# Which is the best immune approach to replace ASCT ?
# CAR T or BiTEs ?
# BiTEs !!

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# Agenda

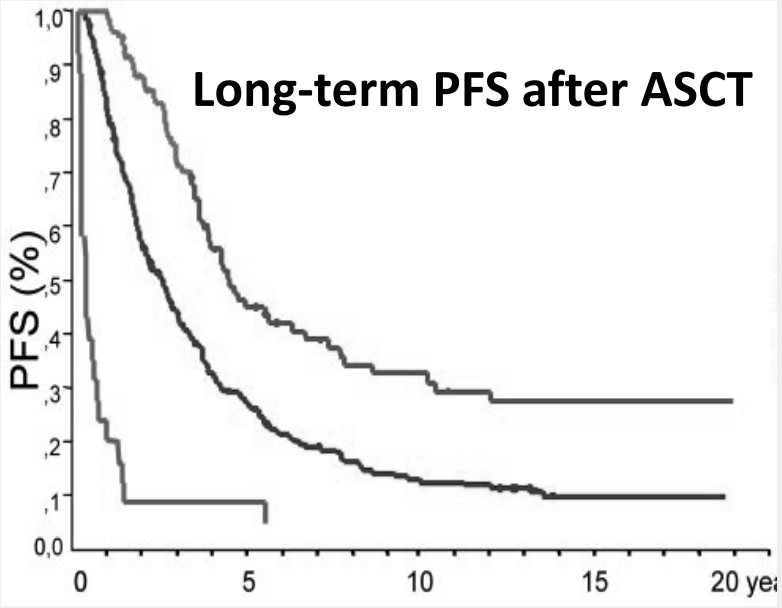
**Will immunotherapy replace ASCT or consolidate ASCT ?**

**Why maintain ASCT ?**

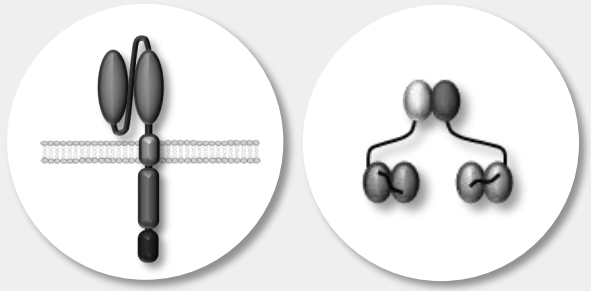
- World-wide access
- Cost-benefit ratio
- Low TRM
- In SR MM long term disease control – Cure fraction
- Increase the cure rate by combination therapy !

**BiTEs vs CAR T**

- Availability
- Drug variability/precise dosing
- One shot therapy vs treatment until PD
- Efficacy/Safety
- Resistance mechanisms




Martinez-Lopez J et al., Blood 2011



Chimeric antigen receptor (CAR)

Bispecific T cell engagers (BiTE)

# Bispecific Antibodies/T Cell Engagers (TCE) (vs CAR T cells)

The poor man‘s CAR T cells
Treatment forever!
Less effective!
Only for elderly/frail patients!

**The race is on !!**

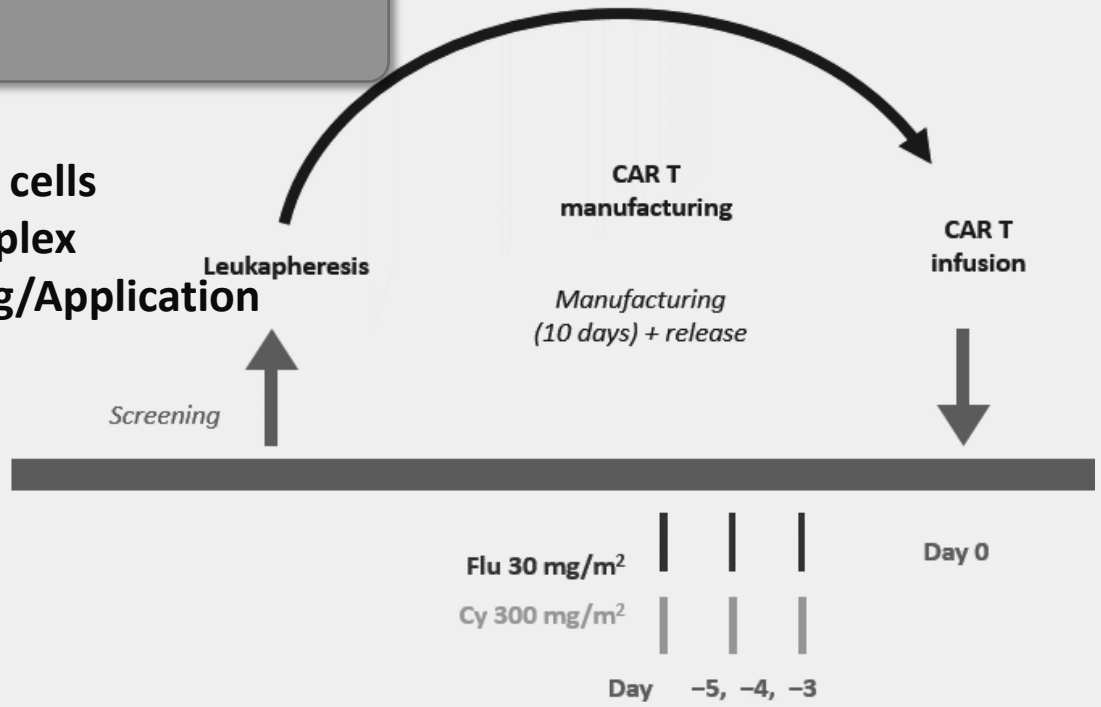

**CAR** START **BiTE**

# BiTEs vs CAR Ts

**What do you get ?**

**CAR T cell product highly variable**
**T cell subset Composition**
**Transduction Efficacy**
**Viability**

**CAR T cells**
**Complex**
**Manufacturing/Application**




→ It can take up to 8 weeks from leukapheresis to CART infusion

**New Strategies: Allo-CAR T cells**

→ But: Immunogenicity/extensive genetic engineering → Persistence?

**T Cell Engaging Antibodies**

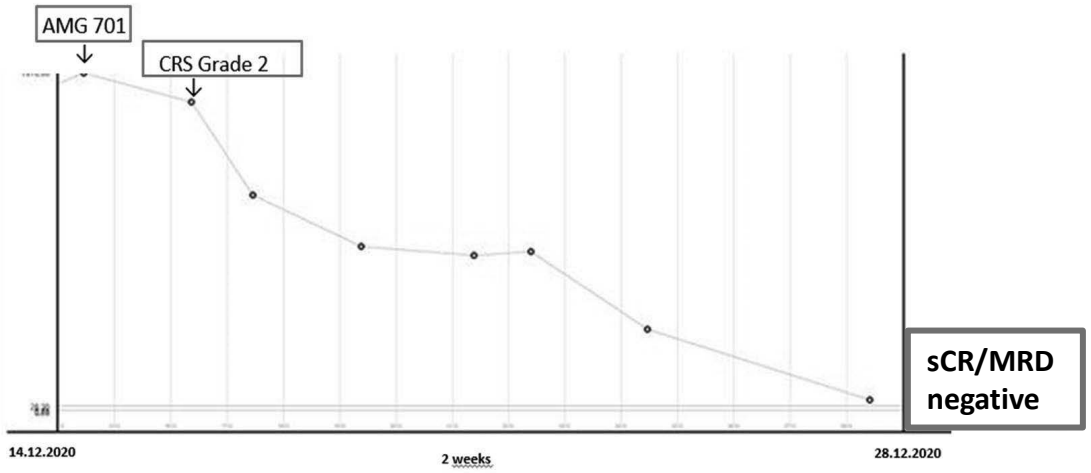
**Off the shelf**

**What do you want?**

**Precise dosing**
**s.c./i.v. application**
**Application qW, q2W, q3W etc.?**
**Which target?**
**BCMA/GPRC5D/FcHR5/CD38?**

# Do we need to give BiTes until PD? No!

Retreatment with BiTEs possible/effective!




Max. response in all our patients after 1-3 mo.
(4-12 applications of BCMA-BiTEs)

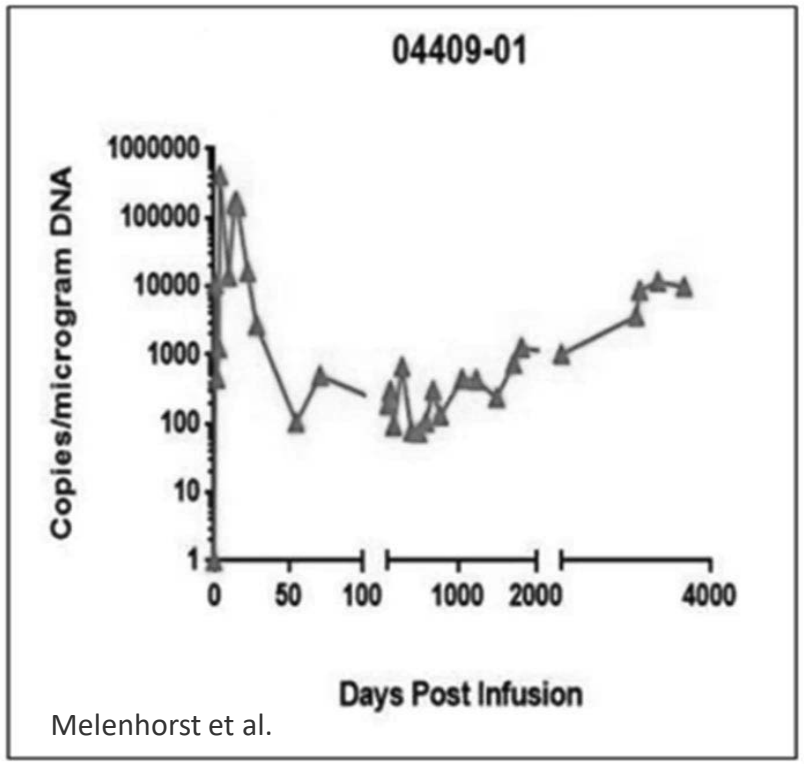
| Pt | Age | Initial treatment | | | Intervening alloHSCT | Retreatment | | | RFS (months) | Overall survival (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Daily dose | Response duration (months) | Blasts at relapse | | Daily dose | Grade ≥3 neurologic event | Best hematologic response | | |
| 1 | 12 | 15–30 µg/m² | 12.4 | — | | 5–15 µg/m² | | PD | | 0.7 |
| 2 | 4 | 5–15 µg/m² | 3.4 | 93% | Yes | 5–15 µg/m² | | No response | | 6.7 |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | 62 | 15 µg/m² | | — | Yes | 15 µg/m² | | CRh | 3.9 | 4.8 |
| 7 | 21 | 5–15 µg/m² | 10.6 | 10% | | 5–15 µg/m² | Yes | — | | 12.3 |
| 8 | 20 | 9–28 µg | 14.2 | — | | 9–28 µg | Yes | CR | 1.7 | 3.7 |
| 9 | 29 | 9–28 µg | 10.5 | — | Yes | 9–28 µg | | PD | | 0.7 |
| 10 | 26 | 9–28 µg | 5.1 | — | Yes | 9–28 µg | | PD | | 1.8 |
| 11 | 25 | 9–28 µg | 11.3 | — | Yes | 9–28 µg | | CRh | 3.7 | 4.6 |
| | | | | | | | | | 3.8 (1.7, 8.6) | 9.4 (0.7, 12.9) |
| Retreatment with BCMA-directed CART cells of limited value: ORR only xx %, PFS only xy mo. | | | | | | | | | | |

**ORR 36% after 2nd application (comparable to the 44% reported for initial treatment!**
**3 out of 4 responding patients still alive up to 20 mo. post retreatment !**

Topp MS et al., Leukemia 2017

Response-adapted therapy and retreatment
→ Reduce duration of therapy / T cell exhaustion/toxicity esp. infectious complications

# CAR T Cell Therapy in MM: One shot treatment? No



Melenhorst et al.

Long-term persistence of CAR Ts,
long term disease control/cure?

**But: BCMA-CAR T limited persistence**

**CAR T Cell persistence over time**

| | Month 1 | Month 3 | Month 6 | Month 12 |
|---|---|---|---|---|
| No. at risk | 24 | 22 | 23 | 10 |
| No. (%) with detectable vector | 23 (96) | 19 (86) | 13 (57) | 2 (20) |

All 33 patients were included in the analysis. Data from samples with <50 ng total DNA input were excluded.

Raje N et al., NEJM 2019

## CAR T Cell Therapy for MM

Combination Therapy (continuous therapy)
- IMiD/CelMODs
- Immune Checkpoint Blockers
- Anti-CD38 Ab ± IMiDs
- TKI, e.g. Ibrutinib

# BCMA-directed CAR T Cell Therapeutics vs BCMA-directed Bispecifics

## Efficacy/Toxicity

| | CAR T | Bispecifics |
|---|---|---|
| ORR | 80 - 100 % | >60 - 83 % |
| CR | 40 - 85 % | 13 - 50 % |
| PFS | > 1 - 1,5 yrs | > 6 mo. |
| CRS Gr. 3 | 3 - 6 % | 0 - 3 % |
| ICANS Gr. 3 | 3 - 10 % | 0 - 1 % |

Following CAR T Cell Therapy grade 3 cytopenia can last for of 2-3 months !!

**→ Hematotoxicity clearly less frequent/less severe/shorter after BiTEs vs CART cells**

Munshi N et al. NEJM 2012; Madduri D et al. ASH 2020 #177; Garfall AL et al. ASH 2020 #180; Lesokhin AM et al. ASH 2020 #3206; Madduri D et al. ASH 2020 #291; Rodriguez et al. ASH 2020 #293; Chari A et al. ASH 2020 #290; Cohen AD et al. ASH 2020 #292; Harrison S et al. ASH 2020 #181; Costello C et al. ASH 2020 #134; Kumar et al. ASH 2020 #133; Piasecki et al. ASH 2020 #2350; Colonna et al. ASH 2020 #2358.

**But:** **Few patients treated with BiTEs in highest dose level: In some trials MTD not reached!**
**Short follow up for bispecifics!**

# Treatment of elderly patients?

**Inclusion:**

| | Ide-cel (all treated) N=128 | Cita-cel N=97 | Bispecific mAbs (pooled data) |
|---|---|---|---|
| Age, medium | 61 yrs (up to 78) | 60 yrs (up to 75) | 64 yrs (up to 88) |

Munshi NC et al., J Clin Oncol 2020;
Berdeja JG et al., J Clin Oncol 2020;
Mailankody S et al., J Clin Oncol 2020;
Costa LJ et al., EHA 2020;
Usmani SF et al., J Clin Oncol 2020

Ide-cel resulted in an ORR of **73 %**
- Patients > 65 yrs (n=45): **84 %**
- Patients ≥ 70 yrs (n=20): **90 %**
- **Tolerability, PFS and DoR are comparable with the ITT population**

**Bispecific TCE successful and safe in frail patients !**

Mosunetuzumab
CD20xCD3-BiTE

| Characteristics | | 1L DLBCL (N=29) |
|---|---|---|
| Median age, years (range) | | 82 (67–100) |
| Age ≥80, n (%) | | 21 (72) |
| Age <80, n (%) | | 8 (28) |
| Female, n (%) | | 21 (72) |
| IPI score ≥3, n (%) | | 15 (52) |
| ECOG PS, n (%) | 0 | 5 (17) |
| | 1 | 15 (52) |
| | 2 | 9 (31) |

| Summary of CRS | 1L DLBCL (N=29) |
|---|---|
| Any grade, n (%) | 6 (21) |
| Grade 1 | 5 (17) |
| Grade 2 | 1 (3) |
| Hypotension related to CRS, n (%) | 1 (3) |
| No TRM! | 0 |

Olszewski A et al., ASH 2020, Abstract #401

# Antigen escape in BCMA CAR T Cell Therapy for MM

## Homozygous *BCMA* gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma

Matteo C. Da Vià[1], Oliver Dietrich[2], Marietta Truger[3], Panagiota Arampatzi[4], Johannes Duell[1], Anke Heidemeier[5], Xiang Zhou[1], Sophia Danhof[1], Sabrina Kraus[1], Manik Chatterjee[1], Manja Meggendorfer[3], Sven Twardziok[3], Maria-Elisabeth Goebeler[1], Max S. Topp[1], Michael Hudecek[1], Sabrina Prommersberger[1], Kristen Hege[6], Shari Kaiser[6], Viktoria Fuhr[7], Niels Weinhold[8], Andreas Rosenwald[7], Florian Erhard[9], Claudia Haferlach[3], Hermann Einsele[1], K. Martin Kortüm[1], Antoine-Emmanuel Saliba[2] and Leo Rasche[1,10]

**B cell maturation antigen (BCMA) is a target for various immunotherapies and a biomarker for tumor load in multiple myeloma (MM). We report a case of irreversible BCMA loss**

has been described in a few patients[3,4], the tumor-intrinsic mechanism underlying relapse from BCMA-directed CAR T cell therapy has yet to be elucidated

## 719 Cite–Seq Profiling of T Cells in Multiple Myeloma Patients Undergoing BCMA Targeting CAR–T or Bites Immunotherapy

Program: Oral and Poster Abstracts
Type: Oral
Session: 651. Myeloma: Biology and Pathophysiology, excluding Therapy II
Hematology Disease Topics & Pathways:
multiple myeloma, Biological, Diseases, CAR–Ts, Therapies, Biological Processes, Technology and Procedures, Plasma Cell Disorders, immunotherapy, Lymphoid Malignancies, Clinically relevant, immune mechanism, integrative –omics, NGS, RNA sequencing

Monday, December 7, 2020: 1:30 PM

***Noemie Leblay, PhD**[1*], Ranjan Maity, PhD[1*], Elie Barakat[1*], Sylvia McCulloch, MD, MSc[2], Peter Duggan, MD, FRCPC[2], Victor Jimenez–Zepeda, MD[2], Nizar Bahlis, MD[3] and Paola Neri, MD[1]*

**Antigen escape is a common mechanism of escape after CART19 in particular in ALL (40-75%), but also in DLBCL (~30%)**

ARTICLE

https://doi.org/10.1038/s41467-021-21177-5 OPEN

Check for updates

## Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma

Mehmet Kemal Samur[1,2,3], Mariateresa Fulciniti[3], Anil Aktas Samur[1,2], Abdul Hamid Bazarbachi[3,4], Yu-Tzu Tai[3], Rao Prabhala[3,5], Alejandro Alonso[3], Adam S. Sperling[3], Timothy Campbell[6], Fabio Petrocca[7], Kristen Hege[6], Shari Kaiser[8], Hervé Avet Loiseau[9], Kenneth C. Anderson[3] & Nikhil C. Munshi[3,5]

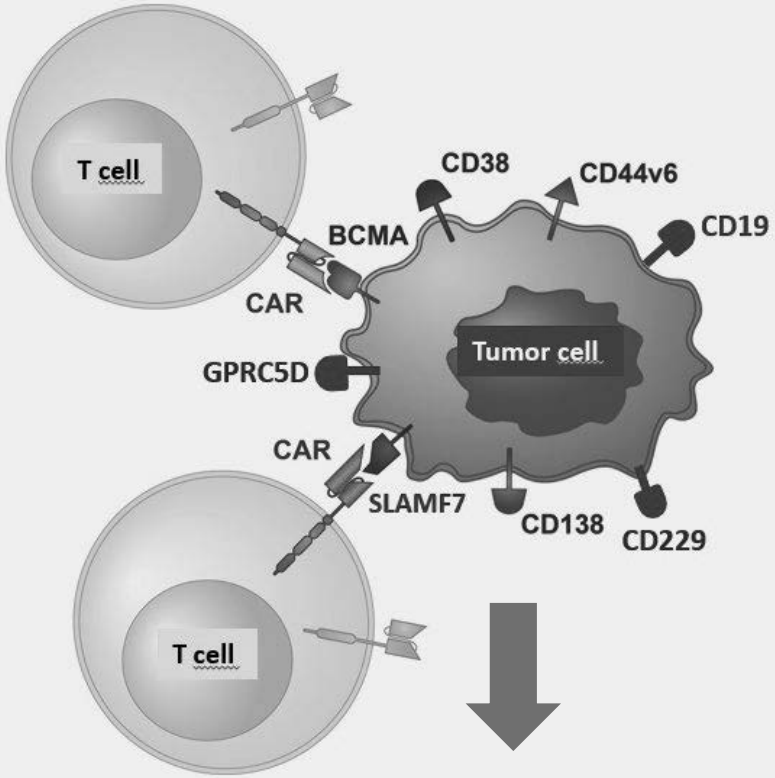
BCMA targeting chimeric antigen receptor (CAR) T cell therapy has shown deep and durable responses in multiple myeloma. However, relapse following therapy is frequently observed,

**HOMOZYGOUS BCMA LOSS IN RESPONSE TO T-CELL ENGAGERS (TCE)**

Truger MS et al. Blood Adv 2021

# How to deal with BCMA loss?

**Produce CAR T cells targeting surface antigens beyond BCMA on MM**




→ But: Time-consuming production / successful production after CAR T cell failure?

Off-the shelf
Bispecific T cell engagers available against various surface antigens:

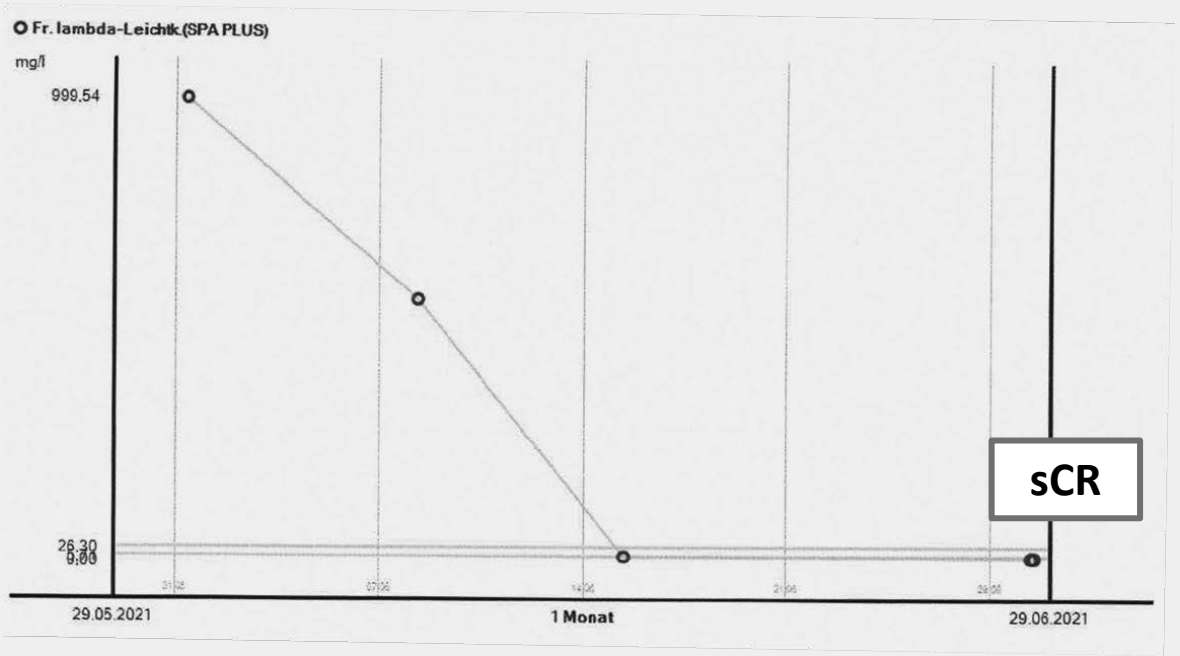
- BCMA
- GPRC5D
- FcHR5
- CD38

→ **Can they be used sequentially?**

# Patient Case

**57 year ♀, LC-MM, ISS-IIIB, acute renal failure, hypercalcemia (short-term dialysis), multiple osteolyses**

**Yes:**
After failure of BCMA BiTE targeting BiTEs targeting other MM-surface Ag with BiTEs like GPRC5D/FcHR5 have been sucessful




**Treatment:**

| | |
|---|---|
| 02/2011 | 3x PAD |
| 05/u. 08/2011 | Tandem-Mel → CR |
| 4/14 | PD → RD 6 cycles |
| 12/15 - 12/16 | RD → 16 cycles |
| | Panobinostat/Bortezomib/Dexa → PD |
| 05 – 11/17 | 6x Ixa/Thal/Dex → PD |
| 11 – 12/12 | 1x Rd → PD |
| 01/18 | BCMA-Bite (AMG420) → sCR |
| 09/19 | PD → KRd 18x |
| 07/20 | PD → Dara/Vel/Dex → PD |
| 12/20 | Belantamab → PD |
| | (**Documented irreversible BCMA-loss**) |
| 12/20 | VTD-PACE 3x → PD |

→ GPRC5D-targeting BiTE!

# Bispecific Antibodies/T Cell Engagers (TCE) vs CAR T cells

The race is finished !!


**CAR** **BiTE**

## And the winner is: Bispecific T cell engager (BiTE)!

# Bispecific Antibodies/T Cell Engagers (TCE)

## = Best immune approach to replace or consolidate ASCT

- Better availability (off the shelf vs time consuming production)
- Precise dosing (vs drug variability)
- Broad range of specificities as off the shelf products (vs long production time/failure)
- Better tolerability (CRS/ICANS/hematotoxicity)
- Retreatment more successful with BiTEs
- Duration of treatment not necessarily longer (optimal response after 1-3 mo BiTE therapy vs CAR T cells > 2 mo therapy)
- Efficacy similar with further dose escalation of Bites or combination therapies ?

# Retreatment with CAR T Cells

## Tumor Response and Progression-Free Survival in All Enrolled Patients and Retreated Patients

| | Total Enrolled (N=140) | Total Retreated (N=28) |
|---|---|---|
| Best overall response—no. (%) | 94 (67) | 6 (21) |
| Stringent complete response | 41 (29) | 0 |
| Complete response | 1 (1) | 0 |
| Very good partial response | 25 (18) | 1 (4) |
| Partial response | 27 (19) | 5 (18) |
| Stable disease | 22 (16) | 5 (18) |
| Progressive disease | 8 (6) | 15 (54) |
| Not evaluable* | 14 (10) | 2 (7) |
| Median progression-free survival (95% CI)—mo | 9.5 (6.9–12.5) | 1.0 (1.0–2.1) |

**Retreatment with CAR T cells (at least the same product) of limited value!**

Munshi NC et al., N Engl J Med 2021

# BCMA-directed CAR T Cell Therapeutics vs BCMA-directed Bispecifics

| | CART | | BiTEs | | |
|---|---|---|---|---|---|
| | Ide-Cel[2] | Cilta-Cel[1] | CC-93268[5] | Teclistamab[4] | AMG 701[3] |
| Neutropenia Grade ≥ 3 | 89% | 80% | 43% | 44% | 25% |
| Anemia Grade ≥ 3 | 60% | 45% | 37% | 26% | 42% |
| Thrombocytopenia Grade ≥ 3 | 52% | 45% | 17% | 21% | 21% |

Following CAR T Cell Therapy grade 3 cytopenia can last for of 2-3 months!!

→ **Hematotoxicity clearly less frequent/less severe/shorter after BiTEs vs CART cells**


1. Berdeja J et al., Lancet 2021
2. Munshi N et al., NEJM 2021
3. Harrison S et al., ASH 2020 Abstract#181
4. Krishnan A et al., ASCO 2021 Abstract#8007
5. Costa LJ et al., ASH 2019 Abstract#143