not been well described. Insight into this population is key in addressing research gaps and unmet pt needs, particularly among different age groups. The Connect® MM Registry is a large, US, multicenter, prospective observational cohort study designed to examine real-world treatment (tx) patterns and clinical outcomes in pts with NDMM. This analysis investigated characteristics and outcomes of NT-1L pts from the Connect MM Registry who received RVd in 1L.
Methods: Adults with NDMM were enrolled during 2009–2016 from 250 community, academic, and government sites. NT-1L pts were those who did not receive a transplant in 1L. Eligible NT-1L pts included those who received Rd and/or R following 1L RVd; pts who received any other regimen or transplant were excluded. Demographics and outcomes were assessed by age group. Pts were also stratified by time to progression (TTP; ≤12 mo vs >12 mo from start of 1L tx). Progression-free survival (PFS) was measured from 1L tx until death or progression (start of new line of tx was censored) using the Kaplan-Meier method. Cox proportional hazards models were used to assess PFS between subgroups.
Results: As of 04 Aug 2021, 314 of 1,979 NT-1L pts (≤65 y: n=135; >65 y: n=179) received only RVd or RVd followed by Rd/R in 1L. Baseline characteristics were comparable between age groups with the exception of renal function, which was more commonly impaired in pts aged >65 y. Among pts aged ≤65 y and >65 y, median duration of 1L tx (DOT) was 6.3 mo and 9.0 mo, median time to next tx line was 15.5 mo and 15.2 mo, and median PFS was 19.3 mo and 23.0 mo, respectively. IMWG high-risk MM, high serum calcium, and low hemoglobin were associated with a higher hazard of progression or death. Adjusting for these confounding factors, PFS hazard ratio with respect to age (≤65 y vs >65 y) was 1.206 (P=0.20). Median overall survival was 60.0 mo in pts ≤65 y and 59.1 mo in pts >65 y. A total of 108 pts had a TTP of 12 mo.
Conclusions: These results from CONNECT MM are consistent with other real-world data (RWD; Medhekar et al. Blood. 2021;138 (suppl1):3782) indicating RVd is effective across age groups. However, PFS outcomes from this analysis are shorter than those observed in SWOG S0777 (Durie et al. Blood Cancer J 2020), which may be due to the gap in DOT vs PFS. Differences in outcomes between age groups were not supported by any differences in the baseline characteristics, suggesting that attempting and understanding outcomes in RWD can be complex. Data also suggest that shorter DOT may translate to shorter time to next tx. One study limitation is that enrollment ended prior to the adoption of novel agents, such as anti-CD38, in earlier lines. However, this analysis provides robust RWD that support further investigation of RVd efficacy among NT-1L pts.

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In-class transition (iCT) from bortezomib (V)-based induction to oral ixazomib-lenalidomide-dexamethasone vs parenteral V-based therapy: comparative effectiveness in newly diagnosed multiple myeloma

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Introduction: Outcomes for patients (pts) with multiple myeloma (MM) can be improved by prolonged proteasome inhibitor (PI)-based therapy. However, this can be challenging to achieve in routine clinical practice with parenteral PIs (e.g. V). US MM-6 (NCT03173092; phase IV, community-based, single-arm study) is evaluating iCT from parenteral V to all-oral ixazomib-lenalidomide-dexamethasone (IRd). INSIGHT MM (global, prospective, observational study of >4,200 MM pts) provides a subset of pts as a comparator cohort. We report on an evaluation of comparative effectiveness in pts transitioning to IRd following V-based induction (US MM-6 pts; 'IRd' cohort) vs those who continued to receive V-based therapy (INSIGHT MM pts; 'V-based' cohort) in newly diagnosed MM (NDMM) pts treated in routine clinical practice in the US.
Methods: Non-transplant-eligible US NDMM pts with ≥stable disease following 3 cycles of V-based induction and a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2 from US MM-6 (Manda CLML 2020) and INSIGHT MM (Costello Future Onc 2019) were included in this secondary analysis. Outcomes included first-line duration of treatment (DOT), overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and reasons for treatment discontinuation. To account for the imbalance of potential confounding factors between the two pt cohorts, analyses were weighted using the inverse probability of treatment weighting (IPTW) method. Time-to-event outcomes were analyzed from the start of therapy by the Kaplan–Meier method. Results are presented throughout for the IRd vs V-based cohorts.
Results: 100 pts from US MM-6 and 111 from INSIGHT MM were included in the IRd and V-based cohorts, respectively. Following IPTW, pts had a median age of 75.0 vs 74.8 years; 56.7 vs 51.3% were male, 37.4 vs 29.1% had an ECOG PS of 2, and 48.8 vs 41.4% had International Staging System stage III at initial diagnosis. Initial induction therapy was VRd/V-cyclophosphamide-d (VCd)/VRCd in 79.5/17.7/2.8 vs 77.3/19.5/3.1% of pts. Adjusted ORRs were 73.2 (95% confidence interval [CI] 65.0–81.3) vs 57.5% (95% CI 47.9–67.1; p< 0.0001). After a median follow-up of 20.3 vs 15.8 months, median DOT was 10.8 (95% CI 6.5–24.4) vs 5.3 months (95% CI 4.3–7.0; p< 0.0001). Median PFS was not estimable (NE) in either cohort, and 24-month PFS rates were 85.7 (95% CI 68.1–94.0) vs 76.5% (95% CI 62.6–85.8). Median OS was NE in either cohort, and 24-month OS rates were 94.0 (95% CI 77.7–98.5) vs 84.9% (95% CI 70.6–92.6). Discontinuation of IRd vs V due to an adverse event occurred in 17.6 vs 24.4% of pts.
Conclusions: NDMM pts who transitioned to IRd following 3 cycles of V-based induction in US MM-6 had a significantly higher ORR and longer DOT compared with INSIGHT MM pts who continued to receive V-based therapy. Thus, iCT from V-based therapy to all-oral IRd may improve outcomes in NDMM pts compared with continued V-based therapy.

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A glimpse into transplant-ineligible newly diagnosed multiple myeloma treatment in real-world practice in Spain: carinae study

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Introduction: Multiple myeloma (MM) is the second most common blood cancer, with an estimated 5-year prevalence of nearly 230,000 cases worldwide.1 In recent years, several treatment regimens have been approved representing effective treatment alternatives and a hope for a better-quality of life for patients, however, real-world evidence (RWE) about effectiveness, tolerability and adherence are required for clinicians in optimizing treatment approaches for MM patients.
Methods: Observational, ambispective, descriptive ongoing study in patients with transplant-ineligible newly diagnosed MM (TIE-NDMM) who started antineoplastic treatment within daily clinical practice. Group A: started treatment with a combination of ≥2 drugs, 1 year before the reimbursement of daratumumab for the treatment of TIE-NDMM in Spain. Group B: started treatment with daratumumab plus bortezomib, melphalan and prednisone (DVMP), within 15 months after its reimbursement in Spain. An interim analysis performed after 6-month study entry is presented.
Results: 117 TIE-NDMM patients were included, 110 were valid for this interim analysis, 53 in group A and 57 in group B. No significant differences were observed in basal clinical and demographics characteristics between groups: mean age 76.1 years; 47.3% female; 29.1% with cardiopathy, 24.5% with renal failure, 9.1% with pulmonary obstructive disease and 2.7% with peripheral neuropathy; median eastern cooperative oncology group performance score was 1; most common myeloma type was IgG (51.9%); mean bone marrow % plasma cell was 34.43%; 12.7% had a high risk cytogenetic profile, defined by one of the following alterations: t(4;14), t(14;16) and del 17p13. More than 90% of the patients in group A started treatment with schemes based on bortezomib, lenalidomide, or both. 87,0% and 90,4% showed partial response or better, group A and B respectively. Significant differences in percentage of patients with very good partial response or better were observed between

group A (63.0%) and DVMP group (75.0%; p=0.0410). Disease progressions were significantly higher in group A (30.2%) than DVMP group (12.3%; p=0.0210). 64.5% of the patients showed adverse drug reactions (ADR) related to the first line treatment, however no significant differences were detected between treatment groups. Most frequent ADRs were blood and lymphatic (25.8%), gastrointestinal (18.1%) and nervous system disorders (16.1%). 13.1% of the reported ADRs were serious with no significant differences between groups. Non unexpected ADRs were observed.
Conclusions: New treatments have been incorporated into the therapeutic scenario of TIE-NDMM in the last years. For the first time, a large RWE study describes their incorporation in clinical practice in Spain. This interim analysis is a preview of the results, which allow us to provide encouraging results about standard of care regimens with monoclonal antibodies as DVMP for TIE-NDMM patients in real-world practice in Spain.

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Real-life experience of the combination of daratumumab, bortezomib, melphalan, and prednisone (DVMP)in patients with newly diagnosed multiple myeloma ineligible for autologousstem-cell transplantation

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Introduction: The combination of daratumumab, bortezomib, melphalan, and prednisone (D-VMP) is an effective and safe alternative treatment for patients with newly diagnosed multiple myeloma (NDMM) ineligiblefor autologous hematopoietic stem-cell transplantation (HSCT) as described in ALCYONEclinical trial. However, real-life data is limited. The objective of this study is to communicate the data derived from real-life experience with this combination.
Methods: This is a Spanish retrospective, multicenter study. Seventy-six adults with NDMM ineligible for autologous HSCT who had started first-line treatment with D-VMP were included. The primaryendpoint was to describe the progression-free survival (PFS), and the secondary endpoints were to describe overall response rate (ORR), very good partial response, complete response, overall survival (OS), and safety profile.
Results: A total of 76 patients were included, 37 (49%) males. The median age was 76 years (IR 72-80), with 63% ≥ 75 years. Nine percent had an ECOG >2,7% severe anemia (Hb <7.5g/dL), 17% creatinine >2mg/dL,and 8% had a first in-hospital dialysis. Forty-six (61%) were IgG MM, 17 (24%) had R-ISS III disease stage, and 22 (29%) had extramedullary disease (24% bone-related plasmacytomas and 5% soft-tissue plasmacytomas). Of the 64 patients evaluable for cytogenetics, 12 (19%) had t(11;14), 24 (37.5%) had at least one poor-prognosis cytogenetic abnormality, and 7 (11%) had > 1.Of all patients, 46 (60.5%) had completed induction, with a median number of cycles of 9 (IR 7-9). Of those, 14 (30%) received combined maintenancewith daratumumab and bortezomib.The ORR was 95%, and the rate of very good partial response or better was 55%. The median time to response was 33 days (IR 20-45), and the median time to best response was 122 days (IR 48-304).Minimal residual disease (MRD) was determined in 31 patients (41%), 12 (39%) reached negative MRD (10-4/-5), 3 of whom were re-evaluated at 12 months, and only 1 maintained MRD negativity (10-5). The median OS was not reached and the median PFS was 26 months (95% confidence interval [CI], 23 to 29). At a median follow-up of 14 months (IR 6-21), the 18-month PFS rate was 84% (95% CI, 78 to 90) and the 18-month OS rate was 90% (95% CI, 85 to 95).The dose of bortezomib was reduced in 34% of patients, mainly due to neuropathy (86%). The dose of melphalan was reduced in 21%, mainly because of myelotoxicity (36%) and kidney failure (29%). Bortezomib was discontinued in 7% of cases and melphalan in 16%. Daratumumab did not require adjustment or early suspension. There were 5 deaths, 2 due to progression, 2 due to infection, and 1 due to a cause unrelated to the MM.
Conclusions: In real-life practice, D-VMP combination in patients with NDMM ineligible for transplant showed comparable efficacy and safety profile with those reported in ALCYONE clinical trial. Further follow-up is necessary to find out the prognosis of these patients.

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Real-world duration of use and dosing frequency of daratumumab in patients with multiple myeloma in the U.S.

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Introduction: Daratumumab (DARA) is an anti-CD38 monoclonal antibody approved for treatment of patients with newly diagnosed and previously treated multiple myeloma (MM). Hence, it is possible that patients initiating DARA may

continue to use it as backbone of their treatment even if their line of therapy (LOT) or treatment regimen changes, sometimes with interruptions. This study examines the continuous duration of DARA treatment and dosing frequency across all LOTs using real-world data from MM patients in the U.S.
Methods: This is a retrospective observational study conducted using Optum Clinformatics Data Mart database consisting of some Medicare and commercially insured MM patients utilizing DARA, between 11/1/2015-3/31/2021. Duration of DARA use was defined as the time interval between first initiation and discontinuation of DARA spanning multiple LOTs as a time-to-event outcome using Kaplan-Meier method. A gap of >60 days between two consequent DARA claim dates was defined as DARA discontinuation. Dosing frequency was calculated as the average number of DARA doses during defined time periods. Compliance ratios were calculated as observed dosing frequency divided by the dosing frequency for FDA approved regimens (DARA-Lenalidomide-Dexamethasone [DRd] and DARA-Pomalidomide-Dexamethasone [DPd]). All results were calculated for patients using DARA across multiple LOTs regardless of treatment regimen.
Results: A total of 2125 patients initiating DARA therapy were included in this analysis with mean age (SD) of 70.9 (9.8) years, 51.3% males, and 64.8% white. The median length of DARA use spanning multiple LOTs, was 16.6 months. During the first year of DARA use, 90.5%, 83.2%, 72.6% and 63.5% of the patients continued DARA at 3, 6, 9, and 12 months, respectively. At years 2 and 3 of DARA use, 33.1% and 14.5% of the patients, respectively, continued DARA treatment. The mean dosing frequency in real world was similar to the dosing frequency on the approved label. The compliance ratio was 0.88 during the first six months of DARA therapy and increased to 0.96 for first 12 months, then to 0.98 for the first 24 months and remained at 0.98 over the period of 36 months.
Conclusions: Patients initiating DARA remain on the therapy for a median of 16.6 months with one-sixth continuing DARA beyond 3 years. The dosing frequency observed in the real-world was consistent with the approved label.

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Solitary pulmonary plasmacytoma: about a case

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Introduction: Extramedullary plasmacytoma is a rare form of plasma cells dyscrasia characterized by the infiltration of soft tissues by monoclonal plasma cells without any other sign of multiple myeloma. It usually involves the head and neck region, more exceptionally the lungs, presenting then as a solitary intraparenchymal nodule or masse.
Methods: We report a case of solitary pulmonary plasmacytoma that presents as a lung cancer.
Results: A 65-year-old Caucasian man was referred to the pneumologist for a 3 months history of dry cough, dyspnea and chest pain. Chest-CT revealed a tumor in the upper lobe of the left lung. Additional work-up identified a unique large hypermetabolic tumor (140x91mm) surrounding the left main bronchi and left pulmonary veins, infiltrating the pericardium, left atrium and venous sinus, and associated with enlarged lymph nodes, left pleural effusion and pleural nodules suggestive of a pleural carcinomatosis. Bronchoscopy failed to show any endobronchial tumor, and transbronchial biopsies performed twice did not identify any malignant cells. Tumoral markers were in the normal range. A third lymph node biopsy finally revealed an important infiltration by CD138 positive plasma cells with a restriction to kappa light chains. Serum protein electrophoresis showed an IgG kappa monoclonal peak at 5.5 g/l, with kappa light chains measured at 108 mg/l. Complete blood count and 24h-proteinuria were normal. Bone marrow aspirate showed a 8% plasma cells infiltration. Because of the size of the tumor, systemic therapy was preferred over radiation therapy. Patient started a VRD (bortezomib, lenalidomide and dexamethasone) regimen for 8 cycles, and achieved a (metabolic and hematologic) partial response after the first 3 cycles, with an improvement of symptoms.
Conclusions: We reported a case of solitary pulmonary plasmacytoma that was initially diagnosed as lung cancer. Although standard treatments for solitary plasmocytomas usually encompasses surgery and/or radiotherapy, we started a systemic therapy with VRD because of the size and its extensive tumor infiltration, without any complications.

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Outcomes of transplant-ineligible myeloma patients using bortezomib/lenalidomide-containing regimens in the real world: a report from the Canadian Myeloma Research Group Database

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Introduction: This study aims to evaluate the outcomes of transplant-ineligible newly diagnosed MM (TI NDMM) patients treated in the Canadian real-world setting with bortezomib/lenalidomide-based regimens. The objectives include assessment of the response rates, progression-free survival (PFS) and overall survival (OS) in this cohort. As the follow-up of these patients is relatively long, we also examined outcomes after second-line therapy in those who progressed after initial therapy.
Methods: The Canadian Myeloma Research Group Database is a national database with input from multiple Canadian centres with now over 8000 patients entered. A total of 1980 TI NDMM patients were identified between the years of 2007-2021.
Results: The four most commonly used initial regimens were VMP (23%), CyBorD (47%), Rd (24%) and VRd (6%). After a median follow-up of 30.46 months (mos) (0.89-168.42), the median PFS (mPFS) of each cohort was 23.5 mos, 22.9 mos, 34.0 mos and not reached (NR), while the median overall survival (mOS) was 64.1 mos, 51.1 mos, 61.5 mos and NR, respectively. The overall response rates (and rates of ≥ VGPR) were 80.5% (15.3%), 83.8% (17.4%), 79.6% (17.4%) and 95.6% (16.5%), respectively. The most common cause of treatment discontinuation of first-line therapy was progressive disease occurring in 45% of the group. At the time of data cut-off, 1128 patients had received second-line therapy. The majority of those who received a PI-based regimen in first-line received a len-based regimen in second-line, and vice versa. The most common second-line regimens were Rd (47.4%), DRd (12.9%), CyBorD (10.3%), and VRd (8.9%). The mPFS after second-line therapy was 17.0, 31.1, 15.4, and 14.0 mos, with a mOS of 34.7, NR, 47.6 and 33.4 mos, respectively. Only 3.3% of patients received DVd with a mPFS of 7.3 mos. The mPFS2 from first-line therapy was 53.3 mos after VMP, 48.4 mos after CyBorD, 62.7 mos after Rd and NR after VRd.
Conclusions: This study represents the real-world outcomes in TI NDMM patients treated in Canada after the introduction of novel agents. While the integration of anti-CD38 monoclonal antibodies into frontline therapy has initiated a new standard of care in TI NDMM, the spectra of therapy presented here reflects regimens still widely used around the world. Moreover, this cohort reflects the type of TI NDMM patient currently experiencing relapse in other real-world settings. Our results highlight the superiority of anti-CD38-based treatment in second-line therapy. Nevertheless, our mPFS with DRd was less impressive than that seen in the second-line setting in the phase 3 POLLUX trial (31 mos vs 53.3 mos). Differences in patient characteristics—such as addition of daratumumab to some patients already on Rd at the time of first relapse and a lower incidence of prior stem cell transplantation in our real-world setting may contribute to this finding. Further analyses to characterize real-world patients are in progress.

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Machine learning-assisted identification of optimal first-line treatment for newly diagnosed, transplant ineligible multiple myeloma

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Introduction: Bortezomib plus melphalan plus prednisone (VMP), and lenalidomide plus dexamethasone (RD) have been administered as the first-line treatment for transplant ineligible, newly diagnosed multiple myeloma (NDMM). We developed the machine learning models that predict response and survival following the VMP or RD chemotherapy to assist optimal selection between the two.
Methods: We used the retrospective data on 514 transplant ineligible NDMM provided by the Catholic Research Network for Multiple Myeloma in Republic of Korea. The initial data consisted of 45 types of demographic and clinical characteristics, as well as time-course of response and survival outcomes. The machine learning models were developed using the XGBoost method. The minimal set of covariates resulting in the highest predictive performance during 5-fold cross validation were chosen as inputs to each model.
Results: The machine learning models utilized up to seven features to predict with the ROC-AUC ranging from 0.781 to 0.931. Using the response and overall survival (OS) prospects generated by the models, we were able to stratify the patients into the high and low risk subgroups. The hazard ratios between the two subgroups were 0.250 (95% CI: 0.161 – 0.387) and 0.204 (95% CI: 0.077 – 0.538) with respect to OS following the VMP or RD chemotherapy, respectively. 18 and 29% of the patients were classified as the high risk to VMP but low risk to RD, or vice versa.
Conclusions: In conclusion, we used the machine learning models to stratify the transplant ineligible NDMM into the high and low risk subgroups with respect to use of VMP or RD chemotherapy as the first-line treatment. A total of 10 clinical characteristics measured during diagnosis are needed as inputs to the trained models, which we plan to validate in a prospective study.

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Early mortality and treatment discontinuation in multiple myeloma patients treated in front-line with bortezomib, lenalidomide and dexamethasone (VRD)

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Introduction: VRD represents a standard treatment in newly diagnosed multiple myeloma (NDMM) patients (pts) both eligible or non-eligible for autologous stem-cell transplantation (ASCT). The risk of early treatment discontinuation (ED) and early mortality (EM) associated to VRD is not well-defined in clinical trials due to the exclusion of pts with short life expectancy. Our aim was to identify the main factors determining EM and ED in a non-selected cohort of NDMM.
Methods: This national multicenter prospective phase IV clinical trial recruited NDMM with IMWG treatment criteria. Inclusion in the trial was unrestricted for any patient aiming for active treatment. Treatment consisted of 28-day cycles of VRD with bortezomib 1.3 mg/m2 D1,4, 8,11; lenalidomide 25 mg/day 21/28 days (dose adjusted if renal impairment) and dexamethasone 40mg (20mg in >70 years) D1,2,4,5,8,9,11 and 12. All patients received up to 8 cycles, additionally, eligible pts received high-dose melphalan and ASCT between cycle 6 and 7. We analyzed the clinical and biological features at diagnosis and determinants associated with EM (≤1 year of diagnosis) and ED (during first year of treatment).
Results: Between 2019 and 2022, a total of 204 NDMM pts were included. Baseline characteristics, Median age (range) in years 65 (40-86), glomerular filtrate (range) in mL/min 68 (4-113), 42% female, 34% ISS III, 4% hemodialysis at treatment initiation, 11% plasmacytomas, 16% high-cytogenetic risk. The median follow-up was 18 months (range 3-28). At time of analysis, 7% of patients had died, EM was 6% (13/204) were EM of which 11/13 occurred during the first three cycles. The main cause of death was infection (85%), 72% of them pneumonias. Progression accounted for all cases of non-EM (>1 year from treatment onset). Pts with EM were older (median age of 78 years versus 64, p< 0,00001) and were more likely to have extramedullary plasmacytomas (22% versus 4%, p< 0,0003). No significant differences were found in type of myeloma, cytogenetics, ISS or R-SS staging and renal function. Twenty-seven pts (13%) suffered ED. Reasons for ED not related to progression were infections 12/21 (57%), comorbidities 5/21 (24%) and drug-related toxicity 4/21 (19%). Infections leading to ED occurred in the first three months in 83% of pts (10/12). Median age of pts with infection-related pts ED was 76 years vs 65 in the rest (p< 0,0001), they also showed a higher rate of plasmacytomas (33% versus 11%, p< 0,009). No other baseline characteristics (including gender, cytogenetics, ISS staging and renal function) were associated to ED or EM.
Conclusions: The main cause of EM and ED in our cohort of non-selected pts with NDMM treated with VRD were infections, particularly pneumonia. Older age and presence of plasmacytomas at diagnosis were non-modifiable risk factors for both EM and ED. Stage or renal function did not have an impact in EM or ED in VRD-treated NDMM.

P-204
In-class transition (iCT) from parenteral bortezomib to oral ixazomib therapy in newly diagnosed multiple myeloma (NDMM) patients (pts): fully accrued data from the community-based US MM-6 study

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Introduction: Prolonged therapy with parenteral proteasome inhibitors (PIs) can be difficult to achieve in routine MM practice due to issues such as toxicity, comorbidities, & the burden of repeated, clinic-based treatment administration. US MM-6 is a prospective, community-based phase 4 study of in-class transition (iCT) from parenteral bortezomib-based induction to all-oral ixazomib-lenalidomide-dexamethasone (IRd) therapy in pts with NDMM (NCT03173092). The objective is to increase the duration of PI-based therapy & improve outcomes while maintaining quality of life (QoL). Results were previously reported for the first 101 pts (median follow-up 18.5 months [mos]; Rifkin ASH 2021). We report

data for the fully accrued study cohort (final enrollment completed May 2021, N=141).
Methods: Transplant-ineligible/delayed-transplant (≥24 mos) NDMM pts with ≥stable disease after 3 cycles of bortezomib-based induction were enrolled at US community sites to receive IRd for up to 39 cycles or until progression or toxicity (Manda CLML 2020). The primary endpoint was 2-year (yr) progression-free survival (PFS) rate. Key secondary endpoints included rates of partial, very good partial, & complete response (PR, VGPR, & CR), & duration of therapy (DOT). Other endpoints included overall survival (OS), safety outcomes, & QoL (all secondary) & actigraphy data (exploratory).
Results: As of Feb-28-2022, 140 pts had received IRd, with median follow-up of 20.0 mos. Median age was 72.5 yrs (range, 48–90) with 79% of pts aged ≥65 yrs (42% ≥75 yrs); 94% had ≥1 comorbidity at the start of IRd. The 2-yr PFS rate (from start of IRd; primary endpoint) was 69% (95% confidence interval [CI]: 59–77%). Overall response rate increased from 62% (CR 8%; VGPR 24%; PR 30%) at the end of bortezomib-based induction to 78% (CR 33%; VGPR 27%; PR 18%) after iCT to IRd. At data cut-off, 28 pts (20%) were ongoing on IRd; median DOT with IRd was 10.0 mos & median duration of all PI-based therapy was 12.7 mos. The 2-yr OS rate (from start of IRd) was 85% (95% CI: 76–90%). Grade (G) ≥3 treatment-emergent adverse events (TEAEs) were observed in 66% of pts (treatment-related, 36%) & serious TEAEs in 44% (treatment-related, 14%); 4 on-study deaths had occurred. The most common TEAEs (any-grade/G≥3) were diarrhea (48%/9%), peripheral neuropathies not elsewhere classified (39%/4%), & fatigue (34%/4%). TEAEs led to modification/discontinuation of any of the 3 study drugs in 59%/15% of pts. Pt-reported QoL (EORTC QLQ-C30 Global Health Status/QoL score) & treatment satisfaction (TSQM-9 Global Satisfaction, Effectiveness, & Convenience scores) were maintained during IRd therapy. Actigraphy data will be presented.
Conclusions: These US MM-6 data confirm that iCT to IRd permits long-term PI-based therapy & improves responses, with promising PFS & OS seen in these mostly elderly, community-treated pts with NDMM & comorbidities. The AE profile of IRd was similar to previous clinical reports. No adverse impact on QoL/treatment satisfaction was observed.

P-205
The use of non cryopreserved peripheral blood stem cells in multiple myeloma: ten years experience from a single center in Algeria

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Introduction: Introduction: The storage of harvested stem cells, in standard refrigerators at +4°C, is a inexpensive alternative to cryopreservation in countries with limited resources. We present the 10 years' experience of our single center from Oran using non-cryopreserved stem cells after conditioning of myeloma patients.
Methods: Patients and methods: From May 2009 to December 2019, autologous stem cell transplantation (ASCT) was carried out in our center, of which 420 with multiple myeloma (MM). The source of stem cells in all patients consisted of mobilized autologous peripheral blood stem cells. A median of one cytapherisis was performed (range, 1-3) and the products of the aphaeresis were stored in a conventional blood bank refrigerator at +4°C. The chemotherapy conditioning regimen (Melphalan 200) started once a minimum of 2×106 CD34+cell/kg was obtained.
Results: Results: The median age at ASCT was 54 years (range; 27-73). Male= ; Female= . The median harvested CD34+ cell count was 3,2x106/kg (range; 1, 22 to 13, 22) and the viability in all cases being >90%. All patients had engraftment on the median of day 9 (range; 7 to 24) and platelet transfusion independence on the median of day 13 (range; 9 to 39). Transplant related mortality at 100 days was 3,5%. The overall response to transplant was 99% (CR=64,5%; VGPR=34%, PR=1,5%). The OS at 5 years was 68% and the median post-transplant PFS was 47 months. On December 31th 2021, 41% patient relapsed and 28% died after disease progression. 305 (75%) patients are alive and 237 (59%) without disease activity after a median follow-up of 52 months (range; 13 to 149).
Conclusions: Conclusion: This study demonstrates the efficacy and safety of intensified therapy followed by autologous non-cryopreserved PBSCs infusion in MM. This method is cheaper, and may potentially enable the widespread use in other hematology centers in Algeria and in developing countries.

P-206
Antibodies to omicron variants are maintained in newly diagnosed MM patients on lenalidomide, cyclophosphamide, bortezomib and dexamethasone (RCyBorD): results from the UK RADAR/Myeloma XV Trial

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Introduction: MM patients mount suboptimal humoral and cellular responses to SARS-CoV-2 vaccine compared to healthy controls.1 Responses wane post-vaccination suggesting MM patients remain at risk of infection.2 Vaccine protection against the Omicron variant is limited, although protection is increased with booster doses.3,4 We assessed antibody (Ab) responses to Wuhan and Omicron variants in patients enrolled onto the RADAR study, effect of prior infection, booster doses during therapy, disease risk and response to induction.
Methods: RADAR is a multi-centre, phase III trial for transplant-eligible NDMM patients receiving induction with 4 cycles of RCyBorD and ASCT, then different consolidation and maintenance treatment based on cytogenetic risk and MRD status. Patients received BNT162b2, mRNA-1273 or ChAdOx1 nCoV-19 vaccines. Sera were centrally assayed by ELISA for Wuhan IgG, targeted IgG, IgA and IgM (IgGAM) and IgG anti-S Ab levels for Omicron BA.1 and BA.2. Results were correlated with patient and disease features, previous infection and vaccine history. High-risk (HR) was defined by the presence of ≥2 of: 1q gain, del(17p), t(4;14), t(14;16), t(14;20).
Results: 39 patients (median age 60y (43-73)) had available vaccine response data at either baseline or post-induction, 27 at both timepoints. At trial entry 34 (87.2%) patients had been vaccinated against SARS-CoV-2 (19 (48.7%): 2 doses, 15 (38.5%): 3 doses, 2 (5.1%): unvaccinated). 76.9% had heterologous prime/ boost with ChAdOx1 nCoV-19 vaccine and either the BNT162b2 or mRNA-1273 vaccine (15.4% mRNA vaccine only; all BNT162b2). For the patients with paired data 77.8% had positive IgG anti-S Wuhan Ab, post-RCyBorD this was 81.5%. Median Wuhan IgG Ab levels did not decline post-induction (1.34 to 1.20 OD450nm, p=0.19). This was also the case with median Wuhan IgGAM (ratio 2.96 to 2.87; p=0.79), IgG Omicron BA.1 Ab (0.86 to 0.86 OD450nm; p=0.96) and BA.2 Ab (0.89 to 0.95 OD450nm; p=0.80). 66.7% of patients had positive IgG Omicron BA.1 Ab pre and post-RCyBorD. For Omicron BA.2, 66.7% of patients were positive at baseline increasing to 70.4% post-induction. 11 out of 39 (28.2%) patients were vaccinated whilst receiving RCyBorD. Median Omicron BA.1 and BA.2 Ab increased in those with available paired data, (n=7; BA.1 0.86 to 1.72 OD450nm, p=0.01; BA.2 0.77 to 1.71, p=0.01) without an increase in Wuhan IgG Ab (p=0.56). Total number of vaccine doses received, ISS score or prior COVID-19 infection did not affect Ab responses post-induction. There was a trend towards higher Ab levels in patients in >=VGPR post-induction for both Wuhan (p=0.11), Omicron BA.1 (p=0.08) and BA.2 (p=0.12) IgG anti-S Ab.
Conclusions: NDMM patients receiving RCyBorD induction maintain serological vaccine responses against Wuhan and Omicron variants. Our findings support ongoing vaccination through therapy to maintain and improve protection against SARS-CoV-2 variants, particularly Omicron, in NDMM patients.

P-207
Impact of the time interval between end of induction and autologous hematopoietic transplantation in newly diagnosed patients with multiple myeloma

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Introduction: Multiple Myeloma (MM) patients eligible for autologous hematopoietic transplantation (AHT) receive 3-6 cycles of induction therapy before transplant. Typically, the last induction cycle is completed 2-4 weeks prior to mobilization. It is unclear whether disease progression during this drug-free period predicts for high-risk disease and worse clinical outcomes post ASCT. In this study, we evaluated the impact of the time interval between end of induction and AHT on progression-free survival (PFS) and overall survival (OS).
Methods: We included all newly diagnosed MM (NDMM) patients from 2004-2018 who were seen in our institution and underwent upfront AHT within a year from diagnosis. Patients that progressed during induction therapy were excluded from the study. We analyzed patients based on the median time to transplant (TTT), calculated from the last chemotherapy date to the date of transplant. The end-points of the study were PFS and OS, measured from the date of transplant. PFS and OS were calculated with the Kaplan and Meier method. Cox proportional hazards models were used for univariable and multivariable analyses. A two-sided p-value < 0.05 was considered statistically significant
Results: A total of 1055 patients were identified. The median TTT was 33 days (27-42 inter-quartile range). We found that

patients with a TTT of less than 33 days had significantly prolonged PFS (35.6 vs. 32.1 months, p< 0.03) but non-significant OS differences compared to patients with a TTT of more than 33 days. When grouping patients based on inter-quartile TTT, we found that patients with a TTT of less than 27 days (1st quartile) had significantly prolonged PFS (36.7 vs. 30.9 months, p< 0.01) but non-significant OS differences compared to patients with a TTT of more than 42 days (4th quartile). In a subgroup analysis based on the biochemical response achieved prior to transplant, we grouped patients into "good" responders (VGPR or better) and "bad" responders (less than VGPR). In quartile comparisons, patients in the 1st quartile had significantly prolonged PFS (36.4 vs. 33.8 months, p< 0.03) compared to the 4th quartile group for the good responders. In the bad responder group, patients in the 1st quartile had significantly prolonged PFS (37.7 vs. 28.7 months, p< 0.04) compared to the 4th quartile group. For OS, no significant differences were found.
Conclusions: This is the first study to evaluate the impact of TTT on clinically relevant outcomes in NDMM patients. We showed that a prolonged TTT is associated with inferior outcomes compared to tighter chemotherapy schedules. This finding was especially prevalent in patients with less than VGPR at induction. We propose that patients should not be given extensive chemotherapy-free periods prior to stem cell infusion, as this may adversely affect their disease course.

P-208
Association of thrombocytopenia with disease burden, high-risk cytogenetics, and survival in newly diagnosed multiple myeloma patients

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Introduction: Multiple Myeloma (MM) is a malignancy of plasma cells in the bone marrow, with a proportion of patients presenting with low platelet count. While thrombocytopenia has been shown to be prognostic in MM, it is yet unclear what the underlying biology and the exact risk posed by thrombocytopenia is for MM patients, especially in the novel treatment era. The study objective is to evaluate the clinical and molecular characteristics and outcomes in MM patients presenting with thrombocytopenia.
Methods: We studied newly diagnosed MM (NDMM) patients between 2008 and 2018 who received at least 2 novel agents for treatment . Thrombocytopenia at diagnosis was defined as a platelet count of less than < 150,000/mm3. Baseline patient and disease characteristics, and the biochemical response at induction were collected. Univariate analysis was conducted via the Kaplan-Meier method, and multivariable analysis was conducted via the Cox proportional hazards regression. A two-sided p-value < 0.05 was considered statistically significant.
Results: A total of 648 patients were identified. Thrombocytopenia was found in 120 patients (18.5%). Baseline disease characteristics associated with statistically significantly higher rates of thrombocytopenia at baseline included IgA heavy chain, p< 0.01, ISS 3 vs. 1 or 2, p< 0.01, R-ISS 3 vs. 1 or 2, p< 0.01, renal failure (CrCl< 30), p< 0.01, hypercalcemia (Ca >11.5 mg/dL), p< 0.01, elevated LDH, p< 0.03, anemia (Hb< 10 g/dL), p< 0.01, higher serum monoclonal protein, p< 0.02, and >60% plasma cells in the bone marrow, p< 0.01. Thrombocytopenia was more prevalent across patients with t(4;14) and t(14;20) translocations, but it was not associated with an overall high-risk FISH classification. Median OS was significantly lower among patients with thrombocytopenia (64.4 vs. 145.0 months, p< 0.01). In multivariable Cox regression, thrombocytopenia was associated with mortality (hazard ratio 2.53, 95% CI 1.71-9.3, p< 0.01) independently of age, sex, renal failure, high-risk FISH, R-ISS stage, response at induction, receipt of upfront transplant, plasma cells in the bone marrow and anemia.
Conclusions: We found that thrombocytopenia at diagnosis was seen among one-fifth of NDMM patients, and was more common in patients with high-risk features and specific cytogenetic aberrations [t(4;14) and t(14;20)]. Thrombocytopenia was found to have an independent association with worse survival, even when accounting for multiple known predictors of earlier mortality in MM.

P-209
Deepening responses post upfront ASCT in newly diagnosed multiple myeloma in the era of novel agent induction therapy

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Introduction: High dose melphalan followed by autologous stem cell transplant (ASCT) remains the standard of care for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM). Achievement of complete response (CR) and Minimal Residual Disease (MRD) negativity are

associated with improved progression-free survival (PFS) and overall survival (OS).
Methods: This study investigated the rates of conversion to MRD negative CR following upfront ASCT in 210 patients with NDMM treated at a single center from May 1st, 2018 to July 31st, 2019.
Results: Pre-ASCT, 23 patients (11%) achieved MRD negative CR which increased to 66 (31%) patients post ASCT. Of 187 patients not in MRD negative CR pre-ASCT, 45 (24%) converted to MRD negative CR. Patients with MRD positive CR before ASCT had the highest rates of conversion to MRD negative CR. HR cytogenetics did not impact rates of MRD negative CR achievement post ASCT irrespective of pre-ASCT IMWG response (p = 1.0). Overall, irrespective of IMWG response, 43 (20%) patients were MRD negative pre-ASCT (19 in VGPR, 24 in CR or sCR) and 102 (49%) patients were MRD negative post-ASCT (36 in VGPR, 66 in CR or sCR). Among 85 patients with VGPR post-ASCT, 36 achieved MRD negativity of which 8 (22%) progressed, while 49 had MRD positive disease of which 24 (49%) progressed (p = 0.014).
Conclusions: Upfront ASCT in patients with NDMM leads to deeper responses with 24% converting to MRD negative CR and more than doubling of the total rate of MRD negativity irrespective of IMWG response depth.

P-210
Impact of pre-transplant disease status on progression-free survival (PFS) in patients with multiple myeloma undergoing auto-HCT

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Introduction: The purpose of the study was to evaluate the impact of pre-transplant disease status on progression-free survival (PFS) post-auto-HCT and also the impact of maintenance therapy on PFS post-auto-HCT
Methods: We retrospectively analyzed 100 patients with multiple myeloma from January 2016 through June 2021 who underwent induction chemotherapy followed by a single auto-HCT. Median age was 63 years (37-77). Conditioning regimen was either Melphalan 200 mg/m2 (n=95) or 70 mg/m2 (n=5) divided over 2 days. International myeloma working group criteria were used to establish the disease status prior to transplant. Complete response (CR) was seen in 14 patients, very good partial response (VGPR) was seen in 26 patients and partial response (PR) was seen in 60 patients. Post-transplant maintenance was administered to 12/14 patients in CR group, 21/26 in VGPR group and 49/60 in the PR group.
Results: At a median follow-up of 33 months, 2/14 (17%) of the patients in CR had relapsed with a median time to relapse of 37.8 months. Of the patients who achieved VGPR, 9/26 patients had relapsed (45%), 5 of whom were on maintenance with a median time to relapse of 17.3 months. In the PR response group, 19/60 patients relapsed (32%), 13 of whom were on maintenance with a median time to relapse at 22 months. Use of post-auto-HCT maintenance with either Lenalidomide or a Proteasome inhibitor (Bortezomib or Ixazomib) showed a statistically significant difference in median PFS (p=0.003) compared to those who did not receive maintenance therapy.

Table 1 - Subgroup analysis of patients with multiple myeloma based on IMWG criteria

	Complete remission (CR)	Very good partial response (VGPR)	Partial response (PR)
Median age in years (range)	64 (54-76)	66 (43-75)	62 (37-77)
Melphalan 200 mg/m2	12	26	57
Melphalan 140 mg/m2	2	0	3
Post-auto-HCT Maintenance therapy	12	21	49
Relapse (%)	2 (17)	9 (35)	19 (32%)
Median time to relapse (months)	37.8	17.3	22.1

Conclusions: Our retrospective analysis suggests that pre-transplant depth of response may influence outcome, even though not statistically significant. Use of post-auto-HCT maintenance therapy may overcome the disadvantage of pre-transplant depth of response with improved PFS.

P-211
Changes in serum alkaline phosphatase levels during induction therapy to predict outcomes in patients with newly diagnosed multiple myeloma

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Introduction: Bone disease in multiple myeloma (MM) occurs in part due to increased osteoclast activity and decreased osteoblast activity, through interactions between MM cells and the bone marrow microenvironment. In addition to anti-MM activity, proteasome inhibitors (PIs) modify the bone microenvironment from a catabolic to an anabolic state and

have favorable effects on MM bone disease. Alkaline phosphatase (ALP) is a marker of osteoblast activity and bone mineralization in MM. Increase in ALP levels during treatment have been correlated with response to therapy and longer time to progression, possibly reflecting underlying bone mineralization/ healing. There have been limited studies assessing the relation of changes in ALP levels and outcomes in newly diagnosed MM (NDMM), and in NDMM patients treated with novel triplet and quadruplet regimens.
Methods: We retrospectively identified 693 NDMM patients who had received at least 4 cycles of induction with 3 or 4 drug regimens. Patients who had progressed during 1st 4 cycles were excluded. The International Staging System (ISS) and mSMART 3.0 criteria were used for risk stratification. Responses were evaluated using the International Myeloma Working Group (IMWG) response criteria. ALP levels were analyzed at baseline & at every cycle (C) until end of C4. Maximum % rise in ALP compared to baseline during C1-C4 (Max % rise), and area under the curve of rise in ALP from C1-C4 over baseline (ALP AUC) were used to predict IMWG response and progression free survival (PFS) using multiple logistic regression and Cox models.
Results: Overall, the median age of the cohort was 63.1 yrs and 61.7% patients were male. 29.4%/28.7%/32.3% were ISS I/II/III respectively and 35.4% had high risk disease at diagnosis. 48.3% received induction with PI + immunomodulatory drug (IMiD) regimens, 36.6% with PI based regimens, and 7% with daratumumab based regimens. % Rise in ALP was greatest after C1 (19.7%) followed by C2 (9.6%). After adjusting for age, high risk FISH, ISS stage, and presence of fracture at diagnosis; quartile (Q) 4 of Max % rise had higher odds of achieving a partial response or better (>=PR) (OR= 5.51, p=0.003), and very good partial response or better (>=VGPR) at C4-C6 (OR= 2.010, p= 0.019) vs Q1. Q4 in subgroups that received PI based regimens (OR= 3.49, p=0.011) and PI containing regimens (OR=2.36, p= 0.006) also had higher odds of achieving >=VGPR at C4-C6. No significant association was seen for overall best response, or PFS among Q1-Q4 (PFS= 48.5, 36.2, 44.3, 36.8 months respectively). No significant associations were found among quartiles of ALP AUC (N=400) in terms of response at C4-C6, overall best response, or PFS.
Conclusions: Rise in ALP is common during C1-C2 of induction and is predictive of early response to MM therapy, possibly acting as a marker of bone healing. This is especially seen with PI based regimens, further highlighting the anabolic effects of PIs on MM bone disease.

P-212
Quantifying the average treatment effect of single vs. tandem autologous stem cell transplantation in newly diagnosed multiple myeloma using causal inference

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Introduction: In the era of novel agents, the role of single vs. double autologous stem cell transplantation (ASCT) in multiple myeloma remains questionable. Even though studies indicate benefits in progression free (PFS) and overall survival (OS) for patients undergoing tandem transplantation, it remains unclear which patients benefit more. Our goal was to estimate the increase or decrease in PFS observed for different patient cohorts who received a single vs. tandem ASCT using causal inference (CI) analysis.
Methods: In this study, we analyzed data from two large tertiary centers in Germany (University Hospital Jena and University Hospital Leipzig) as well as the Multiple Myeloma Research Foundation CoMMpass trial. In a first step, key metrics with a divergent impact on PFS in patients who received single vs. tandem ASCT were identified and corresponding p-values calculated with log-rank tests. Furthermore, we utilized the DoWhy Python Package for CI (v0.6) to calculate the average treatment effect of a tandem transplantation in PFS days in different patient cohorts. With CI analysis, domain knowledge was transformed into a graph from which the actual, independent effect of an action (tandem ASCT) on an outcome (PFS) in a larger system (set of patient features) can be determined. The robustness of the estimation was validated using refutation tests. Censored cases were excluded, thus only the patients who experienced a progress event were included in the analysis.
Results: A total of 491 patients were included of whom 397 underwent single and 94 tandem ASCT. We identified ECOG performance status and remission status before first ASCT as key features to predict difference in PFS comparing single to tandem ASCT. Patients with ECOG 0 and 1 showed benefit from a second ASCT (p=0.006), whereas no difference was shown for patients with ECOG >1. No benefit for tandem ASCT was detected for patients with very good partial response (VGPR) or better after induction therapy (p=0.2), whereas patients with partial response (PR) or stable disease (SD) before the first ASCT benefitted from a tandem ASCT regimen (p=0.01). Using CI, we were able to quantify the estimated benefit in PFS: Patients with ECOG 0/1 and SD after induction profited the most from tandem ASCT and gained estimated 485 progression-free days, while patients with ECOG 0/1 in VGPR or better gained only seven progression-

free days. In contrast, patients with ECOG > 1 and VGPR or better after induction lost an average of 475 days when treated with tandem compared to single ASCT. All refutation tests provided by the DoWhy framework passed.
Conclusions: With this analysis, we showed the potential of applying CI analysis to clinical decision problems. By calculating the exact number of days gained or lost in PFS for different patient cohorts our results can directly guide personalized treatment decisions in the future.

P-213
Efficacy and safety of bortezomib in once weekly vs. twice weekly dosing in the treatment of multiple myeloma

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Introduction: The combination of lenalidomide (R), bortezomib (V), and dexamethasone (D) (RVD) has been the standard of care for multiple myeloma since the publication of the SWOG S0777 trial in 2017. Patients in this study received IV bortezomib on a twice weekly basis for two weeks per cycle, but in clinical practice the frequency of bortezomib dosing is often modified to weekly as peripheral neuropathy (PN) becomes intolerable. There is limited data comparing efficacy and safety outcomes of patients given bortezomib twice weekly (BIW) compared to once weekly (QW) as part of RVD induction. Here, we compare the response rates and outcomes for patients given two different schedules of the RVD induction in a real-world academic center setting.
Methods: Adult patients with newly diagnosed multiple myeloma who received RVD induction treatment from July 1, 2014 – July 1, 2020 were identified via chart review. Electronic medical records were reviewed to obtain baseline demographics, treatment doses and schedules, response rates, and toxicities. Patients were included if they received at least 2 cycles of RVD and split between QW and BIW based on the schedule they were initiated on. The primary efficacy outcome was overall response rate, defined as very good partial response rates or better (> VGPR). Secondary outcomes include progression free survival, duration of response, and rate of bone marrow transplant. Other secondary endpoints include those that evaluate tolerability such as: incidence of common adverse events associated with bortezomib, duration of treatment, median dose accumulation, and frequency of dose reductions interruptions.
Results: Forty patients were identified, 14 QW and 26 BIW. Baseline characteristics were similar in the two groups. Median age at diagnosis was 66.5 (range 50-85), and 69 (range 50-85) vs 63.5 (range 53-82) in the QW and BIW groups. Men comprised 79% of the QW cohort, compared to 46% of the BIW cohort. Stage 1 disease was more common in the QW cohort (7 (50%)) compared to BIW cohort (7 (27%)), while stage 3 disease was seen in 2 (14%) and 11 (42%) respectively. High risk cytogenetics (defined as +1q, t(4;14), t(14;16) or del(17p)) were identified in 16 (40%) of the total cohort and 7 (50%) and 9 (35%) of the QW and BIW cohorts respectively. Stem cell transplant was utilized in 19 (46%) patients: 6 (43%) in QW and 13 (48%) in BIW groups. Mean total bortezomib dose was 52.6mg and 63.7mg in QW and BIW respectively. VGPR or better was achieved in 71% and 63% in QW and BIW respectively (p=1). Median PFS was not reached in either group; Two year PFS in QW was 63% versus 54% in BIW (p=0.7). All grade PN was reported in 36% of QW compared to 58% in BIW patients, resulting in PN related dose reductions in 7% vs 37% of patients respectively (p=0.06).
Conclusions: In RVD induction, weekly bortezomib has similar efficacy to twice weekly, with numerically lower incidence of all grade PN and PN related dose-reductions.

P-214
Busulfan plus cyclophosphamide and etoposide versus high-dose melphalan as conditioning in autologous stem cell transplantation for newly diagnosed multiple myeloma

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Introduction: High-dose melphalan (HDMEL) represents the standard conditioning regimen before autologous stem cell transplant (ASCT) in multiple myeloma, but recent updates have suggested combination of busulfan with melphalan is also associated with favorable outcomes. In patients with hematologic malignancies, previous reports of etoposide, busulfan, and cyclophosphamide as a conditioning regimen have shown high efficacy with a wide maximal tolerated dose range. This retrospective study was performed to determine if the busulfan based conditioning without melphalan would be a tolerable and effective conditioning regimen. We report a single institution's experience with 35 multiple myeloma patients treated with high-dose busulfan, cyclophosphamide, and etoposide (BuCyE), followed by ASCT.
Methods: Between March 2016 and September 2021, patients aged 47-67 (median 57 years) with multiple myeloma were enrolled to receive bortezomib, thalidomide and dexamethasone induction followed by ASCT. All patients received HDMEL or BuCyE as conditioning regimen.
Results: Median follow-up for the group was 33 months. The 3-year progression-free survival (PFS) was 57.7% for the HDMEL conditioning group versus 76.2% for the BuCyE conditioning group and median PFS was 37 months in HDMEL and 60 months in BuCyE (P=0.321). Five year overall survival rate was 73.1% in HDMEL versus 100% in BuCyE (P=0.059). The average time from ASCT to leukocyte recovery (≥ 1000/mm3 of absolute neutrophil count) and platelet recovery (≥50000/mm3 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 study showed that BuCyE is an effective and well-tolerated alternative to HDMEL conditioning, with good PFS.

P-215
D-VTd as induction therapy in newly diagnosed multiple myeloma (NDMM) patients who are candidates for transplantation: a real-life experience in a single center

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Introduction: D-VTd (Daratumumab, Velcade, Thalidomide, Dexamethasone) is approved by EMA/FDA and is recommended by the Therapeutic Guidelines ESMO/NCCN (IA evidence) as standard induction and consolidation therapy in transplant-eligible NDMM patients, according to the Cassiopeia clinical trial, which demonstrated a significant improvement in progression-free survival compared to VTd (HR: 0.47) (Moreau P et al, Lancet 2019; 394: 29–38). We report our real-life practice experience with D-VTd in our transplant-eligible NDMM patients.
Methods: In July 2020 we introduced Daratumumab in the induction treatment of transplant-eligible NDMM patients. We report our initial series in real life practice with 26 patients treated with D-VTd prior to transplantation.
Results: The main characteristics are: 26 Patients included since July 2020. Males: 16 patients (62%) / Females: 10 patients (38%). Median Age: 59 years (33-68). Type of MM: IgG: 62%, IgA: 19%, Bence Jones (BJ): 19%, IgD: 1 patient 4%. ISS: I: 38%, II: 38%, III: 23%. ISS-R: I: 23%, II: 65%, III: 8%, unknown: 4%. High cytogenetic risk (t(4;14), t(14;16), TP53): 6 patients (19%). Responses: After the first DVTd cycle (26 evaluable patients): PR: 62%, VGPR: 27%, Not available: 11%. After 2 DVTd cycles (24 evaluable patients): PR: 21%, VGPR: 67%, CR: 8%, Not available: 3%. Pre-transplant (24 evaluable patients): PR: 4%, VGPR: 63%, CR: 29%, Local progression: 4% treated with radiotherapy After transplantation (19 evaluable patients): PR: 5%, VGPR: 37%, CR: 21%, Stringent CR (sCR): 32%, Biologic progression: 5%. After consolidation (15 evaluable patients): PR: 13%, VGPR 33%, CR: 6%, sCR: 47%. In maintenance (Daratumumab or Lenalidomide or DRd, 13 evaluable patients): PR: 7%, VGPR: 7%, sCR 69%. No patient has required a second line of treatment. The results will be updated with the available follow-up. Toxicity: The most significant toxicity has been Peripheral Neuropathy: 30% (grade 1) and 8% (grade 2), being reversible in all cases with dose reduction of thalidomide and/or velcade. Two patients did not receive consolidation with either velcade or thalidomide due to polyneuropathy. Mobilization and collection of peripheral blood hematopoietic progenitor cells (PBPCs):It was carried out with G-CSF (10 ug/kg/12 hours x 4 days), requiring the association of Plerixafor in 6 patients (23%). The number of the apheresis procedures was: 1 in 10 patients (38%), 2 in 11 patients (42%), 3 in 3 patients (12%). The median number of CD34+ cells collected was 3.6 x 106/kg (2.1-8.74).So far, 23 patients have been transplanted, all with good engraftment.
Conclusions: D-VTd as induction therapy in NDMM transplant-eligible patients is feasible in real-life practice with a very high response rate and acceptable toxicity. Our results are in line with those of the Cassiopeia clinical trial, highlighting the rapid response and the high rate of negative minimal residual disease (MRD).

P-216
Early stem cell transplantation for newly diagnosed multiple myeloma in the era of novel agents: it is time to stop

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Introduction: Early stem cell transplantation (SCT) for multiple myeloma is still the standard of care for eligible patients in first remission. However, highly-effective combination regimens are being used with increasing frequency, and it is time to revisit the concept of whether routine early SCT is still relevant in the era of modern myeloma therapies. Recent results of the GRIFFIN trial showed that the percentage of patients in complete response (CR) in both arms tripled during the time that patients were receiving post-transplant consolidation and maintenance treatment. Such benefit would likely have occurred whether or not transplantation had been performed since the maximal SCT benefit had already happened. To determine whether SCT provides benefit in the setting of modern regimens, the TriNetX database was used to evaluate the outcomes of SCT versus non-SCT myeloma patients within the last five years.
Methods: TriNetX, the federated global database providing anonymized medical record information for over 212 million patients in 92 large healthcare organizations was used for this study. Two cohorts were created, both consisting of patients diagnosed with multiple myeloma within the last five years. One cohort contained patients who underwent SCT within six months of diagnosis, while the other cohort never received transplantation. The cohorts were balanced for age, race, gender, and ethnicity, resulting in 26,036 patients per arm. They were then evaluated for the outcome of multiple myeloma in relapse, with a secondary outcome of overall survival.
Results: Multiple myeloma patients who received early SCT had a risk ratio for relapse of 3.2 (95% CI (3.07,3.36), p value < 0.0001). Transplanted patients also experienced inferior

five-year overall survival (60.8% vs 84.3%), with a hazard ratio for death of 3.47 (p value < 0.0001).
Conclusions: These results indicate that the routine use of early stem cell transplantation for all eligible multiple myeloma patients should be discontinued. Long-term follow up of the IFM2009 trial revealed no benefit for early transplant versus transplant in first relapse, even prior to widespread use of daratumumab or carfilzomib. The GRIFFIN trial and others have established the concept that complete responses develop over time with sustained use of effective agents. It is possible that stopping and restarting these agents to facilitate a stem cell transplant may result in the creation of treatment resistance in a fashion similar to the stopping and restarting of chemotherapy for solid tumors. It may be most appropriate to reserve SCT for patients who do not achieve MRD negativity by a time frame that has yet to be determined, or if maximal response with first line therapy does not result in MRD negativity.

P-217
First line daratumumab-VTd versus VRd for transplant eligible multiple myeloma

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Introduction: The ultimate goal of induction therapy is to achieve adequate disease control. The current guidelines favor triplet (bortezomib-lenalidomide-dexamethasone; VRd) or quadruplet induction regimens (daratumumab plus bortezomib-thalidomide-dexamethasone; DVTd). In the absence of direct comparison between the two, we conducted this retrospective study to compare DVTd vs VRd.
Methods: We conducted a retrospective cohort study of newly diagnosed multiple myeloma patients over 18 years old undergoing induction therapy followed by autologous stem cell transplantation (ASCT) between November 2020 to December 2021. The outcomes of DVTd (N=41) versus VRd (N=41) were compared.
Results: There were no differences between the 2 groups regarding the baseline characteristics. There were 10 patients (24.4%) in DVTd group who were present with extramedullary disease (EMD) at diagnosis, and 9 (22.0%) in VRd group. del17p was present in 27% vs 18.2% (p=0.311) of the patients, and t(4;14) in 8.1% vs 15.2% (p=0.360), respectively. After induction, 7.3% of the DVTd group showed stringent complete remission (sCR), 36.8% complete remission (CR), 51.2% very good partial response (VGPR), and 4.9% partial response (PR). For VRd group, 9.8% showed sCR, 24.4% showed CR, 34.1% showed VGPR and 31.7% showed PR. DVTd was associated with deeper response (VGPR or better, 95.1% vs 68.3%, p=0.002). During the induction 1 patient from each group progressed, thus 40 patients in each group underwent mobilization and ASCT. Initial chemotherapy-mobilization was used in 30% vs 40% of the patients. Additional mobilization was required in 32.5% vs 20.0% of the patients. The difference did not reach statistical difference, and the quantity of the mobilized CD34 cells were not affected per induction regimen. After ASCT, 52.5% of the DVTd group showed sCR, 40% showed CR and 7.5% VGPR. In VRd group, 30% showed sCR, 37.5% showed CR, 17.5% VGPR and 10% PR. There was 1 case of transplant related mortality in VRd group (sudden cardiac death).
Conclusions: Our study supports front-line quadruple induction regimen containing CD38 monoclonal antibody for transplant-eligible newly diagnosed multiple myeloma.

P-218
Real world experience of induction therapy for treatment of newly diagnosed multiple myeloma: an analysis from the Australian and New Zealand, and Asia-Pacific Myeloma and related diseases registries.

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Introduction: Up until 2019, bortezomib, cyclophosphamide and dexamethasone (VCd) was the most commonly used induction treatment regimen in Australia for transplant eligible patients with NDMM. Since June 2020, the addition of bortezomib, lenalidomide and dexamethasone (VRd) onto the Pharmaceutical Benefits Scheme (PBS) for induction therapy has allowed clinicians to access lenalidomide and thus increase its use for patients with NDMM. Another common regimen used in the world for induction treatment is bortezomib, thalidomide and dexamethasone (VTd). However, the use in Australia has been limited by the absence of thalidomide on the PBS. All three lines of induction therapy have high overall response rates (ORR) and rates of achieving a very good partial response (VGPR). We aim to be the first research group to review the RWE of three induction regimens for NDMM patients in the Australian and Asian Pacific region.
Methods: We analysed all patients aged ≥18 years with NDMM, commencing induction therapy between January 2016 and December 2021 with either VCd, VTd or VRd, using data from the ANZ and the APAC MRDR. Progression free survival (PFS), overall survival (OS), ORR (≥ partial response) were assessed. PFS and OS were estimated using Kaplan-Meier methods.

Results: 2939 patients were included. Median age of VCd patients was 65.3 years; VTd: 60.8 years, VRd: 64.9 years (p-value < 0.001). 91% of VTd patients were treated in Korea and 84% of VRd patients in Australia. 11.5% of VCd patients had high risk disease (International Myeloma Working Group criteria); VTd: 25.6%, VRd: 17.4% (p-value < 0.001). 56.4% of VCd patients received an autologous stem cell transplant (ASCT); VTd: 75.1%, VRd: 58.3% (p-value < 0.001). In the ASCT group, ORR for VCd patients was 85.8%, VTd: 98.1%, VRd: 94.7% (p-value < 0.001). Kaplan-Meier survival curves showed a statistically significant difference between treatments in PFS with VRd having the longest PFS, followed by VCd and VTd. There was no difference in OS between treatments. PFS advantage for VRd in ASCT patients remained when adjusted for country - hazard ratio (95% CI) with VCd as reference: VTd 1.46 (0.64-3.37) p = 0.37, VRd 0.61 (0.37-0.99) p = 0.044. In patients who did not have an ASCT, ORR for those on VCd was 83.3%, VTd: 87.8%, VRd: 92.9% (p-value 0.049). No difference was seen on Kaplan-Meier survival curves for PFS and OS between treatments.
Conclusions: For ASCT patients, VRd confers longer PFS than VCd or VTd, but not in OS. In patients not receiving an ASCT, there was no difference in PFS or OS between therapies. Short follow-up time, and different database and patient management between countries may confound results.

P-219
Daratumumab (DARA) + lenalidomide/bortezomib/dexamethasone (RVd) in Black patients with transplant-eligible newly diagnosed multiple myeloma (NDMM): an updated subgroup analysis of GRIFFIN

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Introduction: Optimal treatment for Black patients (pts) with NDMM remains to be defined. In the previously published primary analysis of the randomized phase 2 GRIFFIN study, addition of DARA to RVd (D-RVd) improved the rate of stringent complete response (sCR) by end of consolidation. Moreover, minimal residual disease (MRD)-negativity rates were higher for D-RVd vs RVd at all time points and deepened with longer follow-up. We report updated data from a subgroup analysis of Black pts from GRIFFIN occurring after all pts completed 2 years of maintenance therapy or discontinued (median follow-up, 38.6 mo).
Methods: Pts with transplant-eligible NDMM were randomized 1:1 to 4 D-RVd/RVd induction cycles, autologous stem cell transplant, 2 D-RVd/RVd consolidation cycles, and up to 2 years of maintenance with lenalidomide (R) ± DARA. For induction/consolidation (21-day cycles), pts received R (25 mg PO Days [D] 1-14), V (1.3 mg/m^2 SC D1, 4, 8, 11), and d (40 mg PO weekly) ± DARA (16 mg/kg IV D1, 8, 15 Cycles 1-4 and D1 Cycles 5-6). In maintenance (28-day cycles), pts received R (10 mg PO D1-21; if tolerated, 15 mg Cycles 10+) ± DARA (16 mg/kg IV Q8W/Q4W or 1800 mg SC Q4W per protocol amendments). The primary endpoint was sCR rate by end of consolidation.
Results: Of 207 randomized pts (D-RVd, n = 104; RVd, n = 103), 32 (15.5%) were Black (D-RVd, n = 14; RVd, n = 18) and 161 (77.8%) were White (D-RVd, n = 85; RVd, n = 76). Baseline characteristics were generally similar between Black and White pts. sCR rates by end of consolidation were higher for D-RVd vs RVd in Black (71.4% vs 33.3%, P = 0.0353) and White pts (42.2% vs 29.6%, P = 0.1066). At 1 year of maintenance, sCR rates were higher for D-RVd vs RVd in Black (85.7% vs 38.9%, P = 0.0085) and White patients (61.4% vs 47.9%, P = 0.0927). After 2 years of maintenance, sCR rates deepened and were higher with D-RVd vs RVd in Black (92.9% vs 38.9%, P = 0.0021) and White pts (63.9% vs 49.3%, P = 0.0697), and MRD-negativity (10^–5) rates were higher for D-RVd vs RVd for Black (64.3% vs 22.2%, P = 0.0293) and White pts (65.9% vs 31.6%, P < 0.0001). The most common (≥25%) grade 3/4 treatment-emergent adverse events (TEAEs) with D-RVd/RVd included neutropenia (Black pts, 50.0%/22.2%; White pts, 47.0%/18.9%), lymphopenia (28.6%/38.9%; 22.9%/16.2%), and thrombocytopenia (28.6%/11.1%; 13.3%/8.1%). Infusion-related reactions occurred in 28.6% of Black and 47.0% of White pts (most were grades 1/2).
Conclusions: After 2 years of maintenance in the GRIFFIN study, Black pts continued to derive clinical benefit from the addition of DARA to RVd frontline treatment and Black pts did not have an increase in adverse events. Larger studies are needed to confirm this benefit.

P-221
Nicotine exposure and treatment outcomes in multiple myeloma: a retrospective cohort study

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Introduction: Proteasome inhibitors including bortezomib are a cornerstone of modern multiple myeloma (MM) therapy, and have contributed to significant improvements in treatment response and overall survival rates. Nicotine is known to both inhibit and upregulate the proteasome complex. This may decrease sensitivity to concurrent or subsequent exposure to proteasome inhibitors, similar to the reduced efficacy seen in serial lines of proteasome inhibitor exposure. However, the clinical significance of this effect is unknown. Our study's primary objective was to evaluate the effect of nicotine exposure on treatment outcomes in MM patients receiving bortezomib.
Methods: We conducted a retrospective multi-center study involving MM patients receiving care from January 2003 to February 2021 at 48 participating United States healthcare organizations enrolled in TriNetX, a global health research network that provides de-identified electronic medical record data. On the research platform, we used multiple ICD-10-CM codes to separate patients into two cohorts based on their history of nicotine exposure. All patients received bortezomib, with no prior history of proteasome inhibitor therapy. We used a chi-square analysis to test for associations in bivariate comparisons; unless otherwise noted, statistical significance was determined by $p< 0.05$.
Results: A total of 1,626 patients met the inclusion and exclusion criteria for this study. Group A consisted of 632 patients with a documented diagnosis of tobacco dependence, while Group B had 994 patients without such diagnosis. Group A had a risk ratio (RR) of death of 1.33 (95% CI 1.15-1.54, $p < 0.0001$), as well as a median survival from diagnosis of 2,179 days compared with 2,766 days for Group B (non-significant). Group A patients underwent autologous stem cell transplant sooner than those in Group B, with a median time to transplant of 256 days compared with 2,460 days ($p< 0.0001$). Group A in this outcome had a RR of 1.42 (95% CI 1.28-1.58, $p< 0.0001$). Time to next treatment (considering only regimens listed as category 1 per NCCN MM guidelines as of February 2021) was 1,061 days for Group A compared with 2,239 days for group B ($p< 0.0001$). Group A in this outcome had a RR of 1.40 (95% CI 1.25-1.58, $p< 0.0001$). As the patient data was de-identified, it could not be determined whether transition to next line therapy was due to therapy failure, adverse effects, or other factors.
Conclusions: Our study suggests that nicotine use is associated with significantly shorter times to stem cell transplant and to other treatment transitions in MM patients. This could reflect diminished responsiveness to proteasome inhibitors in these individuals; however, confounding factors surrounding smoking, especially in this de-identified dataset, could explain our findings. Future studies should explore this relationship to help clinicians to better select MM therapy for tobacco-using patients.

A prospective phase 2 study to assess minimal residual disease after ixazomib plus lenalidomide plus dexamethasone (IRd) treatment for newly diagnosed transplant eligible multiple myeloma patients

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Introduction: This phase 2 Nordic Myeloma Study Group (NMSG) trial was conducted to explore the response of ixazomib (Ixa), lenalidomide (Len) and dexamethasone (Dex), (IRd) induction, single ASCT, IRd consolidation and risk-based maintenance either with IR or R. We present the responses and minimal residual disease (MRD) by next generation flow cytometry (NGF) until 18 months (mo) on maintenance.
Methods: 120 pts were included. Pts received 4 IRd cycles (cy) as induction, Ixa 4 mg on days (d) 1,8,15, Len 25 mg on d1-21, Dex 40 mg weekly in 28-d cy. ASCT was performed according to routines. 3 mo post-ASCT all pts received 2 cy of IRd as consolidation followed by risk-based maintenance. High-risk (HR) pts (del17p at least 60%, t(4;14), t(14;16), t(14;20) and/or +1q) received Ixa 4 mg on d1,8,15 and Len 10 mg on d1-21 in 28-d cy. Non-HR (NHR) pts received Len 10 mg on d1-21 in 28-d cy. Study treatment will continue until progression (PD). Len increased to 15 mg after 3 cy if tolerated. The primary endpoint is MRD by flow< 10-4, to be

compared with a previous Finnish Myeloma Study Group trial. The secondary endpoints are NGF-MRD neg< 10-5, overall response rate (ORR), safety and progression-free survival (PFS). MRD was assessed every 6 mo in CR pts. A comparison of NGF with blood mass spectrometry, BM-NGS and blood cell-free DNA is planned.
Results: 47% of 120 pts had HRMM. The most common HR was +1q, alone in 25% and in 35% if co-occurred with other HR. T(4;14) was found in 12%, del17p in 5% of pts. The ORR after induction was 87%. Treatment related mortality (TRM) is 2% (2 pts, 1 pulmonary embolism, 1 unknown). Post-ASCT 48% of pts were in at least VGPR and 58% after consolidation. At 18 mo on maintenance 55% of pts had at least VGPR response. 42 (35%) pts were out of study: 7 (6%) no PR after induction, 23 (19%) due to PD, 2 (2%) deaths, 6 (5%) due to toxicity, 3 (3%) pts were withdrawn and 1 (1%) protocol violation. CR rate was 47/120 (39%). 28% (34/120) achieved CR/flow-neg with 10-4 and 27% (32/120) with 10-5. Among CR/flow-neg pts the number of HR and NHR patients was equal at 18 mo on maintenance, 50% (17/34) vs 50% (17/34), respectively. With the median follow-up of 29 mo in April2022 the median PFS has not been reached in either group. There was no PFS difference between HR and NHR pts (p=0.713) nor between double-hit (n=12) and others (n=108) (p=0.223). 79 different AEs at least grade 3 have been reported in 56 pts, 53% of these were infections. 5 pts discontinued Ixa due to grade 3 peripheral neuropathy. 3% had grade 3 skin reactions. 7 non-fatal SARS-CoV-2 cases were reported.
Conclusions: This NMSG trial reports responses and safety after observation of all pts until the time-point of 18 months on maintenance. The ORR after induction was 87%. TRM is 2%. Consolidation demonstrates an increase of pts with at least VGPR from 48% to 58%. 27% achieved CR/flow-MRD neg with 10-5. HR and NHR pts have had comparable outcomes, in terms of flow-MRD negativity and PFS.

P-223
Busulfan and thiotepa as a conditioning regimen for autologous stem cell transplantation in patients with multiple myeloma

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Introduction: Currently the standard conditioning regimen for autologous stem cell transplantation (ASCT) in multiple myeloma (MM) is high-dose melphalan. Thiotepa is an active alkylating agent against MM, and this study compared the efficacy and toxicity of busulfan and thiotepa (BuTT) and those of high-dose melphalan (HD-MEL) as conditioning regimen for ASCT in patients with MM.
Methods: This study retrospectively reviewed the record of patients who were diagnosed symptomatic MM between March 2008 to May 2020 from 7 institutions. BuTT conditioning regimen was composed of intravenous thiotepa 5 mg/kg once a day from days -7 to -6 followed by intravenous busulfan 3.2 mg/kg once a day from days -5 to -3. HD-MEL conditioning regimen was composed of melphalan 100 mg/m2 once a day from days -3 to -2. Response to treatment was assessed after induction chemotherapy before ASCT and 3 months after ASCT. Maintenance therapy was administered based on the policies of each participating center.
Results: One hundred and fourteen patients received BuTT conditioning and the same number of patients received HD-MEL. The baseline clinical characteristics of the patients were not significantly different between two groups including high-risk chromosomal abnormalities and Revised-International Staging System (R-ISS). More patients in BuTT group received bortezomib-containing induction treatment (100.0% vs. 65.8%) and more patients in HD-MEL group received thalidomide maintenance after ASCT (28.1% vs. 50.0%). The ORR after ASCT was 94.7% in BuTT group and 97.4% in HD-MEL group (p = 0.333). After median follow-up of 47.6 months, median PFS was 41.5 months in BuTT group and 30.3 months in HD-MEL group (HR 0.706, 95% CI 0.497-1.004, p = 0.053). OS was not different between two groups (not reached in BuTT group vs. 101.0 months in HD-MEL group, HR 1.092, 95% CI 0.610-1.956, p = 0.766). Analysis including patients who did not proceed to maintenance or consolidation treatment after ASCT, PFS difference became more significant (41.5 months in BuTT group vs. 24.4 months in HD-MEL group, HR 0.621, 95% CI 0.388-0.993, p = 0.047). OS was not different between two groups (not reached in BuTT group vs. not reached in HD-MEL group, HR 1.038, 95% CI 0.478-2.255, p = 0.924). There was no significant difference in hematopoietic stem cell engraftment in both groups. BuTT group had fewer adverse events such as grade 3 or 4 stomatitis and diarrhea than HD-MEL group (stomatitis, 10.5% vs. 23.7%, p = 0.013; diarrhea, 10.5% vs. 25.4%, p = 0.005). There was no difference in occurrence of venous-occlusive disease (VOD) (2.6% in BuTT. Vs. 0.9% in HD-MEL, p = 0.622).
Conclusions: This study suggested that BuTT is an effective alternative conditioning regimen with reduced toxicity in patients with newly diagnosed MM, and further prospective trial is needed to confirm the efficacy of BuTT conditioning.

P-224
Single versus tandem autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma and high-

risk cytogenetics: a retrospective study of the PETHEMA/Spanish Myeloma Group (GEM)

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Introduction: Several approaches have been developed to try to overcome the bad prognosis of patients with multiple myeloma (MM) and high-risk (HR) cytogenetics. Tandem Autologous Stem-Cell Transplantation (ASCT) has been viewed in some studies as a means to intensify therapy and improved response treatment in these patients. We performed this observational, retrospective study to better understand the outcomes of single and tandem ASCT in this subgroup of patients.
Methods: Overall, 213 patients with MM and HR cytogenetics from 35 hospitals pertaining to the cooperative PETHEMA/Spanish Myeloma Group (GEM) and diagnosed between January 2015 and December 2019 were included in the study. HR cytogenetic status was defined as having ≥1 of the following abnormalities: del(17p), t(4;14), t(14;16) or 1q21 amplification (≥4 copies). Every patient underwent front-line induction therapy with VTD or VRD followed by high-dose chemotherapy and single or tandem ASCT. The decision of performing single or double ASCT depended on each center's policy.
Results: 142 (66.7%) patients received a single ASCT and 71 (33.3%) patients a tandem ASCT. Patients undergoing tandem ASCT were younger (median age 55 vs. 60 years; p = 0.007), were more likely to have R-ISS advanced stage (p = 0.002), and have a higher plasma cell infiltration in bone marrow at time of diagnosis (33% vs. 50%; p = 0.03) than patients in the single transplant group. Most patients receive post-transplant maintenance (88% in the single and 93% in the tandem group), being lenalidomide alone the most commonly regimen used (76.1% patients in the single and 50.7% patients in the double ASCT group). With a median follow-up of 31 months (range, 10-82), median PFS was 41 months and 48 months in the single and tandem ASCT group, respectively (p = 0.33). According to the different subtypes of cytogenetic abnormalities, only patients with isolated del(17p) undergoing tandem ASCT showed a longer PFS than patients receiving a single ASCT (not reached vs. 41 months), but the difference did not reach statistical significance. Post-transplant response rate was 97.9% and 100% in the single and in the tandem ASCT group, respectively, and CR after transplant was 71.3% after single and 83% after tandem ASCT. Finally, 62 patients (43.7%) and 33 (46.5%) in the single and tandem transplant group achieved CR and MRD negativity, respectively.
Conclusions: Tandem ASCT was not associated with a significant clinical benefit in PFS when compared with single ASCT in a homogeneously treated series of young patients. Post-transplant MRD negative rate was similar in patients receiving one or two ASCT which might explain the limited additional benefit of tandem ASCT observed. In conclusion, our data do not show superiority of tandem-ASCT vs single ASCT in young patients with MM and HR cytogenetics when treated with a standard approach of a triplet agent-based induction including PIs and IMiDs and post- transplant maintenance.

P-225
The optimal dose of thalidomide on the treatment of newly diagnosed multiple myeloma: real-world experience in Taiwan

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Introduction: Although VTD regimen (the combination of bortezomib, thalidomide, and dexamethasone) is the most common strategy to treat newly diagnosis multiple myeloma in Taiwan, the optimal dose of thalidomide cannot be clearly defined. Here we conducted a prospective study to investigate the relationship between the toxicity, as well as treatment response, and the dose of thalidomide.
Methods: Patients with newly diagnosed multiple myeloma were recruited from September 2016 through June 2022. All the patients received induction therapy with four 28-day cycles of VTD regimen and thalidomide was started from 50 mg per day in the first cycle. From the second cycle, the dose of thalidomide was titrated according to the adverse effects (AE) happened in the last cycle. The minimal dose of thalidomide was 50 mg per day and the maximal dose was

100 mg per day. The primary end point was adverse event rates of VTD regimen. The secondary end points included response rate and progression-free survival (PFS). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
Results: Of the 52 patients, 41 patients underwent dose escalation of thalidomide to 100 mg per day successfully (79% of the study population), whom we classified into "T100" group. And 11 patients kept 50 mg per day due to intolerable toxicity while dose escalation (21% of the study population), whom we classified into "T50" group. Baseline characteristics were well balanced between the two treatment groups. The most common nonhematologic adverse events of VTD regimen in overall population was herpes zoster infection (13.5%), followed by limb edema (11.5%). The rates of very good partial response (VGPR) were 68% in T100 group and 58% in T50 group after 4-cycle induction therapy (p = 0.731). The 2-year PFS was similar between two groups (67.1% in T100 group and 64.8% in T50 group; p = 0.908). While no one factor had been identified as affecting the dose escalation of thalidomide.
Conclusions: By adjusting the dose of thalidomide, we can greatly reduce the adverse events of VTD regimen. Because thalidomide 50 mg per day is still an effective treatment for newly diagnosed myeloma, it is unnecessary to abandon VTD regimen if the patient is unable to tolerate thalidomide 100 mg per day due to toxicities.

P-226
Bortezomib, lenalidomide and dexamethasone in newly diagnosed multiple myeloma patients: a real-world study of China

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Introduction: In recent years, a series of new drugs such as proteasome inhibitors, immune modulators and autologous stem cell transplantation (ASCT) have been widely used in multiple myeloma (MM) patients and have prolonged the survival of patients. Nowadays Bortezomib/lenalidomide/dexamethasone (VRD) is considered as the first-line induction therapy for newly diagnosed multiple myeloma (NDMM). Because of the data of VRD in China is insufficient, we aimed to evaluate the efficacy of VRD in NDMM patients as well as the effect of the regimen on the long-term prognosis in the real world.
Methods: The clinical characteristics, survival rates, response rates and minimal residual disease (MRD) of 87 NDMM patients in our hospital from January 1, 2013 to January 1, 2020 were retrospectively analyzed. Response was evaluated after 2 courses of induction therapy, before ASCT and at day 100 after ASCT. The best response was defined as the deepest response during the follow-up. MRD was evaluated by multiparameter flow cytometry (MFC) with 10-4 sensitivity.
Results: The median age of the patients was 56 years old (36-78) and males and females accounted for 58.6% and 41.4%, respectively. The overall response rate (ORR) was 95.9% after 2 courses of induction therapy, with 13.5% achieving the deep response (complete response (CR) or better) and 51.3% of patients achieving a very good partial response (VGPR) or better. After 4 courses of induction therapy, the ORR achieved 95.2%, and the proportions of the deep response and VGPR or better grew up to 46.0% and 77.7%. According to the treatment, the patients (≤65 years old) were divided into transplantation group and non-transplantation group. After the induction therapy, 88.8% of patients in the transplantation group achieved VGPR or better, and 55.5% reached the deep response. After the transplantation, the proportion increased to 97.2% (P=0.174) and 77.2% (P=0.055), respectively, with the rate of undetectable minimal residual disease (MRD) increasing from 44.4% to 77.8% (P=0.004). In the non-transplantation group, 74.2% of patients achieved VGPR or better after 4 courses of induction therapy, 35.5% of the patients achieved deep response and the rate of undetectable MRD was 37.0%. Compared with the non-transplantation group, transplantation was associated with a higher rate of response ($P < 0.001$) and a lower rate of MRD detection(78.4% vs 55.2%, P=0.045). The median follow-up time of all patients was 26.3 months (6.2-61.4). The median PFS and OS were not reached. The three-year PFS and OS rates were 78.4% and 87.1%, respectively. None of the standard-risk group, the high-risk group, the transplantation group and non-transplantation group achieved the median PFS and OS.
Conclusions: VRD regimen has promising efficacy and result in a substantial survival benefit. Autologous stem cell transplantation (ASCT) after VRD induction therapy is associated with higher rate of deep response, lower rate of undetectable MRD and longer survival.

P-227
The prognostic role of 1q21 gain/amp in newly diagnosed multiple myeloma: the faster, the worse

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Introduction: The prognostic value of additional copies of chromosome 1q (1q gain/amp) in multiple myeloma (MM) remains controversial. Here, we update the data of 781 real-world newly diagnosed MM patients (NDMM) from our center.

Methods: We retrieved clinical characteristics at the point of diagnosis as well as treatment and transplant information from the electronica medical records.
Results: 1q gain/amp was detected among 405 patients (51.9%) which was associated with aggressive clinical characteristics including ISS stage III (p< 0.001), del (17p) (p=0.02), t (4;14) (p< 0.001), immunoglobulin A (IgA) (p< 0.001), elevated β2MG (p< 0.001), anemia (p< 0.001) and renal failure (p=0.025).Furthermore, comparing to the patients without 1q gain/amp, the duration from diagnosis to the first time very good partial response or better (TVGPR) was significantly shorter in the 1q gain/amp subgroup (77days vs 100days, p=0.001). However, in term of the response depth, patients without 1q gain/amp exhibited more superior than 1q gain/amp group. The univariate survival analysis found that 1q gain/amp patients had shorter progression free survival (PFS) (p< 0.001) and overall survival (OS)(p=0.003). In the multivariate analysis, ISS stage (PFS: p=0.001; OS: p< 0.001), del(17p)(PFS: p=0.001; OS: p=0.005) and 1q gain/amp (PFS: p=0.001; OS: p=0.06) remained independent adverse prognostic factors for survival. Patients with 1q gain/amp receiving doublet or triblet regimen had comparable survival prognosis, whose PFS can be improved by autologous stem cell transplant (ASCT) (p=0.009).
Conclusions: In conclusion, patients with 1q gain/amp achieved VGPR rapidly, but they could not achieve a deep response. 1q gain/amp still acts as an independent adverse prognostic factor even in the setting of novel therapy.

P-228
ASCT does not benefit patients who are MRD negative following induction therapy: updated results from the Phase 2 Cardamon study

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Introduction: The benefit of upfront ASCT for fit newly diagnosed MM (NDMM) patients may depend on the induction regimen, disease risk and depth of response to induction. Studies testing ASCT against chemotherapy consolidation (cons) have largely utilised PI+lenalidomide induction and lenalidomide maintenance. The randomised open-label phase 2 trial Cardamon (ClinicalTrials.gov NCT02315716) evaluated the benefit of ASCT in an IMiD-free carfilzomib-based induction, cons and maintenance protocol.
Methods: NDMM patients received 4 cycles of carfilzomib, cyclophosphamide and dexamethasone (KCd), then randomised 1:1 to ASCT or 4 KCd cons cycles; all received 18 cycles K maintenance. Non-inferiority of KCd cons to ASCT was assessed by 2-year progression free survival (PFS) rate from randomisation in the intention to treat (ITT) population (non-inferiority margin 10% difference). Safety and initial efficacy results were reported at ASCO 2021 with median follow up 30.8m from randomisation. This is an updated analysis focusing on MRD and genetic risk. High risk (HiR) patients were defined as having any of del17p (≥50%), t(4;14), t(14;16) or t(14;20).
Results: Of 281 patients enrolled, 218 proceeded to randomisation (109 KCd cons, 109 ASCT). Post induction ≥VGPR rate was 57·7% (95%CI 51·6%-63·5%) and MRD negative rate 22·8% (95%CI 18·0%-28·1%). Disease response post-randomised treatment was similar between groups (≥VGPR 78·0% KCd cons vs 77·1% ASCT, p=0·8). Median follow-up was 45·5m from registration and 40·2m from randomisation. Observed 2-year PFS for KCd cons was 68% vs 76% for ASCT and calculated difference -7·2% (70%CI -11·1% to -2·8%), just outside the non-inferiority margin. ASCT showed no benefit in MRD negative patients post-induction (restricted mean survival time [RMST] difference KCd cons vs ASCT: -0·6m over 59·5m, p=0·9). However, there were better outcomes following ASCT for MRD positive patients (RMST difference KCd cons vs ASCT: -7·3m over 60·1m, p=0·045). ASCT patients achieved higher rates of MRD negativity at day 100 (30·3% KCd cons vs 47·7% ASCT, p=0·008) and after 6 months maintenance (31·2% KCd cons vs 45·9% ASCT, p=0·03). Of 259 patients with complete FISH data, 52 (20%) were HiR. Response to KCd induction was independent of risk (≥VGPR 59·6% HiR vs 58·0% SR; MRD negativity 23·1% HiR vs 23·2% SR). Despite this, HiR patients had inferior outcomes (2-year PFS 49% vs 75% SR [HR: 2·21 (95%CI 1·49-3·28)], p< 0·001), independent of randomisation (interaction p=0·6). Comparing treatments (KCd cons vs ASCT), the calculated

difference in 2-year PFS for SR patients was -7·4% (70%CI -10·9% to -3·1%), mirroring the result in the ITT population, while HiR patients had a non-significant -3·8m difference in PFS over 42·4m by RMST (p=0·4).
Conclusions: KCd was not statistically non-inferior to ASCT, though PFS difference was marginal. These results indicate that upfront ASCT may be deferred for patients who are MRD negative post-induction.

P-229
Real-world outcomes of sequencing elotuzumab (elo)-based regimens following daratumumab (dara) in patients with relapsed/refractory multiple myeloma: results from the Connect® MM Registry

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Introduction: As treatment options for patients with relapsed/refractory multiple myeloma (RRMM) expand, sequencing of agents has become increasingly complex. Some therapies can potentially affect outcomes with subsequent agents. For example, the mechanism of action of dara results in depletion of natural killer (NK) cells, a cell population through which elo mediates cytotoxicity, which may impact the efficacy of elo in patients previously treated with dara. The Connect® MM Registry (NCT01081028) is a large, US, multicenter, prospective observational cohort study of patients with newly diagnosed multiple myeloma (NDMM). This analysis investigated characteristics and outcomes in patients from the Connect MM Registry who received elo-based therapy after dara.
Methods: Adult patients (n=3011) with symptomatic NDMM ≤2 mo from diagnosis were enrolled from 250 community, academic, and government sites from 2009 to 2016. Patients who received a line of therapy after dara were included. Demographics and outcomes were assessed according to inclusion of elo in subsequent regimens. Progression-free survival (PFS) was measured from elo start date or first non-elo treatment after dara until death or progression and analyzed using the Kaplan-Meier method and Cox proportional hazards models.
Results: As of the 04 Aug 2021 data cut, 66 patients with RRMM had received elo in any line after dara. Most patients (80%) received elo in combination with an IMiD agent (lenalidomide or pomalidomide). Median time between dara stop and elo start was 1.0 mo (range, 0.1–37.6). Median lines of therapy administered prior to dara was 2. Median PFS for patients who received elo after dara was 5.0 mo. In a subgroup analysis of lines of therapy received immediately after dara, 38 patients received elo and 177 patients received non-elo regimens. Median PFS was 7.1 mo and 5.3 mo, respectively for elo and non-elo regimens received immediately after dara. Adjusted hazard ratio (HR) for elo vs non-elo was 0.82 (95% CI, 0.56–1.21; *P*=0.32). In an additional analysis of patients who received either elo-based or non-antibody triplet/quadruplet regimens, median PFS and adjusted HRs were consistent with the previous finding. Of the 35 patients who received elo immediately after dara, the most common elo-based 3+ regimens were elo/lenalidomide/dexamethasone (51%) and elo/pomalidomide/dexamethasone (31%). The most common regimen among the 67 patients who received a non-antibody regimen was carfilzomib/cyclophosphamide/dexamethasone (15%).
Conclusions: This analysis suggests elo may provide clinical benefit similar to that of non-elo therapies, even when given immediately after dara despite the concern of potential NK cell depletion. Although patient cohorts were small, these results from the CONNECT MM Registry provide valuable insights on elo use in the real-world setting. As new targeted agents continue to emerge and move into earlier lines of therapy, comprehensive investigation of treatment sequencing in RRMM is warranted.

P-230
Preclinical and translational biomarker analysis to support further clinical development and dose optimization of mezigdomide (MEZI; CC-92480) in combination with either bortezomib or carfilzomib

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Introduction: MEZI is a novel, potent cereblon E3 ligase modulator (CELMoD®) designed to induce rapid and maximal degradation of the transcription factors Ikaros and Aiolos. Ikaros and Aiolos play a key role in the development and

differentiation of hematopoietic cells and their loss induces tumoricidal and immunomodulatory activity in multiple myeloma (MM). MEZI is currently being investigated for the treatment of relapsed/refractory MM in phase 1/2 studies as monotherapy and in combination with standard of care and novel agents (NCT03374085; NCT03989414; NCT05372354).
Methods: Preclinical studies were performed on MM cell lines treated with MEZI or pomalidomide (POM) in combination with proteasome inhibitors (PIs), bortezomib (BORT) or carfilzomib (CFZ); and in a lenalidomide-resistant H929 xenograft model (n=10/cohort) treated with MEZI or POM plus dexamethasone (DEX) and BORT. Translational studies included pharmacodynamic analysis of Aiolos and Ikaros levels in peripheral blood cells, induction of T/NK cell proliferation, and activation and changes in serum free light chains as a biomarker for tumor burden by dose in patients treated with MEZI monotherapy, in combination with DEX, or a triplet combination with BORT or CFZ.
Results: Analysis of in vitro tumoricidal activity of MEZI or POM in combination with either BORT or CFZ demonstrated MEZI induced significantly deeper apoptosis in combination with either PI at 100-fold lower concentrations than POM. In vivo, MEZI/BORT affected tumor growth rate similarly to POM/BORT/DEX, and the triplet combination of MEZI/BORT/DEX resulted in the greatest tumor regressions, with near complete loss of palpable tumor detection on average by day 41. Survival analysis demonstrated all mice in the MEZI/BORT/DEX cohort remained in regression over the observation period while 8/10 mice relapsed in the POM/BORT/DEX cohort. In the clinic, pharmacodynamic data from patients treated with MEZI in triplet combination with either BORT or CFZ and DEX showed decreases in Ikaros and Aiolos at doses as low as 0.3 mg. However, median decrease for patients treated with the triplet combination at the 0.6 mg and 1.0 mg dose were most like patients treated with DEX doublet. Analysis of changes in peripheral blood immunophenotyping by mid-cycle 3 showed similar dose-dependent trends, with MEZI remaining pharmacodynamically active at all doses in the immune compartment, but with the 1.0 mg dose inducing more consistent and greater changes than lower doses.
Conclusions: These results demonstrate more potent pre-clinical tumoricidal activity of MEZI triplet combinations with PIs and DEX versus POM. Translational studies indicate that proteasome inhibition does not abrogate MEZI pharmacodynamic activity, with the 1.0 mg dose appearing to be the most active. Further exploration of doses between 0.3 and 1.0 mg in combination with either BORT or CFZ are suggested to determine the optimal dose.

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Biomarker analysis to support dose optimization of iberdomide (IBER) as monotherapy and in combination with standard of care treatments for multiple myeloma from a phase 1/2 trial

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Introduction: IBER, a novel cereblon E3 ligase modulator (CELMoD®) agent with tumoricidal and immunomodulatory activity in multiple myeloma (MM), is being investigated for treatment of relapsed/refractory MM (RRMM) in a phase 1/2 study (NCT02773030). Due to the recent focus by health authorities on dose selection for oncology products other than maximum tolerated dose (MTD), a comprehensive analysis of pharmacodynamics (PD) and pharmacokinetics (PK) was implemented to support dose optimization of IBER alone, in combination with dexamethasone (DEX; Iber+d), and with DEX and daratumumab (DARA; IberDd).
Methods: PK samples were collected on treatment cycles (C)1–4 to estimate IBER exposure using population PK (area under the concentration curve over 24-h dosing interval [AUCτ]). Biomarkers included analysis of peripheral blood samples on C1 day (D)1 and mid-cycle through C4 for immunophenotyping, absolute neutrophil counts (ANC), and assessment of serum free light chain (sFLC), as a biomarker of tumor burden. Bone marrow samples were collected at screening and C2D15 for immunohistochemistry.
Results: IBER AUCτ increased in a dose-related manner between 0.3 and 1.0mg as monotherapy and 0.3 and 1.6mg + DEX, with moderate variability. Median time to maximum serum concentration of IBER was 2–4h post dose. Comparable IBER exposure was observed for monotherapy and Iber+d. Reductions of Ikaros/Aiolos in tumor cells were observed at all doses in both cohorts with a >90% reduction at the 0.45mg dose. A >50% decrease in sFLCs was observed only at doses ≥0.9mg, and 1.6mg induced faster and deeper decreases vs lower doses. In the immune compartment, IBER induced similar dose-/exposure-dependent PD changes as monotherapy and Iber+d, which appeared to saturate at higher doses. A >80% reduction in mature B cells and ~2-fold increase in proliferating/activated T and NK cells were observed at doses ≥1.0mg. PD activity of IBER was not attenuated by prior refractoriness to IMiD® agents or anti-CD38 therapy. Based on these results, doses between 1.0 and 1.6mg were tested in the IberDd cohort. PK/PD of IBER were similar with IberDd. In this cohort, reduction in mature B cells and sFLCs was more consistently observed at 1.6mg vs lower doses; however, higher IBER exposures were associated with more pronounced decreases in ANC when compared with Iber+d. This was clinically manageable and the IBER MTD was not determined in any cohort.
Conclusions: Similar PK/PD results were observed in patients receiving IBER alone, Iber+d, and IberDd. Across all cohorts, a

>20% difference in dose was needed for meaningful change in IBER exposure, immune PD began to saturate at doses ≥1.0mg, and decreases in tumor burden were greatest at the 1.6mg dose. Based on these results, 1.0, 1.3, and 1.6mg of IBER were chosen for dose optimization of IberDd for RRMM, and 0.75, 1.0, and 1.3mg were selected for dose optimization of IBER monotherapy in the newly diagnosed MM maintenance setting.

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Adverse event patterns and management with pomalidomide, dexamethasone, and daratumumab in patients with relapsed or refractory multiple myeloma: a safety analysis of the phase 2 MM-014 study

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Introduction: Lenalidomide (LEN) is standard of care for newly diagnosed multiple myeloma (MM), but patients (pts) who had a relapse after or became refractory to LEN were poorly represented in previous trials. In the phase 2 MM-014 trial (NCT01946477), patients with relapsed or refractory multiple myeloma (RRMM) received pomalidomide (POM)-based treatments (Tx) immediately after first- or second-line LEN-based Tx. In Cohort B, POM + daratumumab and low-dose dexamethasone (DEX) (DPd) resulted in an overall response rate (ORR) of 77.7%, a 1-year progression-free survival (PFS) rate of 74.1%, and a median PFS (mPFS) of 30.8 mo (95% CI, 19.3–48.9) (median follow-up, 28.4 mo). Neutropenia was the most common Tx-emergent adverse event (TEAE) (75/112 pts, n=72 grade 3/4). We assessed TEAEs that occurred in Cohort B and whether they could be resolved by dose modification without affecting efficacy.
Methods: Pts with RRMM and 1–2 prior lines of therapy with LEN-based Tx as their most recent received DPd in 28-day cycles. Primary endpoint was ORR; AE assessment was a secondary endpoint. AEs were recorded during each cycle and coded according to the MedDRA (v20.0). POM or DEX administration was interrupted and reduced by 1 dose level for certain TEAEs. Minimum permitted dose for POM was 1 mg and for DEX was 10 mg (age ≤75 years) or 8 mg (age >75 years). Daratumumab administration was unchanged but interrupted for infusion reactions and certain AEs.
Results: In Cohort B (n=112), TEAEs of interest were the most common TEAEs during the first 10 cycles: neutropenia, thrombocytopenia, leukopenia, infections, fatigue, and constipation. All TEAE rates decreased over the first 10 cycles except infections. Most pts (93.8%) experienced TEAEs related to POM, including neutropenia (63.4%), thrombocytopenia (19.6%), leukopenia (8.9%), and infections (25.9%). Median onset was < 1 mo from first dose for TEAEs of interest except fatigue (2.2 mo); all persisted for a median of < 1 mo except fatigue (7.6 mo) and constipation (35.1 mo); and TEAEs that resolved (neutropenia n=67/75, thrombocytopenia n=24/28, leukopenia n=11/12, infections n=76/89, fatigue n=22/52, constipation n=8/20) did so in a median of < 1.5 mo except fatigue (3.9 mo). POM-related TEAEs were mostly managed by dose interruption, reduction, or both; few pts discontinued POM due to TEAEs of interest (thrombocytopenia, n=1; leukopenia, n=1; infections, n=2). A total of 34 (30.4%), 11 (9.8%), and 6 (5.4%) pts received 1, 2, and 3 POM dose reductions, respectively. mPFS was 36.1 mo (95% CI, 23.5–53.6) in pts with a dose modification.
Conclusions: Pts previously treated with LEN remained responsive to DPd when AEs were managed by dose modification. There was no evidence of cumulative toxicity between LEN and POM, and pts with dose modification had a higher mPFS than the overall cohort. Managing AEs through dose modification may improve outcomes for pts with RRMM treated with DPd.

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Retrospective, single-center, real-world experience of belantamab mafodotin in relapsed/refractory multiple myeloma

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Introduction: Belantamab mafodotin (belamaf) is a BCMA antibody drug conjugate approved for treatment of relapsed refractory multiple myeloma (RRMM) patients (pts) based on the pivotal phase 2 DREAMM-2 study (Lonial et al, Lancet Oncology, 2019), which demonstrated an overall response rate (ORR) of 32%, median progression free survival (PFS) of

2.8 months, and overall survival (OS) of 13.7 months in triple class (proteasome inhibitor, IMiD, and anti-CD38) refractory (TCR) MM. In this single-center retrospective study, we report the efficacy and safety of belamaf in RRMM pts administered in a real-world, standard of care (SOC) setting.
Methods: All MM pts treated with SOC belamaf, either as monotherapy or in combination, between 11/1/2020 and 11/30/2021 at the center were included in this study. Response and progression were evaluated using International Myeloma Working Group standard criteria. Keratopathy and best corrected visual acuity (BCVA) adverse events (AEs) were graded per the Keratopathy and Visual Acuity (KVA) scale. The Kaplan-Meier method was used to estimate time to event endpoints.
Results: A total of 39 consecutive pts with a median of 7 prior lines of therapy were included in the analysis, of whom 37 pts (95%) received single agent belamaf. Median age was 66 years (range 39-89), 14 of 37 (38%) pts with available FISH had high risk disease (del 17p, t(4;14, and/or t(14;16)), 14 pts (36%) had extramedullary disease, 37 (95%) pts were TCR, 32 (82%) pts were TCR and alkylator-refractory, and 8 pts (21%) were BCMA-refractory. Notably, the majority (69%) of pts in this analysis would have been ineligible for the DREAMM-2 trial based on key eligibility criteria.Median number of belamaf doses administered was 2 (range 1-9). Among 37 pts with measurable, response evaluable baseline disease, the best ORR (≥ PR) was 27% with ≥ VGPR of 3%. The clinical benefit rate (≥ MR) was 35%. Among 8 BCMA-refractory pts, there was 1 PR and 1 MR. Median PFS was 1.8 months and median OS was 9.2 months with a median follow-up of 10.1 months. Median duration of response has not been reached among 10 responding pts. Among 33 pts with a post-treatment ocular exam, 25 pts (76%) developed any grade keratopathy (Grade 1/2/3/4, 9%/55%/12%/0%, respectively) and BCVA changes (Grade 1/2/3/4, 42%/27%/6%/0%, respectively). Median time to first keratopathy or BCVA AE was 1.3 months. The most common reasons for treatment discontinuation were disease progression (75%) and AEs (9%).
Conclusions: Our study in heavily pretreated RRMM pts, of whom the majority would have been ineligible for the DREAMM-2 study, demonstrates an ORR, PFS, and ocular AE profile with SOC belamaf comparable to outcomes reported in the pivotal registration study. Future studies are needed to further define the optimal use and sequencing of belamaf in MM pts, particularly in context of other BCMA-targeting modalities. Additionally, data regarding BCMA expression and correlation with outcomes is currently being investigated at our institution.

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Real-world belantamab mafodotin (belamaf) use: a US retrospective longitudinal pharmacy and medical open-source claims database assessment

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Introduction: Belamaf is an approved (August 2020), first-in-class, B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate for patients with relapsed or refractory multiple myeloma (RRMM) who have received ≥4 prior therapies including an anti-CD38 monoclonal antibody (mAb), a proteasome inhibitor (PI), and an immunomodulatory agent. The DREAMM-2 study, with single-agent belamaf, reported an overall response rate of 32%, duration of response of 11 months, and progression-free survival of 2.8 months. Belamaf can cause ocular events that can be managed with dose holds/reductions. This study examined prior MM treatments and belamaf treatment patterns for US patients initiating belamaf in real-world clinical practice.
Methods: This descriptive, retrospective cohort study was conducted using IQVIA's longitudinal pharmacy and medical open-source US claims databases. Belamaf claims were identified between August 2020 and February 2022. Index date was the first observed belamaf claim during this period. Belamaf patients were followed for ≥6 months. The treatment period was the index date through last observed belamaf claim + 21 days. Key baseline measures were demographic and clinical characteristics, prior MM treatments, and recycled treatments (used more than once). Belamaf dose and use patterns were examined during follow-up.
Results: Overall, 695 patients received belamaf; 53% were male and median age was 70 years. Prior to belamaf, most had been treated with corticosteroids (99%), PIs (89%), anti-CD38 mAb (83%), and immunomodulators (65%). A median of 4 therapeutic classes were used, and 491 patients (71%) had ≥1 recycled treatment. Among the 210 patients (30%) with at least 6 months of available follow-up, median follow-up was 307 days (range 180–532) from index date and median belamaf treatment duration was 86 days (22–455) with a median of 3 administrations. During the follow-up, 49 patients (23%) had a treatment gap of 29–56 days and 63 (30%) had treatment gap of >56 days. Doses were administered a median of 22 days apart. Median belamaf dose was 170 mg at first dose and 160 mg at fourth dose. Among patients with >1 evaluable dose (n= 167), 119 (71%) had no dose reduction and 48 (29%) had ≥1 dose reduction. Concomitant therapies were received by 80 patients (38%), most commonly dexamethasone (n=66).
Conclusions: Belamaf is an available treatment option for patients with RRMM. Real-world evidence from this study suggests belamaf use in clinical practice is generally consistent with the label indication and managed with dose reductions and holds, and patients remain on therapy consistent with the DREAMM-2 trial. Ongoing belamaf studies are examining alternative dosing schedules and combinations to further optimize use. Funding: GSK (214283).

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Chemo or chemo-free regimens in heavily pretreated multiple myeloma? Role of bendamustine-bortezomib-dexamethasone (BVD) in novel agents' era

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Introduction: The treatment of heavily pretreated Multiple Myeloma continues to be considered as an important unmet clinical need. Bendamustine is an old bi-functional alkylating agent which has proved to be effective in relapsed, refractory and in new diagnosed Multiple Myeloma (MM). Thus, aiming to provide further insights in this field, also in novel agents'era, we present here a retrospective, real-life analysis of patients with relapsed/refractory MM (rrMM), who had received salvage therapy with bendamustine in combination with bortezomib and dexamethasone (BVD).
Methods: 81 patients (44 M/37 F), with rrMM, median age at diagnosis 59.4 years (r. 36-82), median age at start of treatment 63.6 years (r.37-86) treated with several lines of treatments (median 6, r. 2-11), every refractory to all the drugs previously received (also Bortezomib), received BVD (B 90 mg/sqm days 1,2; V 1.3 mg/sqm days 1,4,8,11, D 20 mg days 1,2,4,5,8,9,11,12, Pegfilgrastim day +4) every 28 days, until progression. All patients had previously received bortezomib-based and IMIDs-based treatments, and 32% (26/81) had also received radiotherapy. 69% (56/81) had undergone single or double autologous and three (2%) allogeneic stem cell transplant. All patients were relapsed and refractory to last therapies received before BVD.
Results: Bendamustine was well tolerated, with grade 3-4 transfusion-dependent anemia in 56% (46/81) of patients, and 43% (35/81) grade 3-4 neutropenia (no ospedalization was required, no septic shocks were observed). No severe extrahematologic toxicity was observed, only grade 1 gastrointestinal side effect (nausea), treated by common antiemetic drugs. According to IMWG, ORR was 63% (51/81: 7 CR, 18 VGPR, 15 PR, 11 MR) with 11 PD and 19 patients in SD, which can be considered as an impressive result in this subset of rrMM patients. In particular, for 11 patients, BVD was, after having achieved at least a PR, a bridge to second auSCT, and for two patients a bridge to alloSCT. Eight patients have surprisingly achieved a notable PR after failure of novel agents (i.e. Carfilzomib, Daratumumab and Pomalidomide). Median time to response was 1.3 months (r.1-3), median OS from diagnosis was 67.3 months (r.6-151), median OS from start of Bendamustine was 9.6 months (r.2-36).
Conclusions: The triplet Bendamustine-Bortezomib-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, and, in particular cases, it could be considered as a bridge to a second autologous or allogenic SCT, also after failure of novel agents.

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Addition of carfilzomib as a third agent in lenalidomide-refractory multiple myeloma: switching from doublet to triplet

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Introduction: Carfilzomib is an epoxyketone proteasome inhibitor of second generation, proved to be effective and safe in relapsed and refractory Multiple Myeloma (rrMM), in combination with dexamethasone or lenalidomide and dexamethasone.In this retrospective observational trial, it has been evaluated efficacy and safety of carfilzomib, in combination with lenalidomide-dexamethasone (KRD) as salvage regimen in patients with rrMM, refractory to lenalidomide, where lenalidomide-based regimens have no proven efficacy.
Methods: 41 patients (23 M/18 F), with rrMM, median age at diagnosis 63.7 years (r. 43-82), median age at start of treatment 67 years (r. 48-84) previously treated with several lines of treatments (median 3, r. 2-11), underwent to KRD regimen (ASPIRE trial schedule) for a median treatment cycles of 8 (r 2-18). ISS was equally distributed, and all patients had previously been treated with bortezomib and IMIDs, and were refractory to this agents. 61% (19/31) of them had undergone at least to a single ASCT.
Results: According to IMWG criteria, after a median follow-up of 9 months (r. 2-18), ORR was 68,2% (28/41: 9 CR, 12 VGPR, 7 PR) with 5 progressive diseases (PD) and 8 patients in stable disease (SD): this can be considered as an impressive result in this subset of rrMM patients, refractory to lenalidomide. In particular, for 11 patients, KRD was, after having achieved at least a PR, a bridge to second/third autologous SCT. Median time to response was 1.3 months (r.1-4), median OS from diagnosis was 62 months (r. 9-170), median OS from start of Carfilzomib was 11 months (r. 2-18). Carfilzomib was well tolerated, with grade 2 anemia in 39%(16/41) of patients, successfully managed by ESAs, without necessity of blood transfusions; 29% (12/41) grade 3-4 neutropenia (pegfilgrastim in primary prophylaxis was given, no ospedalization was required, no septic shocks were observed); 34% (14/41) grade 2, 21% (9/41) grade 3 and 12% (5/41) grade 4 thrombocytopenia, without hemorrhagic events and transfusion-dependency. Moreover, it was observed pneumonia in 39% (16/41) of patients, treated by common antibiotic drugs and always solved. A cardiac monitoring was performed for all patients: hypertension (grade 2-3) in 34% (14/41) of patients; fatigue in 39% (16/31) of patients.
Conclusions: Carfilzomib-Lenalidomide-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic

resources, also lenalidomide, and it could be considered as a bridge to a second autologous or allogenic SCT.

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Real-world treatment patterns and clinical outcomes in patients with triple-class exposed relapsed or refractory multiple myeloma in United States clinical practice

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Introduction: Patients with multiple myeloma (MM) are at a persistent risk of relapsing and/or becoming refractory to therapies, and those with relapsed or refractory MM (RRMM) who are triple-class exposed (TCE) to immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs) are particularly challenging to treat, with limited treatment options and poor prognosis. Data regarding real-world (RW) treatments and outcomes in patients with TCE RRMM are limited. The aim of this analysis was to assess the characteristics, treatment patterns, and survival outcomes in RW patients with TCE RRMM.
Methods: Patients with MM from Jan 2011 to Aug 2021 were selected from the Flatiron Health deidentified US Electronic Health Record (EHR)-derived database. Patients with MM who had received ≥3 prior lines of therapy (LOT); were TCE to a PI, an IMiD, and an anti-CD38 mAb; and received ≥1 subsequent LOT were included in the analysis. Multiple observations per patient were considered if each of their respective LOT satisfied TCE eligibility criteria. Index date was defined as date of initiation of the LOT post TCE. Descriptive statistics were reported for patient characteristics and treatment patterns. Time-to-event endpoints, including overall survival (OS), progression-free survival (PFS), and time to next treatment (TTNT), were estimated using the Kaplan-Meier method.
Results: Of the 11571 treated MM patients in the Flatiron Health database,1500 observations for 740 unique patients were eligible for inclusion in the analysis. Median age at diagnosis was 69 years; 53.1% were male. The median time from diagnosis to the index date (start date of eligible LOT post TCE) was 4.2 years, 27.2% had prior stem cell transplant and patients received a median of 5 prior LOT. Prior to the index date, most patients were exposed to daratumumab (100%), lenalidomide (95.8%), bortezomib (89.5%), pomalidomide (71.5%), and carfilzomib (61.3%). The most common post-TCE treatments at any instance were dexamethasone (80.7%), pomalidomide- (31.3%), daratumumab- (30.2%), and carfilzomib-based regimens (23.3%). The most frequently used therapy was triplets (41.2%), followed by doublets (37.7%), monotherapies (15.5%), and quadruplets (5.7%). Median OS, PFS, and TTNT were 12.6 (95% CI 11.8–14.2) months, 3.7 (95% CI 3.5–3.9) months, and 4.7 (95% CI 4.4–5.2) months, respectively.
Conclusions: Results show that patients with TCE RRMM cycle through various treatment regimens and have poor survival and clinical outcomes. These RW results highlight the need for highly effective treatments; emerging novel therapies may improve outcomes in patients with TCE RRMM.

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Clinical impact of time to the best response in relapsed/refractory multiple myeloma patients receiving carfilzomib

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Introduction: In addition to the depth of response to the treatment, time to the response was recognized as a predictive marker in hematologic malignancies. A few data reported that slower response to induction therapy was associated with better survival in newly diagnosed multiple myeloma (MM) patients. In current study, we examined the clinical implication of time to best response in those patients.
Methods: We reviewed medical records of patients with RRMM at Kyungpook National University Hospital, South Korea, from 2014 to 2022. Patients who received a carfilzomib-based regimen: carfilzomib, lenalidomide, and dexamethasone (KRD), or carfilzomib, dexamethasone (KD), as 2nd line of therapy, were included. Time to the best response (TBR) was defined as the period for which a patient reached the best response after carfilzomib initiation. Response evaluation was assessed using International Myeloma Working Group Response Criteria.
Results: In a total of 61 patients, ISS I, II, and III were in 10 (16.4%), 15 (24.6%), and 36 (59.0%). Patients with high-risk cytogenetics were 17 (27.9%). Fifty-seven patients (93.4%) were refractory or relapsed after induction therapy including proteasome inhibitors, and 23 (37.7%) received upfront autologous stem cell transplantation. Median duration of carfilzomib-based therapy was 6.2 months (0.4-25.3). Fifteen patients (82.0%) achieved best response of partial response (PR) or better: 14 (23.0%) in complete response (CR), 19 (31.1%) in very good partial response (VGPR), and 17 (27.9%) in PR. Patients attaining the CR and VGPR had better progression-free survival (PFS) and overall survival (OS) compared with those with PR and non-responders (30.7 months vs 13.7 vs 3.9, $p < 0.001$; not reached (NR) vs 24.3 vs 10.0, $p < 0.001$). Those 50 patients who responded to carfilzomib received median 8 cycles of therapy (range, 1-18) and had 2.6 months of median TBR (range, 0.6-10.5). In an analysis regarding TBR, 31 patients required 2 or more than 2 months to achieve the best response (TBR ≥2 months). Patients with TBR ≥2 months showed significantly superior

survival outcomes compared with those with TBR < 2 months: median PFS was 27.9 months vs 9.9 (p= 0.002), and median OS was 17.1 vs NR (p= 0.041). In multivariate analysis, TBR was an independent prognostic factor to predict longer PFS (hazard ratio (HR), 0.054, 95% confidence interval (CI) 0.009-0.32, p< 0.001) and OS (HR, 0.19, 95% CI 0.042-0.87, p= 0.009) while treatment response was not related with survival outcomes.
Conclusions: Our data demonstrated a significant correlation between time to the best response and survival outcomes in carfilzomib-treated patients with RRMM. The gradual response to the therapy was a favorable prognostic factor for survival outcomes independent of high-risk features, type of previous treatment, and the treatment response.

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Health-related quality of life (HRQoL) in patients with relapsed/refractory multiple myeloma (RRMM) receiving real-life standard of care (SOC) treatments: results from the LocoMMotion study

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Introduction: Patient-reported outcomes (PROs) can inform how real-life SOC treatments (tx) affect HRQoL for patients with RRMM. Here we report measures of symptoms, functioning, and overall HRQoL from LocoMMotion (NCT04035226), the first prospective, multinational study of real-life SOC in triple-class exposed patients with RRMM.
Methods: LocoMMotion is a noninterventional study conducted across 76 sites (63 Europe and 13 United States). Eligible patients had received ≥3 prior lines of therapy (LOT) or were refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), received a PI, IMiD, and anti-CD38 mAb, and had disease progression during/after their last LOT. Real-life SOC therapies were defined as those used in local clinical practice. Patients were given the following questionnaires: EORTC QLQ-C30, EORTC QLQ-MY20 (4 single items), and EQ 5D-5L. HRQoL was evaluated at baseline (BL), day 1 of each tx cycle, end of tx visit, and during follow-up (every 4 weeks). Established thresholds were used to evaluate improvement compared to BL health status. Mixed models for repeated measures were used to evaluate within-group change.
Results: Patients in the LocoMMotion study (N=248; 54.4% male; median age 68 years) had a median of 4.0 (range, 1–20) cycles of SOC. The questionnaire completion rate was 75.6% during SOC tx. Meaningful improvement in PRO scores (defined by a literature-based minimally important difference of 10 points in mean score) was not achieved in most patients. This was most notable in pain symptoms, with 62% of patients showing no meaningful improvement during the first 3 months of tx and 55% showing no improvement during the full tx duration. In the overall population, the least square (LS) mean changes from BL during SOC tx (N=172) and during subsequent tx (SQ, N=87) were as follows – physical functioning: 2.5 during SOC and -11.8 during SQ; global health status: 1.9 during SOC and -2.0 during SQ; thinking about illness: 9.4 during SOC and -7.5 during SQ; worried about dying: 6.1 during SOC and -14.4 during SQ; worried about health: 7.9 during SOC and -9.7 during SQ; and visual analog scale: 2.4 during SOC and -0.6 during SQ (with higher scores indicating better outcomes for all measures); and for pain score: -1.4 during SOC and 1.8 during SQ; fatigue symptoms: -5.3 during SOC and 6.1 during SQ; restless or agitated: -2.6 during SOC and 9.3 during SQ (with higher scores indicating worse outcomes for all measures). Patients with ≥very good partial response during SOC tx had greater improvement in PRO scores, including LS mean change for pain (-14.9).
Conclusions: Limited gains in HRQoL (most notably in pain symptoms) were reported in this first prospective study of real-life current SOC in triple-class exposed patients. Effective therapies are needed to help patients achieve deep responses and delay disease progression, as these are associated with improved HRQoL.

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Real-world assessment of treatment patterns and outcomes in patients with lenalidomide-refractory relapsed multiple myeloma from the SEER-Medicare database

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Introduction: Significant advances in multiple myeloma (MM) therapies have been made in recent years, but data on real-world outcomes with these newer agents in patients with relapsed/refractory disease are limited. Here, we report the treatment patterns and survival outcomes for patients with MM from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database who have received 1–3 prior lines of therapy (PL), including exposure to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and are lenalidomide-refractory.
Methods: Data collected from January 2016 to December 2019 (last available data) were analyzed. Adult patients with MM were included if they had received 1–3 PL, were exposed to a PI and IMiD, and were lenalidomide-refractory. Time zero (T0) was the start date of the first treatment post eligibility. Descriptive statistics were used to assess patient characteristics at baseline and treatment patterns, stratified by PL. Survival outcomes, including overall survival (OS) and time to next treatment (TTNT), were analyzed using the Kaplan-Meier method. OS was defined as the time interval between T0 and all-cause mortality. TTNT was defined as the time interval between T0 and start of subsequent treatment or death, whichever comes first.
Results: From 70,262 patients with MM, 1,319 patients were identified (1 PL: n=466; 2 PL: n=641; 3 PL: n=212), with a median time from MM diagnosis to T0 of 25.1 months. Median age was 75 years, 52.5% of patients were male, 82.6% were white, and 10.9% were black. Patients had a mean Charlson comorbidity index of 3. Approximately 85 unique subsequent treatment regimens were reported overall, and the most common regimens based on hierarchy were daratumumab- (24.2%), pomalidomide- (16.5%), and carfilzomib-based (13.0%). Doublet therapies were most common for patients with 1 PL (36.7%) and 2 PL (38.2%), while triplet therapies were most common for 3 PL (35.4%). Overall, the most common regimens were pomalidomide/dexamethasone (Pd; 7.6%), daratumumab-Pd (6.5%), daratumumab/bortezomib/dexamethasone (6.4%), and bortezomib-Pd (5.6%). Median OS was 32.1 months, 17.7 months, and 10.8 months for 1 PL, 2 PL, and 3 PL, respectively. Median TTNT, serving as a proxy for progression-free survival, was 5.5 months, 5.7 months, and 4.5 months, for 1 PL, 2 PL, and 3 PL, respectively.
Conclusions: Despite many available treatment options, patients who have received 1–3 PL, are PI- and IMiD-exposed, and lenalidomide-refractory progress quickly through currently available therapies, and survival outcomes remain poor. This population-based analysis demonstrates the absence of a clear standard of care for this difficult-to-treat, older, comorbid patient population, and it suggests the need for new and effective treatment regimens, as well as multidisciplinary supportive care.

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Real-world assessment of treatment patterns and outcomes in patients with lenalidomide-refractory relapsed multiple myeloma from the Flatiron database

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Introduction: Despite advances in multiple myeloma (MM) treatment, selecting a treatment regimen in patients with refractory disease remains a challenge. Most patients receive combinations of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and/or anti-CD38 monoclonal antibodies as first-line therapy. There are limited data characterizing subsequent treatments and outcomes in this difficult-to-treat population. We report real-world treatment patterns, survival outcomes, and prognostic variables in lenalidomide-refractory patients from the Flatiron database who have received 1–3 prior lines of therapy (PL), including a PI and IMiD.
Methods: Data were derived from the Flatiron Health deidentified electronic health record database of US patients with MM (Jan 2011 – Aug 2021) and were analyzed starting from January 2016 onward. Patients with MM who received 1–3 PL, were exposed to a PI and IMiD, were lenalidomide-refractory, and had an Eastern Cooperative Oncology Group

(ECOG) performance status (PS) < 2 were included. Time zero (T0) was the time when the first subsequent line of therapy was started after a patient met the inclusion criteria above. A patient may have been included more than once, with a new T0 for each line. Descriptive statistics were used to assess patient characteristics at baseline and treatment patterns stratified by PL. Time-to-event analyses were estimated using the Kaplan-Meier method (starting at T0) for progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS). Univariate Cox regression models were evaluated for exploring prognostic factors.
Results: A total of 1,100 patients were identified from approximately 12,000 patients with MM in the database (1 PL: n=378, 2 PL: n=442, 3 PL: n=280). Median age was 69.5 years; 54% of patients were male, 64% were white, and 17% were black. Median time since diagnosis was 1.8 years. The most common subsequent treatment regimens based on hierarchy were daratumumab- (35.9%), carfilzomib- (19.1%), pomalidomide- (15.2%), or bortezomib-based (11.5%). Most patients had doublet (46.1%) or triplet (43.1%) therapy; daratumumab/pomalidomide/dexamethasone (DPd) was the most commonly used regimen (13.5%). Median PFS was 5.8, 6.1, and 5.9 months for patients who had 1, 2, and 3 PL, respectively. Median TTNT was 7.9, 7.3, and 7.5 months for 1, 2, and 3 PL, respectively, and median OS was 42.3, 34.0, and 35.4 months, respectively. Prognostic factors for OS and PFS were International Staging System (ISS) stage, hemoglobin at T0, ECOG PS, and cytogenetic risk; age was an additional prognostic factor for OS.
Conclusions: This analysis demonstrates that PI-exposed, lenalidomide-refractory patients have poor PFS and move quickly through available therapies, regardless of the number of PL. These data suggest the need for new, effective, and safe treatment regimens for this patient population.

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Efficacy of selinexor in relapsed/refractory multiple myeloma (RRMM) patients with del17p and other high-risk abnormalities: a retrospective single-center study

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Introduction: Selinexor (Seli) is a first-in-class, oral selective inhibitor of a nuclear export protein, exportin-1 (XPO1). Seli exhibits its antitumor effect by blockage of XPO1, which increases nuclear retention of tumor suppressor proteins (TSPs), including p53, thereby limiting translation of oncogenes & triggers cell cycle arrest & death of malignant cells. Multiple Myeloma (MM) patients with del17p are deficient in TP53 and have a particularly poor prognosis. Given its unique mechanism of action, we investigated whether Seli has increased efficacy in RRMM patients with del17p compared to other high-risk cytogenetics (OHRC).
Methods: This is an IRB-approved observational study of RRMM patients with high-risk cytogenetics (del17p, t (4;14), t (14;16) or gain 1q) treated at Levine Cancer Institute (LCI) with a Seli-based regimen between July 2019 and January 2022. Time-to-event endpoints (PFS, OS) were evaluated using Kaplan Meier (KM) methods. Log-rank tests compared time to event endpoints between cohorts [del17p vs. OHRC].
Results: We identified 31 RRMM patients with high-risk cytogenetics, including 12 with del17p and 19 with OHRC. The median age was 60.5 vs. 69 years (del17p vs. OHRC, p=0.55). The median prior line of therapies was 5 (Range: 3-12, p=0.87) with similar rates of prior autologous stem cell transplant in both arms (66.7% vs. 68.4%, p=0.99). The most frequently used regimen was Seli-Pomalidomide-dexamethasone(dex) in the del17p and Seli-Carfilzomib-dex in the OHRC, with no statistically significant difference(p=0.58). The median time to start Seli-based regimen after initial MM diagnosis was 5.6 years for del17p and 4.3 years in OHRC (p=0.88). The median follow-up time after the start of Seli-based regimen was 6.5 months (mos) in the del17p and 7.2 mos in OHRC (p=0.88). In the del17p group, 58.3% had an objective response versus 52.9% in the OHRC (p=0.99). Depth of response was also similar across both arms (16.7% vs. 11.8% ≥VGPR p = 0.99). Median OS was 10.1 mos in the del17p vs. 8.1 mos in the OHRC (p= 0.45). The median PFS was 4.2 mos in the del17p compared to 1.4 mos in OHRC (p = 0.6). Interestingly, the 4 mos PFS was significantly improved in the del17p vs. OHRC (58.3% vs. 31.6%, respectively).
Conclusions: Overall, Seli-based regimens showed promising responses even in this heavily pretreated, high-risk population. Our analysis of a small patient population suggests that Seli-based regimens lead to similar outcomes among RRMM patients with del17p and OHRC. This contrasts with several studies of combinations of novel therapies in this population, where the del17p patients often have a poorer prognosis. Interestingly, our data suggest that using a Seli-based regimen appears to have some initial PFS benefit in del17p patients for 4-6 mos, which suggests it's using as a bridging regimen in patients waiting for subsequent therapies. Further investigation into this population is warranted, including in earlier lines of therapy, in hopes of seeing a more durable response.

P-243
Subgroup analyses from the LocoMMotion study of real-life current standard of care (SOC) in patients with relapsed/refractory multiple myeloma (RRMM)

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Introduction: There is an urgent and currently unmet clinical need in patients (pts) with RRMM who are triple-class exposed (proteasome inhibitor [PI], immunomodulatory drug [IMiD], and anti-CD38 monoclonal antibody [mAb]). Here we present efficacy in subgroups of pts treated with SOC therapies in the LocoMMotion study (NCT04035226), the first prospective multinational study of real-life SOC in triple-class exposed pts with RRMM.
Methods: This noninterventional study was conducted across 76 sites (13 United States; 63 Europe) in pts who had ≥3 prior lines of therapy (LOT) or were double refractory to a PI and an IMiD; received a PI, an IMiD, and an anti-CD38 mAb; and had disease progression during/after their last LOT. Real-life SOC therapies were defined as those used in local clinical practice. Responses and disease progression (per International Myeloma Working Group criteria) were assessed by response review committee. Subgroups were based on the following baseline (BL) characteristics: age, Eastern Cooperative Oncology Group performance status (ECOG PS), renal function, International Staging System stage, presence of extramedullary plasmacytoma, lactate dehydrogenase (LDH) level, % of bone marrow plasma cells, number of prior LOT, triple-class or penta-drug exposure, and refractoriness.
Results: A total of 248 pts were enrolled as of May 21, 2021 (median follow-up 11.0 mo). Pts were treated with a median of 4.0 (range, 1–20) cycles of SOC therapy. Efficacy analyses in subgroups indicated that pts with refractoriness to 3 classes of antimyeloma therapy, presence of extramedullary plasmacytomas, high LDH, and ECOG PS ≥1 had generally worse outcomes compared with pts who did not have these characteristics. In the total population (N=248), median overall survival (OS) and progression-free survival (PFS) were 12.4 mo and 4.6 mo, respectively. Among subgroups, median OS and PFS results were as follows: triple-class refractory (n=183; OS 11.1 mo and PFS 3.9 mo), non-triple-class refractory (n=65; OS not evaluable [NE] and PFS 8.2 mo), BL ECOG PS of 0 (n=63; OS NE and PFS 5.4 mo), BL ECOG PS of ≥1 (n=184; OS 10.8 mo and PFS 4.4 mo), presence of extramedullary plasmacytomas (n=33; OS 8.2 mo and PFS 3.4 mo), absence of extramedullary plasmacytomas (n=215; OS 13.0 mo and PFS 5.1 mo), LDH ≤245 U/L (n=114; OS 13.8 mo and PFS 5.7 mo), LDH >245 U/L (n=72; OS 7.4 mo and PFS 3.3 mo). Across all subgroups, overall response rate ranged from 20.0–43.1%. Age and number of prior LOT did not affect efficacy results.
Conclusions: In this first prospective study of real-life SOC treatment in triple-class exposed pts with RRMM, subgroup analyses demonstrated that specific patient and disease characteristics were associated with poor outcomes. Triple-class refractory and non-triple-class refractory subgroups had poor outcomes; however, the latter had longer median PFS. These data should be considered when planning bridging strategies for pts treated with CAR-T therapy.

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Elotuzumab in combination with pomalidomide and dexamethasone (EloPd) in relapsed refractory multiple myeloma (RRMM): a network meta-analysis

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Introduction: Multiple myeloma (MM) is an incurable, life-limiting disease that accounts for approximately 13% of haematological malignancies. Elotuzumab is a monoclonal antibody aimed to improve outcomes in relapsed/refractory MM and has been investigated in combination with pomalidomide plus dexamethasone (EloPd), in the ELOQUENT-3 trial. Although EloPd has been compared against pomalidomide + dexamethasone (dex) (Pd), it is not known how the final data for EloPd from ELOQUENT-3 compares with other key treatment options. A systematic literature review (SLR) and network meta-analysis (NMA) was

conducted to determine the comparative effectiveness of EloPd with other relevant options.
Methods: An SLR based on searches of Medline, Embase, PubMed and the Cochrane Library was conducted to identify randomised controlled trials of treatments for RRMM. The studies of interest investigated treatments relevant for 3L + MM based on ESMO guidelines. Data from trials that met the SLR's inclusion criteria and the most recent data from ELOQUENT-3 were extracted. There exist two distinct, separate networks in 3L+ MM; those with pomalidomide + dex (Pd) as a control arm; daratumumab + pomalidomide + dex (DPd), isatuximab + pomalidomide + dex (IsaPd), pomalidomide + cyclophosphamide + dex (PCd) and those with a bortezomib + dex (Vd) control arm; daratumumab + bortezomib + dex (DVd), venetoclax + bortezomib + dex (VenVd), Selinexor + bortezomib + dex (SVd). To connect these networks, an external Vd arm was generated for EloPd using patient-level data from the ELOQUENT-3 and OPTIMISMM trials. The main inclusion and exclusion criteria were similar, except for the inclusion of patients refractory to lenalidomide and for the inclusion of patients having one prior line of therapy. Given this difference, a propensity score matching was used (adjusting for treatment effect modifiers), to keep most of the patients in OPTIMISMM (1 prior line patients excluded) and select the closest patients from ELOQUENT-3. For the NMA for progression free survival (PFS) vs. DVd, the impact of fixed duration Vd in the control arm of CASTOR was adjusted for using a matched adjusted indirect comparison (MAIC) to the Vd arm of OPTIMISMM.
Results: Analysis found that EloPd ranked first for both PFS and overall survival (OS) and fourth for overall response rate (ORR) versus the following treatments: IsaPd (PFS HR 0.85 [0.49,1.49], OS HR 0.77 [0.45,1.35]), DPd (PFS HR 0.80 [0.46,1.40], OS HR 0.65 [0.35,1.19]), PCd (PFS HR 0.77 [0.39,1.53], OS HR 0.93 [0.42,2.09]), Pd (PFS HR 0.51 [0.32,0.81], OS HR 0.59 [0.37,0.93]), Vd (PFS HR 0.51 [0.32,0.80], OS HR 0.74 [0.42,1.30]), DVd (PFS HR 0.85 [0.44,1.64], OS HR 0.97 [0.46,2.03]), VenVd (PFS HR 0.87 [0.49,1.52], OS HR 0.51 [0.23,1.09], SVd (PFS HR 0.73 [0.42,1.24], OS HR 0.89 [0.45,1.74]).
Conclusions: Evidence suggests that EloPd is effective in improving PFS and OS in patients with RRMM when compared with other established and new regimens.

P-245
Real-world outcomes in multiple myeloma (MM) patients who received subsequent therapy after daratumumab from the PREAMBLE study

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Introduction: Multiple myeloma (MM) is an incurable, life-limiting disease that accounts for approximately 13% of haematological malignancies. Elotuzumab (Elo) is a monoclonal antibody aimed to improve outcomes in MM and has been investigated in combination with pomalidomide plus dexamethasone (dex) (EPd), ELOQUENT-3 and lenalidomide plus dex (ERd), ELOQUENT-2. Due to the timing of the ELOQUENT studies, few enrolled patients had received prior daratumumab (Dara) and the mechanism of action of Dara results in NK cell depletion, a cell population through which Elo mediates antibody-dependent cellular cytotoxicity. As such real-world evidence from the PREAMBLE registry was analysed to evaluate efficacy for patients who received Elo combinations or other therapies after Dara.
Methods: Four cohorts were identified from the registry. Cohort 1: Elo-post-Dara group (n=37) (patients who received Elo combinations on any line of therapy (LoT) after the first-use of (primary) Dara line); Cohort 2: Elo-immediate-post-Dara group (n=24) (patients who received Elo combinations on the immediate next LoT after the primary Dara line); Cohort 3: non-Elo-post-Dara group (n=148) (patients who received non-Elo containing regimens on any subsequent LoT after the primary Dara line);Cohort 4: Elo-post-non-Dara group (n=56) (patients who received Elo combinations after other (non-Dara containing) MM therapy (with Elo LoT matched to Cohort 1). Elo combinations were combined into a single Elo group due to small sample size and this group was mainly comprised of Elo + lenalidomide combinations followed by Elo + pomalidomide combinations and others. Descriptive statistics were used to describe demographic, clinical characteristics, and treatment patterns. Missing data were not imputed but reported as missing. Adjusted Kaplan-Meier survival curves for progression free survival (PFS) and overall survival (OS) were generated based on Cox proportional hazards regression models to account for prognostic covariates: age, gender, race, ISS stage, and time from initial diagnosis to index date.
Results: There was no statistically significant difference for PFS between Elo-immediate-post-Dara and Non-Elo-Post-Dara or between Elo-Post-Dara and Elo-Post-Non-Dara. OS was limited by lack of reporting of subsequent therapies post index treatment and no statistically significant difference was seen between Elo-immediate-post-Dara and Non-Elo-Post-Dara but was seen between Elo-immediate-post-Dara and Elo-Post-non-Dara, favouring Elo-Post-non-Dara.
Conclusions: Elo combinations remain potent treatment options after Dara and patients are as likely to see a PFS benefit when receiving Elo combinations as when receiving all other standard of care. Elo-treated patients are also as likely to see a PFS benefit whether they've previously received Dara or not.

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Impact of defining refractoriness vs lines of therapy in relapsed/refractory multiple myeloma

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Introduction: Prior treatments for multiple myeloma (MM) have traditionally been described using lines of therapy (LOT) with a LOT defined as ≥1 complete cycles of a single/ combination of drugs, or a planned sequential therapy of various regimens. While number of LOT influences subsequent response to therapy, patients with similar prior LOT may have received vastly different treatments. Further, a LOT can change for reasons other than disease progression- e.g., toxicity, end of planned therapy, inadequate response to therapy, etc. that are more dependent on practice patterns than disease biology. A more meaningful way would be defining refractoriness to drugs/ drug classes, which could better reflect disease biology.
Methods: We retrospectively identified 311 relapsed/refractory MM (RRMM) patients (pts) who started systemic chemotherapy for relapse after January 2015. Pts were classified by prior LOT at index relapse, and refractoriness to number of MM drugs/classes. Refractoriness was defined as disease progression on or within 60 days of last therapy. Drug classes were defined based on mechanism of action. Progression free survival (PFS) and overall survival (OS) were described from date of index relapse using Kaplan Meier (KM) and Cox models.
Results: Overall, the median age was 63.3 yrs; 61.4% pts were male. 27/27.3/28.2% were international staging system (ISS) stage I/II/III, respectively; 27.9% had mSMART high risk disease. Median number of LOT was 2 (range 1-9). Median follow up from index relapse was 45.2 months (mos). Median PFS/OS were 11.6 /48.3 mos, median PFS and OS by 1/2/3/≥4 LOT were 19.5/14.5/11.3/5.0 and 61.4/45.3/39.1/30.8 mos respectively. Median PFS and OS by 0/1/2/≥3 drugs refractory to were 29.5/14.5/10.0/5.0 and NR/48.7/40.2/25.1 mos respectively. Median PFS and OS by 0/1/2/≥3 drug classes refractory to were 29.5/14.5/8.4/4.9 and NR/55.1/33.6/26.0 mos respectively. Harrell's C for LOT/number of drugs/number of drug classes were 0.594/0.645/0.643 for PFS and 0.573/0.632/0.631 for OS. After adjusting for age, high risk FISH, and ISS stage; Cox model PFS and OS hazard ratio (HR)s (95% CI) for 1/2/3/≥4 LOT were 1/1.23 (0.79-1.92)/1.68 (1.05-2.69)/4.38 (2.78-6.91) and 1/1.36 (0.80-2.33)/1.83 (1.01-3.31)/ 2.92 (1.77-4.82); for 0/1/2/≥3 drugs refractory were 1/1.34 (0.85-2.11)/1.95 (1.15-3.30)/5.55 (3.34-9.23) and 1/1.36 (0.75-2.50)/2.79 (1.48-5.30)/ 4.69 (2.55-8.60); and 0/1/2/≥3 drug classes refractory were 1/1.33 (0.85-2.10)/2.38 (1.46-3.89)/5.12 (3.00-8.74) and 1/1.35 (0.74-2.50)/3.15 (1.72-5.80)/ 4.38 (2.34-8.20). Classification by refractoriness led to better separation of KM curves and HRs, and better Harrell's C vs LOT.
Conclusions: Refractoriness to number of drugs/ drug classes is a better way of classifying RRMM patients as compared to number of LOT and can have implications in determining eligibility for advanced MM treatments (e.g., CAR T-cell therapy) and in design of clinical trials.

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Addressing the knowledge gap to optimize treatment sequencing for patients with relapsed/refractory multiple myeloma

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Introduction: Some of the continuing burden of multiple myeloma (MM) may be attributed to the failure of the multidisciplinary team to maintain a working knowledge of emerging data and consensus recommendations that can rationally inform clinical decision making. This study was conducted to determine if an online, case-based continuing medical education (CME)/nursing continuing professional development (NCPD)–approved activity could identify and close practice gaps caused by the rapidly changing treatment landscape of relapsed/refractory MM (RRMM).
Methods: The activity, Optimizing Treatment Sequencing for Patients With Relapsed/Refractory Multiple Myeloma, chaired by Shaji Kumar, MD, of the Mayo Clinic Cancer Center, was made accessible on September 13, 2021. Learners participated in a 1-hour activity that assessed recent clinical trial findings on novel sequential treatment approaches for RRMM and evaluated strategies to monitor and manage adverse events associated with these novel therapies. A repeated-pairs pre- and post-activity assessment consisting of case-based questions gauged learners' ability to apply emerging data to clinical decision making. Knowledge gaps and learning gains were calculated based on percentages of learners obtaining correct responses on the pre- and post-activity assessments. Significance was assessed using a chi-squared test.
Results: As of May 26, 2022, 230 clinicians had completed the activity for credit. Baseline assessment data revealed gaps in knowledge regarding the timing and indications for initiating therapy in relapsed MM (57.8% knowledge gap at baseline); the efficacy of idecabtagene vicleucel for RRMM (86.5% knowledge gap); the efficacy of isatuximab/pomalidomide/dexamethasone for RRMM (67.8% knowledge gap); the management of grade 2 selinexor-related diarrhea (85.2% knowledge gap); and adverse event monitoring for belantamab mafodotin (69.6% knowledge gap). The post-activity assessment revealed a statistically significant decrease in all knowledge gaps, including timing and indications for initiating therapy in relapsed disease (56.1% mean improvement); efficacy of idecabtagene vicleucel for RRMM (79.6% improvement); efficacy of isatuximab/pomalidomide/dexamethasone for RRMM (62.6% improvement); management of grade 2 selinexor-related diarrhea (73.5% improvement); and adverse event monitoring for belantamab mafodotin (67.4% improvement), with $P < .000001$ for all values.

Conclusions: These data demonstrate an educational need regarding the latest developments in the treatment of RRMM. They also demonstrate that online, case-based CME/NCPD–approved activities can result in statistically significant improvements in clinicians' knowledge of therapeutic advances and management of treatment-related adverse events for patients with RRMM.

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A prospective, multicenter, observational study of ixazomib plus lenalidomide-dexamethasone in 295 Japanese patients with relapsed/refractory multiple myeloma

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Introduction: Ixazomib (Ixa) plus lenalidomide (Len)-dexamethasone (Dex) has proven efficacy and is approved for relapsed/refractory multiple myeloma (RRMM), but real-world data are limited, especially in frail and elderly patients (pts). This study examined the real-world effectiveness and safety of Ixa-Len-Dex (IRd) in pts with RRMM and collected cytogenetic risk and frailty data in clinical practice in Japan, the world's first super-aged society.
Methods: A multicenter, prospective, observational study enrolled Japanese adults (aged ≥20 years) with RRMM who were scheduled to initiate IRd. The primary endpoint was progression-free survival (PFS), defined as the time from the first IRd dose to confirmed progressive disease or death. Secondary endpoints were overall survival (OS), time to next treatment (TTNT), duration of response (DOR), overall response rate (ORR) and very good partial response or better (≥VGPR) rate. Subgroup analyses by frailty score, number of prior regimens, type of relapse and cytogenetic risk [t(4;14), t(14;16), t(11;14), del(17p) or 1q gain] were conducted. The median time-to-event for endpoints were estimated using the Kaplan-Meier method.
Results: 295 pts were included in the full analysis set (median age 74 years; 56.9% male; median number of prior lines of therapy was 2; 37.3% had creatinine clearance < 60 mL/min; 28.5% had an International Myeloma Working Group frailty score ≥2). After a median follow-up of 25.0 months, median PFS was 15.3 (95% confidence interval 12.4–19.5) months; median OS was not reached. Median TTNT and DOR were 13.2 and 29.7 months, respectively, and the ORR and ≥VGPR rate were 53.9% and 31.5%, respectively. By frailty score, median PFS was 13.5, 15.7 and 16.0 months in the frail, intermediate fitness and fit subgroups, respectively. Median PFS was 29.0, 19.2 and 6.9 months for pts receiving 1, 2 and ≥3 prior regimens, respectively. By type of relapse, median PFS was 7.9 and 16.0 months for pts with clinical relapse and paraprotein relapse, respectively. By cytogenetic risk, median PFS was 12.6 and 30.2 months in pts with at least one of t(4;14), t(14;16), del(17p) or 1q gain and pts without them, respectively. Median relative dose intensity (RDI) was 66.7%, 40.0% and 39.9% for Ixa, Len and Dex, respectively. Adverse events (AEs) of any grade were reported in 84.4% of pts, grade ≥3 AEs in 58.0%, serious AEs in 32.5%, AEs leading to discontinuation in 24.7% and AEs leading to death in 8.1%. The most common AEs were diarrhea (27.1%), platelet count decreased (26.4%), neutrophil count decreased (25.8%) and white blood cell count decreased (23.7%); no new safety concerns were identified.
Conclusions: In this real-world study, pts receiving IRd were frailer, older, more heavily treated and with a lower RDI than pts included in clinical trials. These results suggest that IRd

therapy is an effective and tolerable treatment option in real-world settings outside of clinical trials.

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Real world evidence and outcomes of patients who are exposed or refractory to lenalidomide at the time of first relapse: a Greek registry analysis

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Introduction: Lenalidomide (Len) is an integral part of first line (1L) therapy of multiple myeloma (MM). Len resistance critically affects treatment decisions but there is limited clinical or real-world (RW) data on treatment strategies and outcomes of patients who progress on or after 1L Len therapy. Here, we describe the characteristics, treatment patterns and outcomes of adults with MM, who relapsed and were either Len-refractory (LR) or not (NLR).
Methods: We analyzed the medical records of sequential patients from a RW registry in a single Greek center, who received 1L Len therapy between 2015 and 2018 and had initiated 2L therapy. Len refractoriness was defined according to IMWG criteria (Rajkumar et al. Blood 2011).
Results: The Len-exposed (LE) cohort (N=249) included 138 (55.4%) LR patients after 1L. At start of 1L, ISS stage distribution was similar for LR and NLR patients (36% and 32% were ISS-3), but high risk (HR) cytogenetics (30% vs 13%) and lactate dehydrogenase levels above the upper limit of normal (22% vs 11%) were more common in LR than NLR patients, respectively, as reflected in the revised ISS-3 (26% vs 12%). In 2L therapy, 13% of LR and 51% of NLR patients received Len-based regimens; 65% of LR and 45% of NLR patients received a triplet. A proteasome inhibitor (PI), pomalidomide (Pom) or anti-CD38 was used in 69%/28%/22% of LR patients vs 57%/8%/9% of NLR patients, respectively. An IMiD-only (Pom or Len) or PI-only regimen was used in 22%/38% of LR vs 36%/28% of NLR patients, respectively. The overall response rate (ORR) was 64% for the whole LE cohort (N=159): 67% in LR vs 72% in NLR patients. Use of a triplet (vs doublet) was associated with improved ORR (LR: 68% vs 38%; NLR: 80% vs 68%); a PI+IMiD regimen (vs not) was associated with higher ORR in both subgroups (LR: 82% vs 53%; NLR: 100% vs 67%), while use of anti-CD38 (vs not) was associated with higher ORR in LR (75% vs 52%) but not in NLR patients (67% vs 74%). Median PFS in 2L was 12.5 months for the whole LE cohort, but shorter for LR than NLR patients (10.7 vs 19.1 months). Median OS from start of 2L was 32 months and was shorter for LR than NLR patients (23.8 vs 53.6 months). Regardless of subgroup, the use of triplets was associated with longer 2L PFS and OS than doublets. In LR patients, the use of a PI-based regimen (vs not) was associated with longer PFS (11.7 vs 6.4 months) and OS (28.1 vs 19.1 months) in 2L. In NLR patients, Len-based regimens remained effective (ORR: 81%, 2L PFS: 29.9 months, OS: 81.6 months). LR patients with HR cytogenetics had shorter 2L PFS (7.3 vs 11.7 months) and OS (18.7 vs 28.1 months) than those without. 2L PFS was shorter in patients receiving < 10 mg of Len as last dose than in those receiving a 10-25 mg dose.
Conclusions: In this real-world Len-exposed cohort, Len refractoriness during 1L was associated with poor PFS and OS in 2L despite the relatively high response rates, emphasizing the need for novel strategies to overcome Len resistance.

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Predictive factors for outcomes after salvage autologous hematopoietic cell transplant for patients with relapsed/refractory multiple myeloma: a single-institution experience

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Introduction: Novel therapies, including CAR-T cell therapy and bispecific targeting agents, have emerged as treatment options in relapsed/refractory multiple myeloma (RRMM). However, salvage autologous hematopoietic cell transplant (AHCT2) remains a viable option in the era of modern MM therapy. As data from prospective clinical trials is sparce, we look to build upon pre-existing retrospective data with our own experiences to better evaluate the role of salvage AHCT2 and determine the factors that influence outcomes.
Methods: We conducted a single-institution, retrospective analysis of patients who received salvage AHCT2 at The Ohio State University from 2000-2018. A transplant was defined as 'salvage' if the patient had received a prior AHCT1 and underwent AHCT2 after evidence of disease progression, regardless of the number of prior lines of therapy since AHCT1. Patients who received a second transplant as part of a planned tandem or auto-allo transplant were excluded.
Results: 58 patients aged 41-74 (median 62) were treated with salvage AHCT2. Patients had 1-17 (median 2) lines of

therapy post-AHCT1 prior to salvage AHCT2; 39 (70%) had prior immunomodulatory imide drugs (IMiDs), 46 (82%) had prior proteasome inhibitor (PIs), and 11 (20%) had prior anti-CD38 monoclonal antibodies as part of re-induction therapy; 24 (41%) patients attained complete response (CR) or very good partial response (VGPR) prior to salvage AHCT2. 42 (72%) were treated with melphalan 200mg/m^2 as conditioning regimen before infusion of a median of 3.8 x10^6 CD34+ cells/kg. 33 (57%) patients had maintenance therapy and 46 (79%) patients attained CR/VGPR as best response after salvage AHCT2. The median progression free survival (PFS) after salvage AHCT2 was 1.6 years and the median overall survival (OS) was 3.6 years. On univariable analysis of pre-salvage AHCT2 factors, beta-2-microglobulin, ISS 3, R-ISS 2 and 3, presence of high-risk cytogenetics, and not having attained CR/VGPR were predictive of inferior PFS. Furthermore, less than 2 years of remission after AHCT1 and having more than 2 lines of therapy post-AHCT1 before salvage AHCT2 were associated with inferior PFS. Melphalan 140mg/m^2 compared to melphalan 200mg/m^2 and no maintenance therapy compared to maintenance therapy were not associated with shorter PFS. Multivariable analysis and overall survival outcomes will be updated during the meeting. There was no transplant-related mortality in this patient cohort.

Conclusions: For patients deriving benefit after their AHCT1, salvage AHCT2 was safe and resulted in deep and durable remissions. Factors associated with inferior PFS in published studies with AHCT1 were also associated with inferior PFS with salvage AHCT2. Efforts aimed at maximizing pre- and post-salvage AHCT2 depth of remission may translate to improved outcomes. Large randomized clinical trials are needed to identify the patient population that derive the most benefit from this therapy.

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Comparative effectiveness of teclistamab versus real-world physician's choice of therapy for patients with triple-class exposed relapsed/refractory multiple myeloma

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Introduction: Teclistamab is a B-cell maturation antigen × CD3 bispecific antibody currently being evaluated in MajesTEC-1 (NCT04557098), an open-label, single-arm, phase 1/2 trial in patients with RRMM who had received ≥3 prior lines of therapy (LOT) and were triple-class exposed (TCE) to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Given the absence of a control arm in MajesTEC-1, we assessed the comparative effectiveness of teclistamab versus physician's choice of therapy using an external control arm from a real-world database.

Methods: An external control arm for MajesTEC-1 was created from eligible patients in the nationwide de-identified electronic health record-derived Flatiron Health multiple myeloma cohort database who started a new line of therapy (physician's choice) following triple-class exposure between January 2011 and August 2021, received ≥3 prior LOT, progressed within 12 months of last LOT, and satisfied key MajesTEC-1 eligibility criteria. Individual patient data from MajesTEC-1 included patients (N=150) who received teclistamab (1.5 mg/kg weekly) at a clinical cutoff of Nov 9, 2021. Inverse probability of treatment weighting (IPTW) was used to adjust for imbalances in baseline covariates of prognostic significance: refractory status, progression on last LOT, cytogenetic risk, International Staging System stage, number of prior LOT, time since diagnosis, age, and hemoglobin. Outcomes of interest included overall survival (OS), progression-free survival (PFS), and time to next treatment (TTNT). These outcomes were analyzed as time-to-event data using IPTW adjusted Kaplan-Meier estimates and a weighted Cox proportional hazards model. A sensitivity analysis weighted patients on prior stem cell transplant, Eastern Cooperative Oncology Group performance status, race, sex, and type of MM, in addition to the base case variables.

Results: After IPTW, 364 patients in the Flatiron cohort contributed to 766 observations. Baseline characteristics were comparable between cohorts. Patients treated with teclistamab had improved OS (hazard ratio [HR] 0.73 [95% confidence interval (CI) 0.50–1.07]; P=0.1084), PFS (HR 0.43 [0.32–0.57]; P< 0.0001), and TTNT (HR 0.39 [0.28–0.53]; P< 0.0001) versus real-world physician's choice of therapy. Outcomes for the sensitivity analysis were consistent with those from the base case analysis.

Conclusions: Teclistamab showed improved effectiveness for OS, PFS, and TTNT compared with real-world physician's choice of therapy in patients with TCE RRMM who received ≥3 prior LOT. These findings highlight the clinical benefit of teclistamab in patients with TCE RRMM who have limited treatment options.

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Phase II study of the combination of daratumumab, ixazomib, pomalidomide, and dexamethasone as salvage therapy in relapsed/refractory multiple myeloma

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Introduction: The combination of daratumumab, pomalidomide, and dexamethasone (DPd) has previously demonstrated deep and durable responses including high rates of minimal residual disease (MRD) negativity, in patients with relapsed/refractory (R/R) MM. Quadruplet regimens may further improve results. We report interim findings from a phase 2 multicenter trial of the addition of ixazomib to DPd (DIPd) in patients with early R/R MM.
Methods: This is a prospective, multi-center, open-label, single arm phase II trial with a primary objective evaluate the overall response rate (ORR), safety, and efficacy of DIPd. Secondary endpoints include progression-free survival (PFS), overall survival (OS), and MRD-negativity rate. A Simon's optimal 2-stage design was used, with 14 subjects in stage 1 and 32 patients for stage 2. Eligible patients may not have had exposure to daratumumab or ixazomib, may not have progressed on pomalidomide, and may have received ≥1 and ≤3 prior lines of therapy. The first six patients in the safety run-in received daratumumab 16mg/kg IV weekly x 8 doses, biweekly x 8 doses, then monthly, pomalidomide 4mg orally on days 1-21 of a 28-day cycle, ixazomib 4mg orally on days 1, 8, 15 every 28 days, and dexamethasone 20-40mg weekly. Grade 3-4 neutropenia was observed in 100% of patients in the safety run-in, prompting dose reduction to ixazomib 3 mg and pomalidomide 3 mg by the DSMB. An amendment allowed for subcutaneous daratumumab. MRD assessments are being performed by EuroFlow for patients in suspected CR. Pharmacodynamic changes in patients' tumor microenvironments were established by custom panel mass cytometry to include T-cell memory and activated subpopulations, B-cell content, NK-cell subpopulations as well as MDSCs, Tregs and T-exhaustive markers, monocytes and dendritic cells.
Results: To date, 14 subjects were treated in stage 1, and 18 of 32 planned subjects in stage 2. Median age is 61.8y (range 41-87), with 50% female and 72% white. Patients have had a median of 1 prior line of therapy (range 1-3), and 47% (11/23) have high-risk cytogenetic features: -17p, +1q, t(14;16), t(14;20), or t(4;14) . Grade 3-4 treatment emergent adverse events include neutropenia (63%), lymphopenia (9%), non-specific leukopenia (3%), thrombocytopenia (9%), febrile neutropenia (13%), infection (22%), electrolyte disturbance (6%), respiratory condition (6%), infusion reaction (3%), thrombosis (3%), and psychiatric condition (3%). Median time on treatment is 4.8 months (range 0.4-30.8 mo), with 12 patients remaining on DIPd and 6 deaths (4 PD, 1 sepsis, 1 surgical complication). ORR to date is 83% (25/30), and best responses include 7 (23%) sCR, 7(23%) VGPR, 11 (37%) PR. After a median follow up of 15.1 months, the median OS is 38.9 months and PFS is 11.6 months.
Conclusions: The quadruplet regimen DIPd is a well-tolerated combination that has shown early safety, efficacy, and high ORR for patients with R/R MM, and appears beneficial for patients with high-risk genetic abnormalities

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Impact of adjusting bortezomib dose in the pomalidomide, bortezomib, and dexamethasone (PVd) combination: a post hoc analysis of the OPTIMISMM study

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Introduction: The phase 3 OPTIMISMM study demonstrated that PVd significantly improved progression-free survival (PFS) in lenalidomide (LEN)-pretreated patients (pts) with relapsed/refractory multiple myeloma (RRMM) vs bortezomib (BORT) and dexamethasone alone (Vd). As a large proportion of pts with RRMM may not be fit enough to remain on some therapies, including PVd, due to advanced age and comorbidities, dose adjustment may be required to improve treatment (Tx) tolerability and optimize clinical benefit. This post hoc analysis assessed the effect of BORT dose adjustment on the efficacy and safety of PVd vs Vd in OPTIMISMM.
Methods: Pts with RRMM and 1–3 prior lines of therapy (including a LEN-containing regimen) were randomized 1:1 to PVd or Vd. Pts receiving PVd could have BORT dose adjustment of 3 (not mutually exclusive) types: any dose reduction, any dose interruption (intermittent dose skipped), or dose withdrawal (no further BORT; remained on pomalidomide+dexamethasone). PFS, overall response rate

(ORR), safety, and quality of life (QOL) outcomes were assessed by Tx group and BORT dose adjustment.
Results: In the safety population (N=548) (data cutoff Oct 26, 2017), 278 (50.7%) received PVd, of whom 240 (86.3%) received a BORT dose adjustment and 270 (49.3%) received Vd. Median (range) time to first BORT dose adjustment was 1.5 mo (0.1–16.5). ORR was higher in PVd pts with a dose adjustment vs Vd (85.4% vs 51.5%; odds ratio [OR], 6.16; P< 0.001) than in pts without vs Vd (68.4% vs 51.5%; OR, 2.19; P=0.055). PVd pts with a dose adjustment had a higher median PFS vs Vd (12.1 vs 7.4 mo; hazard ratio [HR], 0.57; P< 0.001) than did pts without adjustment vs Vd (8.4 vs 7.4 mo; HR, 0.94; P=0.807). Median Tx duration was substantially longer in PVd pts with a dose adjustment vs those without (9.3 vs 4.5 mo) or Vd (5.0 mo). Incidence of grade ≥3 (G3) Tx-emergent adverse events (TEAEs) with PVd was similar for pts with or without a dose adjustment (90.4% vs 89.5%, respectively), and higher than with Vd (70.4%). For TEAEs of interest, only G3 peripheral neuropathy was substantially higher with a dose adjustment than without (12.5% vs 2.6%) or with Vd (5.2%). Tx discontinuation due to G3 TEAEs was higher in pts without a dose adjustment vs with an adjustment or Vd (28.9% vs 21.3% or 18.9%, respectively). Further analysis demonstrated that dose adjustment frequency was not affected by frailty (frail, 39.7% vs non-frail, 38.4%). However, dose adjustment in frail pts resulted in a reduced risk of progression vs Vd (HR, 0.6; P=0.011) compared to without a dose adjustment vs Vd (HR, 1.56; P=0.269). QOL was maintained.
Conclusions: In pts who received PVd, BORT dose adjustment did not negatively impact efficacy vs Vd. Longer and more continuous PVd Tx, with fewer Tx discontinuations, appears to be more important for efficacy than receiving the full BORT dose. Selection bias was possible as pts without an adjustment may have progressed early and pts on Tx longer were more likely to have an adjustment.

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Trends in attrition between first and second line therapy among older adults with multiple myeloma: a SEER-Medicare analysis

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Introduction: In clinical trials, novel therapeutics have improved outcomes in patients with relapsed multiple myeloma (MM). It remains to be seen whether real world outcomes for patients have also improved. Prior studies report that many patients never receive therapy for relapsed MM. Factors associated with risk of attrition are not well-described. We aimed to identify characteristics of patients who do not receive second-line therapy (SLT), and to explore how rates and patterns of attrition may have changed over time.
Methods: People diagnosed with MM (2007–2017) were identified in the SEER-Medicare database. Patients were excluded if diagnosed at death/autopsy, enrolled in managed care, discontinuously enrolled in Medicare parts A, B and D from diagnosis to 12 months after the end of first line therapy (FLT) or death, or did not have FLT. Patients were followed for 12 months after the end of FLT. FLT was defined as the combination of MM agents initiated within 30 days of first agent claim. The end of FLT was defined as the first of, the last FLT claim before a gap of more than 180 days, the initiation of any non FLT MM agent, or death. Any new MM agent claim after the end of FLT was considered SLT. We describe changes over time in the proportion of MM patients who did not receive SLT, and changes in the proportion who died during follow up without SLT using linear regression controlled for age, sex, race, marital status, National Cancer Institute (NCI) comorbidity index, rurality, SEER region, census tract poverty, and whether treated at an academic or NCI designated cancer center.
Results: Of the 10,014 patients with MM identified, 3,956 (40%) did not go on to receive SLT in the 12 months following FLT. Of patients not receiving SLT, 51% had died during follow up. Patients who did not receive SLT were significantly more likely to be Black, Hispanic, older, not married, received front line lenalidomide monotherapy or doublet, have more comorbidities, higher levels of poverty, were from the South and were less likely to have been treated at academic or NCI Cancer Centers. There was no significant change over time in the proportion of MM patients not receiving SLT in our follow up window in both unadjusted (B=0.01, p=0.93) and adjusted models (B=0.03, p=0.68). We found a statistically significant decline over time in the proportion of patients who died within 12 months of FLT without SLT in the unadjusted model (B=-0.20, p=0.03), though this relationship was nonsignificant in the adjusted model (B=-0.12, p=0.20).
Conclusions: Therapy discontinuation after FLT remains common for patients with MM, with significant disparities in receipt of SLT. Rates of attrition, including death prior to receipt of SLT, have not changed significantly over time. These findings support further investigation into causes of therapeutic attrition and development of strategies to reduce attrition to ensure that novel strategies translate into improved outcomes for patients with relapsed MM.

P-255
Isatuximab plus pomalidomide and dexamethasone in patients with relapsed and/or refractory multiple myeloma (RRMM) in real-life context: interim analysis of the retrospective IMAGE study

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Introduction: Isatuximab (Isa), an anti-CD38 monoclonal antibody, induces myeloma cell death by targeting a specific epitope on CD38. Based on the Phase 3 ICARIA-MM study, Isa plus pomalidomide (P) and dexamethasone (d; Isa-Pd) is approved in patients (pts) with RRMM who received ≥2 prior therapies. Prior to its approval, Isa was available in France under early access programs (EAP). This planned interim analysis of the non-interventional, retrospective IMAGE study describes baseline characteristics, progression-free survival (PFS), and safety among French pts with RRMM treated with Isa-Pd under the EAPs.
Methods: Data was collected from medical records of pts ≥18 years old with RRMM who received ≥1 dose of Isa under the EAPs. Effectiveness analysis was restricted to pts with ≥1 year of follow-up after Isa initiation. 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 AEs were coded using the Medical Dictionary for Regulatory Activities; AEs were not graded for severity.
Results: The effectiveness population included 294 pts from 62 study sites in France who met all inclusion/exclusion criteria and received ≥1 Isa dose under the EAPs from 29 Jul 2019 –1 Sep 2020; the safety population included all 299 pts who received ≥1 Isa dose. Unlike ICARIA-MM, the IMAGE study included daratumumab-refractory pts (19%) and pts who had received only 1 prior line of therapy (LOT). Pts in IMAGE had received fewer prior LOT (median of 2 vs 3 in ICARIA-MM) and a lower proportion of pts in the IMAGE effectiveness population were refractory to lenalidomide (73% vs 94%) and to last line of therapy (70% vs 97%) compared to those in the Isa-Pd arm of ICARIA-MM. At data cutoff, median (IQR) duration of Isa exposure for pts in IMAGE was 38.7 (14.0–65.4) weeks; Isa was permanently discontinued in 24.8% of pts, most commonly due to disease progression. At a median follow-up of 14.2 months, median PFS (mPFS) was 12.4 months (95% CI 9.0–15.0); this is in-line with investigator-assessed PFS (median 11.1 months [95% CI 7.8–13.8]) from the Isa-Pd arm of ICARIA-MM. Among pts who received only 1 prior LOT, mPFS was not reached (NR; 95% CI 9.6–NR). At least 1 AE was reported in 79 (26.4%) pts; the most common AE was neutropenia in 28 (9.4%) pts. AEs led to permanent Isa discontinuation in 4 (1.3%) pts. No pts experienced viral re-infection during Isa treatment; 1 (0.3%) pt developed a secondary primary malignancy.
Conclusions: In this IMAGE study reporting Isa-Pd use in real-life context from France, Isa-Pd demonstrated meaningful PFS with a manageable safety profile. Despite a few differences in study populations, similar mPFS in IMAGE and ICARIA-MM support Isa-Pd as a standard of care for RRMM. This is the first study to report meaningful PFS for Isa-Pd among pts at first relapse suggesting that Isa-Pd is a potential new treatment option in earlier lines of therapy. Funding: Sanofi

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Proteasome inhibition prolonged by in-class transitioned ixazomib-based regimen in newly diagnosed and first-line relapsed multiple myeloma patients in China: a real-world study

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Introduction: Bortezomib, is important in the treatment of multiple myeloma (MM), but it always discontinued by adverse event (AE). Assessing in-class transition (iCT) by ixazomib-based oral regimen is a good method for improving PI-based continuous therapy with efficiency, safety and convenience.
Methods: In this real-world retrospective study from Chinese eight hospitals during Oct, 2017-Feb, 2022, we analysed newly diagnosed multiple myeloma (NDMM) and first-line relapsed multiple myeloma (FRMM)patients without transplantation, who achieved at least partial response of bortezomib-based introduction, and then received ixazomib-based three drug oral regimen for 2 years or until progression/intolerant toxicity. Primary endpoint: progression-free survival (PFS). Key second endpoints included response rate, therapy duration and adverse event (AE).
Results: 199 patients were enrolled in this study (NDMM 81%, FRMM 19%, median age 63 years; 37% ≥ 65 years; 54% male; ISS stage I/II/III 14%/44%/42%. 53% high risk (HR,69/129) and 47% standard risk (SR,60/129) were tested by metaphase fluorescence in situ hybridization (M-FISH) according to Mayo clinic risk stratification. All patients received median 4 cycles (1-10) of bortezomib-based regimen including V-based introduction, and median 4 cycles (1-20) of iCT regimen including IRD1/ITD1/ICD1 (145/199, 18/199, 36/199). Median duration of total PI therapy was 10 months and of ixazomib-based regimen was 5 months(without the treatment discontinued by COVID 19 pandemic and economy), 58% patients remain on therapy. With 16 months median follow-up, 18-month progression free survival (PFS) rate was 76% (95% confidence interval,65-86) from the start of bortezomib-based induction and 55% (95% confidence interval,70-94) from the start of ixazomib-based treatment

(cause of COVID 19 pandemic and economy). ORR rate was 100% (sCR, 18/199, 9%; CR, 47/199, 24%; VGPR, 54/199, 27%; PR, 80/199, 40%) and 95% (sCR 17/76, 18%; CR, 22/76, 29%; VGPR, 11/76, 14%; PR, 22/76, 29%) after 6 cycles ixazomib-Based Regimen. ORR of HR (24/56) patients were 100% and 92%, ORR of SR patients (32/56) were 100% and 100% before and after ixazomib-based regimen, respectively. The ixazomib-safety profile was consistent with previous clinical trial data. In our study, 47% (94/199) of patients had any grade adverse events AE. In which, the most frequent grade < =2 one-hematological AEs were PN (27%), nausea and vomiting (6%), diarrhea (7%), hematological AEs were thrombocytopenia (2%),granulocytopenia (1%). The most frequent grade 3/4 AEs were agranulocytosis (1%) , rash (1%), pneumonia(1%), PN (1%).
Conclusions: In real-world China MM population, NDMM and FRMM patients are sensitive to PI-based continuous therapy with satisfied response rate; ixazomib-based iCT can permit prolonged PI-based therapy with promising efficacy and tolerated adverse events.

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A phase 3, two-stage study of iberdomide, daratumumab, and dexamethasone (IberDd) versus daratumumab, bortezomib, and dexamethasone (DVd) in relapsed or refractory multiple myeloma: EXCALIBER-RRMM

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Introduction: Trial in progress. New treatments (Txs) are needed to deepen and extend remissions in relapsed/refractory multiple myeloma (RRMM). Iberdomide (IBER) is a novel, potent oral cereblon E3 ligase modulator (CELMoD®) agent with enhanced tumoricidal and immune-stimulatory effects compared with IMiD® agents. IBER overcomes IMiD-resistance and has synergy with dexamethasone (DEX), daratumumab (DARA), and bortezomib (BORT) in vitro. IberDd demonstrated efficacy with a manageable safety profile and increased NK/T cell proliferation in a phase 1/2 trial in patients (pts) with RRMM. The EXCALIBER-RRMM phase 3 trial (NCT04975997) will compare the efficacy and safety of IberDd with that of DVd in pts with early-line RRMM.
Methods: This multicenter, open-label study will be conducted in 2 stages: in stage 1, ≥200 pts will be randomized 1:1:1:1 to 1 of 3 IBER doses (1.0, 1.3, or 1.6mg) +Dd or to the DVd arm to identify the optimal IBER dose in conjunction with DARA and DEX; in stage 2, ≈664 additional pts will be randomized 1:1 to IberDd at the selected IBER dose or to DVd, for efficacy and safety analyses (stage-1 pts in the selected dose cohort and DVd arm will also be included). Pts will be stratified by number of prior Tx lines (1 vs 2), age (≤70 y vs >70 y), and ISS staging at study entry (I–II vs III). Key eligibility criteria include age ≥18 y, < 2 prior lines of antimyeloma Tx, a partial response or better to ≥1 prior Tx, and confirmed disease progression during or after the last regimen. Prior anti-CD38 Tx is permitted only in stage 2 (≤10% of pts). Tx in the IberDd arm will consist of 28-day (D) cycles (C) with IBER on D1–21; 1800mg subcutaneous (SC) DARA on D1, 8, 15, and 22 of C1–2, D1 and 15 of C3–6, and D1 of ≥C7; and 40mg oral DEX on D1, 8, 15, and 22. Tx in the DVd arm will consist of 21-D cycles for C1–8 and 28-D cycles for ≥C9; 1800mg SC DARA on D1, 8, and 15 for C1–3, D1 for ≥C4; 1.3mg/m² SC BORT on D1, 4, 8, and 11 for C1–8; and 20mg oral DEX on D1, 2, 4, 5, 8, 9, 11, and 12 for C1–8. Tx will continue until confirmed progressive disease (PD), unacceptable toxicity, death, or consent withdrawal. Primary efficacy endpoint is progression-free survival (PFS), defined as time from randomization to PD or death. Assuming a decrease in PFS risk by 25% (HR=0.75) with IberDd, under exponential distribution assumption of PFS (1-sided α=0.025) and adjusted for 3 interim analyses, 458 PFS events will have ≈84% power to detect an improvement in Tx effect. The 3 planned interim analyses are: for IBER dose selection at end of stage 1; for PFS, to examine futility and superiority when ≈138 (30%) and ≈344 (75%) events, respectively, have been accumulated. Secondary endpoints include overall survival, duration of response, time to progression, overall response rate, minimal residual disease negativity rate, safety, and quality of life. Enrollment is expected to begin in Q2 2022.

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Real-world experience with isatuximab in patients with relapsed and/or refractory multiple myeloma (RRMM): IONA-MM first interim analysis

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Introduction: Isatuximab (Isa) is an anti-CD38 monoclonal antibody that targets a specific CD38 epitope and induces myeloma cell death via multiple mechanisms. Based on the Phase 3 ICARIA-MM and IKEMA studies, Isa plus pomalidomide (P) and dexamethasone (d; Isa-Pd) or carfilzomib (K) and d (Isa-Kd), respectively, are approved in patients (pts) with RRMM. Currently, limited real-world evidence (RWE) exists for pts treated with Isa-Pd/Isa-Kd. This first interim analysis of the non-interventional, observational IONA-MM study (NCT04458831) details baseline characteristics, treatment exposure, and TEAEs for pts with RRMM treated with Isa in the real-world setting.
Methods: Pts ≥18 years old with RRMM who received ≥1 prior treatment line were eligible for the study. Pts were enrolled prospectively and retrospectively (Isa-exposed ≤3 months pre-enrollment). The treating physician determined Isa treatment prior to and independent of enrollment; treatment duration was based on local prescribing regulations. AEs and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.
Results: Between 13 August 2020 and 22 February 2022, 112 pts were enrolled across 38 study sites spanning 6 countries and received ≥1 dose of Isa-Pd (n=81), Isa-Kd (n=26), or other Isa regimens (n=5). Compared to the baseline characteristics in the corresponding Phase 3 Isa studies, a higher proportion of pts who received Isa-Pd/Isa-Kd in IONA-MM were ≥75 years-old and were ISS stage III, and a lower proportion of Isa-Kd pts had high-risk cytogenetics. Among the pts in the Isa-Pd and Isa-Kd groups, 31.5% and 23.1% respectively, had received ≥4 prior lines of therapy. Data on prior treatments received and relative dose intensities of study drugs will be shared at the Congress. At data cutoff, median (min–max) duration of Isa exposure was 5.4 (0–18.8) months for Isa-Pd and 6.2 (0–10.6) months for Isa-Kd, with 79.0% pts still receiving Isa-Pd and 74.1% still receiving Isa-Kd. All-grade TEAEs occurred in 52 (64.2%) pts with Isa-Pd and 16 (61.5%) pts with Isa-Kd; Grade 3–4 TEAEs in 36 (44.4%) and 10 (38.5%) pts; serious TEAEs in 21 (25.9%) and 8 (30.8%) pts; fatal TEAEs during study treatment in 4 (4.9%; 2 [sepsis], 1 [septic shock], and 1 [failure to thrive]) pts and 1 (3.8%; pneumonia) pt; and TEAEs leading to Isa discontinuation in 6 (7.4%) and 3 (11.5%) pts with Isa-Pd and Isa-Kd, respectively. Response data are forthcoming.
Conclusions: In this IONA-MM first interim analysis, we report comparable pt baseline characteristics to those seen in ICARIA-MM/IKEMA with a few imbalances. Both Isa-Pd and Isa-Kd have a manageable safety profile in routine clinical practice. These data provide RWE to support the use of Isa in RRMM outside of clinical trials and in wider populations. Enrollment in IONA-MM is ongoing and will continue until the sample size (1100 pts) is reached. Funding: Sanofi

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Ciltacabtagene autoleucel (cilta-cel) versus real world clinical practice in triple-class exposed multiple myeloma: adjusted comparison of patient reported outcomes from CARTITUDE-1 and LocoMMotion

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Introduction: Adjusted comparisons of the CARTITUDE-1 study of cilta-cel and the LocoMMotion study of treatments used in real-world clinical practice (RWCP) have demonstrated response and survival benefit of cilta-cel in patients with triple-class exposed multiple myeloma (TCE-MM). However, health-related quality of life (HRQoL) is reduced in patients with TCE-MM compared with age- and sex-matched populations. Here we present adjusted comparisons of patient-reported outcomes (PROs) from TCE-MM patients treated with cilta-cel in CARTITUDE-1 vs RWCP in LocoMMotion.

Methods: EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires were administered at baseline, day 7, day 28 and every 4 weeks up to 52 weeks to all patients in the single-arm, phase 2 CARTITUDE-1 study and the prospective LocoMMotion study. Changes from baseline (CFB) for each patient cohort and differences in CFB between cilta-cel and RWCP over time were analyzed using mixed model repeated measures (MMRM), which included baseline PRO score and prognostic characteristics as covariates to balance patient cohorts and adjust for confounding bias. Sensitivity analyses were used and assigned the worst PRO values to patients who dropped out of the main analyses due to death.
Results: 61 patients in CARTITUDE-1 and 202 patients in LocoMMotion had PRO assessments at baseline and follow-up. In both cohorts, PRO scores worsened at day 7 compared with baseline; cilta-cel patients had more pronounced worsening in physical, role and social functioning, fatigue and lack of appetite and constipation, corresponding to short-term adverse events associated with cilta-cel infusion and lymphodepleting chemotherapy. From week 4 onwards, PRO values for cilta-cel patients significantly improved over time vs baseline, whereas improvement from baseline was lower for RWCP patients for most domains and symptoms. In analyses of the average improvement vs baseline from week 4 onwards (corresponding to the absolute difference in CFB between both cohorts), significantly better outcomes for cilta-cel vs RWCP were observed for Visual Analogue Scale (8.0), Global health status (8.5), pain (-11.4), dyspnea (-8.9), constipation (-8.3), future perspective (16.5) (all $p< 0.01$), emotional functioning (7.4), and feeling restless or agitated (-7.2) ($p< 0.05$). All other PROs (except for nausea and vomiting and lack of appetite, which showed small differences in improvement that numerically favored RWCP) numerically favored cilta-cel across the follow-up period. Sensitivity analyses showed that results are inherently biased against the more effective treatment on survival and underestimate PRO benefit of cilta-cel.
Conclusions: Cilta-cel showed significant improvements vs RWCP increasing over time in multiple PRO endpoints in patients with TCE-MM. In addition to its significant efficacy benefits (response, progression free and overall survival), cilta-cel can significantly improve HRQoL and help address unmet patient needs.

P-260
Daratumumab (DARA) plus bortezomib and dexamethasone (D-Vd) or lenalidomide and dexamethasone (D-Rd) in relapsed or refractory multiple myeloma (RRMM): subgroup analyses of CASTOR and POLLUX

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Introduction: In the phase 3 CASTOR and POLLUX studies, D-Vd and D-Rd significantly improved progression-free survival (PFS) and overall survival versus Vd or Rd alone in patients with RRMM. Here, we present post hoc analyses of CASTOR and POLLUX among clinically relevant subgroups (high cytogenetic risk [t(4;14), t(14;16), and/or del17p abnormality], International Staging System [ISS] stage III disease, renal impairment [creatinine clearance ≤60 mL/min], age ≥75 years, 1 prior line of therapy [1 PL], prior autologous stem cell transplant [ASCT], prior bortezomib or lenalidomide, and lenalidomide- or bortezomib-refractory disease) after a median follow-up of >6 years.
Methods: In CASTOR and POLLUX, patients with RRMM and ≥1 PL were randomized to D-Vd/Vd or D-Rd/Rd, respectively. The primary endpoint was PFS. In these post hoc analyses,

PFS was compared between study treatments in subgroups based on a log-rank test; hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model with treatment as the sole explanatory variable.
Results: After a median follow-up of 72.6 months in CASTOR and 79.7 months in POLLUX, PFS consistently favored DARA-containing regimens across subgroups. In CASTOR, PFS was prolonged with D-Vd versus Vd among patients with high cytogenetic risk (HR, 0.37; 95% CI, 0.21-0.64), ISS stage III disease (HR, 0.43; 95% CI, 0.27-0.69), renal impairment (HR, 0.32; 95% CI, 0.20-0.50), age ≥75 years (HR, 0.22; 95% CI, 0.10-0.47), 1 PL (HR, 0.25; 95% CI, 0.18-0.35), prior ASCT (HR, 0.39; 95% CI, 0.30-0.51), prior bortezomib (HR, 0.35; 95% CI, 0.27-0.46), and lenalidomide-refractory disease (HR, 0.42; 95% CI, 0.28-0.61; P< 0.001 for all). In POLLUX, PFS was improved with D-Rd versus Rd among patients with high cytogenetic risk (HR, 0.47; 95% CI, 0.28-0.79), ISS stage III disease (HR, 0.49; 95% CI, 0.32-0.77), renal impairment (HR, 0.42; 95% CI, 0.28-0.62), age ≥75 years (HR, 0.48; 95% CI, 0.27-0.85), 1 PL (HR, 0.50; 95% CI, 0.38-0.67), prior ASCT (HR, 0.54; 95% CI, 0.42-0.70), prior lenalidomide (HR, 0.40; 95% CI, 0.25-0.65), and bortezomib-refractory disease (HR, 0.47; 95% CI, 0.30-0.72; P< 0.01 for all). In a pooled analysis of CASTOR and POLLUX, PFS was prolonged with the addition of DARA to control regimens among patients with high cytogenetic risk (HR, 0.45; 95% CI, 0.31-0.65), ISS stage III disease (HR, 0.53; 95% CI, 0.39-0.72), renal impairment (HR, 0.39; 95% CI, 0.29-0.52), age ≥75 years (HR, 0.41; 95% CI, 0.27-0.63), 1 PL (HR, 0.43; 95% CI, 0.35-0.53), and prior ASCT (HR, 0.54; 95% CI, 0.45-0.65; P< 0.0001 for all).
Conclusions: Post hoc analyses of CASTOR and POLLUX, both individually and pooled, showed that the addition of DARA to standard-of-care regimens prolonged PFS across many RRMM subgroups, including patients with high-risk disease, after a >6-year median follow-up. These results support the use of DARA-containing regimens in RRMM patients across clinically relevant subgroups.

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Treatment attrition rates in multiple myeloma (MM): a Canadian Myeloma Research Group (CMRG) analysis

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Introduction: Most patients diagnosed with MM receive 1st line therapy although reported attrition rates for subsequent treatment lines are high. An understanding of the attrition rates and characteristics of patients who do not receive subsequent therapy can aid in planning for MM stakeholders. Studies using administrative data may overestimate attrition as it can be challenging to distinguish 'true attrition' (defined as patients who do not receive a subsequent line of therapy due to death or those who are alive with progressive MM) from 'perceived attrition' (defined as those who do not receive 2nd line therapy due to death, planned fixed-duration initial therapy and ongoing response, or ongoing 1st line therapy). We therefore performed analysis of attrition rates in a large disease-specific database.
Methods: This is a retrospective observational study using the MM-specific CMRG database. Consecutive patients with newly diagnosed MM who received at least one line of therapy between Jan 1, 2010-Dec 31, 2020 were included. The primary objective was to evaluate attrition at each line of therapy, stratified by time of therapy initiation (2010-15, 2016-20) and category (ASCT-eligible, ASCT-ineligible). Attrition was defined as failure to receive a subsequent line of therapy due to death or despite progression of MM. The secondary objective was to identify factors associated with attrition at each line of therapy.
Results: 5548 patients were identified, 2961 in the 2010-15 cohort and 2587 in the 2016-20 cohort. In the 2010-15 cohort, attrition in ASCT patients was 10.4% after line 1 (n=1721), 12.6% after line 2 (n=1031) and 22% after line 3 (n=627). In ASCT-ineligible patients, attrition was 20.9 % after line 1 (n=1240), 28.5% after line 2 (n=773) and 42.3% after line 3 (n=443). In the 2016-20 cohort, attrition in ASCT patients was 4.4% after line 1 (n=1390), 12.4% after line 2 (n=427) and 26% after line 3 (n=160). In ASCT-ineligible patients, attrition was 17.7% after line 1 (n=1197), 23.7% after line 2 (n=559) and 38.7% after line 3 (n=214). Death was the dominant contributor to attrition across all cohorts, with a minority of patients alive with progressive disease in the absence of further therapy. Multivariable analysis identified older age, shorter time to progression, and inferior response rates as independent risk factors for attrition.
Conclusions: In this large observational study using a MM-specific database, we show that attrition rates increase with each line of therapy and are higher in ASCT-ineligible patients but are appreciably lower than what has been previously

reported. Death accounted for the vast majority of patients lost to attrition, with most patients not receiving subsequent therapy due to continuation of their previous therapy or ongoing remission. Our data revises the previous definition of attrition, and our demonstration that the majority of patients with MM go on to 2nd, 3rd and even 4th line therapy may be of utility to MM stakeholders.

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Estimation of post-infusion costs of care for patients in the US with relapsed and refractory multiple myeloma (RRMM) who received idecabtagene vicleucel (ide-cel, bb2121) in the KarMMa clinical trial

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Introduction: Ide-cel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T cell therapy, demonstrated frequent, deep, and durable responses in triple-class exposed patients (pts) with RRMM in the pivotal phase 2, multicenter KarMMa clinical trial (NCT03361748). Prior research has indicated a high economic burden among pts with RRMM (Chari A, et al. Poster presented at EHA 2020. Abstract EP1756). This abstract provides a US- specific update to the previously presented analysis on the healthcare resource utilization (HCRU) and estimated cost of care across a 1-year time period among pts treated with ide-cel in the KarMMa study (Hari P, et al. Poster presented at ISPOR 2021. Abstract PCN58).
Methods: Patient-level case report forms detailing HCRU data, including length of hospital stay (LOS) (standard inpatient [IP] and intensive care unit [ICU] days), diagnostics, procedures, and medications, were analyzed from the KarMMa clinical trial database from the day of ide-cel infusion through 1-year follow-up. Post-infusion costs (not including the cost of ide-cel) were estimated using a micro-costing methodology. Using a US health system (provider) perspective, HCRU in the 1-year time frame were identified and unit costs were sourced from public databases or peer-reviewed literature, adjusted to 2022 US dollars (USD), and applied to each HCRU. Average total cost by ide-cel post infusion month was calculated among pts with ongoing status in that month. Standard descriptive statistical analyses were conducted. Pts censored due to data cutoff were excluded.
Results: Among the 94/128 US pts who received ide-cel infusions, estimated mean 1-year post-infusion total cost of care was USD 116,181. Most (57%) 1-year costs were incurred in the first month following infusion and were primarily driven by facility costs, namely standard IP hospitalizations and ICU stays. Mean (standard deviation [SD]) hospitalization time was 20.4 (11.7) days for IP stays and 1.2 (3.3) days for ICU stays. Total LOS ranged from 15 to 114 days with a median of 18 days and a mean (SD) of 21.5 (11.8) days (protocol required stay ≥ 14 days). No pts needed dialysis, while some needed an ICU stay (18%), and few needed intubation (4%). Over the 1-year time frame, most pts received antibiotics (95%) and tocilizumab plus corticosteroids (54%), some received corticosteroids only (46%), and few (13%) had vasopressor use; medication usage may have been used for management of toxicity or progression of disease.
Conclusions: Most costs after ide-cel infusion related to IP HCRU in US pts in the KarMMa trial. Results of this study indicate that, compared with other RRMM therapies, the mean estimated 1-year total ide-cel post-infusion cost of USD 116,181 is substantially less costly, likely due to the significantly reduced HCRU following the initial treatment period. Future assessment of real-world evidence in this population is needed to more accurately reflect clinical practice, resource use, and cost in the US.

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Matching-adjusted indirect treatment comparison (MAIC) of teclistamab vs approved therapies for the treatment of patients with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM)

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Introduction: Teclistamab is a T-cell redirecting bispecific antibody targeting B-cell maturation antigen × CD3 being evaluated in the multicohort phase 1/2 MajesTEC-1 trial (NCT04557098). This study estimated the comparative efficacy of teclistamab vs belantamab mafodotin (bel) and selinexor-dexamethasone (sel-dex) for the treatment of patients (pts) with RRMM who were TCE to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
Methods: An unanchored MAIC was performed using individual pt-level data (IPD) from MajesTEC-1 (teclistamab 1.5 mg/kg weekly; N=150; clinical cutoff Nov 2021) and published summary-level data from each comparator (2.5 mg/kg cohort in DREAMM-2 [NCT03525678], N=97; treated pts in STORM Part 2 [NCT02336815], N=122). Treated pts from MajesTEC-1 who satisfied comparator trial eligibility criteria were included. IPD from MajesTEC-1 were weighted to match the aggregated baseline pt characteristics from each comparator. Baseline characteristics of prognostic significance (refractory status, cytogenetic profile, International Staging System stage [ISS; revised ISS used to compare teclistamab and sel-dex], presence of extramedullary disease, and number of prior LOT) were adjusted for in the analysis. Comparative efficacy of teclistamab vs bel and sel-dex was estimated for overall response rate (ORR), complete response or better (≥CR) rate, overall survival (OS), progression-free survival (PFS), and duration of response (DOR). For binary endpoints, relative effects of teclistamab vs comparators were quantified using an odds ratio (OR) and 95% CI derived from a weighted logistic regression analysis. For time-to-event endpoints, hazard ratios (HRs) including 95% CI were estimated using a weighted Cox proportional hazards model.
Results: Baseline characteristics for reweighted MajesTEC-1 pts were balanced with each comparator population. Pts treated with teclistamab had improved ORR (OR 2.07 [95% CI 0.93–4.63]; P=not significant [NS]; response ratio [RR] 1.54), ≥CR rate (OR 2.68 [1.02–7.05] P≤0.05; RR 2.39), PFS (HR 0.65 [0.36–1.17]; P=NS), and DOR (HR 0.29 [0.10–0.86]; P≤0.05) vs bel. OS HR of 1.03 ([0.56–1.88]; P=NS) indicates similar outcomes for the 2 therapies for this endpoint. Compared with sel-dex, pts treated with teclistamab had improved ORR (OR 3.14 [1.48–6.69]; P≤0.05; RR 2.01), ≥CR rate (OR 19.93 [4.27–93.03]; P≤0.05; RR 15.21), OS (HR 0.49 [0.28–0.88]; P≤0.05), PFS (HR 0.57 [0.29–1.09]; P=NS), and DOR (HR 0.04 [0.02–0.10]; P< 0.05). Cross-trial differences in baseline characteristics led to reduced effective sample size (33 vs DREAMM-2; 37 vs STORM Part 2) after adjustment, which may account for the lack of statistical significance for some outcomes.
Conclusions: These analyses demonstrated improved efficacy of teclistamab vs bel or sel-dex for most outcomes, highlighting the clinical benefit of teclistamab over these approved therapies in pts with TCE RRMM who received ≥3 prior LOT.

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Updated results from LocoMMotion: A prospective, noninterventional, multinational study of real-life current standards-of-care in heavily pretreated patients with relapsed/refractory multiple myeloma

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Introduction: LocoMMotion (NCT04035226) is the first prospective, noninterventional study of real-life standard-of-care (SOC) treatments in heavily treated patients with relapsed/refractory multiple myeloma (RRMM), conducted

across 86 sites in 9 European countries and the US. Initial results at 11-month median follow-up (MFU) were previously reported, with an overall response rate (ORR) of 29.8%, median progression-free survival (mPFS) of 4.6 months, and median overall survival (mOS) of 12.4 months (Mateos, et al. Leukemia 2022). We report updated results with longer MFU (16.1 months).

Methods: Adult patients with MM were included if they received ≥3 prior lines of therapy (LOT) or were refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD); had measurable disease at screening; received a PI, IMiD, and anti-CD38 monoclonal antibody (triple-class exposed) with progressive disease since their last LOT; and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 (enrolled August 2019–October 2020). SOC treatments were those used in local clinical practice. Endpoints included ORR, assessed by review committee per International Myeloma Working Group criteria (primary), complete response (CR) and very good partial response (VGPR) rates, PFS, OS, duration of response (DOR), and treatment-emergent adverse events (TEAEs) (secondary).

Results: As of November 2, 2021, the 248 enrolled patients had a 16.1-month MFU (range 0.1–25.9). Median age was 68 years (range 41–89), 135 (54.4%) were male, 179 (72.2%) had a baseline ECOG PS of 1, and median time since initial MM diagnosis was 6.3 years (range 0.3–22.8). Patients received a median of 4 prior LOT (range 2–13), 182 (73.4%) were triple-class refractory, and 230 (92.7%) were refractory to last LOT. Ninety-one unique regimens were used as SOC after enrollment, and 65.3% of patients were treated with a combination of ≥3 drugs. ORR to SOC was 31.5% (95% CI: 25.7–37.6), 1 patient had CR, and 32 (12.9%) had VGPR. Median DOR was 7.7 months (95% CI: 5.1–13.1) in 78 responders. mPFS was 4.6 months (95% CI: 3.9–5.6), and mOS was 13.8 months (95% CI: 10.8–18.5). Overall, 56% of patients received subsequent LOT (1 subsequent LOT, 30.6%; ≥2 subsequent LOT, 25.4%). mPFS from the start of SOC through subsequent LOT (PFS2) was 9.9 months (95% CI: 7.6–12.0). TEAEs were reported in 213 (85.9%) patients; 140 (56.5%) patients had grade 3/4 TEAEs, most commonly thrombocytopenia (18.5%), neutropenia (16.1%), and anemia (10.1%). Nineteen (7.7%) patients died due to TEAEs, most commonly infection (n=12). Forty-one (16.5%) patients had ongoing SOC treatment after data cutoff, with 92 (37.1%) still on study.

Conclusions: Updated data from LocoMMotion confirm initially reported results, demonstrate rapid disease progression and poor outcomes with current SOC treatments, even in subsequent lines, and highlight the need for novel therapies in triple-class exposed patients with RRMM.

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Treatment patterns and outcomes of patients with triple-class exposed relapsed or refractory multiple myeloma: analysis of the Optum electronic health records and commercial claims database

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Introduction: Patients (pts) with relapsed or refractory multiple myeloma (RRMM) who have undergone therapy with proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies (mAbs) are challenging to treat, with limited treatment (tx) options and poor prognosis. Little is known about real-world (RW) tx patterns and outcomes for this pt population. Here, we assessed the characteristics, tx patterns, and survival outcomes in RW pts with triple-class exposed (TCE) RRMM.

Methods: Data were retrospectively extracted from the US-based Optum Electronic Health Record (EHR) and the Clinformatics Data Mart (claims) databases (dbs). The analysis included pts who had a diagnosis date of MM between Jan 1, 2010, and Dec 31, 2020. The key eligibility criteria included pts who had received ≥3 prior lines of therapy (LOT), including a PI, an IMiD, and an anti-CD38 mAb, ≥1 LOT after TCE, and were progressing on last LOT. Multiple observations (obs) per pt were considered if each of their respective LOT satisfied TCE eligibility criteria. Index date was defined as date of initiation of the LOT post TCE. Descriptive statistics were reported for pt characteristics and tx patterns. Time to next tx (TTNT) and overall survival (OS) were estimated using the Kaplan-Meier method.

Results: Pts from the EHR db (n=511 with 1011 obs) and the claims db (n=234 with 439 obs) were included in the analysis. Median age at index date was 69 years (EHR)/73 years (claims); 26.1% (EHR) and 39.6% (claims) of pts had prior stem cell transplant. The median duration from diagnosis to index date was 46 months (mos) for EHR and 36 mos. for claims, and 52.5% and 45.1% of pts, respectively, received ≥5 LOT prior to their index date. The most common comorbidities were hypertension (EHR: 66.3%, claims: 78.6%) and fluid and electrolyte disorders (EHR: 57.9%, claims: 67.9%). Tx patterns were similar between the two dbs. Prior to index date, pts were exposed to daratumumab (100% in each db), bortezomib (EHR: 89.0%, claims: 96.0%), lenalidomide (EHR: 89.0%, claims: 95.0%), pomalidomide (EHR: 66.0%, claims: 59.0%), and carfilzomib (EHR: 58.0%, claims: 56.0%).The most frequently used post-TCE therapy regimens were triplets (EHR: 40.4%, claims: 45.6%) and monotherapies (EHR: 26.1%, claims: 23.5%), with carfilzomib- (EHR: 23.9%, claims: 24.6%) and pomalidomide-based regimens (EHR: 25.4%, claims: 23.5%) being the most common. The median OS and TTNT for pts from the EHR db were 10.3 (95% CI 8.9–11.9) mos. and 3.3 (95% CI 3.0–3.7) mos; respectively. Pts from the claims db had a median OS and TTNT of 8.6 (95% CI 7.3–11.0) mos. and 3.6 (95% CI 3.0–4.1) mos; respectively.

Conclusions: These findings demonstrate that pts with TCE RRMM cycle through several tx regimens with poor outcomes. This RW evidence highlights the poor outcomes and the need for highly effective txs; emerging novel therapies may improve outcomes and reduce the disease burden in pts with TCE RRMM.

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Favorable outcomes of 3-weekly daratumumab-based regimens in relapsed/refractory multiple myeloma: impact of MRD, rapid doubling time, LDH, triplets and quadruplets

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Introduction: In relapsed or refractory MM (RRMM), addition of daratumumab (dara) rendered superior response rates and survivals. Herein, using 3-weekly dara as the backbone, we evaluated the outcomes of dara-based regimens in RRMM.
Methods: Forty patients with RRMM were treated at Queen Mary Hospital, Hong Kong, using either dara-IMid-dexamethasone (dara-IMiD-triplet), dara-IMiD-dexamethasone + proteasome inhibitor (dara-IMiD-quadruplet) or dara-(non-IMid) regimens (dara-cyclophosphamide/carfilzomib-dexamethasone or dara-carfilzomib-cyclophosphamide-dexamethasone). Daratumumab was used every 3 weekly until maximum response or at least 8 doses, followed by either IMiD maintenance till disease progression, or no maintenance, after maximal response. Responses were documented after one cycle and four cycles, and at best responses. Overall survival (OS), event free survival (EFS) and progression free survival (PFS) were computed. Minimal residual disease (MRD) was studied by next generation sequencing using LymphoTrack System. Risk factors for OS and PFS were also evaluated.
Results: Of the forty patients, the median age was 64.5 (range: 46 - 91 years), and number of prior lines of treatments was two. Ten patients (25%) were refractory to bortezomib, 21 (52.5%) to lenalidomide, and 24 (62.5%) to last treatment. Twenty-five patients (62.5%) have undergone ASCT. High-risk cytogenetics occurred in 7 (25.9%) patients. All patients achieved a response with 33 (80%) achieving ≥very good partial response (VGPR) at best responses. Median time to VGPR is 2.5 months. The median OS was not reached in both dara-IMiD-triplet and dara-IMiD-quadruplet but 17 months in dara-non-IMiD regimens (p=0.004), and median PFS was not reached in dara-IMiD-quadruplet, 23 months in dara-IMiD-triplet and 15 months in dara-non-IMiD regimen (p=0.014). Among the dara-IMiD group, dara-IMiD-quadruplet yielded superior PFS than the dara-IMiD-triplet (median not reached vs 23 months, P=0.02) while the median OS were both not reached (P=0.813). In the entire cohort, inferior OS was associated with high lactate dehydrogenase (LDH) at relapse (median: 27 months vs not reached, P=0.004). Shorter PFS was noted in patients with 1q gain (16 months vs 39 months, P=0.02) and a rapid doubling time of paraprotein (18 months vs not reached, p=0.016). Among the fifteen patients with MRD studied at ≥near CR, MRD-negativity was achieved in three (37.5%) of dara-IMiD-triplet and 3 (75%) of dara-IMiD-quadruplet (p=0.545). MRD negativity rendered superior median EFS (not reached vs 14 months, p=0.013).
Conclusions: A 3-weekly daratumumab-based regimen, especially in combination with IMiD, is highly effective in RRMM. Risk factors for survival included LDH, rapid doubling time, 1q gain and MRD. A prospective study is warranted.

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Subcutaneous isatuximab administration by an on-body delivery system in combination with pomalidomide-dexamethasone in relapsed/refractory multiple myeloma patients: interim phase 1b study results

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Introduction: Intravenous (IV) isatuximab (Isa) + pomalidomide-dexamethasone (Pd) is approved for treatment of relapsed/refractory multiple myeloma (RRMM) patients (pts). Subcutaneous (SC) delivery would optimize convenience of administration. Prior results showed that SC Isa administered by syringe pump has efficacy and safety

profiles comparable to IV Isa; recommended Phase 2 dose (RP2D) was 1400mg (IMW21 P-207).
Methods: This multicenter Phase 1b study (NCT04045795) evaluated safety, pharmacokinetics (PK), and efficacy of SC vs IV Isa+Pd in RRMM pts after ≥2 prior treatment lines. Pts were randomized 2:1 to SC1000mg or IV 10mg/kg and to SC1400mg or IV. An expansion cohort was later implemented with SC Isa administered at RP2D via on-body delivery system (OBDS), a wearable bolus injector applied to abdomen by healthcare professional. Primary endpoints (EPs) were safety, including injection site (IS) reactions (ISRs) and PK. Main secondary EPs were overall response rate (ORR) and progression-free survival (PFS).
Results: 56 pts were randomized and treated: 12 Isa IV, 12 Isa SC1000, 10 Isa SC1400, and 22 OBDS pts. At study entry, ISS stage II–III was 67% in IV, 33% in SC1000, 60% in SC1400, and 50% in OBDS pts. On 20Jan2022, 33% IV, 25% SC1000, 50% SC1400, and 86% OBDS pts remained on treatment. Due to sequential accrual, median follow-up (FU) was longer in IV (20.6 mo) and SC1000 (23.8 mo) than SC1400 (18.1 mo) and OBDS (6.5 mo) pts. Infusion reactions (IRs) were infrequent (≤10% in each cohort, all Grade [G] 2), only at first IV or SC infusion/injection, with no IRs in OBDS. Local tolerability of OBDS was very good, with 5 (22.7%) pts experiencing 7 ISR episodes, all G1, out of 305 administrations (2.3%): 5 IS erythemas, 1 IS hemorrhage, and 1 IS induration. Median duration of OBDS injection was 10min. Lower % of ≥G3 treatment-related TEAEs in OBDS (77%) vs other cohorts (≥80%) may be due to shorter FU; most common ≥G3 TEAEs in OBDS pts were neutropenia (77.3%) and anemia (13.6%). None of the patients discontinued Isa due to TEAEs. ORR, ≥VGPR, CR, and PR rates were: 66.7%, 50%, 16.7% and 16.7% in IV, 66.7%, 41.7%, 25% and 25% in SC1000, 80%, 40%, 20% and 40% in SC1400 and 77.3%, 40.9%, 13.6% and 36.4% in OBDS and 78.1%, 40.6%, 15.6% and 37.5% in SC1400+OBDS(R2PD); longer FU is needed for OBDS pts. Median PFS was 22 mo in IV, 12.5 mo in SC1000, and not reached in SC1400 and OBDS pts. Mean Ctrough of Isa at end of weekly dosing period was higher after Isa OBDS and SC vs IV. Mean CD38 receptor occupancy was 78% in Isa OBDS, 81% in SC1400, and 76% in IV pts.
Conclusions: SC Isa administered by OBDS shows safety profile consistent with IV administration with no IRs and excellent local tolerability. Efficacy in SC cohorts was comparable to Phase 3 ICARIA results. PK results in OBDS pts were similar to those receiving SC1400. Isa SC administration by OBDS is well-tolerated, requires short duration of injection, and provides convenient hands-free option.

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INSURE: a global pooled analysis of patients (pts) with relapsed/refractory multiple myeloma (RRMM) treated with ixazomib-lenalidomide-dexamethasone (IRd) in routine clinical practice

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Introduction: IRd was approved for the treatment of RRMM based on results from TOURMALINE-MM1 (median progression-free survival [PFS] with IRd vs placebo-Rd, 20.6 vs 14.7 months [mos]; Moreau NEJM 2016). Here, we evaluate the effectiveness of IRd used to treat RRMM in routine clinical practice, overall, by line of therapy (LoT), & by frailty status.
Methods: INSURE, a pooled analysis of three observational studies (INSIGHT MM, UVEA-IXA, & REMIX), included adult pts with RRMM who had received IRd in ≥2nd LoT. Primary outcomes were PFS & time-to-next therapy (TTNT); secondary outcomes included duration of treatment (DOT), overall response rate (ORR), & safety. Effectiveness outcomes were analyzed overall, by LoT (i.e., pts who received IRd in 2nd/3rd/≥4th LoT), & in subpopulations of frail vs non-frail pts (defined by a simplified International Myeloma Working Group frailty score assessed at the start of IRd therapy: non-frail, 0–1; frail, ≥2). Safety data were reported separately for each study.
Results: 564 pts were included (INSIGHT MM/UVEA-IXA/REMIX, n=181/195/188). Median follow-up was 18.5 mos. Median age was 68 years (range 36–92); 17.5% of pts had an Eastern Cooperative Oncology Group performance status ≥2 (missing pts excluded from percentage). Pts received a median of 2 LoTs before IRd; 40.8/38.1/21.1% received IRd as 2nd/3rd/≥4th LoT. Overall, 164 out of 406 pts with frailty scores recorded (40.4%) were defined as frail (41.0/39.3/41.6% in 2nd/3rd/≥4th LoT). Median DOT was 14.0 mos overall, 16.9/14.8/7.5 mos in 2nd/3rd/≥4th LoT, & 16.1/9.7 mos in non-frail/frail pts. Median TTNT was 18.4 mos overall, 20.7/17.2/12.8 mos in 2nd/3rd/≥4th LoT, & 21.4/12.6 mos in non-frail/frail pts. Median PFS was 19.9 mos overall,

21.7/19.7/11.6 mos in 2nd/3rd/≥4th LoT, & 21.6/11.8 mos in non-frail/frail pts. OS data were not mature. The ORR in 404 response-evaluable pts was 64.6% overall, 70.5/63.1/52.8% in 2nd/3rd/≥4th LoT, & 67.1/59.2% in non-frail/frail pts. In INSIGHT MM, 29.8/22.7/18.2% of pts discontinued ixazomib/lenalidomide/dexamethasone due to adverse events (AEs); 13.8/19.3/11.6% had dose reductions of each drug to manage AEs. In UVEA-IXA, 16.9/14.9/9.7% of pts discontinued ixazomib/lenalidomide/dexamethasone due to AEs; 9.2/9.2/1.0% had dose reductions. The most frequently occurring AEs leading to ixazomib discontinuation in INSIGHT MM/UVEA-IXA were thrombocytopenia (18.5/24.2%), diarrhea (9.3/18.2%), & infections & infestations (14.8/6.1% [infection only in UVEA-IXA]). Further safety data will be presented.
Conclusions: The effectiveness of IRd reported here is consistent with its efficacy in TOURMALINE-MM1 (median PFS, 19.9 vs 20.6 mos), with no new safety signals. Our findings suggest a treatment benefit with IRd in earlier vs later lines, consistent with results from previous, smaller real-world studies of IRd in RRMM. This analysis also provides insight into the effectiveness of IRd in frail pts; this is important for improving understanding of achievable outcomes in this pt population.

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COVALENT-101: a Phase 1 study of BMF-219, a novel oral covalent menin inhibitor, in patients with relapsed/refractory (R/R) acute leukemia, diffuse large B-cell lymphoma, and multiple myeloma

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Introduction: Trial in Progress Background: Menin, a protein involved in transcriptional regulation, impacting cell cycle control, apoptosis, and DNA damage repair, plays a direct role in oncogenic signaling in multiple cancers. Inhibition of menin is a novel approach to cancer treatment. Preclinical data of BMF-219, a highly selective, orally bioavailable, small-molecule covalent inhibitor of menin, show sustained potent abrogation of menin-dependent oncogenic signaling in vitro and in vivo. BMF-219 exhibited a strong anti-proliferative effect on various menin-dependent acute myeloid leukemia (AML) cell lines, diffuse large B-cell lymphoma (DLBCL) lines representing Double/Triple Hit Lymphoma (DHL/THL) & Double Expressor Lymphoma (DEL), and MM cell lines with diverse mutational backgrounds. BMF-219 also showed high potency ex vivo in patient samples from MLL-rearranged and NPM1-mutant AML, THL and MYC-amplified DLBCL, and bone marrow mononuclear cells from treatment-naive and R/R MM.
Methods: COVALENT-101 (BF-MNN-101; NCT05153330) is a prospective, open-label, multi-cohort, non-randomized, multicenter Phase I study evaluating the safety, tolerability, and clinical activity of escalating doses of once daily oral BMF-219 in patients with R/R acute leukemia (AL), DLBCL, and MM who have received or are ineligible for standard therapy. 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 (DLT). At that point, the cohort will switch to a classical “3 + 3” design. Treatment will continue in 28-day cycles until progression or intolerability. Expansion cohorts for each indication will enroll patients to obtain further safety and efficacy data.Patients with R/R AL who have failed or are ineligible for any standard therapies, R/R DLBCL following ≥ 2 but ≤ 5 prior therapies, and R/R MM who have received ≥ 3 therapies are eligible. Patients must have ECOG PS ≤ 2, and adequate organ function. Key exclusion criteria include known CNS disease involvement, prior menin inhibitor therapy, and clinically significant cardiovascular disease.
Results: The primary objective is to determine independently for each cohort/indication the optimal biological dose (OBD)/ recommended Phase 2 dose (RP2D) of BMF-219 oral monotherapy. Key secondary objectives include further evaluation of safety and tolerability, characterization of the pharmacodynamics and pharmacokinetics of BMF-219, and assessment of its antitumor activity based on best overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and time to progression (TTP) per disease-specific response criteria as assessed by the investigator. Food-effect studies will be performed in DLBCL and MM patients at certain dose levels.
Conclusions: Enrollment in COVALENT-101 commenced in January 2022.

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GO41036: a Phase Ia/Ib open-label, multicenter study evaluating the safety and pharmacokinetics of tiragolumab in combination with atezolizumab and daratumumab in patients with R/R MM

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Introduction: Treatment of relapsed/refractory (R/R) multiple myeloma (MM) is challenging, especially in later lines where drug resistance reduces therapeutic options and remission duration. With the approval of daratumumab, and with other anti-CD38 monoclonal antibodies in development, there will be a growing need for combination options for patients who fail these therapies. Prognosis is poor (estimated survival: < 1

year) for patients with MM who have received >3 prior lines of therapy and are triple class refractory to immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and anti-CD38 agents (Gandhi et al. 2019). Treatment of refractory patients remains challenging because of disease heterogeneity and the lack of clear understanding of the mechanisms that lead to resistance. This study explores the feasibility and tolerability of administering tiragolumab in combination with daratumumab and atezolizumab in the R/R MM patient population, including patients that were refractory to, or relapsed during, prior to daratumumab therapy. The preliminary safety and efficacy data from the ongoing studies of tiragolumab as a single agent or in combination with atezolizumab across different solid tumor indications support a favorable benefit-risk profile for the combination. This favorable benefit-risk profile, as well as, the potential for combined TIGIT and PD-L1 blockade to enhance the activity of daratumumab in multiple myeloma, and the significant unmet medical need in heavily pre-treated R/R MM are key reasons for the current study.
Methods: Patients must be aged ≥18 years, have an ECOG performance status of 0 or 1 and a life expectancy of >12 weeks. Patients must have R/R MM and have received at least 3 prior lines of therapy, including a proteasome inhibitor, an IMiD, and an anti-CD38 antibody. Patients must have experienced at least a PR while receiving the anti-CD38 therapy, not have relapsed within 60 days of the first response, and must have at least a 6-month treatment-free interval from last dose of anti-CD38 treatment received and first dose of study treatment on trial. Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on day 1 of each 21-day cycle until disease progression. Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until disease progression. Daratumumab will be administered by SC injection at a dose of 1800 mg/30,000 U rHuPH20 weekly for a total of 6 doses, then every 3 weeks for a total of 16 doses (first dose given at week 7), then every 4 weeks from week 55 onward until disease progression. The primary objective is to evaluate the safety and tolerability of the combination. Secondary objectives include assessment of activity, PK, immunogenicity, and pharmacodynamic biomarkers.
Results: N/A - Trial in Progress.
Conclusions: N/A - Trial in Progress.

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Comparative effectiveness of lenalidomide/dexamethasone-based triplet regimens for treatment of relapsed and/or refractory multiple myeloma in the United States

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Introduction: Clinical trials have demonstrated the efficacy of proteasome inhibitors, ixazomib (I), calfilzomib (K), and bortezomib (V), as well as monoclonal antibodies, elotuzumab (E) and daratumumab (D), in combination with lenalidomide and dexamethasone (Rd) in relapsed/refractory multiple myeloma (RRMM). Head-to-head comparisons of Rd-based triplets are limited due to lack of trials and heterogeneity of study populations. This real-world study compared the effectiveness of IRd, KRd, VRd, ERd, and DRd with respect to treatment outcomes among RRMM patients in the United States (US).
Methods: This retrospective longitudinal study used the Flatiron Health Database (01/01/2014–09/30/2020). Adult RRMM patients who initiated IRd, KRd, VRd, ERd, or DRd in line of therapy 2 or later (LOT2+) on or after 01/01/2014 were included. Index was the date of initiation for each LOT (multiple LOTs per patient were included); baseline period was 6-months pre-index. Duration of therapy (DOT), progression free survival (PFS), time to next therapy (TTNT), and overall survival (OS) were compared between regimens with multivariable Cox proportional hazards models. Patients who had not experienced the event were censored at end of observation. Analyses were conducted in overall cohort and by LOT.
Results: A total of 1,185 patients contributed to 1,332 LOTs (IRd: n=245; KRd: n=222; VRd: n=568; ERd: n=83; DRd: n=214). Median age was 71 years, most (63.5%) regimens were in LOT2, and the majority of patients (89.6%) were treated in a community setting; median follow-up was 18 months. DRd was associated with longer DOT compared to IRd (adjusted hazard ratio [95% confidence interval]: 1.58 [1.23–2.04]), KRd (1.84 [1.42–2.38]), VRd (1.54 [1.18–2.00]), and ERd (1.65 [1.20–2.28]). Similarly, DRd was associated with prolonged PFS in comparison to all triplets (IRd: 1.61 [1.23–2.11]; KRd: 1.59 [1.20–2.12]; VRd: 1.93 [1.42–2.63]; ERd: 1.62 [1.14–2.30]). TTNT was also longer for DRd when compared to IRd (1.49 [1.15–1.93]), KRd (1.75 [1.35–2.27]), VRd (1.43 [1.09–1.87]), and ERd (1.58 [1.15–2.19]). KRd was associated with shorter OS compared with DRd (1.45 [1.01–2.08]) and VRd (1.32 [1.01–1.73]). No statistically significant differences were found for other comparisons of the triplet regimens, as they were generally comparable with respect to the endpoints under study. Analyses stratified by LOT yielded similar results.
Conclusions: In this real-world study of RRMM patients treated primarily within US community settings, PI-containing Rd-based triplet regimens showed comparable effectiveness as measured by the study outcomes. Consistent with prior evidence, DRd was associated with statistically significantly better PFS, DOT, TTNT, and in some cases OS, compared to other Rd-based triplet regimens. Data on the effectiveness of therapies in routine clinical care settings provide key supplemental evidence to clinical trials, thereby informing treatment recommendations.

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Efficacy and safety of ixazomib plus lenalidomide and dexamethasone following injectable proteasome inhibitor-based therapy in patients with relapsed/refractory multiple myeloma

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Introduction: Background: Long-term proteasome inhibitor (PI)-based therapy improves outcomes in multiple myeloma (MM). However, physical, social, and geographic access to health services and treatment toxicity may interfere with long-term PI therapy in clinical practice. Aims: Evaluate the efficacy and safety of treatment with the oral PI, ixazomib (IXA), lenalidomide (LEN) + dexamethasone (DEX) [IRd] in relapsed/refractory MM (RRMM) following injectable PI-based therapy.
Methods: Nationwide, multicenter, open-label, single-arm study in Japan. Patients aged ≥20 years with RRMM (including

those not refractory to bortezomib [BOR], carfilzomib [CFZ], or LEN) were enrolled. Patients received BOR, LEN + DEX (VRd), or CFZ, LEN + DEX (KRd) for 3 cycles. Patients with at least a minor response to VRd or KRd transitioned to IRd. After transition, patients received 4 mg IXA on days 1, 8, and 15, 25 mg LEN on days 1 through 21, + 40 mg DEX on days 1, 8, 15, and 22 in 28-day cycles until progressive disease (PD) or unacceptable toxicity. Endpoints were progression-free survival (PFS) from the start of injectable PI-based therapy, overall survival (OS), overall response rate (ORR), percentage of patients with a very good partial response (VGPR) or better, healthcare resource utilization, time to next treatment (TTNT), and safety.
Results: Of 45 RRMM patients enrolled, 36 achieved minor response or better after 3 cycles of VRd (n=6) or KRd (n=30) and received IRd, and were followed up for at least 12 months after the last patient started injectable PI-based therapy. Mean age was 70.7 (SD±9.2) years, the median (min, max) number of prior lines of therapy was 2 (1, 4), and 95.6% had an ECOG PS of 0−1. At a median follow-up of 20.8 (95% CI: 17.4-23.7) months, median PFS and TTNT were 29.0 (95% CI: 21.3−NE) months and 32.3 (95% CI: 14.9−35.4) months, respectively; median OS was not reached. The ORR was 73.3% (95% CI: 58.1−85.4) and 42.2% (95% CI: 27.7−57.8) of patients had a VGPR or better. The length of hospital stay, and outpatient visits during the initially 3 cycles of injectable PI-based treatment and following IRd treatment were 5.3 vs 1.0 days per person-month, and 4.2 vs 1.9 visits per person-month, respectively. The safety profile of IRd was similar and consistent to that previously reported. Frequent (≥10% incidence) Grade ≥3 treatment emergent adverse events were neutrophil count decreased (n=7 [15.6%]) and platelet count decreased (n=7 [15.6%]); the only SAE with a ≥10% incidence was pneumonia (n=5 [11.1%]). Two deaths occurred during the study, one during KRd treatment (pneumonia, bacterial, n=1 [2.2%]) and one during IRd treatment (pneumonia, n=1 [2.2%]), which was related to IRd.
Conclusions: Long-term treatment with the oral PI, IXA, + LEN and DEX after injectable PI-based treatment was tolerable and had favorable efficacy in patients with RRMM. This treatment strategy may be useful in clinical practice.

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Impact of early relapse on survival of patients with multiple myeloma after autologous cell transplant

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Introduction: The survival of multiple myeloma (MM) patients have improved in the last decade. However, while some patients experience prolonged remission, the prognosis remains inferior for high risk MM. Early relapse (ER) after treatment has been recognized as an independent risk factor for lower survival.
Methods: Objectives: To assess overall survival (OS) in patients with ER and to analyze associated factors and progression free survival to second-line therapy (PFS2) Design: Retrospective study of a single center that included 214 consecutive patients with MM all of whom received bortezomib-based induction therapy and autologous stem cell transplant (ASCT) from 2010 to 2020. ER was considered as relapse or progression within 12 months after ASCT. Patients with ER were compared with those without early relapse (NER).
Results: A total of 35 patients (16.5%) presented ER, with a median relapse time of 7 months (95% CI; 4.9). The most common induction treatment used was VCD (75% vs. 70%; p 0.15) followed by VTD and VRD.These patients had more frequently ISS III (46% vs 32%; p 0.3) and partial response to treatment (32% vs 14%; p 0.02) with less frequent of maintenance (31% vs 60%; p 0.002) or consolidation therapy (3% vs 13%; p 0.08). The median PFS2 was 15 months (IC95%; 11,17) vs. 53 months (IC95%; 43,64) [HR 4.85 (95% CI; 2.6,8.9); p< 0.001]. The median of follow-up was 44 months (IQR; 18,71). The median OS was significantly worse for ER at 21 months (95% CI; 13,27) vs not reached (NR) (95% CI; 106,NR) for those with late relapse [HR; 10.9 (95% CI; 6.1,19.5); p< 0.001], with a 5-year OS of 23% (95%CI; 10.39) vs. 87% (95%CI; 79.92) respectively. In multivariate analysis, early relapse (HR; 8.61; p< 0.001) and elevated LDH (HR; 10.1; p< 0.001) were the most important prognostic factor for poor survival after ASCT, even adjusted for cytogenetic risk.
Conclusions: ER represents a poor prognosis even with new treatment options and beyond cytogenetic risk. Identifying prognostic factors associated with ER could be useful for performing a risk-adapted treatment.

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Treatment patterns among patients with relapsed/refractory multiple myeloma (RRMM) in Taiwan

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Introduction: Patients with relapsed/refractory multiple myeloma (RRMM) have poor prognosis and effective treatment options remain limited. Pomalidomide-based regimens used for RRMM patients who have failed two prior lines of treatment have been reimbursed by Taiwan's National Health Insurance since 2018; however, treatment patterns and characteristics of these RRMM patients who received pomalidomide-based regimens is unknown here. The study objective was aimed to understand the treatment pattern of pomalidomide-based treatment in Taiwan.

Methods: Charts of RRMM patients of age ≥ 20 who receiving pomalidomide-based regimens between 1st Jan 2017 and 31st Dec 2020 at five hospitals (NTUH, CGMH-KH, CMUH, NCKUH and TCVGH) were reviewed for this retrospective study. The initial treatment date of pomalidomide-based regimens was then defined as index date. Patients with non-secretory MM or had enrolled in pomalidomide-based interventional study were excluded. By using retrospective chart-review, data (including characteristics, cytogenetic tests and treatments) were collected from the date of diagnosed with MM until 2021 30th April.
Results: Total 84 patients received pomalidomide-based regimens were enrolled. The average age (SD) was 67.2 (+ 9.0), 48% were female, 7.1% (n=6) had received Autologous Stem Cell Transplant after relapsed or refractory disease, and the median number of treatment regimens was 7 (ranged 6-9) in total. Disease progression was the most common reason for these patients to receive pomalidomide-based regimens, including 76.8% of patients who chose doublet regimens and 46.7% of those who chose triplet regimens. Before entering pomalidomide-based regimens, around 5 and 4 regimens were taken for doublets and triplets. And prior to commence pomalidomide-based regimens, 54.8%, 47.6% and 13.1% of these RRMM patients were refractory to lenalidomide, bortezomib, and carfilzomib, respectively. 82.1% of these RRMM patients received triplet regimens for their pomalidomide-based regimens (e.g., pomalidomide plus dexamethasone), and the others (17.9%) received triplet regimens. The median treatment duration and cycles for pomalidomide-based doublet and triplet regimens were 118 (ranged 50.5-213.5) days with 4 (ranged 2-7) cycles and 122 (ranged 62-198) days with 5 (ranged 2-7) cycles respectively. Patients who received triplet regimens had higher overall response rate, in terms of partial response or better, than those who received doublet (46.7% vs 33.3%, respectively. P=0.3287). Among 36 patients (42.9%) tested for genetic abnormalities, we found deletion 17p in 4 patients, t(4;14) in 2 patients, and t(11;14) in one patient.
Conclusions: The real-world treatment pattern and characteristics of RRMM patients who received pomalidomide-based regimens in Taiwan is likely comparable to the rest of world. Triplet regimens for pomalidomide-based regimens might be a better choice than doublet regimens. (This study was funded by Sanofi. Review and feedback on the abstract were provided by Sanofi.)

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Bendamustine therapy for advanced relapsed/refractory multiple myeloma

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Introduction: Over the last three decades the use of non-selective chemotherapies in multiple myeloma has been mostly abandoned and replaced by new targeted agents in combination with autologous stem cell transplant in eligible patients. However, despite advances in treatment and an increase in survival rates in the majority of patients, disease progression is inevitable. Among the considerations in choosing salvage therapy for relapsed/refractory multiple myeloma (RRMM) is the attempt to provide previously unused therapy that has no/minimal cross-resistance to drugs used in prior lines, and the ever-shrinking range of treatment options. Bendamustine is a unique bifunctional alkylating agent that causes single and double DNA strands breaks that are more profound and durable than those of other alkylators. It carries only partial cross-resistance with other alkylators and has a relative safe and tolerable toxicity profile, making it a viable option for heavily pretreated RRMM. Data on bendamustine monotherapy in this patient population is lacking.
Methods: We analyzed the outcomes of 18 heavily pretreated RRMM patients (median age 73 years, range 60-91) who were treated with bendamustine and dexamethasone at our center. Intravenous bendamustine 60-120 mg/m2 and dexamethasone 10-20 mg intravenously/orally were given on days 1 and 2 of 3-4-week cycles. Treatment response was assessed every cycle according to International Myeloma Working Group response criteria.
Results: Twelve patients (67%) had ECOG ≥2. The median number of prior treatment lines was 6 (range 4-11). All patients had at least triple-refractory disease, 6 (33%) had quad-refractory disease and 9 (50%) had penta-refractory disease. A median of 4 cycles (range 1-17) was given. Median follow-up was 351 days (interquartile range 323-405 days). Three of the 18 (17%) patients died after the first cycle due to progressive disease. Fifteen patients were treated with ≥2 cycles. The overall response rate was 22.2% (95% CI: 2.9-41.1). One patient (6%) achieved complete response, 2 patients (18%) achieved partial response and 11 patients (65%) had stable disease. Median progression-free survival and median overall survival were 130 days (95% CI: 84–not reached) and 433 days (95% CI: 221-not reached), respectively. Safety was evaluated in patients treated with ≥2 cycles. The most common adverse events were anemia (73%; grade 3 20%), thrombocytopenia (66%; grade 3-4 60%) and neutropenia (60%, grade 3-4 40%). Sepsis was documented in 13% of patients. Therapy was not discontinued due to any adverse event.
Conclusions: Our series suggests that bendamustine with dexamethasone may be a reliable salvage therapy in heavily pretreated RRMM. The relatively low bendamustine doses given may explain the low toxicity profile observed. This easily attainable salvage therapy should be considered in heavily pretreated patients as it may halt disease progression, utilizing this period as a bridge until a new treatment may become available.

P-276
Real-world study of the efficacy and safety of belantamab mafodotin (GSK2857916) in relapsed or refractory multiple

myeloma based on data from the nominative ATU in France: IFM 2020-04 study

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Introduction: Patients with relapsed or refractory multiple myeloma (MM) need novel treatment strategies as MM is still incurable. Belantamab mafodotin (BM), an anti-BCMA antibody drug conjugate (GSK2857916), represents an alternative option with promising results, according to the phase 2 DREAMM-2 study. DREAMM-2 led to a temporary utilization program in France. We sought to assess the efficacy and safety in real-world of BM in patients who benefited from this early-access program.
Methods: We conducted an observational, retrospective, multicenter study. Eligibility criteria were treatment of relapsed or refractory multiple myeloma in monotherapy in adult patients who have received at least 3 lines of therapy previously, including at least one immunomodulatory agent (IMiD), a proteasome inhibitor (PI) and an anti-CD38 monoclonal antibody, and whose disease progressed during the last treatment period. The primary endpoint of the study is to assess the overall survival of patients after starting belantamab mafodotin treatment. The trial was sponsored by the French group IFM ("Intergroupe Francophone du Myélome") and by GSK (GlaxoSmithKline).
Results: A total of 106 patients were treated with BM between July 2019 and December 2020 of whom 97 were eligible for the efficacy evaluation and 104 for safety. Median age was 66 (range: 37-82) years. High risk (HR) cytogenetics were found in 40.9% patients.Fifty-five (56.7%) patients were triple class refractory (IMiDs, PIs, anti-CD38 mAbs) and 11 (11.3%) were refractory to bortezomib, lenalidomide, carfilzomib, pomalidomide, daratumumab. Median of prior lines of treatment was 5 (range: 3-12). The median number of BM cycles administered was 3 (range: 1-22). The overall response rate was 54% and 11.4% achieved a complete response Median OS was 9.3 months (95%CI: 5.9; 15.3) and median progression free survival was 3.5 months (95%CI: 1.9; 4.7). No significant difference was found in OS according to HR cytogenetics or frailty status. The median duration of response was 9 months (range 4.65-10.4) Treatment discontinuation was observed for 55 (52.9%) patients whose 36.5% for treatment-related toxicity. Dose reductions were reported for 22.1% patients. Ophthalmic adverse events, mainly grade ≤2, were the most common toxicity (48%). The rate of keratopathy was 37.5%.
Conclusions: Overall, our data are concordant with the results from DREAMM-2 in terms of efficacy and safety on a non-biased population.

P-277
Carfilzomib, lenalidomide and dexamethasone followed by a second autologous hematopoietic cell transplantation is an effective strategy in first-relapsed multiple myeloma

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Introduction: Multiple myeloma (MM) is an incurable hematologic malignancy despite recent therapeutic advances. Carfilzomib-lenalidomide-dexamethasone (KRd) is one of the preferred options from EHA/ESMO and IMWG recommendations in the context of lenalidomide-sensitive relapse. An autologous hematopoietic cell transplantation (auto-HCT) is also an option in case of a prolonged remission after frontline auto-HCT in eligible patients. Only few data are available on the combination of KRd followed by a second auto-HCT in first relapse.

Methods: This international retrospective study was performed in 22 centers in Europe. Patients with MM were included if they received a second line of treatment with KRd induction followed by a second auto-HCT between January 2016 and December 2018. Primary objective was to estimate progression-free survival (PFS) and overall survival (OS) in this population. Secondary objectives were to assess the response rates and identify statistically significant co-variables on PFS and OS in this population.
Results: A total of 51 patients were included. Median age was 62 (range 35 – 69), 27 patients (52.9%) were of standard cytogenetic risk and 11 (21.6%) of high cytogenetic risk according to IMWG criteria while data was missing for 13 (25.5%). ISS at diagnosis was stage I for 18 patients (35.3%), stage II for 11 (21.6%), stage III for 14 (27.5%) and missing for 8 (15.7%). Median time between transplants was 40.4 months (range 17.9–87.9). Regarding the total number of KRd cycles received, 25 patients received 3 or 4 cycles (49.0%), 17 patients 5 or 6 cycles (33.3%) and 9 patients 7 to 12 cycles (17.7%). Conditioning chemotherapy was melphalan in 46 patients (90.2%), melphalan and another drug in 4 (7.8%) and cyclophosphamide in 1 (2.0%). Median follow-up was 36.7 months (range 5.3-58.0). Median PFS was 32.6 months (95%CI: 30–39.9) and median OS was not reached, while 36- and 48-months OS rates were 87.5% (95%CI: 78.5–97.4) and 72.8% (95%CI: 57.0–92.8) respectively. In univariate analysis, 2 co-variates were found to be associated with a longer median PFS: an interval between transplants greater than 4 years (mPFS of 36.1 vs 30.6 months, p=0.02) and the achievement of a very good partial response (VGPR) or better at the 2nd transplant (mPFS of 33.5 vs 27.8 months, p=0.01). These results were also observed in multivariate analysis, with HR of 0.41 (95%CI: 0.17-0.96, p = 0.04) and HR of 0.45 (95%CI: 0.21-0.98, p = 0.04), respectively. No statistical association was found between the duration of PFS and cytogenetic risk profile. Regarding OS, no co-variables were found to be statistically significative in uni- or multivariate analysis.
Conclusions: KRd induction followed by a second auto-HCT is an effective treatment for patients with a first lenalidomide-sensitive relapse of MM. Our study suggests that patients who achieved a VGPR or better after KRd induction or with over 4 years of remission after a frontline auto-HCT benefit the most from this therapeutic strategy.

P-278
Post-authorization safety of lenalidomide + dexamethasone in patients with relapsed/refractory multiple myeloma in Turkey

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Introduction: Lenalidomide (LEN) in combination with dexamethasone (DEX) has become a common treatment in the relapsed/refractory multiple myeloma (RRMM) setting. Our aim was to investigate the safety profile of LEN + DEX therapy under routine real-world clinical practice in RRMM patients in Turkey.
Methods: This was a non-interventional, multicenter, observational, post-authorization safety study which included patients aged ≥18 years with RRMM and prescribed LEN + DEX treatment. Patients who had previously received LEN and discontinued or who had a treatment interruption for ≥4 weeks were excluded from the study. Patients were observed during and up to 30 days after LEN treatment period for safety and then every 6 months for up to 36 months to assess second primary malignancy (SPM).
Results: Between December 16, 2015, and June 30, 2021, 500 patients across 35 institutions in Turkey were enrolled. Results of 499 patients with available data are presented. Median follow-up was 123.4 weeks (range, 0-337.6). Median age was 63 years (range, 23-87) and 54.9% were male. Median number of prior therapies was two (range, 1-6). Prior autologous stem cell transplantation was reported in 48.7% of the patients. 16 patients (3.2%) had a history of venous thromboembolism (VTE) at baseline. The overall incidence of peripheral neuropathy (PN) at the baseline was 19.6%. Eastern Cooperative Oncology Group (ECOG) performance status were recorded in 443 patients at entry, 88.7% had good performance status (ECOG status 0-1). Majority of the patients (68.5%) started lenalidomide at a dose of 25 mg. Dose modifications were required 174 times in 78 patients during the study. Overall, 3853 adverse events (AEs) were recorded, of which hematologic AEs were observed most frequently (59.7% of patients). 167 patients (33.5%) observed ≥ grade 3 AEs. ≥Grade 3 neutropenia, anemia, pneumonia, and thrombocytopenia were reported in 20.6%, 12.6%, 11.4%, and 10.4% of the patients, respectively. During the study, 12.9% (58/451) of patients had PN, while six patients (1.3%) were recorded as grade 3-4. Prophylaxis for VTE was performed in a total of 84.9% (383/451) of the patients with aspirin (314/451, 69.6%), low molecular weight heparin (82/451, 18.2%) and warfarin (21/451, 4.7%). VTE was reported in seven patients (1.4%). Treatment was discontinued in 174 (34.9%) patients due to AEs, in 101 (20.2%) patients due to disease progression. Of 397 patients who attended 6-month follow-up visits, nine patients (2.3%)

were diagnosed with SPM: 6 non-hematologic malignancies (pancreatic adenocarcinoma, prostate cancer, breast cancer, laryngeal cancer, squamous cell carcinoma, peritoneal carcinomatosis), and 3 hematologic malignancies (two myelodysplastic syndrome, one Hodgkin's lymphoma). There were 195 deaths (39.1%), most frequently due to disease progression (44 of 195; 22.5%).
Conclusions: LEN + DEX treatment had a manageable tolerability and safety profile in adult Turkish RRMM patients which are in line with previous clinical trials.

P-279
Efficacy, safety, and pharmacokinetics of iberdomide plus dexamethasone in patients with relapsed/refractory multiple myeloma by renal function: a subgroup analysis of the CC-220-MM-001 trial

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Introduction: Iberdomide (IBER) is a novel potent cereblon E3 ligase modulator (CELMoD®) with enhanced tumoricidal and immune-stimulatory effects compared with immunomodulatory drugs (IMiDs®). IBER is extensively metabolized, constituting only 16% of intact drug in urine. In this analysis from the phase 1/2 study CC-220-MM-001 (NCT02773030), we investigated the impact of renal impairment (RI) on the efficacy, safety, and pharmacokinetics (PK) of IBER in relapsed/refractory multiple myeloma.
Methods: Eligible patients (pts) had ≥3 prior therapies (including an IMiD agent, a proteasome inhibitor [PI], a glucocorticoid, and a CD38 monoclonal antibody [mAb]); progressive disease < 60 days (D) of last myeloma therapy; and refractoriness to an IMiD agent, a PI, a glucocorticoid, and a CD38 mAb. IBER (1.6mg) was given orally on D1–21, plus dexamethasone (DEX) (40mg; 20mg if >75y of age) on D1, 8, 15, and 22 of each 28-D cycle. Baseline creatinine clearance (CrCl; mL/min) identified pts with no RI (≥90), mild RI (60–89), and moderate RI (30–59). Primary endpoint was overall response rate (ORR), with further efficacy and safety assessments included as secondary endpoints. IBER clearance (CL/F) and PK exposure (AUC, Cmax) were estimated from an integrated population PK (popPK) model over a dose range of 0.3–1.6mg.
Results: At data cutoff (June 2, 2021), 107 pts had received IBER+DEX. Median (range) age was 64y (44–83). Median time since diagnosis was 6.9y (1.6–24.5). Median number of prior regimens was 6 (3–23). Of 107 pts assessed at study entry, 28 had no RI, 47 had mild RI, and 32 had moderate RI. No pts had CrCl < 30 mL/min. ORR (≥partial response) was 26.2% (all pts), 25.0% (no RI), 29.8% (mild RI), and 21.9% (moderate RI); clinical benefit rate (≥minimal response) was 36.4%, 35.7%, 40.4%, and 31.3%, respectively. Median (95% CI) duration of response (weeks) was 30.3 (19.6, 49.1) (all pts), 30.3 (12.0, not reached [NR]) (no RI), 25.3 (12.1, NR) (mild RI), and 33.1 (2.9, NR) (moderate RI). Grade (Gr) 3/4 treatment-emergent adverse events (TEAEs) were observed in 82.2% (all pts), 82.1% (no RI), 83.0% (mild RI), and 81.3% (moderate RI). Gr 3/4 neutropenia was observed in 44.9%, 39.3%, 53.2%, and 37.5%, respectively. Occurrence of other TEAEs (eg, infections) and dose modifications were similar regardless of RI. Based on the popPK analysis, RI did not impact IBER CL/F over the dose range of 0.3–1.6mg. No correlation was observed between RI and IBER PK exposure. Consistent with the clinical results, logistic regression analyses identified no correlation between RI and key efficacy or safety endpoints (ORR, Gr 3/4 neutropenia, and Gr 3/4 thrombocytopenia).
Conclusions: Similar efficacy, safety, and PK results with IBER+DEX indicate that RI (no RI, mild RI, and moderate RI) does not influence the clinical outcome of IBER, and that IBER dose modifications are not required for pts with mild to moderate RI. IBER dosing in severe RI or kidney failure requires further study.

P-280
Efficacy of thalidomide therapy in patients with relapsed or refractory multiple myeloma: a meta-analysis

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Introduction: Multiple myeloma (MM) is the second most frequent malignancy of the blood, which accounts for ~1% of neoplastic diseases and 13% of hematologic cancers. The treatment of MM had undergone significant development

during the past decades. Relapse and Refractory MM was still difficult to cure and require a long-term disease control. Despite recent advances in systemic and supportive therapies, multiple myeloma remains an incurable plasma cell malignancy. Some clinical trials showed that the most of MM patients often had a good respond to initial standard therapy, but the disease ultimately recurred and became refractory to further treatment over the course of time. Thalidomide has recently been recognized as an effective new agent for previously untreated, refractory or relapsed myeloma. This study aims to determine the proportion of response rate (CR/PR) for patients with relapsed and refractory multiple myeloma treated with thalidomide therapy.
Methods: : Literature was searched using MEDLINE, PubMed, EMBASE, Trip Database, Cochrane library, Google Scholar and clinicaltrial.gov to identify studies on relapse and refractory multiple myeloma treated with thalidomide therapy till May 2022. Data was extracted independently by three reviewers. Studies with thalidomide therapy for relapsed and refractory MM were, which reported the data of response rate (CR/PR) included in the proportional meta-analysis. STATA version 13.0 software was used for conducting the proportional meta-analysis.
Results: 37 studies consisting of 2564 patients with mean age 64 year were included in the present meta-analysis. Pooled analysis observed that response rate of thalidomide therapy was 51% with 95% confidence interval 48% to 55%.
Conclusions: The present meta-analysis suggests that satisfactory response rate for the patients with relapsed and refractory multiple myeloma undergoing the thalidomide therapy.

P-281
Adjusted comparison of teclistamab versus physician's choice of therapy in the long-term follow-up of daratumumab trials in patients with triple-class exposed relapsed or refractory multiple myeloma

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Introduction: Patients (pts) with relapsed or refractory multiple myeloma (RRMM) who receive ≥3 prior lines of therapy (LOT) have limited treatment options. Teclistamab is a T-cell redirecting bispecific antibody targeting B-cell maturation antigen × CD3 currently being evaluated in the multicohort, phase 1/2 MajesTEC-1 trial (NCT04557098) in pts with RRMM who received ≥3 prior LOT and were triple-class exposed (TCE) to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Given the absence of a control arm in the MajesTEC-1 trial, we assessed the comparative effectiveness of teclistamab vs physician's choice of therapy.
Methods: An external control arm for MajesTEC-1 was created from pts in 4 clinical trials of daratumumab (CASTOR, POLLUX, EQUULEUS, and APOLLO) who were subsequently treated with physician's choice of therapy after discontinuing trial treatments and met the key eligibility criteria for MajesTEC-1 (N=427 unique patients with 806 observations). Disease progression and best treatment response were based on investigators' assessment. Individual patient-level data from MajesTEC-1 pts who received teclistamab (1.5 mg/kg weekly) at a clinical cutoff of Nov 9, 2021 were included in the analysis. Baseline characteristics of prognostic significance (base case: refractory status, cytogenetic risk, International Staging System stage, extramedullary plasmacytoma, time to progression on last LOT, number of prior LOT, time since diagnosis, age, and hemoglobin) were adjusted by using the inverse probability of treatment weighting (IPTW) method. Outcomes of interest included overall response rate (ORR), very good partial response or better (≥VGPR) rate, overall survival (OS), progression-free survival (PFS), and time to next treatment (TTNT). For binary endpoints, a weighted logistic regression method was used to derive an odds ratio (OR) and 95% confidence interval (CI). A weighted Cox proportional hazards model was used to compute hazard ratios (HRs) and 95% CIs for time-to-event endpoints. A sensitivity analysis weighted patients on prior stem cell transplant, Eastern Cooperative Oncology Group performance status, race, sex, and type of MM, in addition to the base case variables.
Results: After IPTW adjustment, baseline characteristics were comparable between cohorts. Pts had improved outcomes with teclistamab vs physician's choice of therapy: ORR (OR 4.72; 95% CI 2.91–7.75; P < 0.0001); ≥VGPR rate (OR 11.96; 95% CI 6.67–22.60; P< 0.0001); OS (HR 0.46; 95% CI 0.32–0.66; P< 0.0001); PFS (HR 0.61; 95% CI 0.45–0.81; P=0.0009); and TTNT (HR 0.35; 95% CI 0.26–0.48; P< 0.0001). Results of the sensitivity analysis were in favor of teclistamab and consistent with the base case.
Conclusions: Teclistamab showed significantly improved effectiveness vs physician's choice of therapy for all clinical

outcomes, highlighting its clinical benefit in pts with TCE RRMM who have limited treatment options.

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Addition of ixazomib to pomalidomide-dexamethasone improves progression-free survival for myeloma patients progressing on frontline lenalidomide: results of the randomized alliance study A061202

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Introduction: Frontline lenalidomide (LEN) therapy until disease progression (PD) is standard of care. As such, an increasing number of patients (pts) in need of 2nd line therapy have LEN-refractory disease. Best treatment in this setting has not been rigorously assessed in randomized studies. The phase I portion of A061202 demonstrated the safety of the ixazomib (IXA)-pomalidomide (POM)-dexamethasone (DEX) combination for the treatment of pts with relapsed and relapsed/refractory MM. In the randomized phase II portion, we evaluated the addition of IXA to POM-DEX for pts progressing on LEN as part of 1st line therapy.

Methods: Pts were randomized 1:1 to IXA-POM-DEX or POM-DEX and stratified by prior bortezomib exposure, ISS stage and the presence of high-risk cytogenetics. Pts had received one prior line of therapy, had progression of disease on frontline LEN, and could not have PI refractory disease. Treatment was continued until disease progression or the emergence of unacceptable side effects. Patients with disease progression on POM-DEX could cross over to IXA-POM-DEX.

Results: 38 and 39 eligible pts were assigned to IXA-POM-DEX and POM-DEX, respectively. A planned 1st interim analysis was conducted after 43 out of 57 required events had occurred. A stratified log-rank test found that PFS was superior for the triplet after adjusting for stratification factors (one-sided stratified log rank test value = 5.8371; p=0.0157), adjusted hazard ratio 0.451 (upper 90% bound = 0.694). At data lock, the median PFS was 20.35 months vs 7.5 months (adjusted HR 0.377, upper 90% bound 0.572). The overall response rate (ORR) favored IXA-POM-DEX (65.8% vs 43.6%, respectively), and the ≥very good partial response was 26.3% vs 5.1%, respectively (p=0.01). The most common grade 3/4 adverse events included lymphopenia, neutropenia, anemia, and fatigue in 40%, 37%, 16% and 16% of IXA-POM-DEX-treated pts and 26%, 21%, 13%, and 15% of POM-DEX-treated pts. Therapy was discontinued for disease progression in 47.4% of pts on IXA-POM-DEX and 76.9% of pts on POM-DEX and for adverse events in 7.9% and 7.7% of pts, respectively. 26 of the 30 pts who discontinued POM-DEX for disease progression chose to cross over to IXA-POM-DEX, and their response to therapy will be updated at the meeting.

Conclusions: The addition of IXA to the POM-DEX backbone improved the depth of response and PFS for pts relapsing on LEN as part of first line therapy. Side effects were manageable. The ease of administration of this all-oral combination allowed for safer, uninterrupted treatment during the COVID pandemic. Our results should be confirmed in phase III trials but lend support for this regimen as part of 2nd line therapy for this pt population. Longer follow-up, particularly for those who crossed over to the triplet, will help address questions about optimal treatment strategy (i.e., combination therapy vs sequential treatment).

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TRIATLON - triple class exposed/refractory multipLe myeloma patients: a real world analysis (RWA) from the Austrian Myeloma Registry (AMR)

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Introduction: Clinical trials are heavily biased towards the younger and fitter. Effectiveness can also be compared in clinical registries. TRIATLON compared a real-world (RW) population of MM pts. in triple exposed (TE) and/or

refractory (TR) settings treated by alternative approaches to a reference population from KarMMa.
Methods: Pts. were identified by the Austrian Myeloma Registry (AMR) modelled from inclusion criteria of KarMMa. 2 cohorts were defined: C1: TE, not refractory and ongoing therapy & C2: TE/TR and already in the next line of therapy (LoT).
Results: 181 pts. were recruited, 103 in C1 and 78 in C2. 55%/53% of pts. were male. 14% of pts. in C1 were over the age of 75 years, slightly more in C2 (21.5%). Duration of disease (DoD) – until d1 of the index treatment , defined as the first LoT, meeting inclusion criteria, was 18.6 mo. in C1 vs 10.5 mo. in C2. ISS stage distribution was typical with ~ 25% of pts. diagnosed with ISS III disease in C1 & C2. Cytogenetic risk factors were evaluable for all pts.(!) and high risk aberrations [t(4;14), t(14; 16) and del17p] were found to be slightly enriched in C2 vs. C1 (18,8% vs. 24.8%). A panoply of diverse combinatorial regimes were applied in in both cohorts with no clear favorites. Frequently used approaches were re-cycling of anti-CD38-MoABs (100% Isatuximab or Daratumumab in both C1 and C2), as well as the use of Carfilzomib (42,7%, 44%) and Pomalidomide (35%, 61%) as treatment building blocks. With respect to response rates, depth of response and TTnT significant differences between triple exposed and triple refractory clinical settings could be observed in the ORR with 68.1% vs 37.8%, the clinical benefit rate (CBR defined as SD or better) 89.2% vs. 76.8%, and a VGPR or better response with 34.3% vs. 16.2%. Furthermore responses were more durable with TTnTs of 5.5 vs. 3.7 mo.
Conclusions: Being TR defines an unmet ultra-high risk status, with a TE status being only slightly better. TE and TR MM patients should be treated in clinical trials, and/or their data collected in clinical registries at least. In the last year several RW populations of heavily pre-treated MM pts. have been presented, among others: KarMMa-RW, a belgian multi-center analysis, LoccoMMotion and Connect-MM. We will comparatively present our data in detail. Outcome data from the KarMMa trial outperform the results of all RWA in the TE or TR setting by far and are expected to increase further with follow up. In all pts. eligible for CAR-T cell therapy, CARs should be preferentially applied, whenever available. On the other hand applicability of CAR-T cell therapy has limitations based on performance status and organ functions, as new toxicities (ICANS, CRS) can pose a serious threat to pts. Furthermore turn-around times, bridging therapies and technical limitations substantiate the need to develop additive and/or synergistic new therapeutic principles.

P-284

Updated progression-free survival (PFS) and depth of response in IKEMA, a randomized Phase 3 trial of isatuximab, carfilzomib and dexamethasone (Isa-Kd) vs Kd in relapsed multiple myeloma (MM)

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Introduction: The anti-CD38 antibody Isa in combination with Kd is approved in various countries for patients with relapsed MM after ≥1 prior therapy, based on primary interim analysis (IA) of the Phase 3 IKEMA study (NCT03275285). Here we report updated efficacy and safety results from IKEMA.
Methods: This prespecified analysis (179 patients randomized to Isa-Kd, 123 patients to Kd) evaluated PFS (primary endpoint) at 159 PFS events, PFS2, minimal residual disease negativity (MRD-) rate, complete response (CR) rate, MRD- and CR rate in all patients, and safety. Isa 10 mg/kg was given IV weekly for 4 weeks and then every 2 weeks; Kd (20/56 mg/m²) was administered in both arms.
Results: At cutoff, Jan 14, 2022, with a median follow-up of 44 months, 49 (27.4%) patients in Isa-Kd and 11 (8.9%) in Kd were still on treatment. Updated PFS consistent with the IA results, demonstrated significant benefit in favor of Isa-Kd (vs Kd): HR 0.58 (95.4% CI 0.42–0.79) with median PFS 35.7 vs 19.2 months in Isa-Kd vs Kd. PFS2 HR was 0.68 (95% CI 0.50–0.94) with median PFS2 47.2 vs 35.6 months in Isa-Kd vs Kd. A consistent benefit was noted for Isa-Kd vs Kd in PFS all subgroup analyses including poor prognosis patients such as elderly by age ≥65 years, impaired renal function (< 60 mL/min/1.73 m²), high-risk cytogenetics, 1q21+ status and refractory to lenalidomide. With additional follow up and using the Hydrashift Isa immunofixation assay to rule out potential Isa interference in CR determination, final CR rate (Isa-Kd vs Kd) was 44.1% vs 28.5% (Odds Ratio [OR]=2.09, 95%CI=1.26–3.48); MRD- was reached in 33.5% vs 15.4% patients (OR=2.78, 95%CI=1.55–4.99); rate of MRD- CR patients was 26.3% vs 12.2% (OR=2.57, 95%CI=1.35–4.88). A trend in OS was observed in favor of Isa-Kd vs Kd patients, with HR 0.78 (95% CI: 0.54 to 1.12), and survival probability of 68.7% vs 62.9% at 36 months and 66.3% vs 54.5% at 42 months. Safety profiles in both arms (n=177 Isa-Kd, n=122 Kd) remain consistent with prior IKEMA findings; for Isa-Kd vs Kd,

grade ≥3 TEAEs were observed in 83.6% vs 73.0% patients, serious TEAEs in 70.1% vs 59.8% patients; TEAEs leading to definitive discontinuation in 12.4% vs 18.0% patients; and TEAEs during study treatment in 5.6% vs 4.9% patients. The most common, any-grade non-hematologic TEAEs in Isa-Kd were infusion reaction (45.8%), diarrhea (39.5%), hypertension (37.9%) and upper respiratory tract infection (37.3%).
Conclusions: These results show unprecedented median PFS, CR rate, MRD- and MRD-CR rates in a non-lenalidomide containing regimen with benefit maintained through subsequent therapies and a manageable safety profile. Our findings support Isa-Kd as a standard of care treatment for patients with relapsed MM.

P-285
Single-cell RNA-seq reveals XBP1-SLC38A2 axis as a player in immunosuppressive T lymphocytes in multiple myeloma

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Introduction: Functional impairment of T lymphocytes results in immune escape of multiple myeloma (MM). How to correct the immunosuppressive state of T cells in MM and enable them to restore normal immune function becomes the principal focus of MM research. The growing field of immune metabolism has provided new insights into anti-myeloma immunity. The fate and function of T cells are intrinsically related to metabolism, through which cells need to produce bioenergy intermediates to support proliferation and effector functions. The mechanisms of immunosuppression and metabolic reprogramming of T lymphocytes in MM have not been fully elucidated.
Methods: We applied single-cell RNA sequencing to mononuclear cells of bone marrow and peripheral blood samples from 3 healthy volunteers and 10 newly-diagnosed MM patients before and after two cycles of bortezomib/cyclophosphamide/dexamethasone treatment, and analyzed the differential expressed genes, enriched signaling pathways and developmental trajectories of T cell subsets. Flow cytometry was used to validate the immune suppressive profiles of T cells in MM. Spearman correlation analysis was performed to evaluate the correlation among SLC38A2, XBP1 and markers of T cell dysfunction. Luciferase reporter assay was used to detect the direct binding of XBP1s and the promoter of SLC38A2. XBP1 shRNA and overexpression vector were transfected into CD8+ T cells to investigate the regulation of XBP1 on SLC38A2.
Results: We identified 15 T cell clusters through single-cell data. Cytotoxic T (Tc) cell clusters are extensively characterized by senescence, while some cells in each cluster concurrently show exhaustion features. The senescence markers KLRG1/CTSW and exhaustion markers LAG3/TIGIT were representatively expressed in Tc cells in MM. The upregulation of GZMK and CXCR4 in Tc cells further supported T cell dysfunction. Impaired metabolism and unfolded protein response (UPR) pathway enrichment in Tc cell clusters in MM were revealed, along with decreased and increased expressions of glutamine transporter gene SLC38A2 and UPR hallmark XBP1 respectively. Meanwhile, SLC38A2 expression negatively correlated with XBP1, exhaustion markers HAVCR2/TNFRSF14 and senescence markers FGL2/CTSW. The transcription factor XBP1s could directly bind to the promoter of SLC38A2. Overexpressing XBP1s in healthy CD8+ T cells downregulated expressions of SLC38A2 and effector marker GZMA, while silencing XBP1 upregulated expression of SLC38A2 and downregulated expression of senescence marker KLRG1.
Conclusions: Our integrative single-cell transcriptome analysis dissects the immunosuppression profiles of Tc cells in MM and the underlying dysfunction mechanism. We have demonstrated that UPR hallmark XBP1 directly binds to SLC38A2 promoter and inhibits its gene expression, leading to T cell dysfunction. This study reveals a novel metabolic regulating mechanism in Tc cells and provides new insights to the immunotherapy for MM.

P-286
Identification of myeloma-initiating cells and novel therapeutic target by single-cell sequencing

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Introduction: The origin and evolution of multiple myeloma (MM) remain elusive. Recurrent relapse is an inevitable problem for most patients. Targeting the tumor-initiating cells may offers a feasible strategy to resolve the recurrent relapse in MM. The aim of our study is to infer the identity of myeloma-initiating cells (MICs) and explore the novel therapeutic target for MM.
Methods: We applied single cell RNA sequencing to fresh bone marrow mononuclear cell samples collecting from 7 healthy donors and 12 newly diagnosed MM patients utilizing 10x Chromium platform.
Results: Firstly, we identified 10 tumor subpopulations in total. We performed copy number variation analysis to each tumor cluster. Notably, cluster 4 presented the most

abundant chromosomal aberrations among the tumor subpopulations. Next, to explore the evolution trajectory, we performed a trajectory analysis by integrating the pro-B and pre-B cells with the tumor subpopulations together. We found that cluster 4 ranked at the early phase of B cell development. Additionally, cluster 4 displayed high expression of B-cell gene signatures (CD19, CD27, MS4A1 and CD79B) and specifically showed high level of CD24, which has been validated to be the marker gene for MICs. Gene enrichment analysis also implicated that Wnt, Notch, stem cell differentiation and Hedgehog pathway were enriched in cluster 4. We next examined proliferative capability and utilized the 70 high-risk gene model and 56 drug resistance-related gene model to further distinguish subpopulations with the most malignant gene expression features. Notably, we found that cluster 4 possessed characteristics of high proliferation, drug-resistance and high-risk gene profiling myeloma. Differentially expressed gene (DEG) analysis identified LILRB4 as the most highly expressed gene in cluster 4 comparing with other tumor subpopulations. LILRB4 has been investigated as a potential immunotherapeutic target in acute myeloid leukemia. Thus, we explored its biological function in MM. We showed that the level of LILRB4 was significantly increased in precursor plasma cells and mature MM cells compared with normal plasma cells. We genetically overexpressed LILRB4 in MM cell line. We found that over-expression of LILRB4 promoted colony formation capacity and induced a less-mature state of MM cells in vitro. Altogether, we suggested that LILRB4 may act as a symbol of MM initiation and a pivotal factor in regulating plasma cell differentiation and its potential therapeutic role in MM are in need to explore.
Conclusions: Our work presents an integral profiling for tumor cells in myeloma. We inferred MIC population with characteristics of higher proliferation, drug-resistance and high-risk gene profiling at single-cell resolution. We suggested LILRB4 as a symbol of MIC. Over-expression of LILRB4 promoted colony formation capacity and induced a less-mature state of MM cells. LILRB4 may act as a potential therapeutic target in MM.

P-287
ATRA works synergistically with γ-secretase inhibitors to augment BCMA on multiple myeloma and the efficacy of BCMA-CAR T-cells

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Introduction: B cell maturation antigen (BCMA) is the lead antigen for CAR T-cell immunotherapy in multiple myeloma (MM). A challenge is inter- and intra-patient heterogeneity in BCMA expression on MM cells and BCMA down modulation under therapeutic pressure. Accordingly, there is a desire to augment and sustain BCMA expression on MM cells in patients that are treated with BCMA-CAR T-cells and other BCMA-targeted immunotherapies.
Methods: We evaluated treatment with all-trans retinoic acid (ATRA) – an epigenetic modifier and clinically available drug – on BCMA expression on MM cells and efficacy of BCMA-CAR T-cells in pre-clinical models.
Results: We show that ATRA treatment leads to an increase in *BCMA* RNA transcripts and BCMA protein expression in MM cells by RT-qPCR and flow cytometry. Analysis with super-resolution microscopy confirmed increased BCMA expression and revealed an even distribution of BCMA molecules on the MM cell membrane after ATRA treatment. The enhanced BCMA expression on MM cells after ATRA treatment leads to enhanced cytolysis, cytokine secretion and proliferation of BCMA-CAR T-cells *in vitro*, and increased anti-myeloma efficacy in a murine xenograft MM model *in vivo* (NSG/MM1.S). The addition of a gamma-secretase inhibitor to ATRA treatment further enhanced BCMA expression and the anti-MM efficacy of BCMA-CAR T-cells.
Conclusions: Taken together, the data show that ATRA treatment augments BCMA expression on MM cell liens and primary MM cells and support the clinical evaluation of ATRA in combination with BCMA-CAR T-cells to augment response rates and duration of response.

P-288
Interventions and outcomes of multiple myeloma patients progressing after BCMA-directed chimeric antigen receptor (CAR) T cell therapy

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Introduction: BCMA-directed CAR T has demonstrated remarkable efficacy in patients with relapsed/refractory

multiple myeloma (RRMM). The outcomes of patients with disease recurrence after BCMA-directed CAR T has not been comprehensively studied and such an analysis would help define optimal treatment strategies.
Methods: We analyzed salvage treatments and outcome of 79 patients with RRMM from 2 academic institutions who had progression of disease after treatment with BCMA-directed CAR T. We retrospectively collected demographics, baseline disease characteristics, pre- and post-CAR T treatment regimens, responses to post-CAR T salvage therapy, and clinical outcomes.
Results: The 79 patients had a median age of 60 years (range 37-78 years) at the time of PD after CAR T (T0) and 59.5% were male. Sixty-four patients (83.1%) had high-risk cytogenetic characteristics by FISH. Of the 79 patients, 66 (83.5%) were triple-class refractory and 30 (38%) were penta-drug refractory.
The overall response rate (ORR) to the first post-CAR T salvage regimen was 43.4%, with a median progression-free survival of 3.5 months (mo) (95% CI 2.5-4.6 mo). In total, 237 salvage treatment lines were used among all patients, and patients received a median of 2 (range 1-10) treatment lines. Overall, the following salvage treatments were commonly used: T cell-engaging therapy (n=38, ORR=62.9%) (incl. BCMA-directed bispecific Ab (n=9), non-BCMA-directed bispecific Ab (n=23) and non-BCMA-directed CAR T (n=6)), autologous stem cell transplant (Auto-SCT) (n=14, ORR=71.4%), Allo-SCT (n=7, ORR=100%), chemotherapy (e.g. DCEP/PACE) with/without stem cell support (n=53, ORR=56.9%), doublet-triplet combinations of approved anti-MM agents (n=56, ORR=28.3%), venetoclax-based therapy (n=14, ORR=35.7%), selinexor-based therapy (n=15, ORR=21.4%), BCMA-directed ADC (n=9, ORR=12.5%) and other (n=31, ORR=38.7%).
In the whole cohort, the median overall survival (OS) from the date of relapse post-CAR T was 17.9 mo (95% CI 14.0-NE mo) after a median follow-up time of 22.4 mo. The median OS for penta-drug refractory patients (13.9 mo, 95% CI 6.8-NE mo) was significantly lower (p=0.02) than patients that were not penta-drug refractory. OS in patients that received a subsequent T cell-engaging therapy (bispecific antibody or subsequent CAR T) was not reached. OS in patients that received a stem cell transplant was 23.3 mo (95% CI 17.6-NE mo).
Conclusions: Patients with RRMM who relapse after BCMA-directed CAR T have a limited prognosis but can be treated with multiple lines of salvage therapy contributing to an observed OS of almost 18 months. Salvage treatment is guided by patient characteristics: our data suggests that subsequent use of T cell-engaging therapies appears to maintain pronounced clinical activity, and that stem cell transplant is feasible and can lead to deep and durable responses in eligible patients in this setting.

P-289

OM301, a synthetic polypeptide containing the p53TA (transactivation) domain, attenuates myeloma cell proliferation by inhibiting Bcl-2 and mitochondrial functioning

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Introduction: Despite new treatments that have improved outcomes in multiple myeloma (MM), the majority of patients eventually relapse. Moreover, high-risk and refractory MM necessitates novel and robust approaches. Mitochondrial rewiring is found in many aggressive and resistant cancers including MM, and Bcl-2 maintains mitochondrial function and physiology. OM-301, a synthetic peptide constructed to inhibit the p53-MDM2 interaction, in fact induces anti-cancer effects independent of p53.
Methods: Co-immunoprecipitation, Western blot, and RNA sequencing data confirmed its p53 independency. Streptavidin-biotinylated OM-301 pull-down followed by proteomic and pathway analysis indicated the OM-301-Bcl-2 interaction.
Results: In MM, OM-301 was anti-proliferative with an IC_{50} of ~5µm. At 20 mg/kg/bw and twice-a-day dosing, OM-301 significantly reduced tumor burdens in MM1.S xenografted and transplanted NSG mice.
Additional streptavidin-biotinylated OM-301 pull-downs confirmed the Bcl-2 interaction in cell lysates of MM cells with different *TP53* statuses. Biotinylated OM-301 also displayed a direct interaction with purified Bcl-2. OM-301-Bcl-2 molecular docking further corroborated this interaction. Surface plasmon resonance data confirmed a robust Bcl-2 interaction, with potent binding efficiencies for both OM-301 and biotinylated OM-301. OM-301 induced mitochondrial depolarization as monitored by JC-1 dye, fission observed by transmission electron microscopy (TEM), superoxide production, and DNA damage. Immunofluorescence and TEM data also showed OM-301 localization within mitochondria. Further, metabolomic profiling data demonstrate a differential OM-301 signature, with down-regulation of mitochondrial metabolites, indicating mitochondrial dysfunction. Molecularly, OM-301 leads to ubiquitination of Bcl-2–protected HMGB1 and NRF2 proteins. HMGB1 ubiquitination further leads to downregulation of its transcriptional protein target HSPB1, perturbing mitochondrial redox homeostasis. OM-301–mediated NRF2 ubiquitination leads to dual effects. Where on one hand it increases ROS generation by downregulating HO-1 and NQO1 gene expression, on the other hand it induces mitochondrial fission by upregulation of DRP1 protein.
Conclusions: We report that OM-301, although designed for p53-selective cells, may instead interact with Bcl-2 and induce mitochondrial dysfunction, leading to cell death irrespective of *TP53* status. Venetoclax is a bona fide Bcl-2 antagonist. However, in MM, its lethality is mostly restricted to (11;14) translocation. Thus, there is an unmet need for a potential Bcl-2 inhibitor in heterogenous MM cell types. OM-301

exhibits prominent anti-proliferative effects in a multitude of cell types, providing a novel and effective therapeutic option for MM. Our data suggest an indispensable function of Bcl-2 in MM heterogeneity, warranting a redefinition of the role of the Bcl-2 axis.

P-290
Autologous Stem Cell Transplantation in Multiple Myeloma Patients in a Peruvian Cancer Center from 2012 to 2020

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Introduction: Autologous stem cell transplant (ASCT) is the standard treatment in fit patients < 65 years old.
Methods: We evaluated retrospectively transplant-eligible patients who were defined as patients ≤65 years old, fit to undergo the transplant procedure from November 2012 to December 2020.
Baseline characteristics at diagnosis and frontline therapy outcomes, including outcomes of ASCT.
The baseline characteristics of the patients were planned to be presented descriptively. The progression-free survival was either biochemical or clinical relapse after ASCT. The overall survival was from diagnosis to death.
Results: Since 2012 to 2020 457 transplants were performed (303 ASCT and 154 allogeneic transplants). 121 patients were included, 1 patient underwent 2 transplants (122 total, 40% of ASCT). The median of transplants per year was 10 (2012 two transplants, 2019 25 transplants pre covid pandemic, 2020 10 transplants during pandemic). The number of newly diagnosed multiple myeloma (NDMM) transplant eligible patients during the study period was 452 (27% undergo ASCT). The median age was 54 (range 25-70), 63% were male. Ig G was the most common type with 55% followed by Ig A (24%) and light chain (9%). The light chain most frequent was kappa (63%). 45% were ISS 3. 75% of transplant had a public funding and 19% private funding. Cyclophosphamide thalidomide and dexamethasone (CTD) was the frontline treatment in 53% of cases followed by bortezomib, thalidomide dexamethasone (VTD) in 15%. Complete response, very good partial response and partial response was seen in 38%, 19% and 24%, respectively. Maintenance was given in 69% of patients, thalidomide was the regimen in 87% of cases. All patients had autologous peripheral stem cell transplantation, cyclophosphamide was used as the regimen for mobilization and conditioning regimen was melphalan 200mg/m2 divided into two consecutive days. 78% of relapses were biochemical. 10% of biochemical relapse had clinical progression with a median of 10 months (range 0-55). The median interval from diagnosis to transplant was 15.5 m (range 5-211). 11% patients had early relapse after transplant (< 12 months). With a median follow-up of 30 months, the median progression-free survival (PFS) was 33 months (IQR 15-77). The 3y PFS was 44.7 (95% IC, 34.3-54.5). The 5y PFS was 35% (95% IC, 24.8-45.3). With a median follow-up of 58.5 months, the median overall survival (OS) was 199 months (IQR 73-244). The 5y OS was 77.3 (95% IC 68.2- 84.1) and the 10y OS was 59.7% (95% IC 46.7-70.5).
Conclusions: 27% of transplant eligible NDMM patients underwent ASCT, which is similar to other public institutions. The numbers of transplant per year is increasing constantly, with a marked decrease in 2020 due to the covid-19 pandemic. 40% of ASCT is for MM. The median interval from diagnosis to transplant is high (15.5 months). Most patients have late relapse after ASCT. The most frequent type of relapse is biochemical. The overall survival is good.

NS-001
Characterization and management of oral and dermatological toxicities in patients receiving the CD3 X GPRC5D bispecific antibody talquetamab for the treatment of relapsed/refractory multiple myeloma

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Introduction: Talquetamab is a humanized IgG4 bispecific antibody that targets the CD3 receptor complex on T cells and G-protein-coupled receptor class 5 member D (GPRC5D) a transmembrane receptor protein overexpressed on malignant plasma cells in Multiple Myeloma (MM). After 6.3 months of follow-up in relapsed/refractory (RR) MM, talquetemab monotherapy at the recommended phase 2 dose yielded an overall response rate of 70%. Here we describe the presentation and management of dermatologic and oral adverse events (AEs) in 78 patients (pts) enrolled at a single center that is part of a multi-center, multi-national study.
Methods: As of July 2021, 78 pts received talquetamab, 53 (67.9%) by IV and 25 (32%) by SC route. Treatment emergent dermatologic AEs were observed in 20 (25.6%) pts. The most common AEs were palmar/plantar desquamation in 22 pts (28.2%, grade 1/2), nail disorders in 14 pts (17.9%, all grade 1), systemic rash in 11 patients (14%, grades 1-3), and injection site reaction in 7 pts (8.9%, all grade 1). Time of onset was within the first 30 days of therapy.
Results: Management of palmar/plantar desquamation, nail disorders, and injection site reaction is ammonium lactate 12% cream, triamcinolone 0.1% cream, with plain Vaseline and Vanicream applied twice daily. Of the 11 pts with rash, 10 were at or above a dose of 405 µg /kg. Five pts had grade 3 rash requiring dose hold and systemic steroids with topical agents. All pts have resumed dosing without recurrence of grade 3 rash. Four of these pts were at a dose level of 800 µg/kg SC. Grade 1-2 rash did not require dose hold and was managed with early intervention of 3 topical agents.

Treatment emergent oral AEs were observed in 38 (48.7%) pts, all grade 1-2. 42 pts developed dysgeusia (53.8%), 16 developed dry mouth (20.5%), and 17 developed dysphagia (21.8%). Dysgeusia resulted in 3 pts requiring drug interruption. 1 pt required dose reduction and 1 discontinued treatment. Time to onset was 26.5 days. Dry mouth resulted in no drug interruptions, reductions, or discontinuations, and had an onset of 6.7 days. Dysphagia ranged from grades 1-2, with 3 pts requiring drug interruption. There were no dose reductions or treatment discontinuation. Time to onset was 41.5 days. Dry mouth, dysgeusia, and dysphagia were more prevalent with higher doses. Oral AEs have been successfully managed with saliva substitute sprays and rinses. These interventions are instituted at time of onset of symptoms.
Conclusions: Dermatologic and oral AEs have unknown etiologies and are currently under investigation. These AEs are low grade, rarely require dose holds or modifications, and have been manageable with early and consistent supportive care. One patient to date has discontinued treatment due to an oral or dermatologic side effect. Talquetamab has favorable risk/benefit profile in RRMM with durable responses and manageable toxicities. A regimen of topical and oral supportive care can be beneficial in the management of dermatological and oral side effects.

NS-002
Value-based care: engaging myeloma patients in the selection of patient reported outcome measures

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Introduction: Background: With a global shift towards a value-based health care agenda, where value is defined as what matters to patients, there is need to ensure that patient reported outcome measures (PROMs) chosen to assess health-related quality of life (HRQoL) in clinical trials are informed by patient preference. In a systematic review of PRO data reported in 32 myeloma randomised controlled trials (RCTs) between 2014-2021, no studies described engagement with patients when selecting PROMs.1 Aim: To establish a suite of validated, patient endorsed PROMs for use in future trials with multiple myeloma patients.
Methods: Method: An exploratory, descriptive study using semi-structured, telephone-based interviews with myeloma patients. Patients who had completed at least one line of therapy were invited to provide feedback on 10 validated, commonly used PROMs. Interview data were analysed using a manifest content analysis approach and a series of summary statements regarding preferences for PROMs, generated.
Results: Results: Twenty-six participants were recruited (13 male, 13 female) with a mean age of 67 years (range 54-76). Although all PROMs were deemed acceptable, the My-POS was preferred over the EORTC QLQ-C30 and QLQ-MY20 because it allowed for free text reporting of concerns or issues not included in the questionnaire. Fatigue and financial impact were identified as important domains not adequately covered by the My-POS. Therefore, the Brief Fatigue Inventory and COST-FACIT PROMs were included in the final suite alongside the My-POS.
Conclusions: Conclusion: Our patient cohort really valued having the opportunity to voice what matters most to them when assessing HRQoL. No single PROM fully captured the wide range of concerns prioritised by participants. We will use the set of patient-informed PROMs in a future study to assess impact of bortezomib, lenalidomide and dexamethasone on the HRQoL of the newly diagnosed, transplant ineligible patients. 1. Efficace F, Cottone F, Sparano F et al. Patient-Reported Outcomes in Randomized Controlled Trials of Patients with Multiple Myeloma: A Systematic Literature Review of Studies Published Between 2014 and 2021. Clinical Lymphoma, Myeloma and Leukaemia, 2022 https://doi.org/10.1016/j.clml.2022.01.009

NS-003

Development of a nursing care pathway for monitoring pneumocystis pneumonia risk in relapsed refractory multiple myeloma

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Introduction: Pneumocystis jiroveci (PJP) is an opportunistic organism that causes a severe pneumonia (PJP PNA). Patients with MM are at risk due to their disease and treatment. Data specific to MM patients' risk for developing PJP PNA is lacking, especially in the era of novel therapies, such as bispecific therapy and CarT therapy. Historically, patients treated with high-dose steroids or autologous stem cell transplant have been identified as high risk for developing PJP PNA. Recently, we noted an increase in PJP PNA and saw the opportunity for a nursing intervention. Adequate prophylaxis with specific antimicrobials is a necessary intervention and can dramatically reduce the incidence of PJP PNA. The project was developed with the objective of creating a process that empowers clinic nurses to identify patients at highest risk for PJP PNA and clarify the appropriate timely intervention.
Methods: A PJP PNA prophylaxis algorithm was created. Nurses worked with IT to develop a report from the EHR. It identified patients with RRMM who had received CarT, or had a history of PJP PNA, or had received a transplant (allo or auto) within 6 months. The data elements were: patient name, attending provider, cellular therapy, type of donor, date and 2 last CD4 values, prophylaxis, and if infectious diseases consulted. The report also notes when the patient is scheduled to have labs and whether there is an order for CD4 count.An algorithm mapping a prophylaxis path for patients following transplant, CarT, and subsequent treatments was created to standardize prophylaxis.Patients identified were evaluated utilizing the algorithm and fell into three distinct and actionable categories: Initiate prophylaxis, discontinue it, or continue to monitor with CD4.
Results: 52 patients were identified at risk and evaluated for prophylaxis with the algorithm. Of these, 18 had received CarT, 29 were within 6 months post-autoHCT, and 5 patients had received bispecific therapy. 15 patients' monitoring plans have been adjusted utilizing the algorithm. Since initiation, there have been no new instances of PJP PNA in the period of 6 months, compared to 3 instances of PJP PNA in the 3 months prior. A gap in CD4 monitoring for patients who have received standard of care CarT has been identified, and we are still trying to refine the algorithm to determine the best frequency and optimal duration of monitoring.
Conclusions: Utilizing the developed algorithm, nurses have created a better understanding of the risk for PJP PNA in RRMM patients. Education was provided by the nursing staff on how to utilize the algorithm. Identification of patients during clinic preparation assisted in including these patients' prophylaxis and monitoring plan as a discussion point during the next provider visit. While we await more refined data related to PJP PNA risk with CarT therapies and other anti-BCMA therapy, we rely on the example of this real-world clinical experience. We plan to expand this project to other teams.

NS-004

Increasing clinical trial accrual of minority patients by expanding clinical operations at satellite sites: a nursing lead initiative

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Introduction: Multiple myeloma (MM) is the most common blood cancer among African Americans (AA). Despite the fact that AA comprise ~20% of the population of MM patients, they only represent 6% of patients in clinical trials. Moreover, the MM mortality rate among AA is two-times greater than Whites with a 5-year age-adjusted mortality rate of 6.2 per 100,000 vs. 3.1 per 100,000 among Whites. However, when enrolled in clinical trials, AA patients fare as well as, or better than, White patients underscoring the critical need for inclusion of underserved minority patients in our clinical trials. There is also a clinical and regulatory need to generate efficacy and safety data in minority patient populations that are representative of the background incidence of the disease for inclusion in labeling. Our center sees more than 500 new patients each year, making us a center of excellence for MM care in New York City. We are also home to one of the largest and most diverse patient population which affords us the opportunity to have an inclusive clinical trial program. There are many factors contributing to suboptimal clinical trial enrollment among AA MM patients including being presented with the option to enroll in a trial, lack of awareness of clinical research, socioeconomic factors, and general mistrust of research due to historical maltreatment of AAs in medicine and research. One of the main contributing factors is that trials are often not conducted at community sites where minority MM patients are treated. This is due in part to lack of clinical trial resources including study coordinators and research nurses.
Methods: Underserved areas in NYC were identified by using the NYC.gov. A heat map of the MM patient population using underserved area parameters was created. We identified areas of the most need and matched the locations with our closest satellite sites: Brooklyn and lower Manhattan. We hired 2 advanced practice providers (APPs) to lead the MM focused clinics and to advance the clinical trials programs at the sites. AAPs assess the feasibility of each clinical to the site population and clinical operations. AAPs train infusion

nurses, laboratory, pharmacy, and support staff on clinical trials and Good Clinical Practice.
Results: As of 5/30/2022, we have successful opened 4 clinical trials at our satellite sites and enrolled 2 patients. In addition we have several clinical trials currently in the study start up process.
Conclusions: AAs continue to be underrepresented in clinical trials. There are many barriers to clinical trial enrollment. Travel, cost and lost wages from work can significantly impact enrollment. By deploying research APPs into the community, we can attempt to reduce the stressors of clinical trials and improvement overall patient representation.

NS-005
The Cleveland Clinic Survivor Care Program Model for patients living with multiple myeloma and plasma cell disorders

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Introduction: Background and significance: Successes in the treatment of plasma cell disorders (PCDs) have led to dramatic improvements in the overall health of those with the disease and survival rates. However, a longer life span is counterbalanced by cumulative physical, financial, and psychosocial issues that require a multidisciplinary team to monitor and manage. Because of these advancements in drug discovery and supportive measures, many patients with plasma cell disorders (PCDs) live longer than the projected survival rates, which underscores the importance of survival care planning. Advanced practitioners (APs) are well suited to conduct patient visits and intervene with treatment and supportive recommendations when needed. Thus, the purpose of this quality improvement initiative is to implement an AP-led, multidisciplinary survivorship clinic to provide an individualized care plan to patients with PCDs. Survivorship visits will be offered to all patients with PCDs who underwent autologous stem cell transplant (ASCT) to monitor secondary cancers, health maintenance practices, psychosocial and financial concerns.
Methods: Patients are identified as candidates for survivorship care planning (SCP) visits if they have a confirmed diagnosis of PCD and underwent ASCT. The transplant team will inform patients they are a candidate and arrange SCP a visit if the patient agrees. The AP will meet with the patient to conduct a comprehensive review of health history and generate a care plan in a 1-hour visit either virtually or in person at 3 and 6 months following ASCT. If patients remain in remission, the AP will schedule a follow-up survivorship visit at every 12 months. Key survivorship care plan domains to be assessed at each visit were identified from a comprehensive review of literature, components from the International Myeloma Nurse Leadership Board Survivorship Care Plan, and current ASCO and NCCN recommendations.
Results: Data collection: The electronic health record (EHR) will be leveraged to document survivorship visits on a standard template.Routine quality of life (QOL) and psychometric measures available in the medical chart and obtained at each visit as the standard of care will also be obtained and recorded from EHR. Additional outcomes such as (faster time to secondary cancer diagnosis, QOL over time, and improved patient and caregiver satisfaction compared to those who do not opt into survivorship visits) will also be obtained.
Conclusions: Conclusion: Survivorship begins at diagnosis; yet, the inclusion of routine SCP for patients with PCDs is conspicuously absent. This initiative provides a systematic, innovative approach to include patients in the process of SCP via telehealth or in-person methods, who would not otherwise have access to this benefit.

NS-006
Minimal residual disease in myeloma: a patient's perspective

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Introduction: Minimal Residual disease (MRD) assessment is becoming routine in patients with Multiple Myeloma (MM). MRD -negativity is an important treatment goal because it has the potential to predict for significantly superior survival outcomes1. Whilst the merit of MRD assessment is becoming established amongst clinicians, its value has it to the patients and the impact of a MRD result remains poorly studied. We performed this study to understand patients' knowledge of MRD, its impact on their treatment journey, their feelings around their MRD status and to assess their need for increased education and psychological support as a result.
Methods: An online, anonymous questionnaire designed by the authors via Microsoft Forms. This questionnaire surveyed Myeloma/Amyloidosis patients who had undergone a bone marrow biopsy.
Results: 62 patients were surveyed; of those 40 (65%) had MRD assessment, MRD was negative for 21, positive for 19 and not tested for 22. MRD negative patients had a better understanding compared to those who are positive/not investigated for MRD. 100% of these patients reported that they were glad they know their MRD result and felt more confident and optimistic, "I felt a massive reduction in anxiety, I can plan for a future." Based on the MRD results, 4 of the MRD negative patients reported a treatment plan change. 12 patients continued with the same treatment plan

and 5 did not know. All MRD negative patients were keen to have annual MRD assessments. 19 patients tested MRD positive and of those, 15 felt as though they had been adequately counselled on the result. Following the MRD result 9 patients stated that their treatment strategy remained the same, 7 patients stated the treatment strategy changed and 3 did not know. Half of the patients noticed their attitude changed after knowing the results. Patients report feeling vulnerable, disappointed, anxious, "Felt less invincible". 10 out of the 19 patients felt that the result had a negative psychological impact on them, "It feels like a step backwards despite having zero paraprotein, it took time to recover from the news". Only 10 of these patients felt they would want a yearly MRD reassessment. Nevertheless, If given an option, 100% of these patients are glad they know the result. Out of 22 patients who answered 'MRD not tested' half of those had no understanding of MRD in Myeloma and its utility.
Conclusions: Patients who are MRD negative have a better understanding of the significance compared to MRD positive patients/patients not investigated for MRD, which could be due to clinician bias in explaining the results. Those with MRD negative results felt more optimistic with a massive reduction in anxiety. Conversely those who were MRD positive felt disappointed and concerned about their prognosis. This survey suggests that there appears to be physician bias in discussions about MRD results. There is a greater need to educate the patients about MRD and support them through this element of their treatment journey.

NS-007
Using feedback to understand and improve the experience of myeloma patients in the UK

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Introduction: Background Ensuring patients with cancer have the best possible experience throughout their treatment and care is central to health service development and strategy. The Clinical Service Excellence Programme (CSEP) is a Myeloma UK best-practice initiative, designed to support hospitals in delivering high-quality, patient-focused care. An integral component of the CSEP assessment process is asking myeloma patients about their experience and any changes they would like to see. Such feedback can help clinicians evaluate the care they provide and contribute to resource planning and service development, demonstrating a process that is dynamically responsive to patient need. Aims CSEP provided an opportunity to look at patient experience across a range of UK hospitals. Our aim was to identify the most common concerns patients report and what areas of service development could most improve the patient experience.
Methods: Method Feedback was gathered from patients treated at CSEP participating hospitals via an anonymous online or paper survey. The survey contains 26 questions on their experience of care. The survey ends with the optional question 'If you could change one thing about your myeloma treatment and care, what would it be?', which is the focus of this analysis. Responses were thematically categorised.
Results: Results Comments were submitted by patients from 41 CSEP participating hospitals. Of the 698 responses to the above highlighted question, the majority were positive and are not included in these results. Eight categories emerged from the remaining 290 replies: communication, continuity of care, coordination of care, holistic needs, hospital facilities, travel, treatment options and waiting times. From these categories, three areas dominated: waiting times across departments, communication with healthcare professionals, and coordination of care. The areas least mentioned related to hospital facilities and travel. Discussion Overall, the eight categories indicate areas of improvement most important to patients. The most common concerns point to systemic logistical problems within the health service, caused in part by the increased numbers of patients seen, as myeloma treatment options and survival rates improve. Large caseloads impact on clinic sizes, waiting times, quality of consultations, effective communication and care coordination. The CSEP process provides teams with the opportunity to reflect, evaluate and improve their service and can highlight where increased resource is needed. Interestingly, patients appeared less concerned about areas often outside the myeloma team's control: facilities and travel.
Conclusions: Conclusion These findings are used to facilitate increased resource and local myeloma service improvement projects at CSEP participating hospitals. The data also informs wider clinical practice and allows the CSEP programme to develop support strategies and initiatives that have the greatest impact on improving the experience of myeloma patients.