Società Italiana di Ematologia

# 3rd MEETING ON T-CELL AND NK-CELL BASED IMMUNOTHERAPIES FOR LYMPHOID MALIGNANCIES

Hermann Einsele

**Resistance and combination of bispecifics in MM**

*University Hospital Würzburg, Germany*

BOLOGNA, ROYAL HOTEL CARLTON

September 13-14, 2024

# Disclosures of Einsele, Hermann

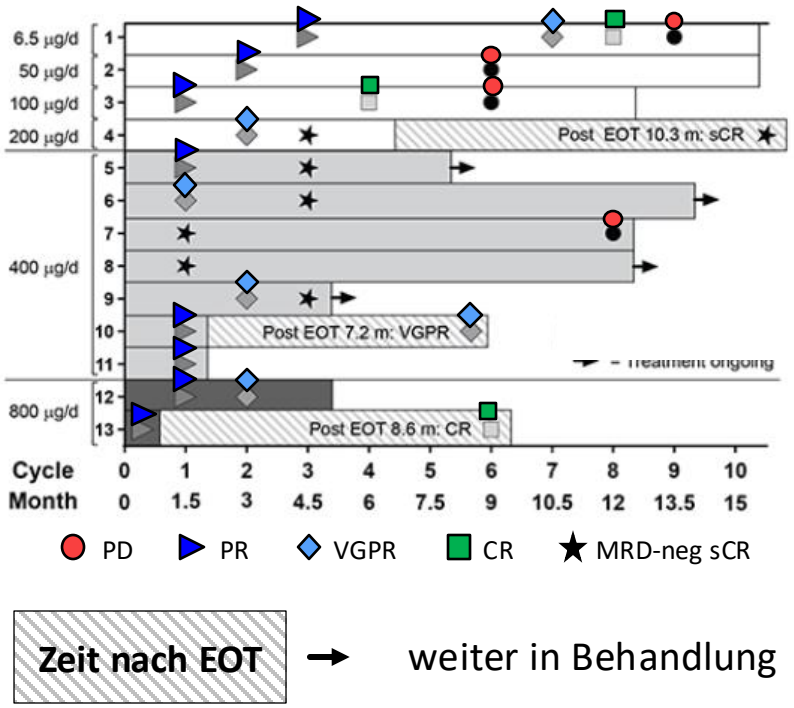
| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| BMS/Celgene | x | | x | | | x | x |
| Janssen | x | | x | | | x | x |
| Amgen | x | | x | | | x | x |
| Takeda | | | x | | | x | x |
| Sanofi | x | | x | | | x | x |
| GSK | x | | x | | | x | x |
| Roche | | | x | | | x | x |
| Novartis | x | | x | | | x | |
| - | | | | | | | |

# Proof-of-Concept-Study: AMG 420
# Updated results from a FIH phase 1 dose escalation study

## Efficacy

- Response
  - Total: 6 sCRs, 3 CRs, 2 VGPRs, 2 PRs
  - At 400 µg/day: **70% response rate**
- **5 MRD-negative sCRs, 1 VGPR and 1 PR**
- Median time to response: 1 month,
- response in the first cycle 9 of 13 pts.
- Duration of response: 5.6-10.4 months
- 4 patients under treatment
- **In some patients, response lasting >1 year**

## Patients with RRMM responding to AMG 420 since February 2019




**Zeit nach EOT** → weiter in Behandlung

Topp MS, … Einsele H, J Clin Oncol 2020

# BCMA targeting bispecific antibodies in RRMM

| | Teclistamab[1,2] | Elranatamab[3] | Elranatamab[4] | Linvoseltamab[5] | Alnuctamab[6,7] | ABBV-383[8] |
|---|---|---|---|---|---|---|
| Patients (n) | 165 | 55 | 123 | 117 | 73 | 124 |
| Dosing schedule | weekly /q2w SC | weekly / q2w SC | weekly/q2w IV | weekly/ q2 or 4 w IV | weekly/ q2-4w IV/SC | q3 weeks IV |
| med Prior LOT | 5 | 6 | 5 | 5 | 4 | 5 |
| ISS III / ↑↑PC (%) | 12.3 / 11.2 | 20 / -- | 15.4 /21.1 | 18.8 /22.2 | 16 / -- | 31 / -- |
| HR / EMD (%) | 25.7 / 17 | 29.1/ 30.9 | 25.2 / 31.7 | 35.9/ 13.7 | 26 / 21 | 18 / -- |
| TCR (%) | 77.6 | 90.9* | 100 | 73.5 | 63 | 82 |
| ORR / ≧ CR (%) @ RP2D | 63 / 45.5 1500 µg/kg SC | 64 / 38.2 76 mg SC | 61 / 35 76 mg SC | 71 / 30 200 mg IV | 69/ 43 30 mg SC | 57 17 40-60 mg IV |
| mDOR | 21.6 mos | 17.1 mos | 71.5% @ 15 mos | -- | -- | 72.2 % @ 12 mos† |
| mPFS | 11.3 mos ≦ 3 LOT 18.1 mos | 11.8 mos | 50.9% @ 15 mos | 72.7% @ 6 mos | 53% @ 12 mos | 10.4 mos 57.9% @ 12 mos† |
| mOS | 21.9 mos | 21.2 mos | 56.7% @ 15 mos | -- | -- | -- |
| CRS (%) | 72.1 (0.6 G3) | 87.3 (0 G3) | 56.3 (0 G3) | 45.3 (0.9 G3) | 56 (0 G3) | 57 (2 G3) |
| Infections (%) | 80 (55.2 G3-4) | 74.5 (27.3 G3-4) | 69.9 (39.8 G3-4) | 59.8 (36.8 G3-4) | 62 (16 G3-4) | 41 (5 G3-4) |

LOT = lines of therapy, HR = high risk cytogenetics, EMD = extramedullary disease, ↑↑PC = > 50-60% bone marrow plasma cells, TCR = triple class refractory, ORR = overall response rate, DOR = duration of response, PFS = progression free survival, OS = overall survival, SC = subcutaneous, IV = intravenous, mos = months, * = 23.6% prior anti-BCMA, -- = not reported, †mPFS at ≥ 40 mg dose level

1. Moreau et al NEJM 2022.; 2. Van de Donk et al ASCO 2023, 3. Bahlis et al Nat Med 2023; 4. Lesokhin et al Nat Med 2023; 5. Lee et al J ASCO 2023 ; 6 Wong et al ASH 2022 ; 7. Barr ASH2023, abstract # 2011; 8. D'Souza A J Clin Oncol 2022

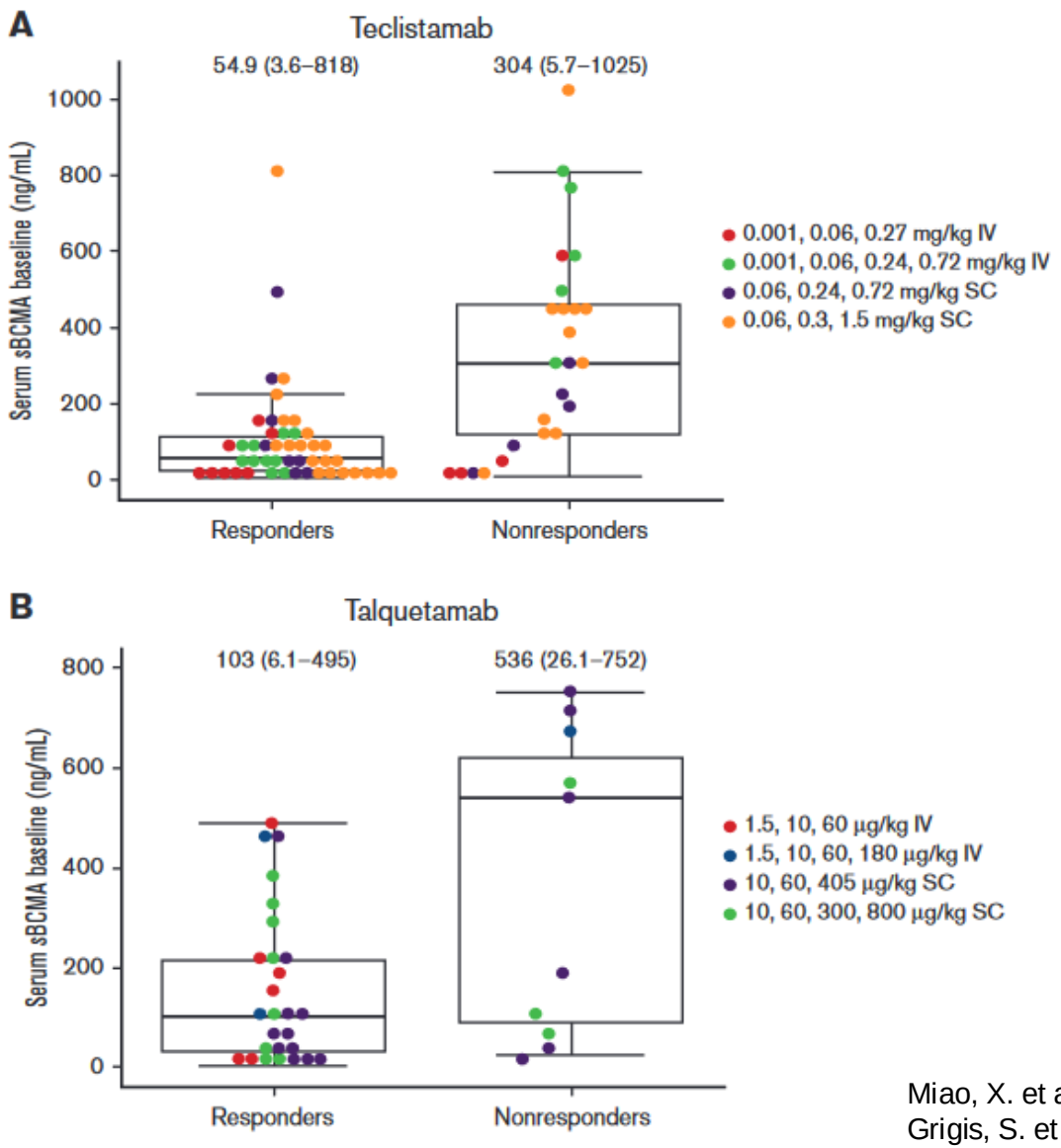
# GPRC5D or FcRH5 targeting BsAb in multiple myeloma

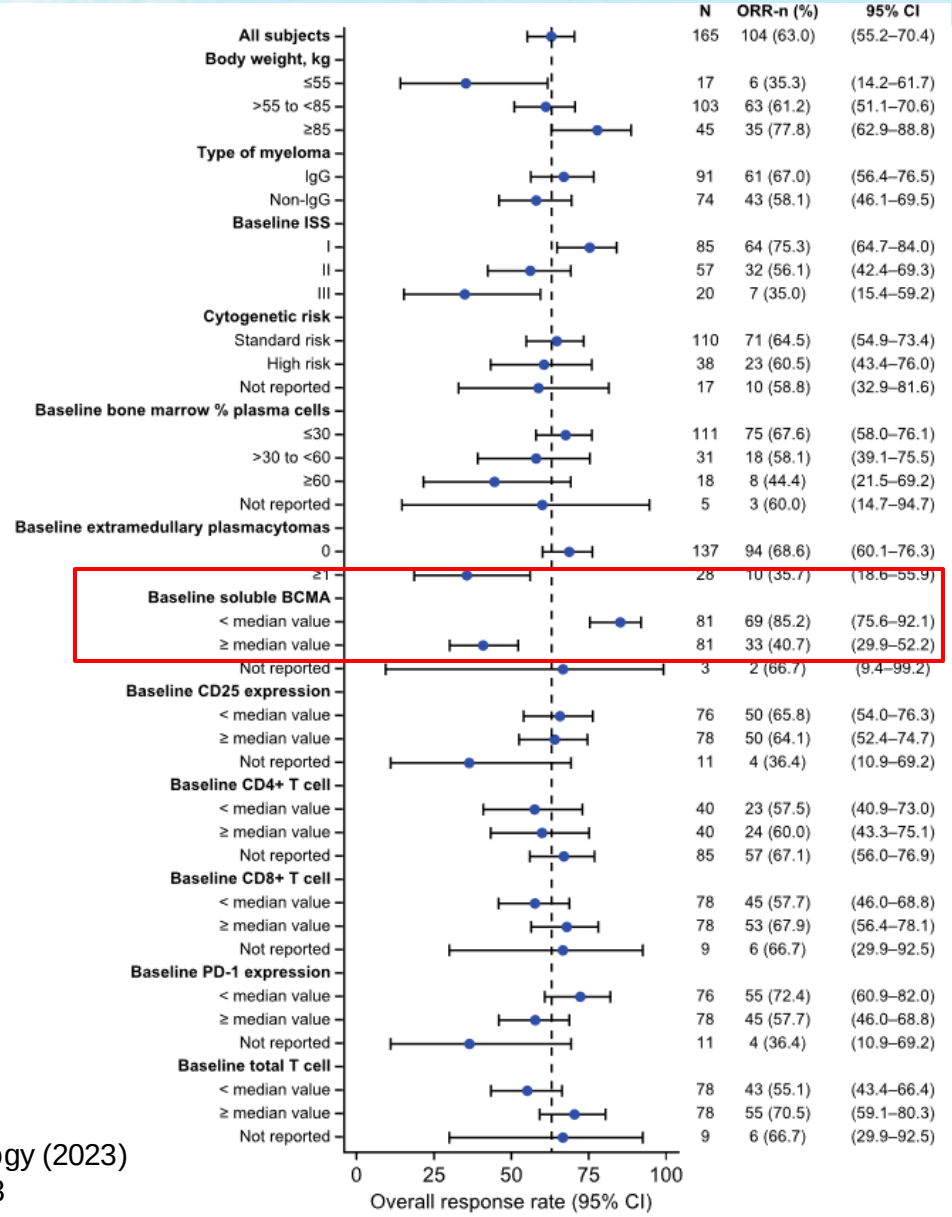
| | Anti-GPRC5d Talquetamab[1,2] | | | Anti-GPRC5d Forimtamig[3] | | Anti-FcRH5 Cevostamab[4,5] |
|---|---|---|---|---|---|---|
| Patients (n) | 143<br>T-cell redirecting Rx naïve<br>Anti-BCMA ADC allowed | 145<br>T-cell redirecting Rx naïve<br>Anti-BCMA ADC allowed | 51<br>Prior anti-BCMA<br>CAR/BsAb allowed | 51<br>Prior anti-BCMA ADC/<br>CAR/BsAb allowed | 57<br>Prior anti-BCMA ADC/<br>CAR/BsAb allowed | 161 |
| Dosing schedule | 405 µg/kg SC QW | 800 µg/kg SC Q2W | 5-1600 µg/kg SC | 18-10000 µg IV Q2-3W | 1200-7200 µg SC Q2-3w | 20-198 mg IV q3w |
| med Prior LOT | 5 | 5 | 6 | 5 | 4 | 6 |
| ISS III / ↑↑PC (%) | 19.6 / 12.3 | 24.3 / 22.7 | 17.6 / 17 | -- | -- | -- |
| HR / EMD (%) | 31.1 / 23.1 | 28.9 / 25.5 | 40.9 / 31.4 | 46.7 / 27.5 | 47.7 / 31.6 | 39.8 / 21.1 |
| TCR / Penta-refr. (%) | 74.1 / 29.4 | 69/ 23.4 | 84.3 / 41.2 | 62 / 36 | 71.9 / 42.1 | 84.5 / 68.3 |
| ORR / ≧ CR (%)<br>ORR prior BCMA (%) | 74.1 / 33.6 | 71.7 / 38.7 | 64.7 / 35.3 | 71.4 / 34.7<br>50 | 63.6 / 25.5<br>54.5 | 56.7 /8.4 × |
| mDOR | 9.5 mos | NR | 11.9 mos | 10.8 mos | 12.5 mos | 11.5 months |
| 12-month PFS (%) | 34.9 | 54.4 | 38.1 | -- | -- | -- |
| 12-month OS (%) | 76.4 | 77.4 | 62.9 | -- | -- | -- |
| CRS (%) | 79 (2.1 G3) | 74.5 (0.7 G3) | 76.5 (2.0 G3) | 82.4 (2.1 G3) | 78.9 (1.8 G3) | 79.5 (2.3 G3)* |
| Infections (%) | 58.7 (19.6 ≧G3) | 66.2 (14.5 ≧G3) | 72.5 (27.5 ≧G3) | 60.8 (21.5 ≧G3) | 45.6 (26.4 ≧G3) | 43 |
| Dysgeusia (%)<br>Skin/Nail (%) | 72<br>55.9 / 54.5 | 71<br>73.1 / 53.8 | 76.5<br>68.6 / 62.7 | 72.5<br>23.5 | 77.2<br>28.1 | na |

* 2-step-up 0.3/3.6/target dose 60-160 mg, * at the132-198 mg dose level, na not reported

1. Schinke at al ASCO 2023 , 2. Chari et al NEJM 2023; 3. Carlo-Stella et al. ASH 2022; 4. Trudel et al. ASH 2021; Harrison et al IMS2023

# Tumor Load/sBCMA determines Efficacy and Safety of BCMA-directed TCE




Miao, X. et al., Targeted Oncology (2023)
Grigis, S. et al., Blood Adv 2023

# Patient Case

♂ **66 yrs., R-ISS III, BM-Infiltration 85 %, FISH: 17p del, gain 1q21, IgA 7,4 g/dl**

- Hyperviscosity Syndrome
- Hypercalcemia

→ DSMM XX Study: **Tec/DaraRd - start with Teclistamab** → no response

→ Plasmapheresis 2x

→ Dexamethasone 40 mg x 4

→ **Restart DSMM XX Tec/DaraRd (4 Cycles)**

→ **CR, MRD-neg. ($10^{-6}$)**

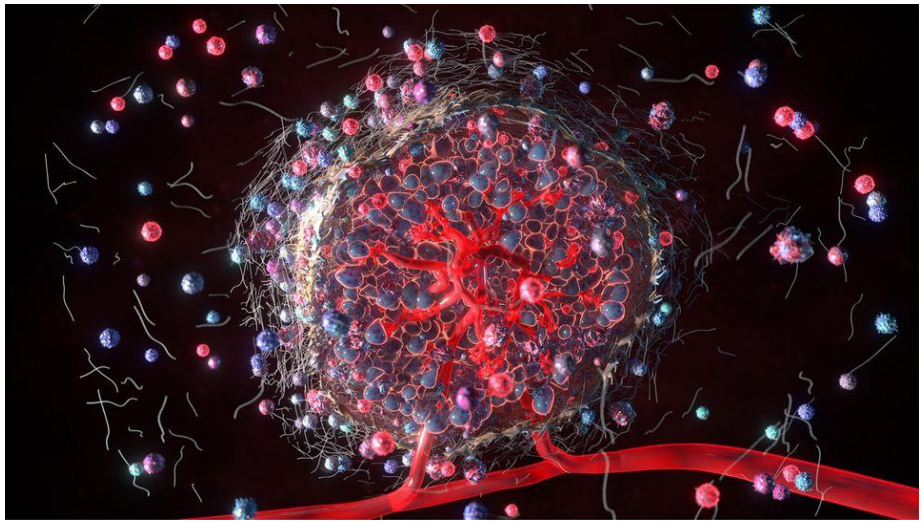
# Acquired Resistance to Bispecific Antibodies

Uniklinikum Würzburg

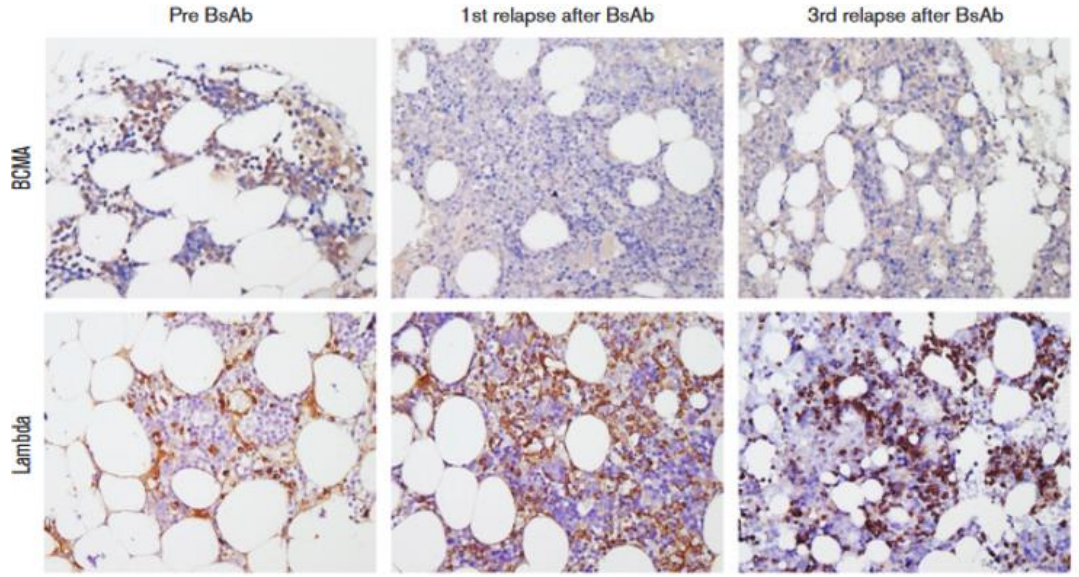
→ Target Antigen Loss

→ T Cell Exhaustion

→ Tumor Microenvironment, esp. Tregs

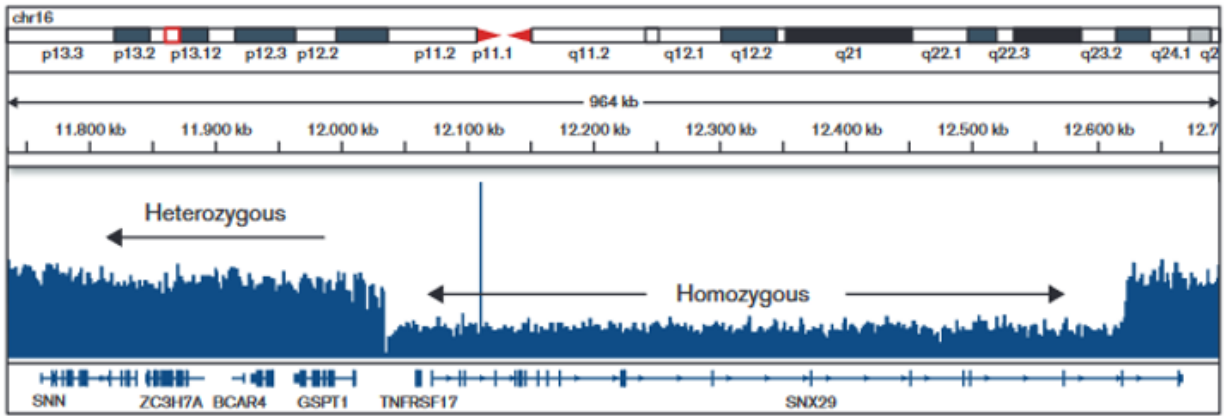


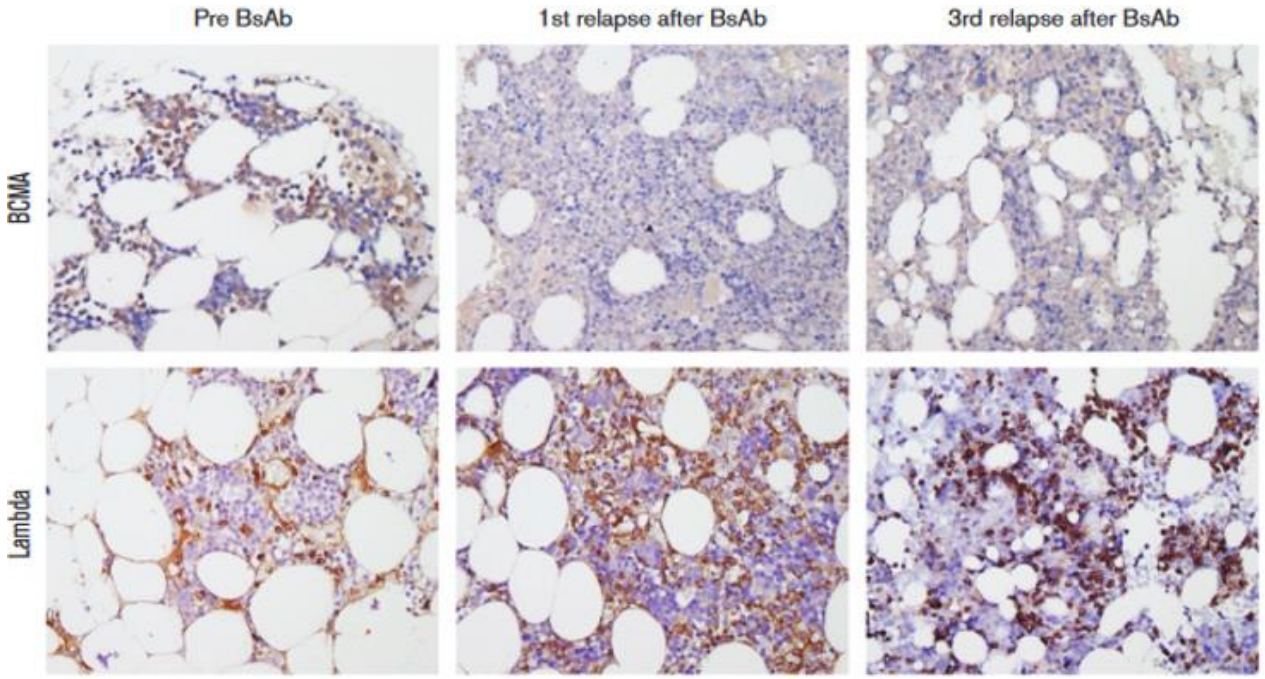
Tumor microenvironment
Halliday A, TechnologyNetworks Cancer Research 2022




Truger, M. et al., Blood Adv 2021
Lee, H., Nat Med 2023

# Acquired Resistance to Bispecifics:
# BCMA biallelic antigenic loss and resistance to AMG420



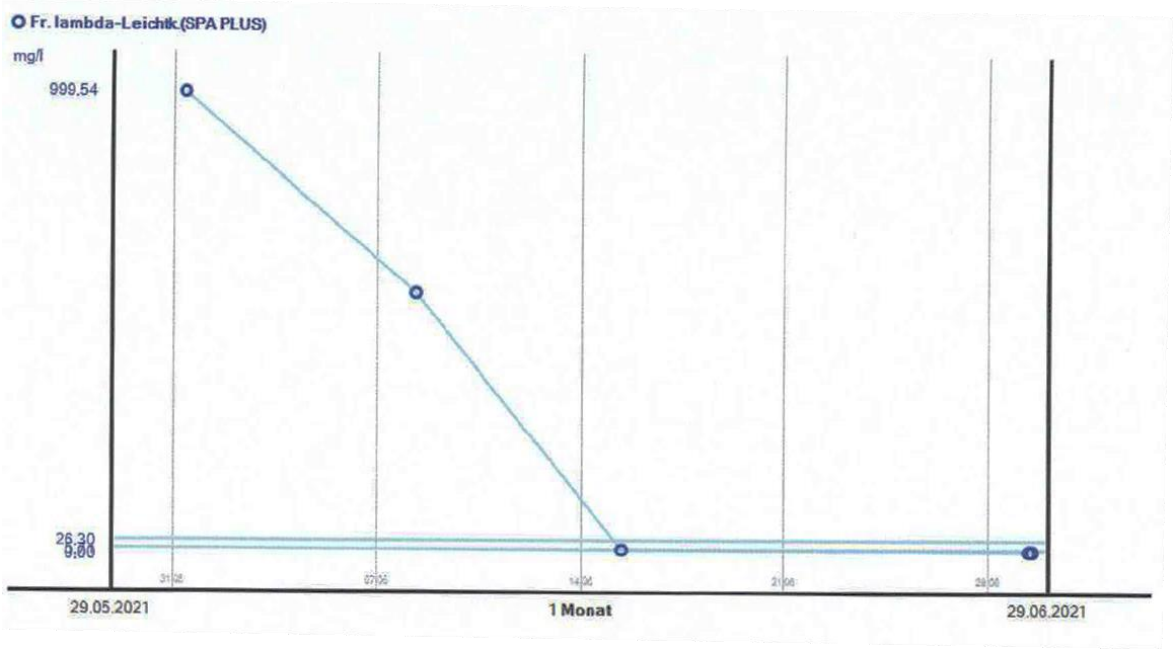

→ **Irreversible loss of Efficacy of Bispecific Antibodies**

Truger, M. et al., Blood Adv 2021

# Patient Case

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

**GPRC5D-directed T-cell Therapy**




**Treatment:**

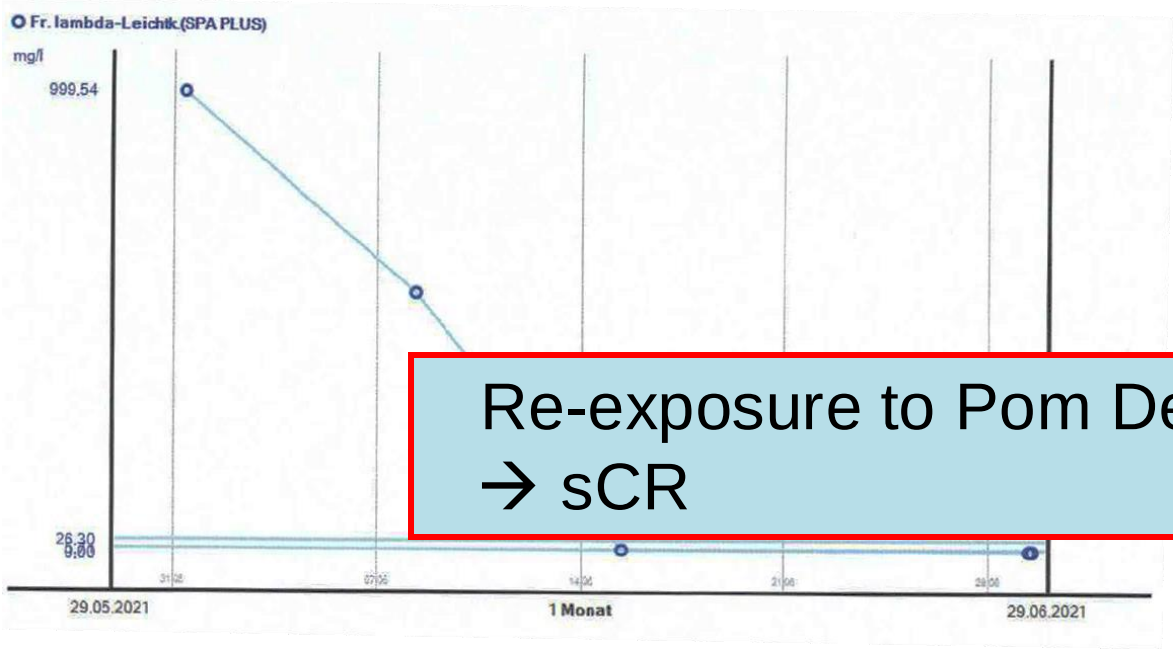
| | |
|---|---|
| 02/2011 | 3x PAD |
| 05/u. 08/2011 | Tandem-Mel → CR |
| 4/14 – 12/16 | RD → 16 cycles |
| | Panobinostat/Bortezomib/Dexa →PD |
| 05 – 11/17 | 6x Ixa/Thal/Dex → PD |
| 11 – 12/12 | 1x Rd → PD |
| 01/18 | BCMA-directed T-Cell-Therapy |
| 9//19 | PD → KRd |
| 07/20 | PD → Dara/Vel/Dex → PD |
| 12/20 | Belantamab → PD |
| (**Documented irreversible BCMA-loss**) | |
| 12/20 | VTD-PACE 3x → PD |

Personal Treatment Experience

# Patient Case

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

**GPRC5D-directed T-cell-therapy**




**Treatment:**

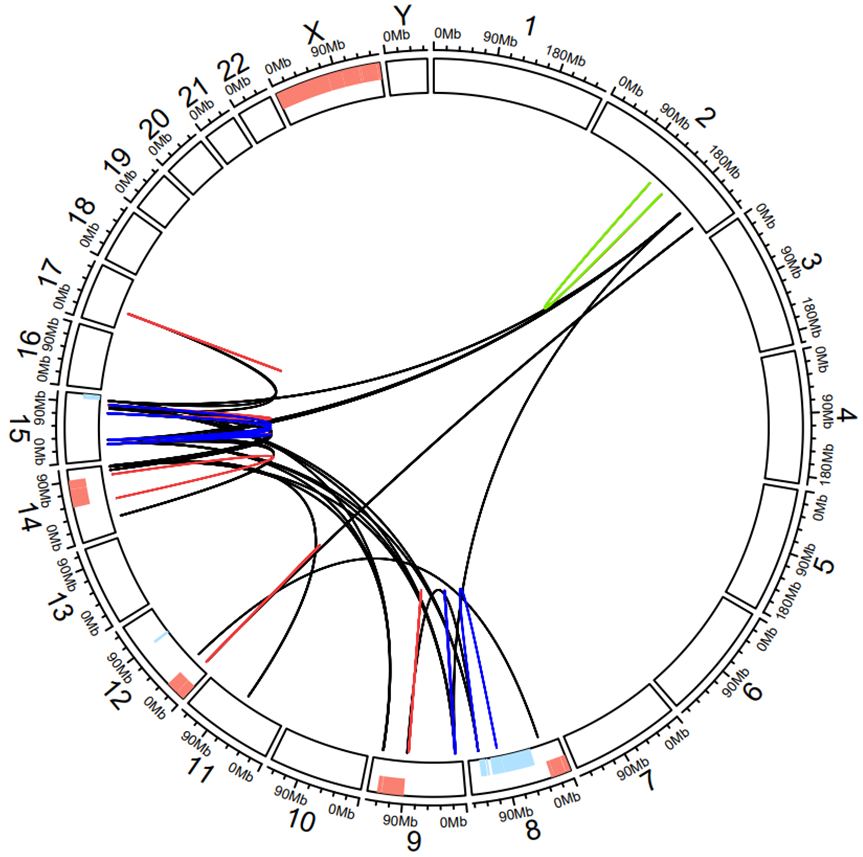
| | |
|---|---|
| 02/2011 | 3x PAD |
| 05/u. 08/2011 | Tandem-Mel → CR |
| 4/14 – 12/16 | RD 16 cycles |
| 12/15 - 12/16 | RD → 16 cycles |
| | Panobinostat/Bortezomib/Dexa →PD |
| 05 – 11/17 | 6x Ixa/Thal/Dex → PD |
| 11 – 12/12 | Rd → PD |
| 01/18 | BCMA-directed T-Cell-Theray |
| 9//19 | PD → KRd |
| 07/20 | PD → Dara/Vel/Dex → PomDexDara |
| | Belantamab → PD |
| | **ed irreversible BCMA-loss**) |
| | VTD-PACE 3x → PD |

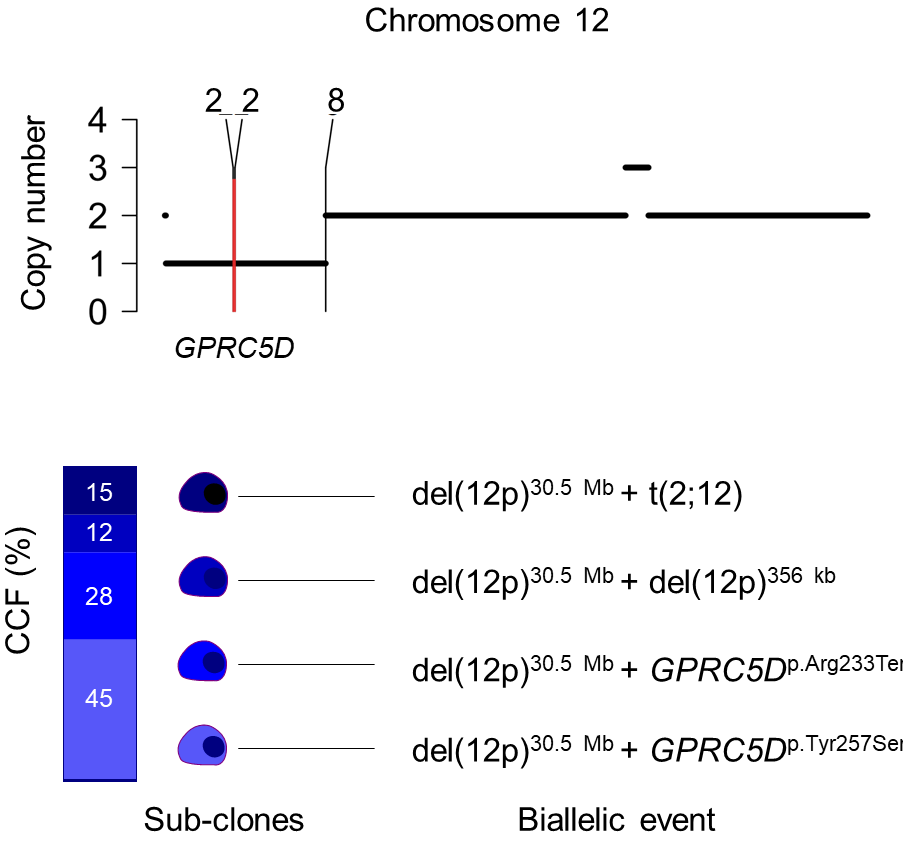
Re-exposure to Pom Dex Dara
→ sCR

After 15 mo. PD!

Personal Treatment Experience

# Biallelic GPRC5D loss after Talquetamab



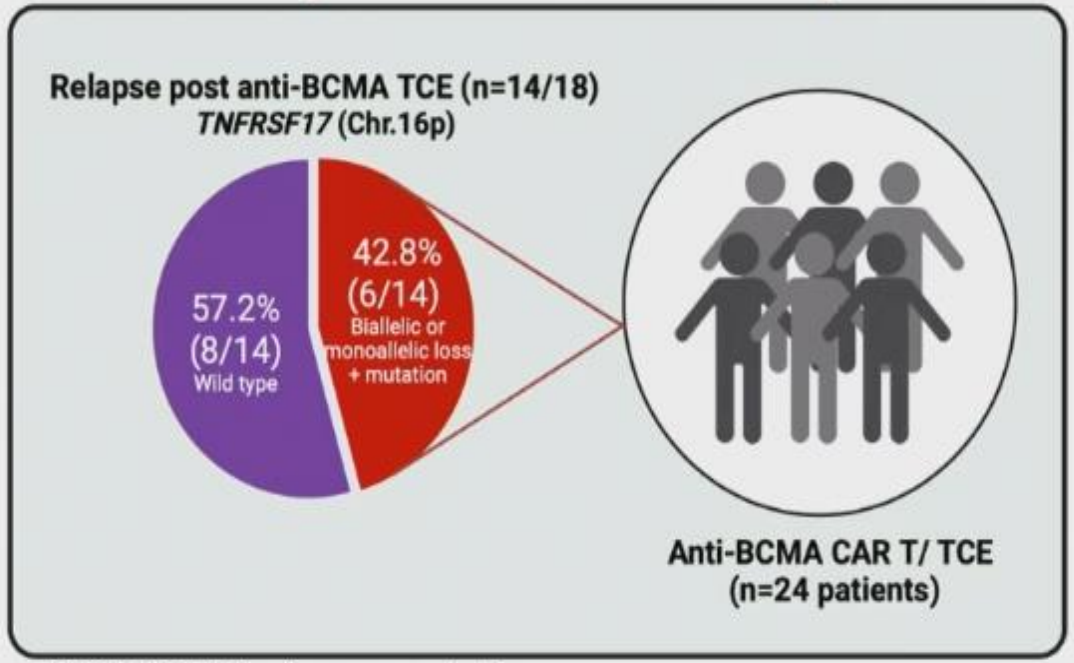

SV Deletion | Duplication | Inversion

Translocation | CNV Deletion | CNV Gain

Holly, E. et al., Nat. Med. 2023

Derrian, J. et al., Nature Cancer 2023

# Frequent BCMA functional antigenic loss with BCMA extracellular domain mutations post BCMA x CD3 bispecific T cell engagers

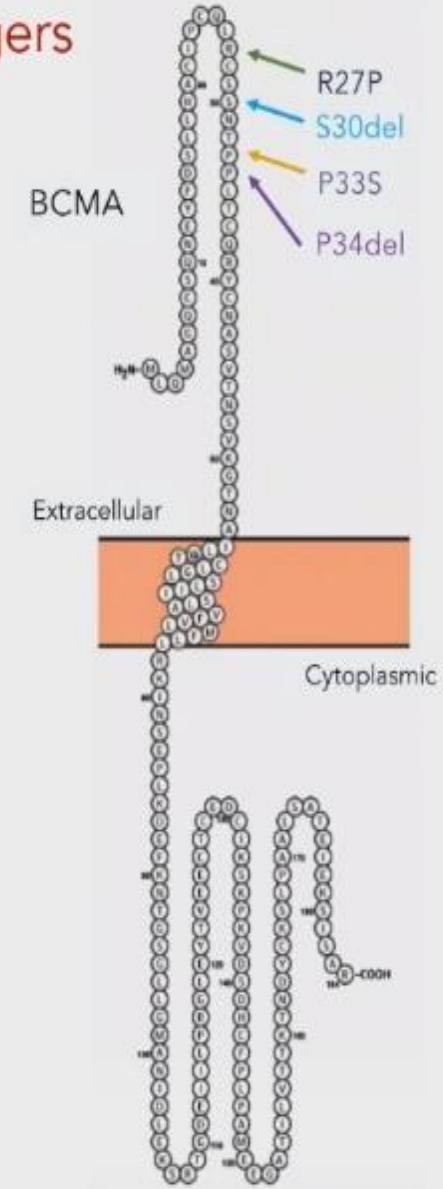



1) TNFRSF17 missense mutations
- p.Arg27Pro (n=1)
- p.Pro33Ser (germline mutation, n=1)

2) TNFRSF17 in-frame deletions
- p.Pro34del (n =3)
- p.Ser30del (n=2)

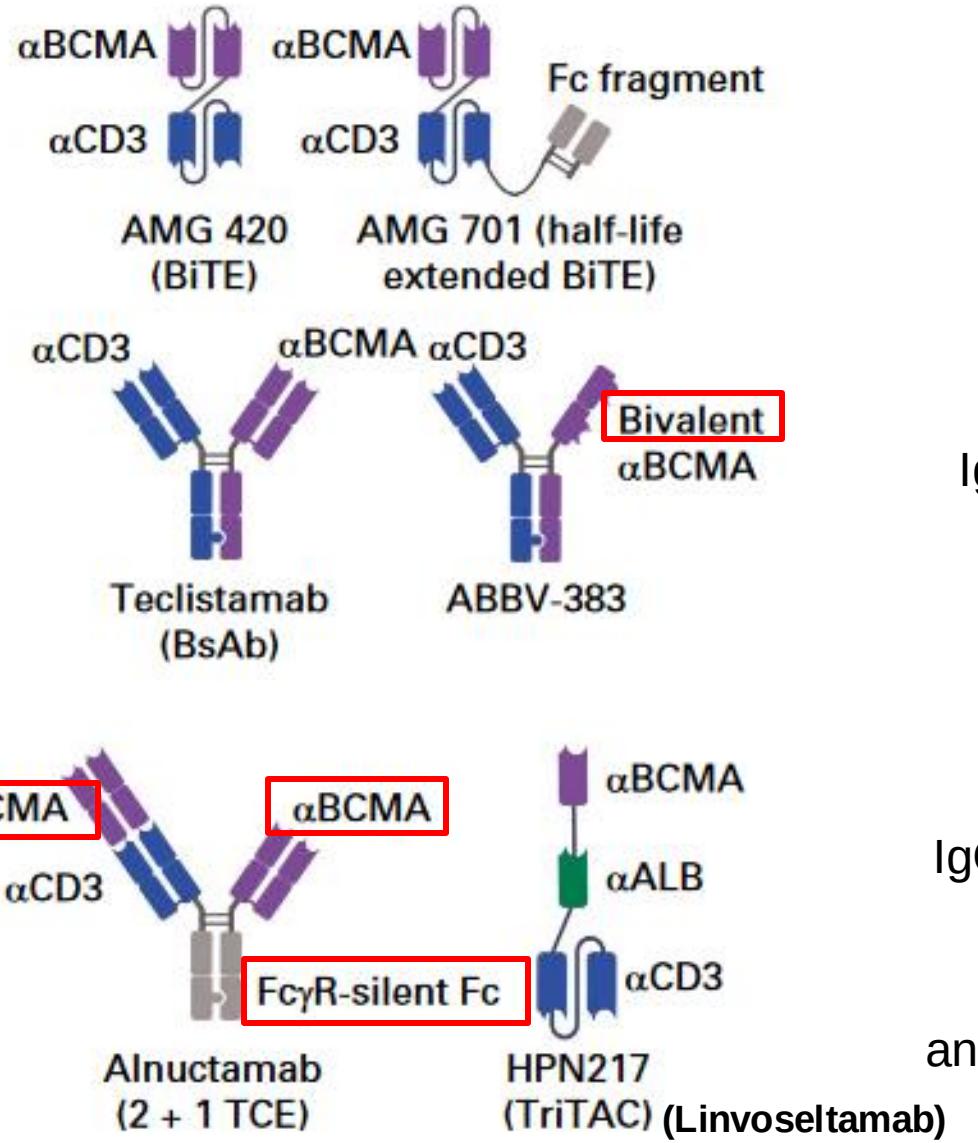
3) TNFRSF17 biallelic deletion (n=1)

* 1 patient with p.Ser30del and p.Pro34del (convergent evolution)




Lee H et al. Nature Medicine. 2023;29:2295-2306

# But: There are differences in MM directed bispecific Antibodies!
# → Antibody Format/Binding Domain (monovalent – bivalent)




BiTE
Tandem-scFv

IgG-like Bsab design +
bivalent BCMA-Fab

IgG-like BsAb design

Additional
anti-Albumin domain

**(Linvoseltamab)**

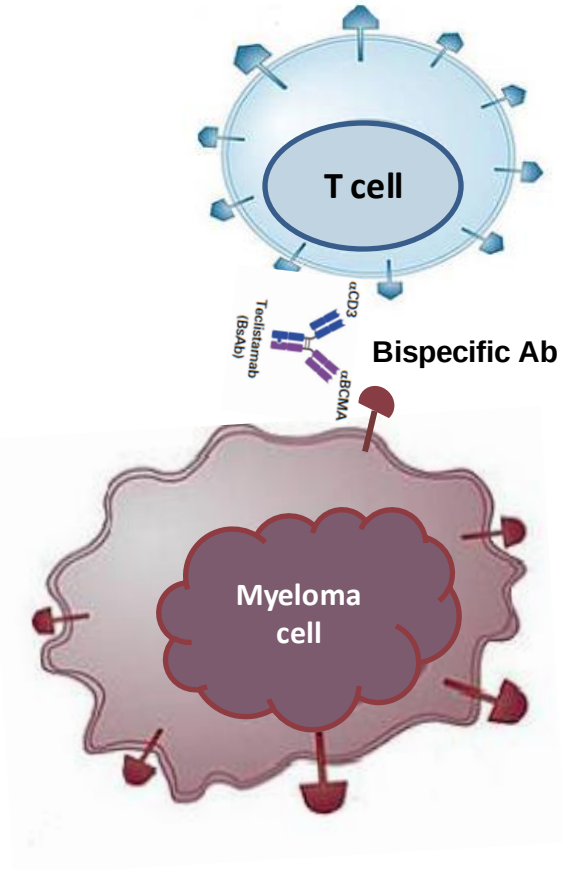
Holstein, S. et al., *JCO* 41, 4416-4429(2023)

# Are there also functional Differences between MM directed Bispecific Antibodies?

1. **CD3 binding Domain – low vs high affinity binding to CD3 (lower affinity binding Alnuctamab/ABBV-383)**
   - ➡ reduce CRS/ ↑tolerability
     - impact on biodistribution: tumor vs. CD3 + rich lymphoid tissues
   - ➡ ↑ serum exposure 3 fold by weak CD3-affinity TCE

2. **Tumor-targeting domain - low vs. high affinity binding - 1 vs 2 BCMA-binding domains**
   - ➡ impact on distribution and clearance
   - ➡ Alnuctamab/ABBV-383: 2 BCMA-binding domains/low affinity binding to CD3

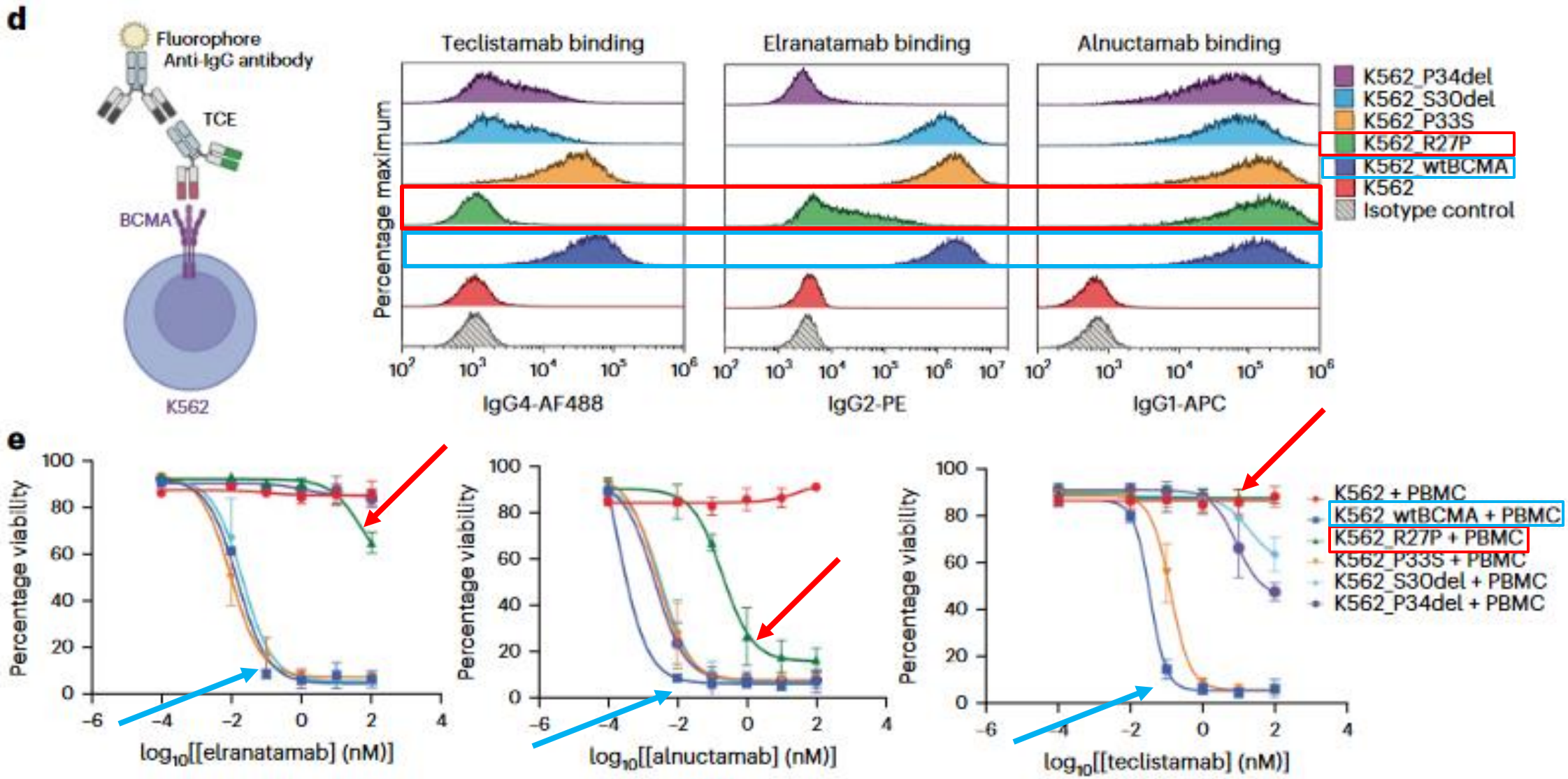
3. **FC Domain**
   - active or mutated (stability, immune response, CRS):
     Modification to minimize binding to FcγRI and C1q (e.g. Alnuctamab)



# BCMA-directed bispecific construct matters!

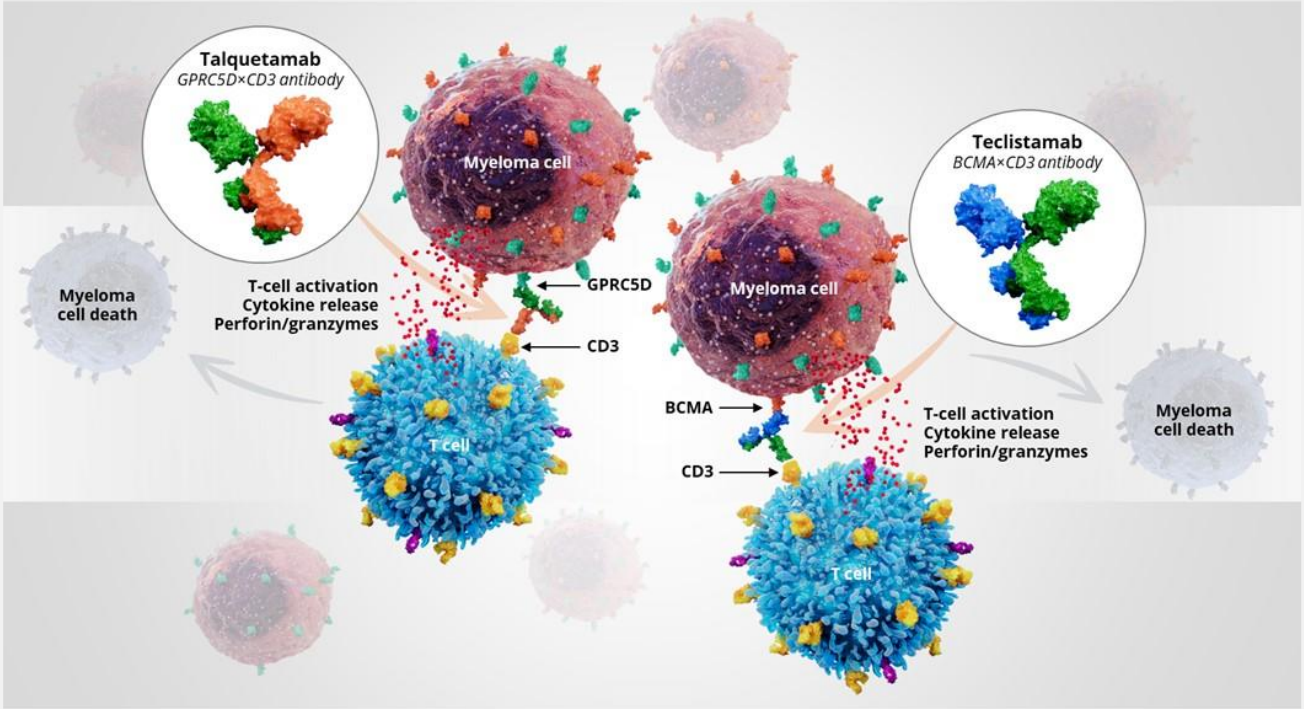
Differential sensitivity of BCMA mutant clones to BCMA xCD3 T-cell engaging BsAb

Lee, H. et al., Nat Med, September 2023



# Teclistamab and Talquetamab: First Combination of Bispecific Antibodies to Target 2 Distinct Myeloma Antigens

- **Teclistamab is the only approved BCMA×CD3 BsAb** with a personalized, weight-based, and flexible dosing schedule for the treatment of TCE RRMM[1]
  - ORR of 63% in MajesTEC-1[2]
- **Talquetamab is the most advanced GPRC5D-directed BsAb**, with promising efficacy in patients with RRMM[3]
  - ORR of >70% in MonumenTAL-1[3]
- Targeting 2 distinct antigens may overcome some resistance mechanisms to monotherapy[4]
- We report the first results from the phase 1b **RedirecTT-1** trial (NCT04586426) in patients with **RRMM**, **including a subset with EMD**




BCMA, B-cell maturation antigen; BsAb, bispecific antibody; EMD, extramedullary disease; GPRC5D, G protein–coupled receptor family C group 5 member D; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma; TCE, triple-class exposed. 1. TECVAYLI (teclistamab-cqyv). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2022. 2. Moreau P, et al. *New Engl J Med* 2022;387: 495-505. 3. Chari A, et al. *Blood* 2022;140 (suppl 1):384-7. 4. Fernandez de Larrea C, et al. *Blood* 2019;134 (suppl 1):136.



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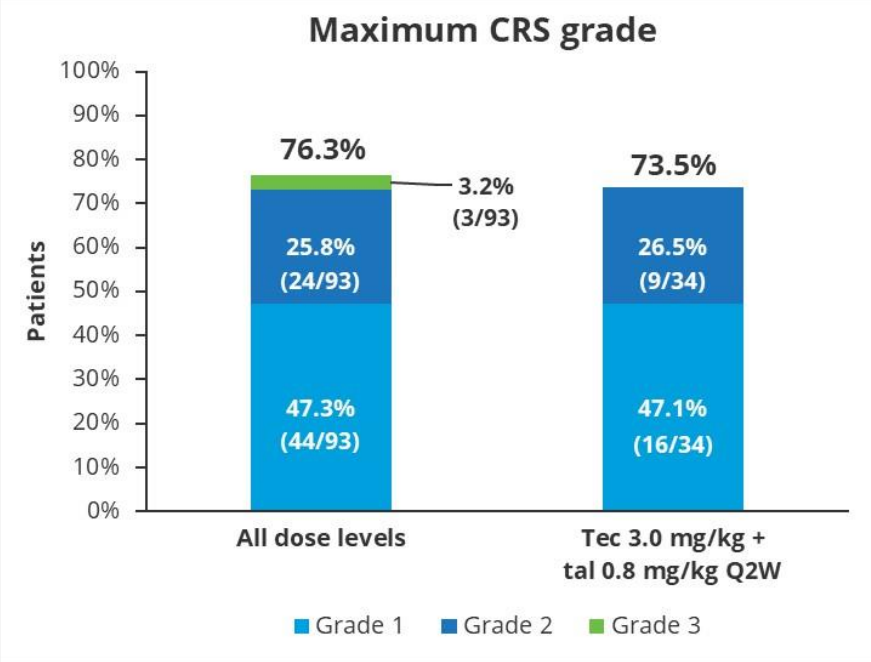
# RedirecTT-1: Incidence and Severity of Cytokine Release Syndrome Consistent With Monotherapies

| | All dose levels (N=93) | Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34) |
|---|---|---|
| Patients with CRS,[a] n (%) | 71 (76.3) | 25 (73.5) |
| Time to onset (days)[b], median (range) | 2 (1–5) | 2 (1–4) |
| Duration (days), median (range) | 2 (1–8) | 2 (1–4) |
| Patients who received supportive measures,[c] n (%) | | |
| Tocilizumab[d] | 25 (26.9) | 7 (20.6) |
| Steroids | 4 (4.3) | 0 |
| Oxygen | 7 (7.5) | 0 |
| Vasopressor | 1 (1.1) | 0 |

- The majority of CRS events occurred during step-up dosing or cycle 1
- All CRS events resolved




Data cut-off date, March 16, 2023
[a]CRS was graded by ASTCT criteria. [b]Relative to the most recent dose. [c]Patients could receive >1 supportive therapy. [d]Tocilizumab was allowed for all CRS events and was allowed at grade 1 CRS; the protocol did not recommend prophylactic tocilizumab use.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; Q2W, every other week.



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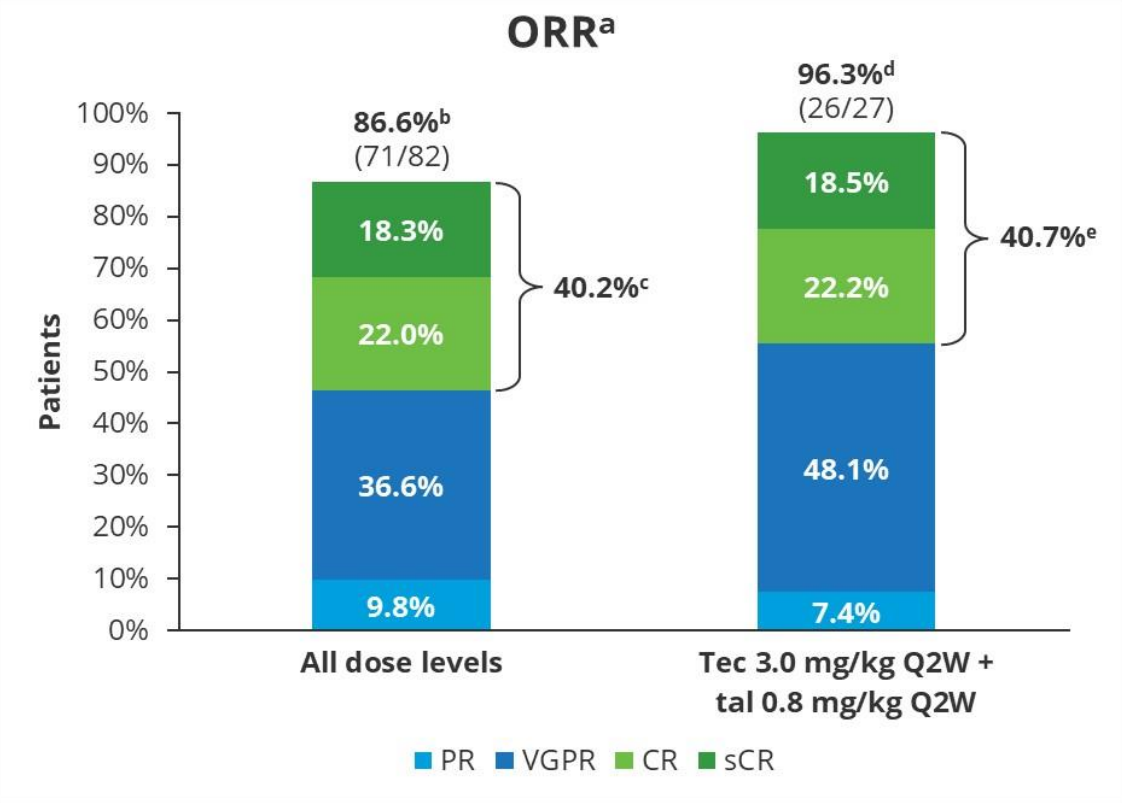
# RedirecTT-1: Efficacy




- ORR was high (86.6%) across all dose levels and 96.3% at the RP2R
- At data cut-off, 61% (57/93) of patients remained on treatment

| | All dose levels (N=93) | Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34) |
|---|---|---|
| Median follow-up, months (range) | 13.4 (0.3–25.6) | 8.1 (0.7–15.0) |
| Median DOR,[f] months (95% CI) | NE (NE–NE) | NE (NE–NE) |
| Median time to first response,[f] months (range) | 1.97 (0–7.7) | 1.48 (0–4.0) |
| Median time to best response,[f] months (range) | 3.98 (1.1–15.7) | 3.22 (1.4–10.7) |
| Median PFS,[g] months (95% CI) | 20.9 (13.0–NE) | NE (9.9–NE) |
| 9-month PFS rate[g] (95% CI) | 70.1 (58.0–79.4) | 77.1 (50.8–90.5) |

Data cut-off date, March 16, 2023.
[a]Response was assessed by investigators, based on International Myeloma Working Group criteria; response-evaluable patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator. [b]95% CI, 77.3–93.1%. [c]95% CI, 29.6–51.7%. [d]95% CI, 81.0–99.9%. [e]95% CI, 22.4–61.2%. [f]Includes patients with confirmed responses. [g]All treated patients. CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every other week; RP2R, recommended phase 2 regimen; sCR, stringent complete response; VGPR, very good partial response.



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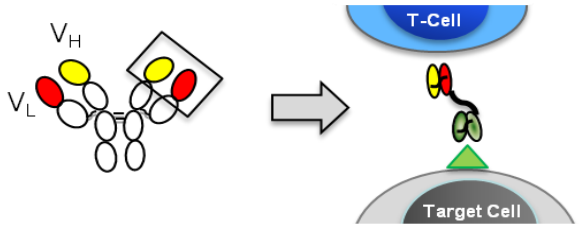
# New Generation of T cell engaging Antibodies:

## NOVEL BI-MOLECULAR T-CELL ACTIVATING ANTIBODIES

### Antibody mediated therapy today

- IgG
- BiTEs, DARTS, Tribodies etc.




**Point of attack:**

**A singular target antigen**

### Problem

- No singular tumor antigens

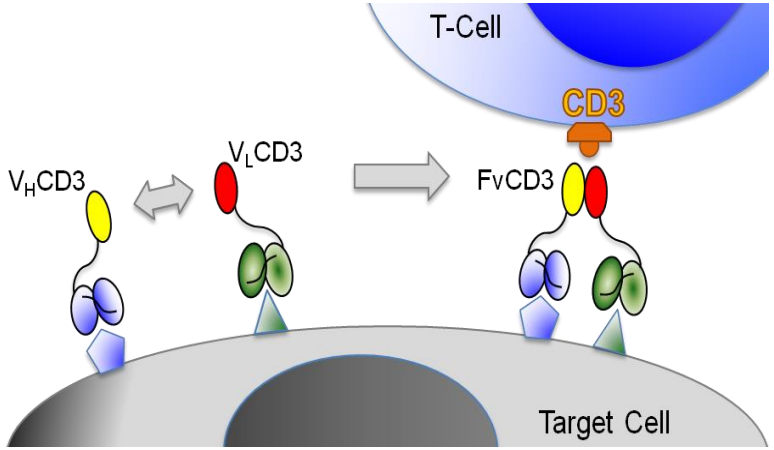
➢ Poor specificity

- Active CD3 binding side

➢ Unspecific T-cell activation

### Hemibody Solution

- bimolecular T cell-engaging antibody constructs




**A target antigen-signature**

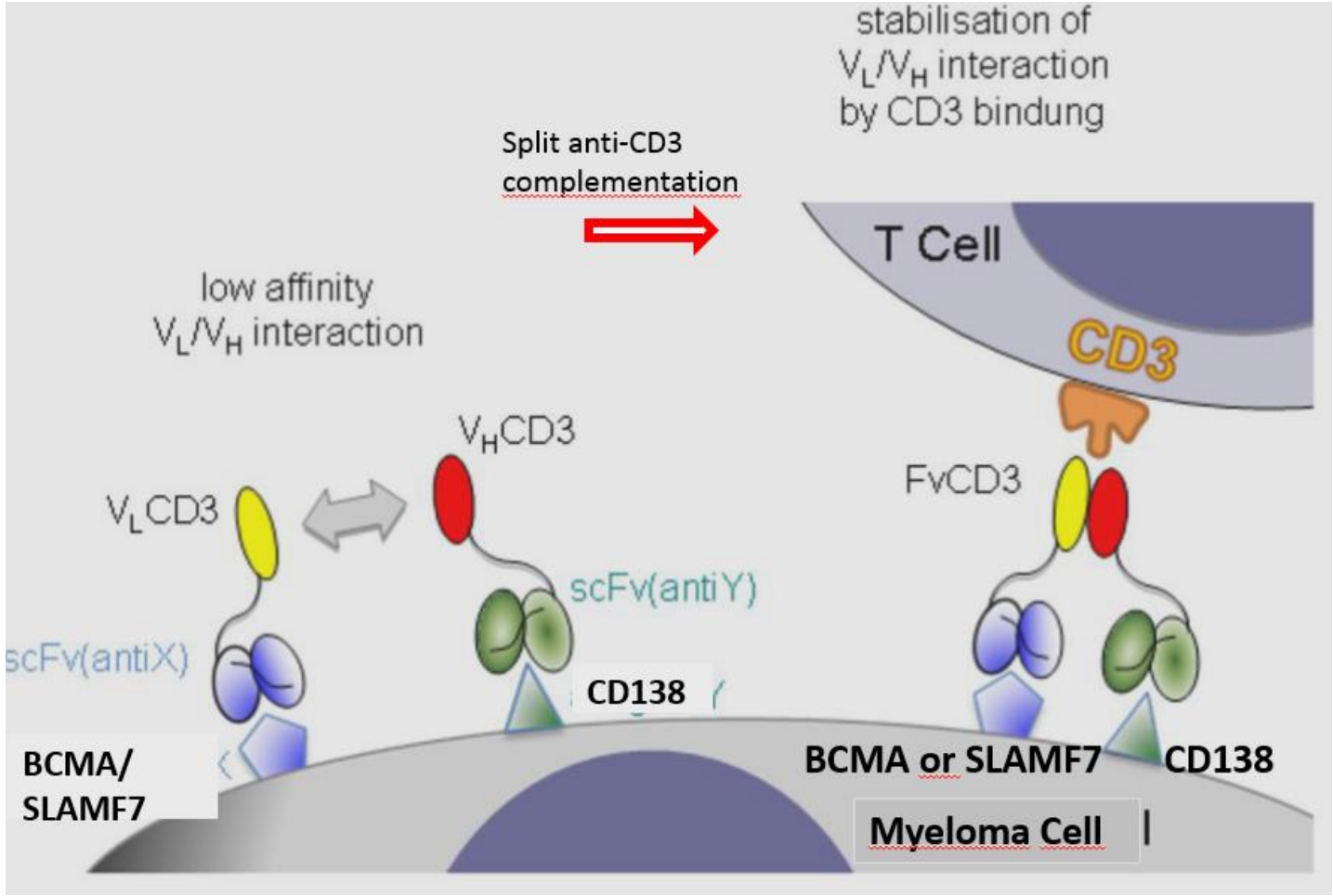
➢ Higher specificity

- No unspecific T-cell activation

➢ Lower side effects

Banaszek A et al,
Nat Comm 2019

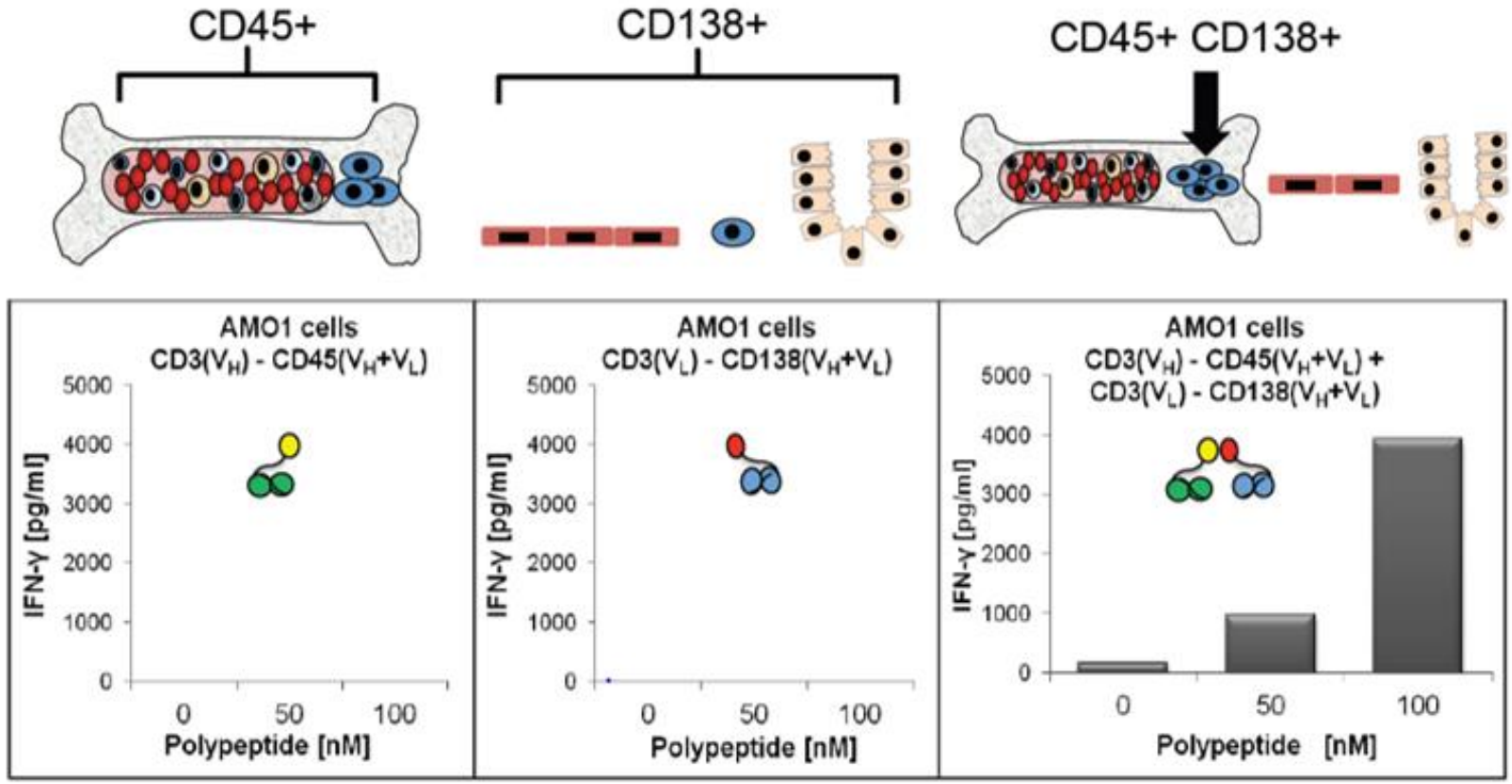
# Combinatorial Approach: Trispecific Antibodies - Hemibodies




- high precision targeting of dual-antigen positive cancer cells (enhanced specificity)
- very low off-tumor toxicity because T cell activation is restricted to cancer sites
- antigen signatures of three and more target molecules can be addressed (enhanced sensitivity)

Banaszek A et al, Nat Commun 2020

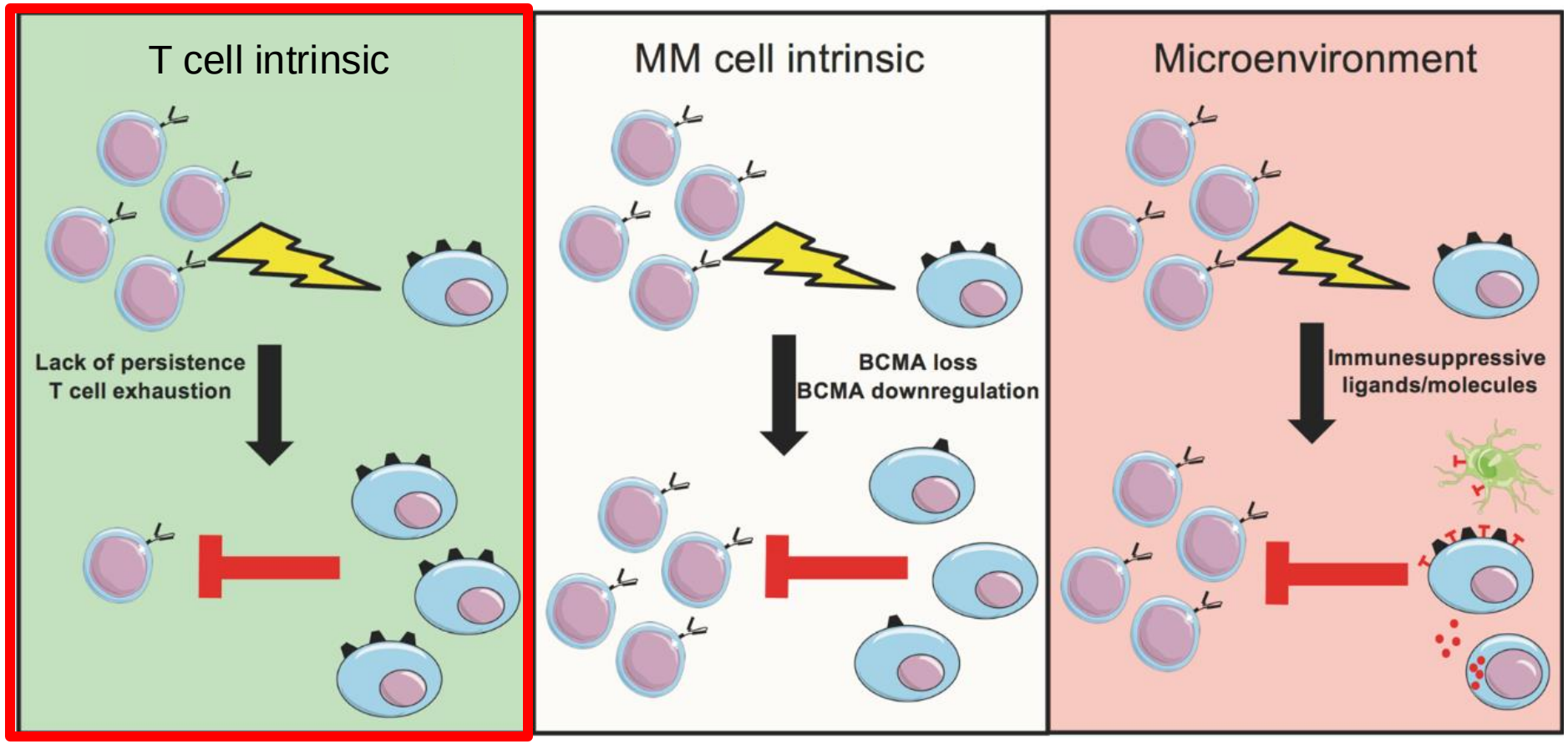
# Efficacy of an MM-specific Hemibody targeting CD138 and CD45 (or CD138 and CD38)




Banaszek A et al, Nat Commun 2019

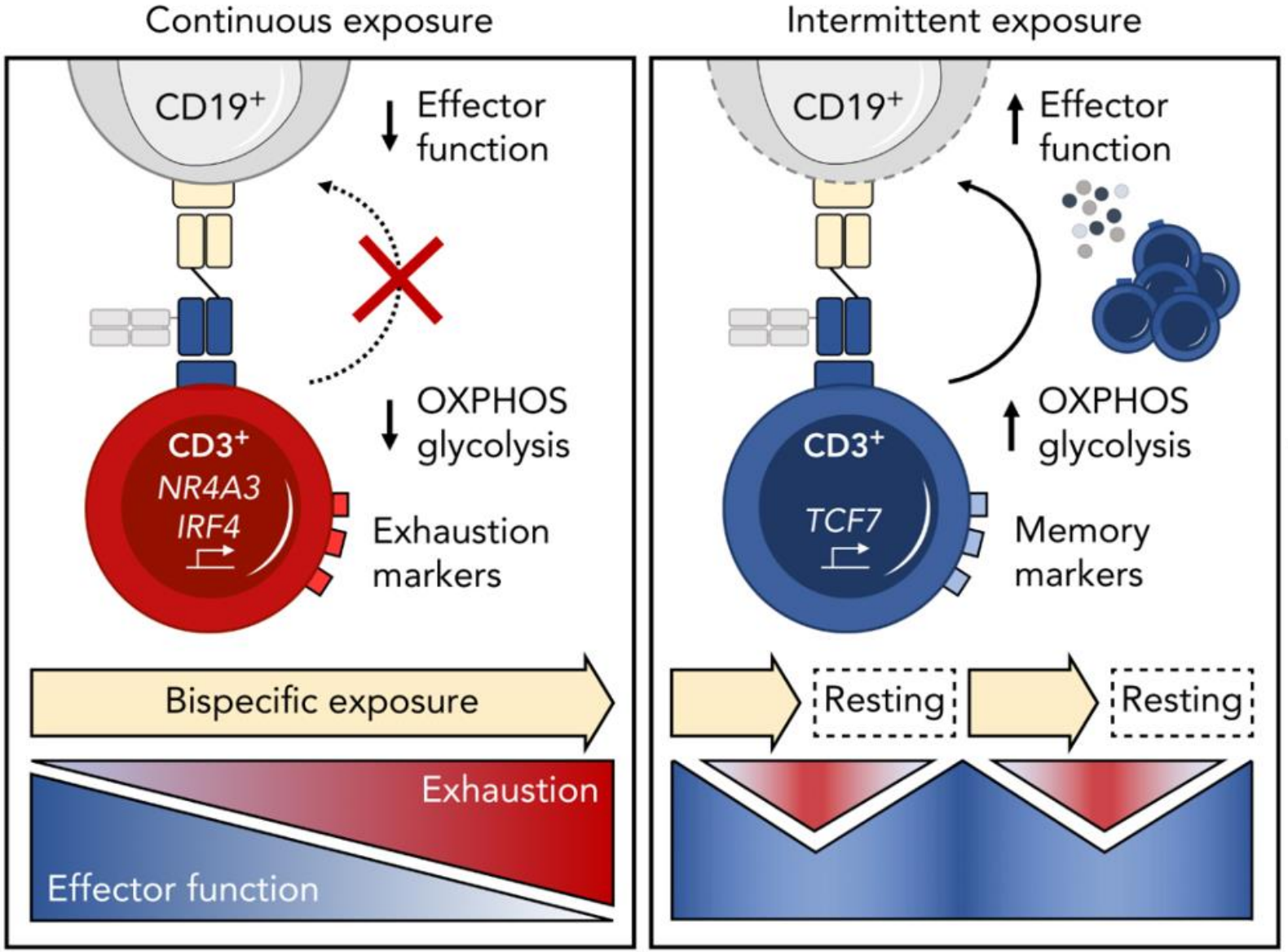
# Bispecific Antibodies in Multiple Myeloma: Can we do better?

## Proposed mechanisms of resistance to T cell engaging antibodies in MM



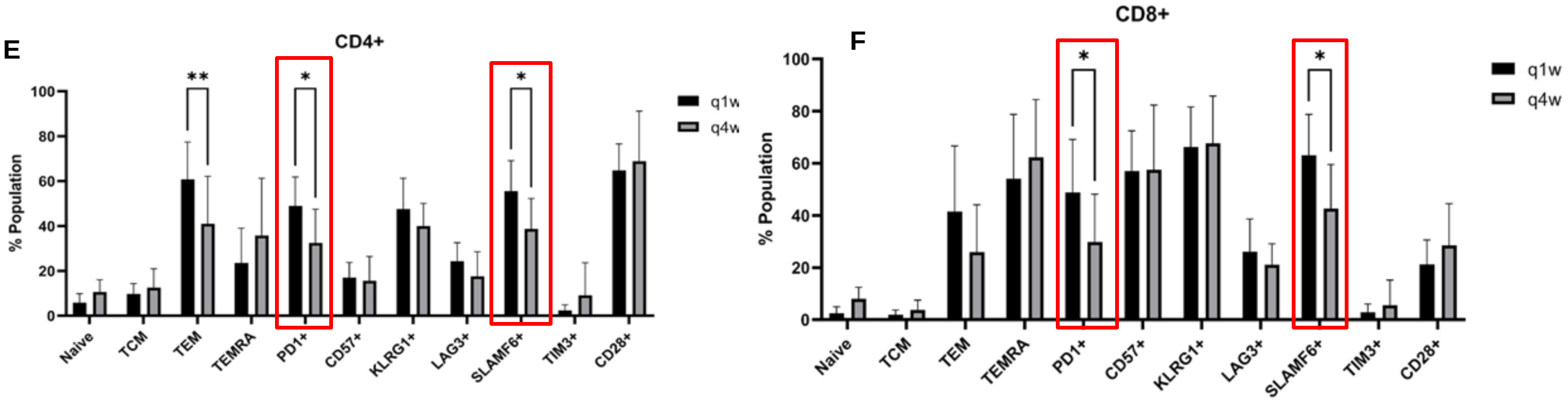

D'Agostino M et al, Leukemia 2020

# Continous exposure to T Cell engaging antibodies induces T Cell exhaustion
# Rest ameliorates T-cell exhaustion by bispecifics




Philip et al., Blood, 8 September 2022

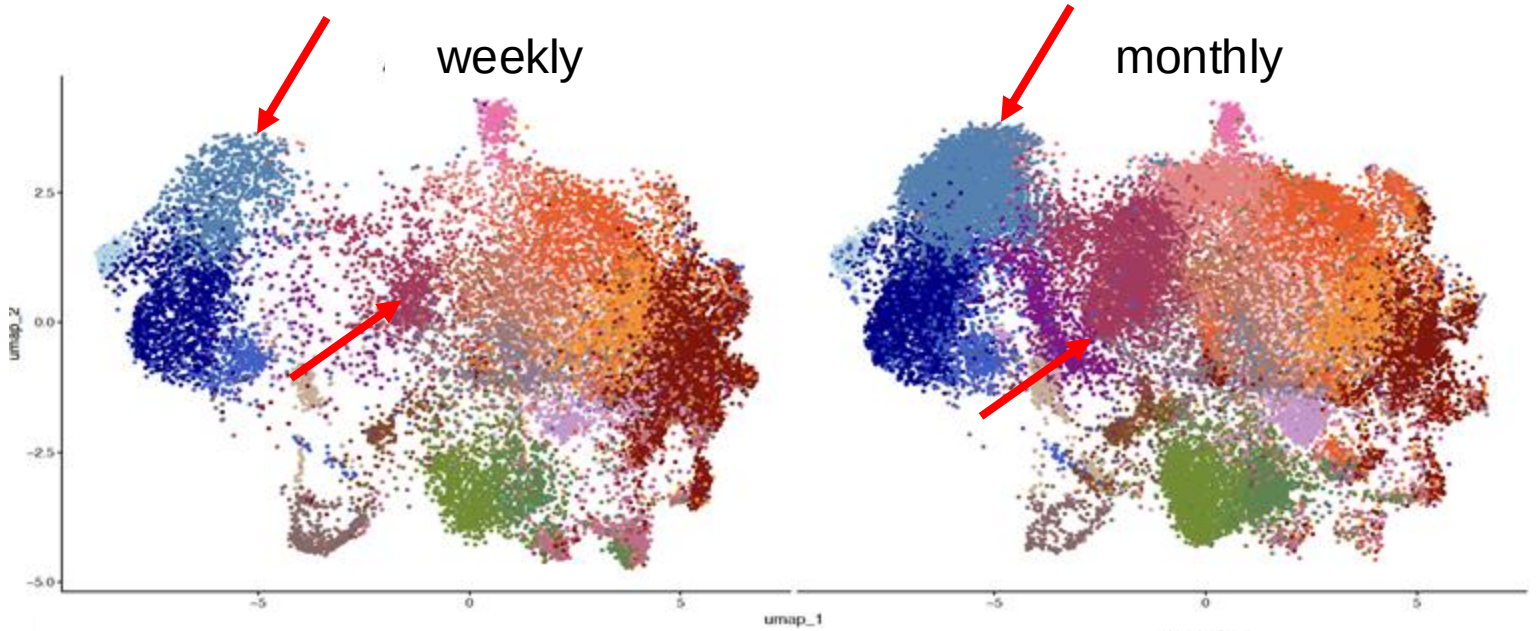
# The Impact of Treatment-Free Intervals on T-Cell Exhaustion with BCMA Bispecific Antibodies

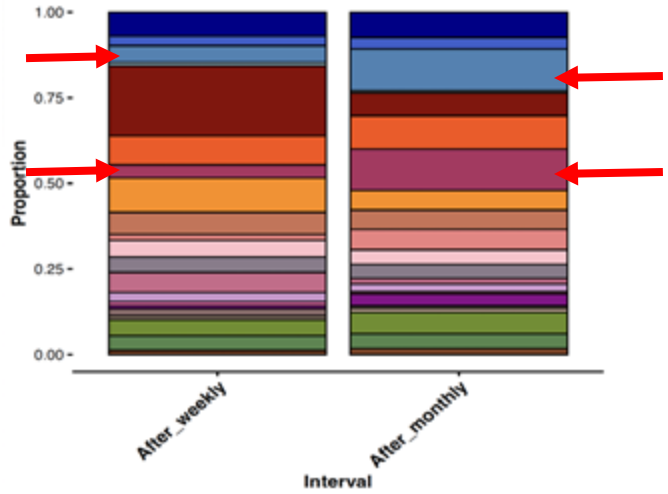


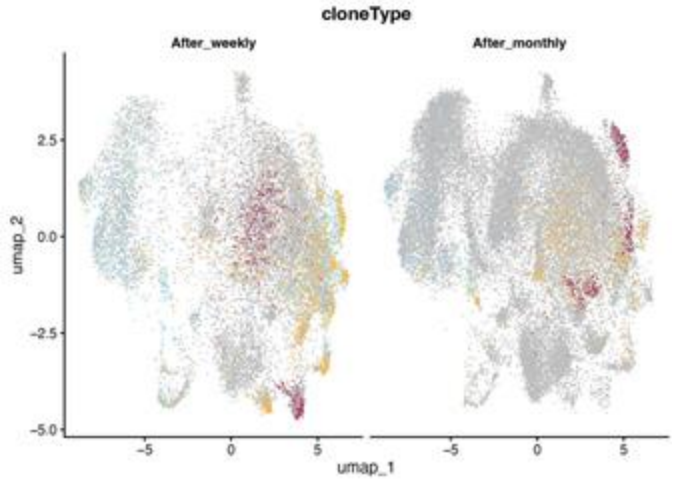

Eisele, F. et al., ASH 2023

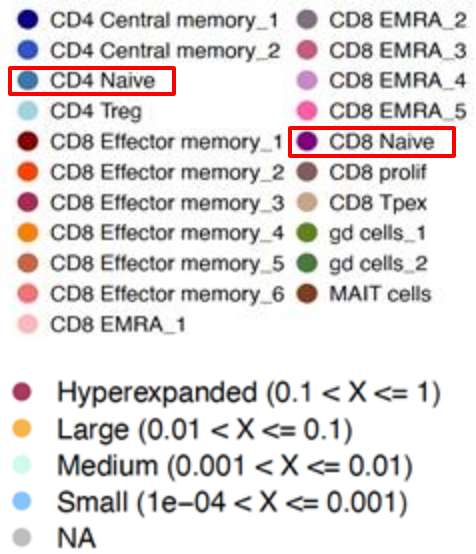
***Flow cytometry analysis of T-cell subsets demonstrate a significant decline in exhaustion markers in monthly treated patients:*** *Longitudinal (A-C) and cross-over analysis (E-G) of exhaustion markers show a significant decrease in expression of PD-1 and SLAMF6 comparing weekly and monthly treated patients. A significant decline in the CD4+ effector memory subset (E) could be observed, conclusive with a significant reduction in CD4+GzB+ T-cells (H) (CD4+ CTL). Paired (longitudinal) and unpaired (cross-over) t-test were used for statistical testing. *P<0.05, *P<0.01*

# Flow analysis and CITE-seq reveal an increase in naïve T-cells, suggesting a restoration of T cell homeostasis



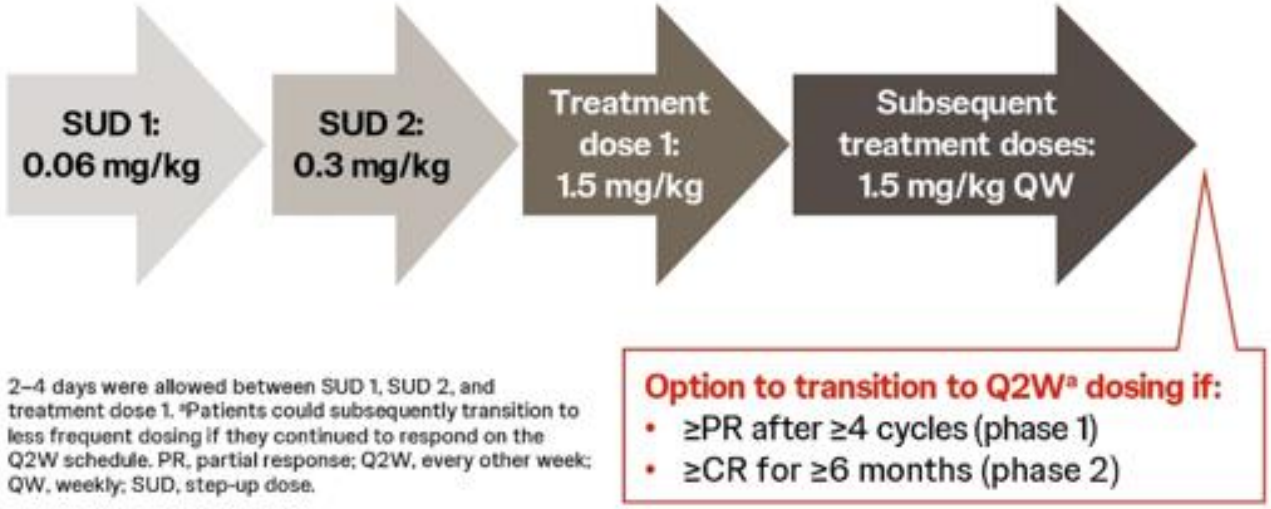




***CITE-seq and TCR-seq demonstrate a gain of naïve T-cells and a change in effector memory subsets:*** *UMAP for CD3+ cross-over comparison of weekly and monthly treated patients (A + B) show a rise in CD4+ and CD8+ naïve T-cells. Furthermore we see a change in T-cell effector memory subsets. A further characterisation of these subsets is pending. The monthly group shows a more diverse RNA-expression profile than the weekly group. Hyperexpanded subsets can be shown in both groups but their localisation on the UMAP differs distinctly.*

Eisele, F. et al., ASH 2023

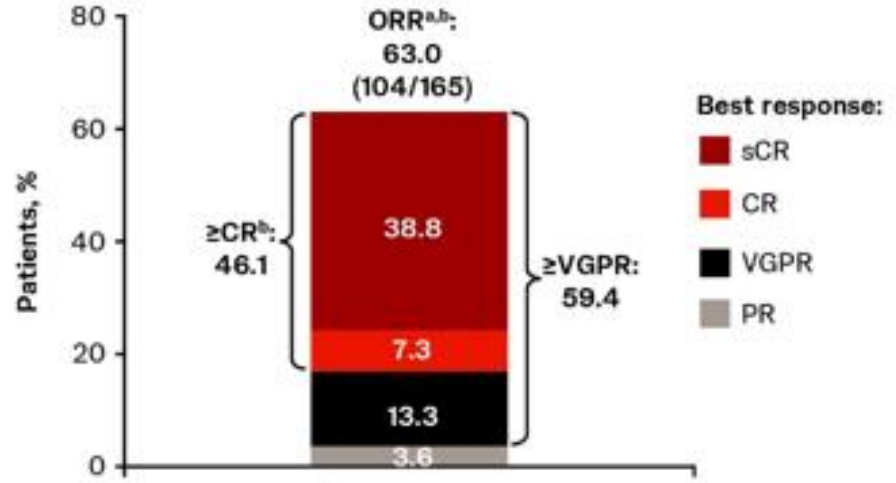
# Long-Term Follow-up From the Phase 1/2 MajesTEC-1 Trial of Teclistamab in Patients with r/rMM

**Figure 1: Teclistamab dosing schedule**




2–4 days were allowed between SUD 1, SUD 2, and treatment dose 1. [a]Patients could subsequently transition to less frequent dosing if they continued to respond on the Q2W schedule. PR, partial response; Q2W, every other week; QW, weekly; SUD, step-up dose.

**Figure 2: ORR**

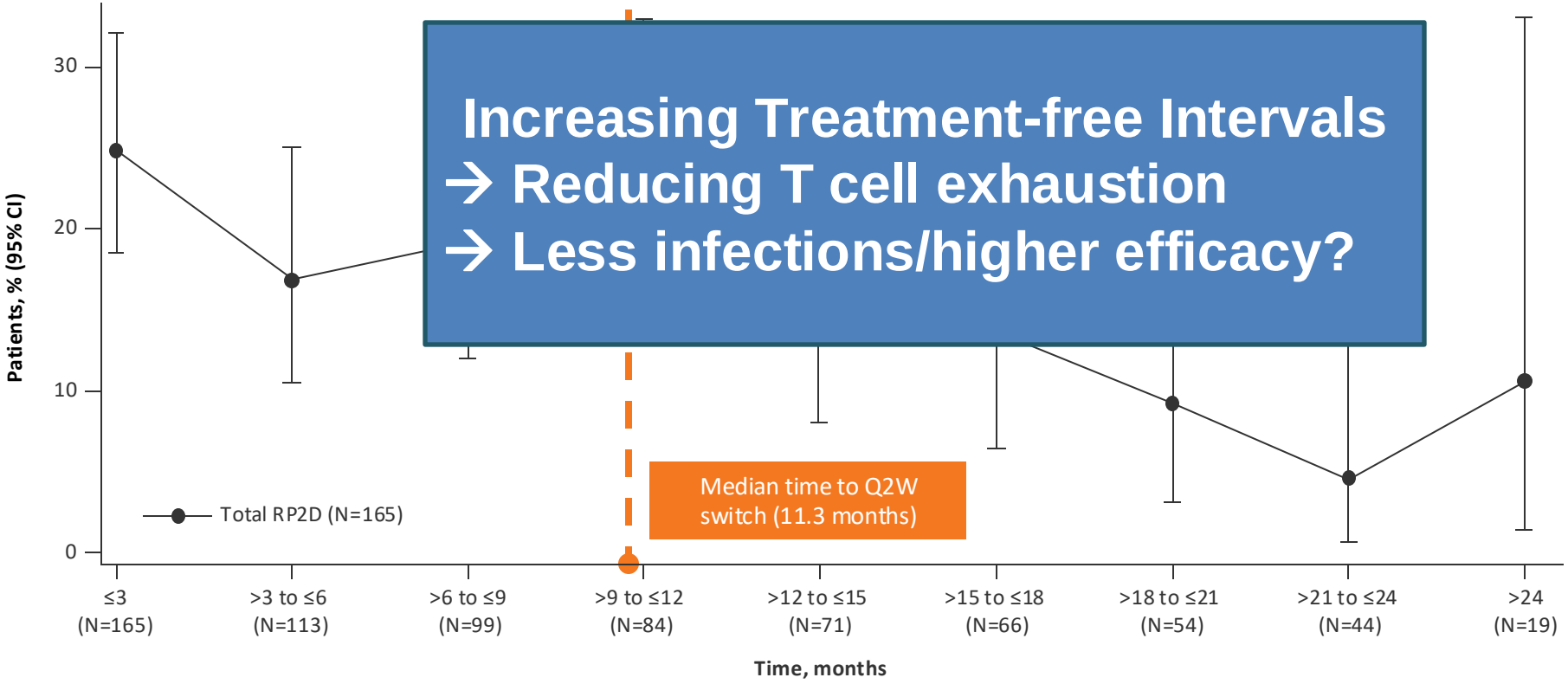



[a]Response assessed by independent review committee. [b]At 30-month mFU of the phase 2 efficacy population (patients enrolled in cohort A on or before March 18, 2021; n=110 patients supporting the USPI[1]): ORR, 61.8%; ≥CR, 46.4% (n=51). sCR, stringent complete response; USPI, United States prescribing information.

Garfall, A. et al., Poster 7540, presented at ASCO 2024

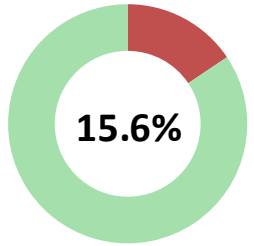
# New-Onset Grade ≥3 Infections Decreased Over Time in MajesTEC-1, With Fewer Infections in Patients Switching to Q2W

**New-onset grade ≥3 infections in the overall MajesTEC-1 study population**

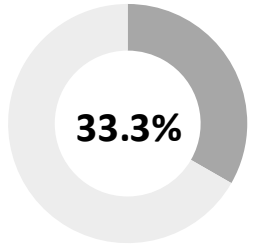



**New-onset grade ≥3 infections at 1–1.5 years[1]**

Patients switching to Q2W dosing by 1 year




Patients remaining on QW dosing at 1 year

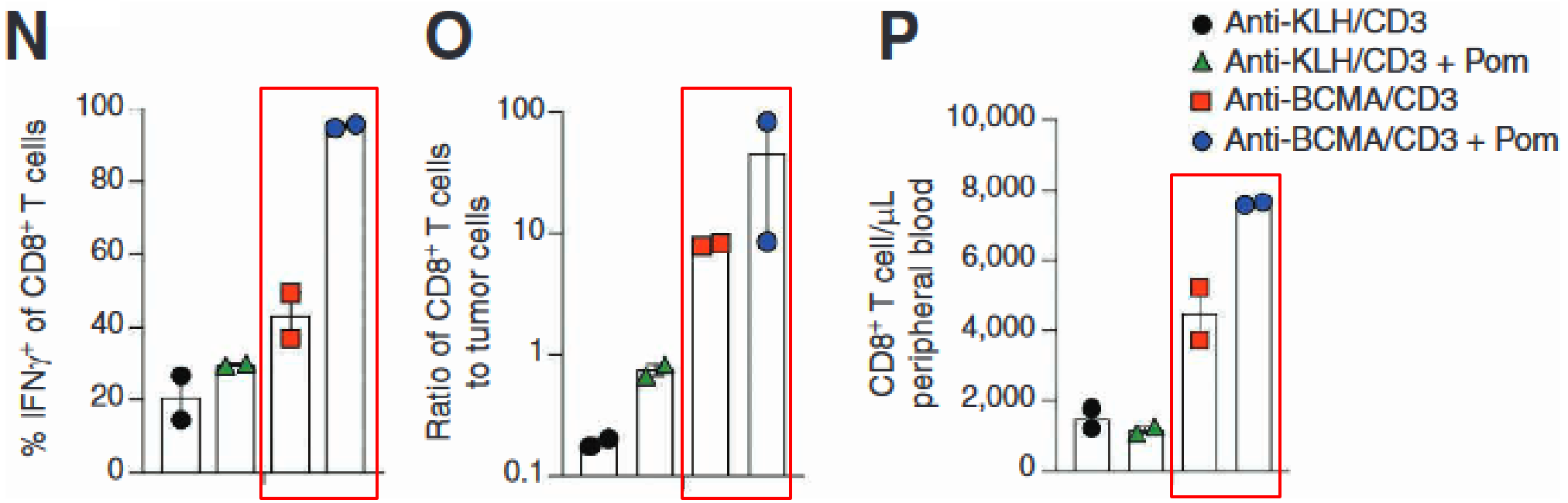



- **25 (32%) switched from weekly to every-other-week (n=24)** or monthly (n=1) Tec after a median time of 3.1 mos from Tec initiation and based on achieving ≥ PR (n=19) and/or toxicity (n=11)
- **At mFU of 5.3 mos** since switch, **96% (24/25) of patients still in response**

Usmani SZ, et al. J Clin Oncol 2023

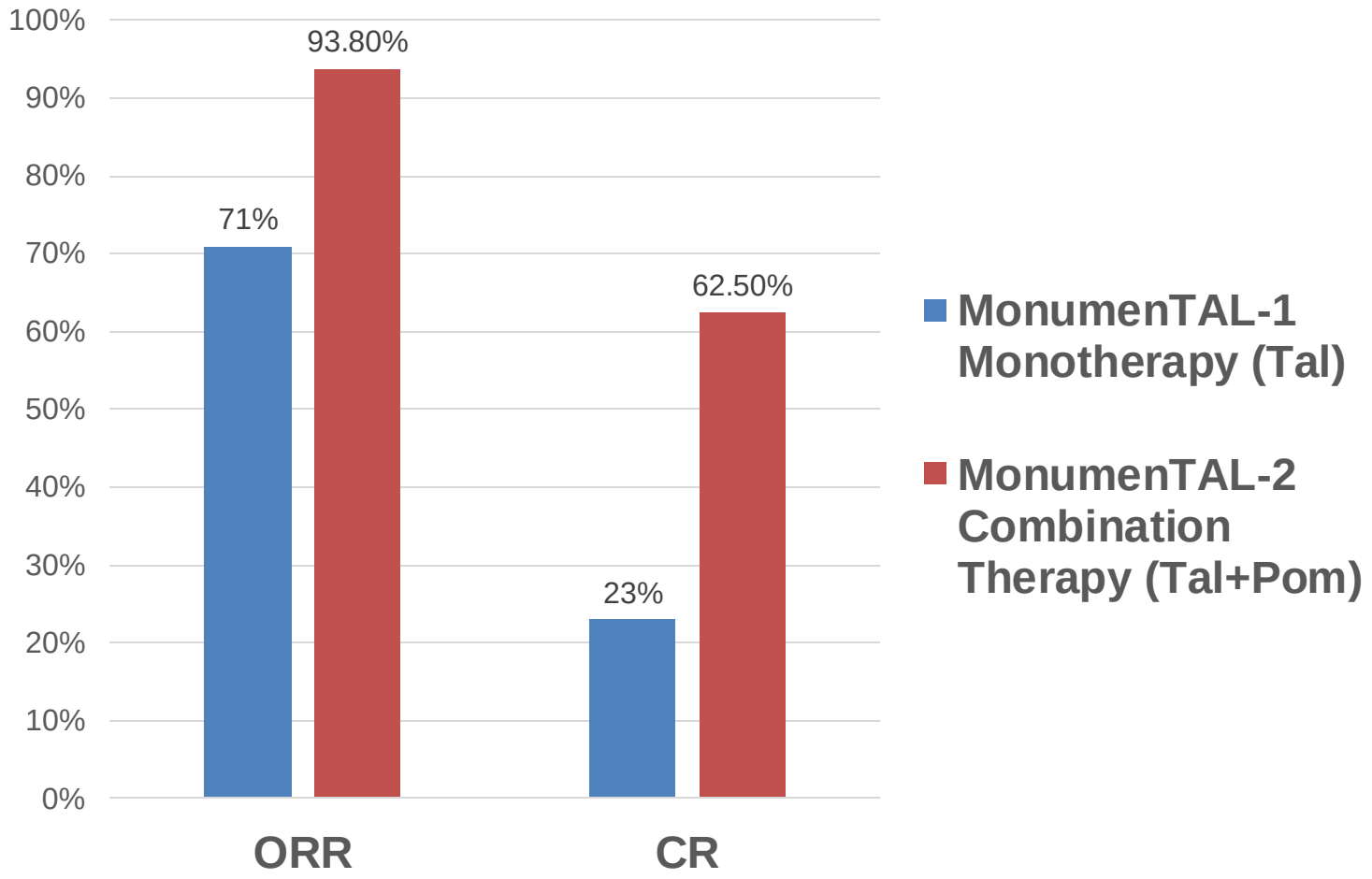
# Combination Therapy to improve T cell Function

**Pom enhances hCRBN transgenic CD8+ T-cell proliferation, cytokine production, and tumor killing induced by anti-BCMA/CD3 in IMiD-resistant tumors**
**→ Reduces T-cell exhaustion**




Meermeier EW et al., Blood Cancer Discov. 2022

# Combination Therapy to improve T cell Function

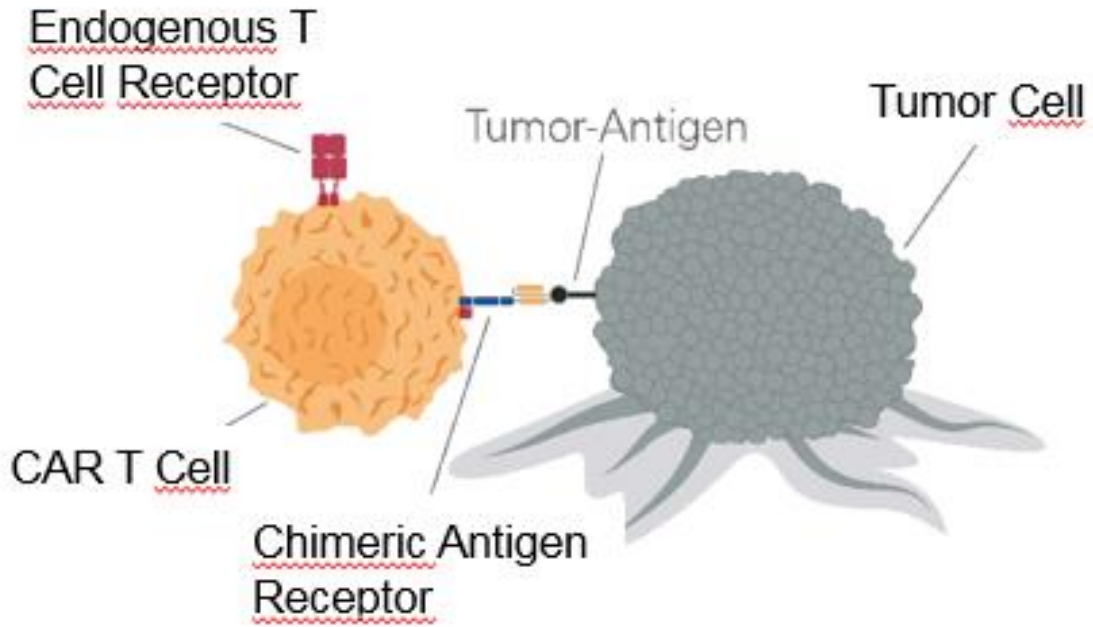



Searle, E. et al., EHA 2024
Chari A et al. N Engl J Med 2022

➡ Combination therapies with IMiDs, CelMODs or bridging therapies with the agents like selinexor were shown to improve T cell function, reduce T cell exhaustion and to improve efficacy of TCEs

# Why earlier application of Bispecifics?

- Fitter T cells
  - Improved Myeloma Cell Killing
- Increased Immunogenicity of Tumor cells
  - No selection of resistent clones
  - Lower tumor burden
  - Lower proliferative potential of tumor cells
- Better Tolerability
  - High Attrition Rate with each treatment line
  - Lower hematotoxicity
  - Lower risk of secondary malignancies



# MajesTEC-7: SRI Cohorts Inform Phase 3 Design

**Key eligibility criteria[a]:**

- NDMM either ineligible or not intended for ASCT
- ECOG PS 0–2

**SRI cohort 1: Tec-DR**

**SRI cohort 2: Tec-DR + DRd lead-in[b]**

**SRI cohort 3: Tal-DR + DRd lead-in[b]**

**SRI period** to establish safety prior to enrolling the randomized study

**N=1500 1:1:1 Randomization**

- → **Tec + DR**
- → **Tal + DR**
- → **DRd**

**Dual primary endpoints:**

- PFS
- 12-mo MRD-neg CR

**Secondary endpoints:**

- ≥CR
- OS
- Sustained MRD-neg CR
- PFS2
- Safety
- PROs
- PK

| SRI cohort 1: Tec-DR | mFU | Cycle 1 | Cycle 2 | Cycle 3–6 | Cycle 7+ until PD |
|---|---|---|---|---|---|
| | 13.8 mo (range, 2.0–15.4) | Tec step-up[c] + D | Tec 1.5 mg/kg QW + DR | Tec 3 mg/kg Q2W + DR | Tec 3 mg/kg Q4W + DR |

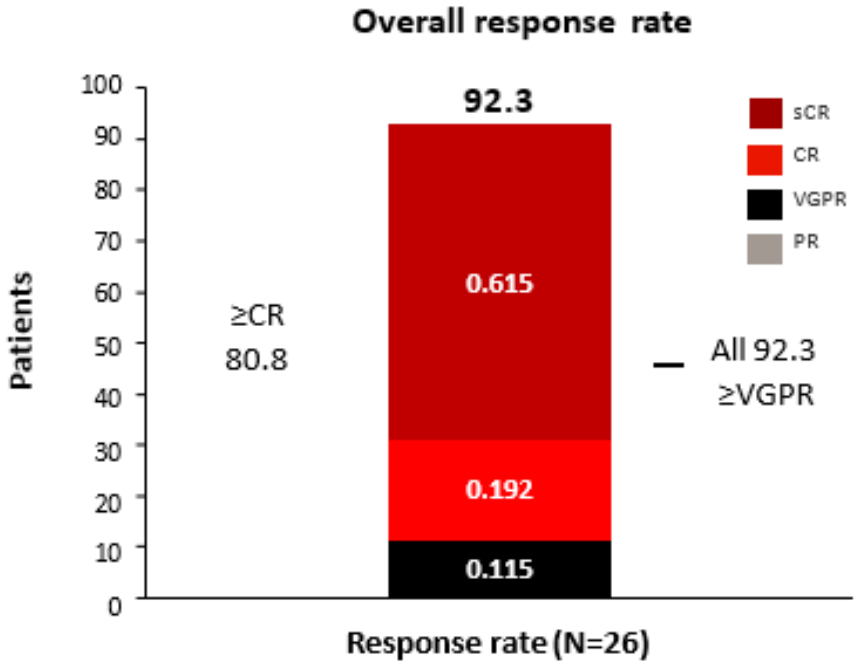
[a]SRI cohort 2 and SRI cohort 3 required an International Myeloma Working Group frailty score <2 (except when score is due to age a lone). [b]DRd lead-in (dara SC 1800 mg QW; len oral 25 mg on days 1–21; dex oral/IV 20 mg QW) in cycle 1; Tec-DR or Tal-DR started in cycle 2. [c]0.06 and 0.3 mg/kg step-up doses on days 2 and 4 followed by treatment doses (1.5 mg/kg) on days 8, 15, and 22.

ASCT, autologous stem cell transplant; CR, complete response; D, daratumumab; dara, daratumumab; dex, dexamethasone; DR, daratumumab and lenalidomide; DRd, daratumumab, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; len, lenalidomide; mFU, median follow-up; mo, months; MRD, minimal residual disease; neg, negative; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival as time from randomization to first PFS event on first subsequent line of therapy; PK, pharmacokinetics; PRO, patient-reported outcome; Q2W, every other week; Q4W; every 4 weeks; QW, weekly; SC, subcutaneous; SRI, safety run-in; tal,

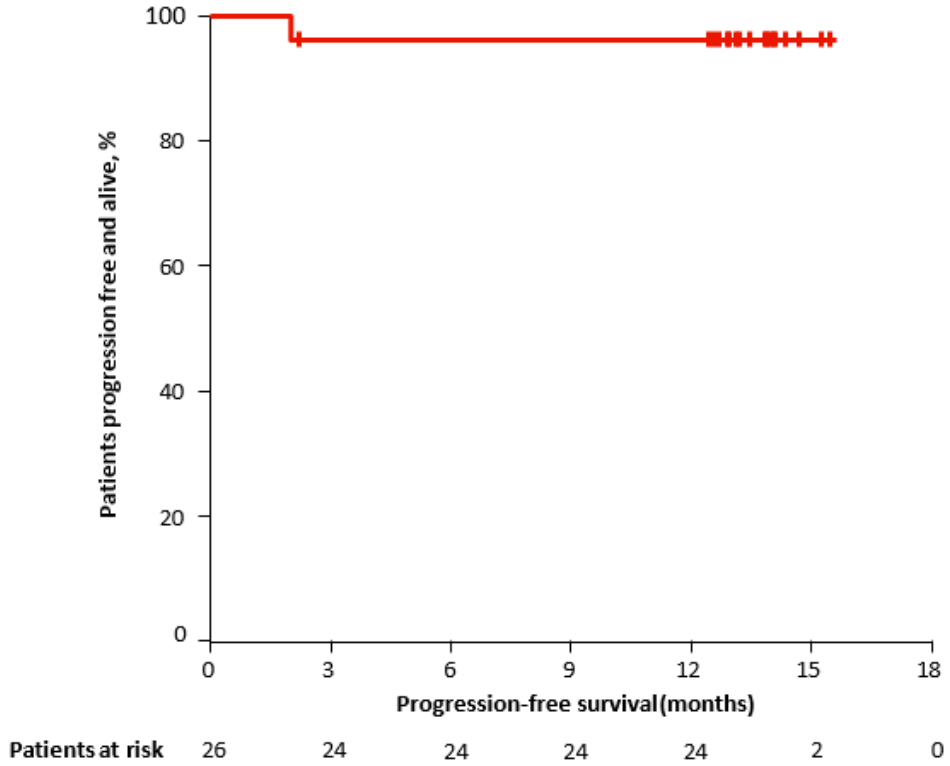
Presented by S Manier at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA & Virtual

# MajesTEC-7 (Tec-DR) SRI Cohort 1: Efficacy and Progression-free Survival Median follow-up of 13.8 months

- 92.3% ORR (80.8% ≥CR); all patients achieved ≥VGPR
- No disease progressions occurred

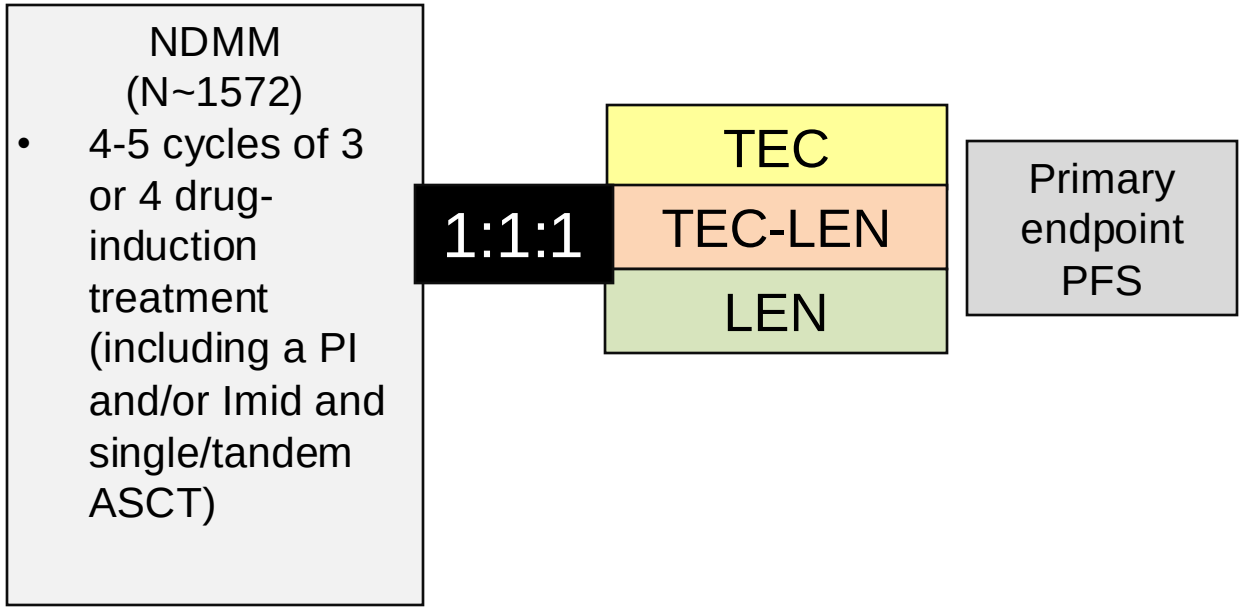



- At median follow-up of 13.8 months, one PFS event has occurred
- Estimated 12-month DOR and PFS were 100.0% and 96.2%, respectively

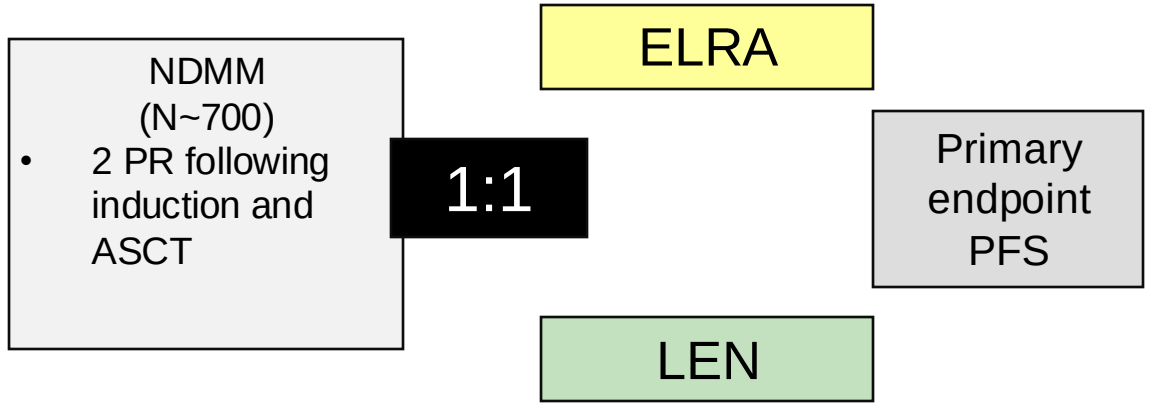


# Bispecific antibodies as mainenance treatment after autologous transplant

## MajesTEC-4 (NCT05243797)




## MagnetisMM-7 (NCT05317416)




→ Prior debulking to optimise effector: target ratio (rational sequencing)
→ T cell fitness is better in earlier lines of therapy

Van de Donk, N., EMMA Madrid 2024

# DSMM XX / GMMG-HD10 / MajesTEC-5

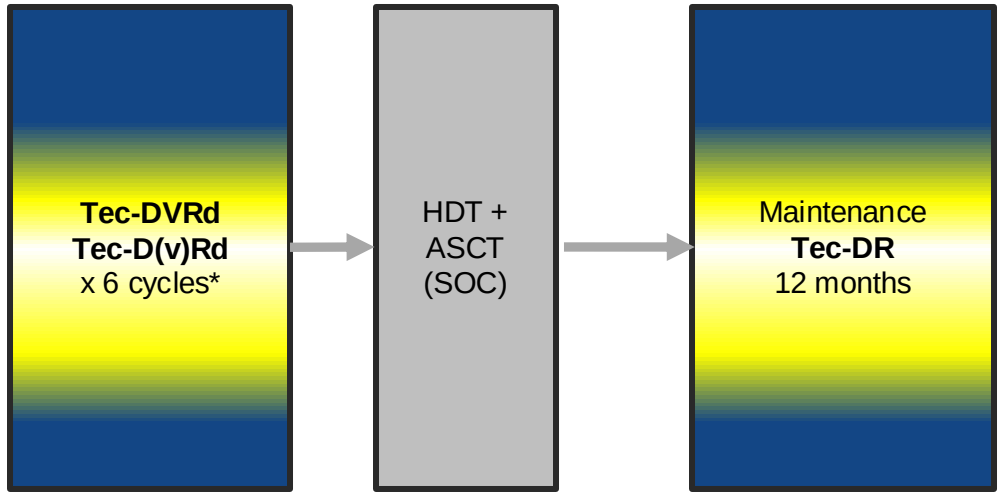
→ BsAb plus ASCT

→ BsAb replace ASCT

**Arm A**
**N = 20-40**

**Arm B**
**N = 20-40**

Study population
- **TE NDMM**
- ECOG ≤2
- 18-70 yrs
- Measurable disease:
  - SPEP ≥1.0 g/dL or
  - UPEP ≥200 mg/24 hrs or
  - FLC ≥10 mg/dL and abnormal FLC ratio
- No Radiotherapy
  - within 14 days or focal radiation within 7 days of confirmation of eligibility

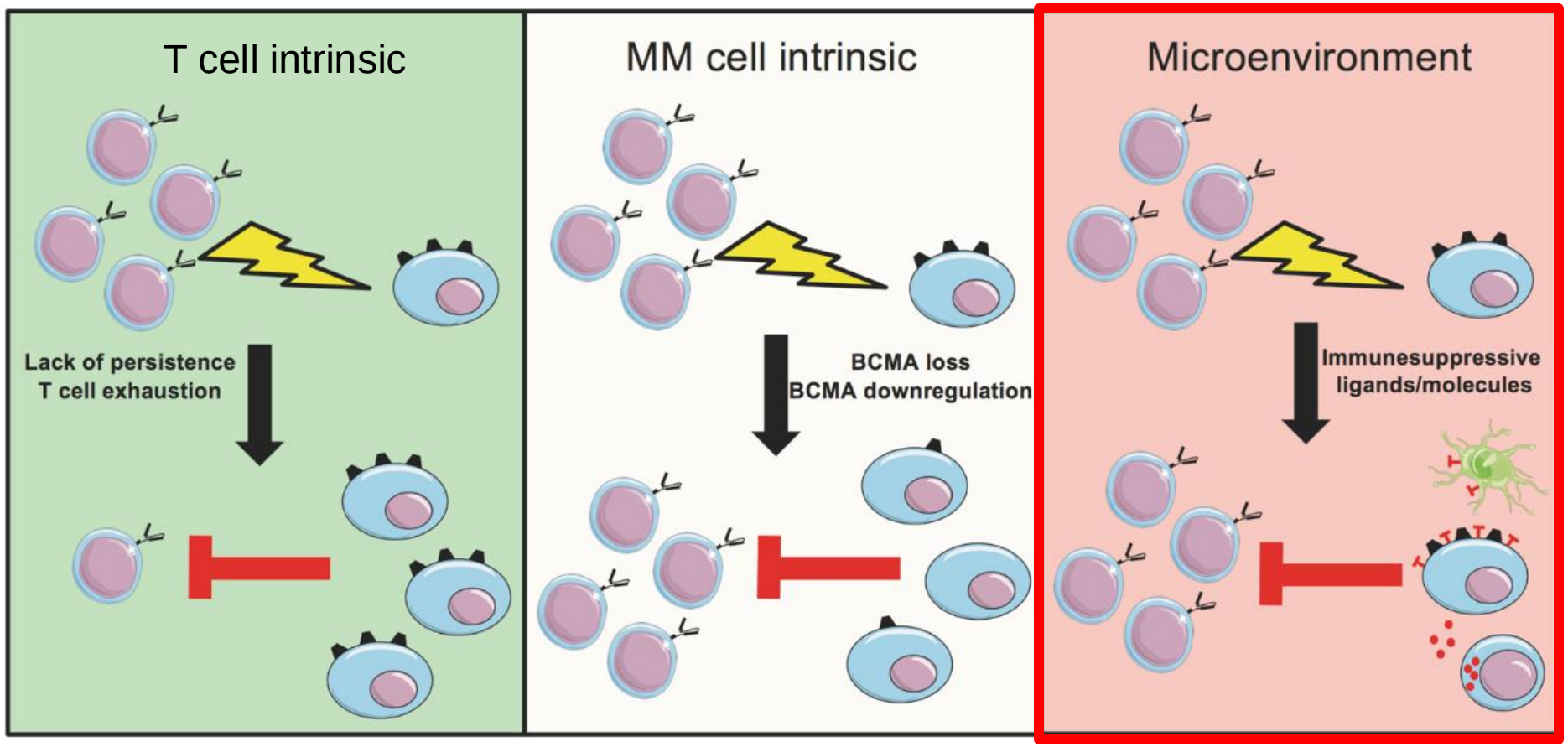



Primary Endpoint:
- **Rate and severity of AEs**

Key Secondary Endpoints
- Ability to mobilize stem cells
- Efficacy incl. MRD

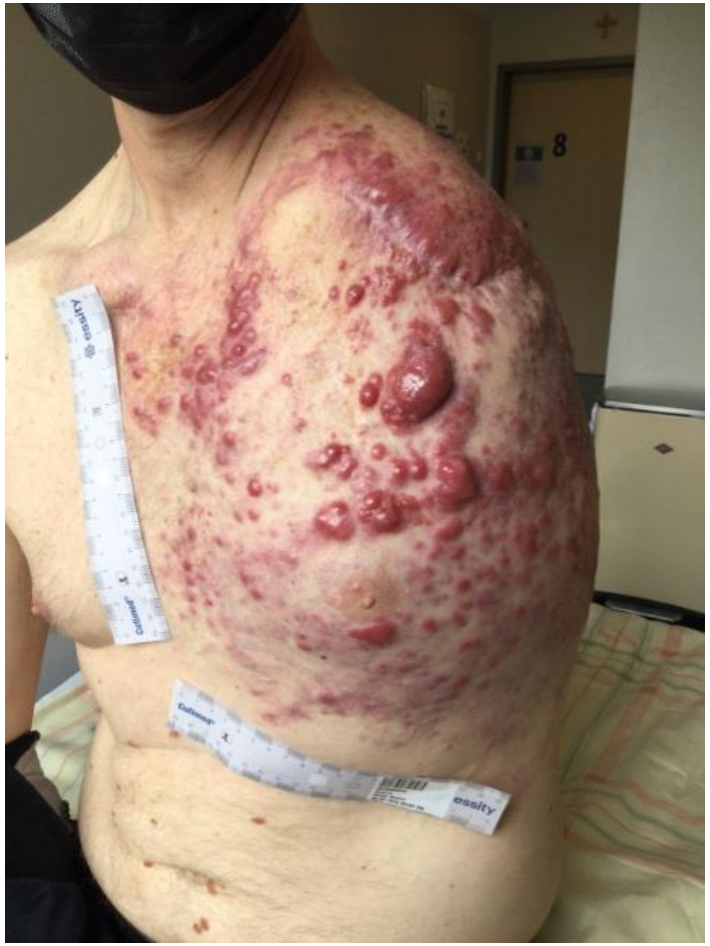
Co-PIs **Raab/Rasche**

## Proposed mechanisms of resistance to anti-BCMA CAR T-cell therapy in MM




D'Agostino M et al, Leukemia 2020

# EMD



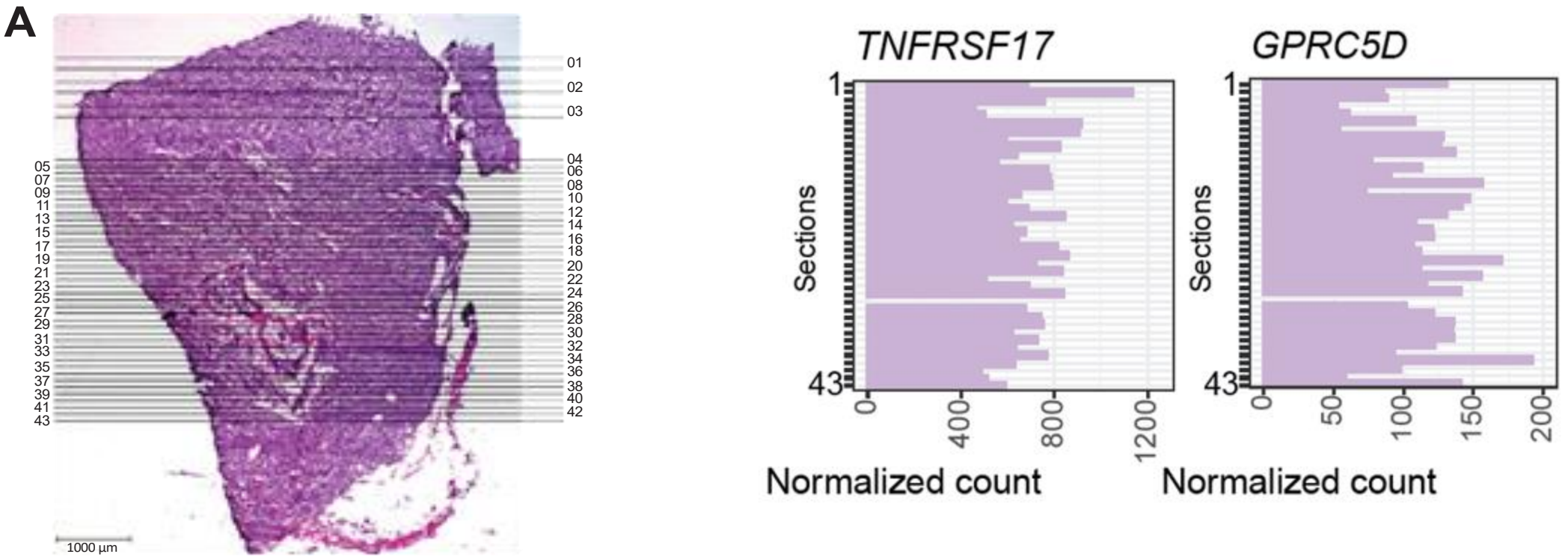
**Trial**

- Ide-cel: ORR 59% vs. 75% (Hansen *et al*)
- Teclistamab: ORR ~35 vs 70%
- Talquetamab: ORR ~40 vs 80%
- Cilta-cel: PFS lower in EMD

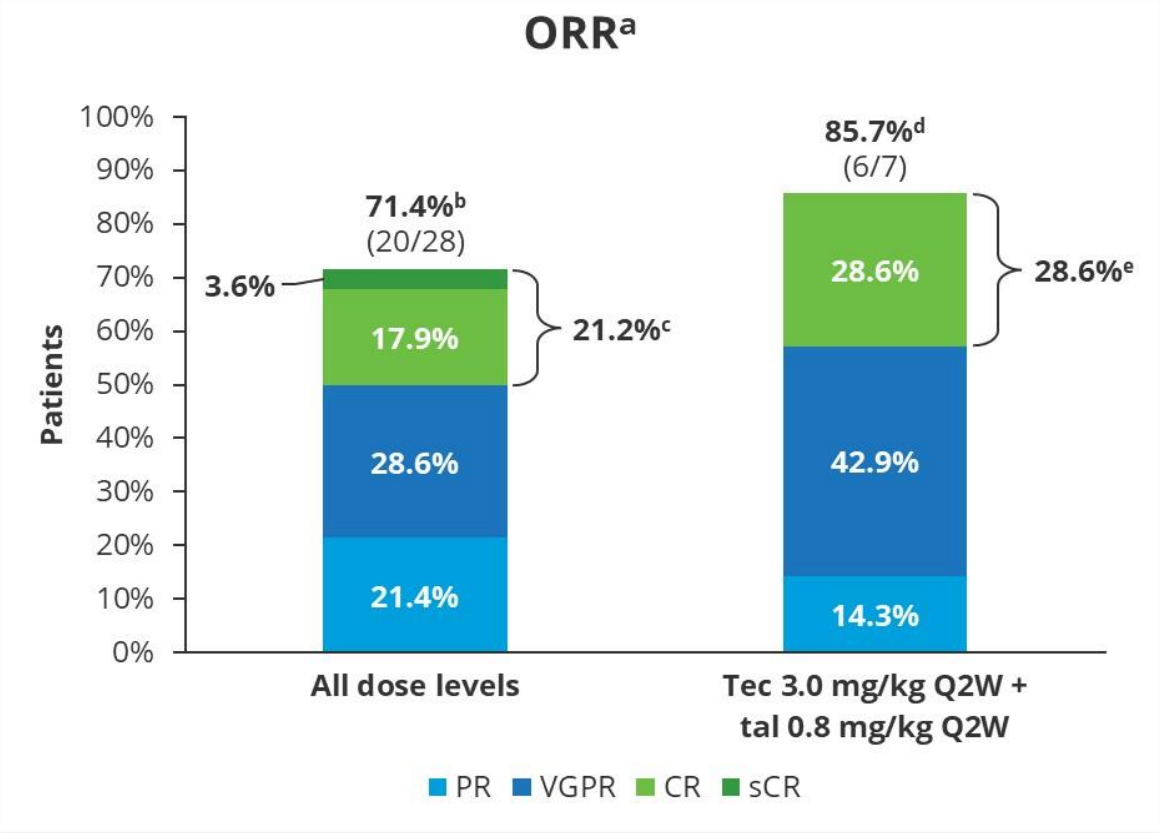
Is there a microenvironment in extramedullary MM as well?

# Tomo-seq Highlights the Spatial Heterogeneity of a Whole Tumor Lesion

Figure 2



# RedirecTT-1: High ORR in Extramedullary Disease




- All were soft tissue plasmacytomas
- At the RP2R (n=11):
  - Median follow-up, 7.2 mo (range 0.7–14.2)
  - 85.7% (6/7 evaluable) ORR
  - 28.6% (2/7 evaluable) ≥CR

| | All dose levels (N=35) | Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (N=11) |
|---|---|---|
| Median DOR,[f] months (95% CI) | 12.9 (4.17–NE) | NE (4.17–NE) |
| Median PFS,[g] months (95% CI) | 6.1 (2.5–9.9) | 9.9 (2.4–NE) |

Data cut-off date, March 16, 2023.
[a]Response was assessed by investigators, based on International Myeloma Working Group criteria; response-evaluable patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator. [b]95% CI, 51.3–86.8%. [c]95% CI, 8.3–41.0%. [d]95% CI, 42.1–99.6%. [e]95% CI, 3.7–71.0%. [f]Includes patients with confirmed responses. [g]All treated patients.
CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every other week; RP2R, recommended phase 2 regimen; sCR, stringent complete response; VGPR, very good partial response.



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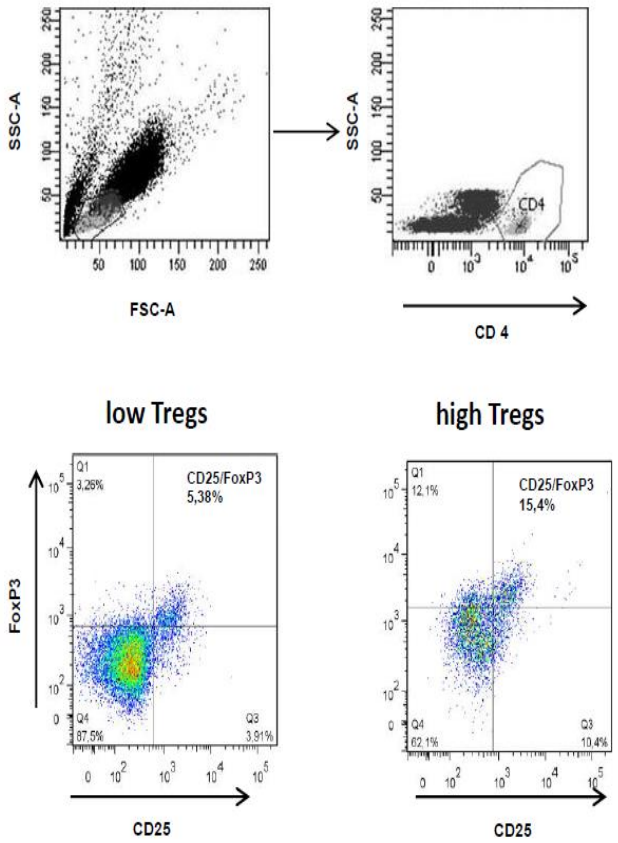
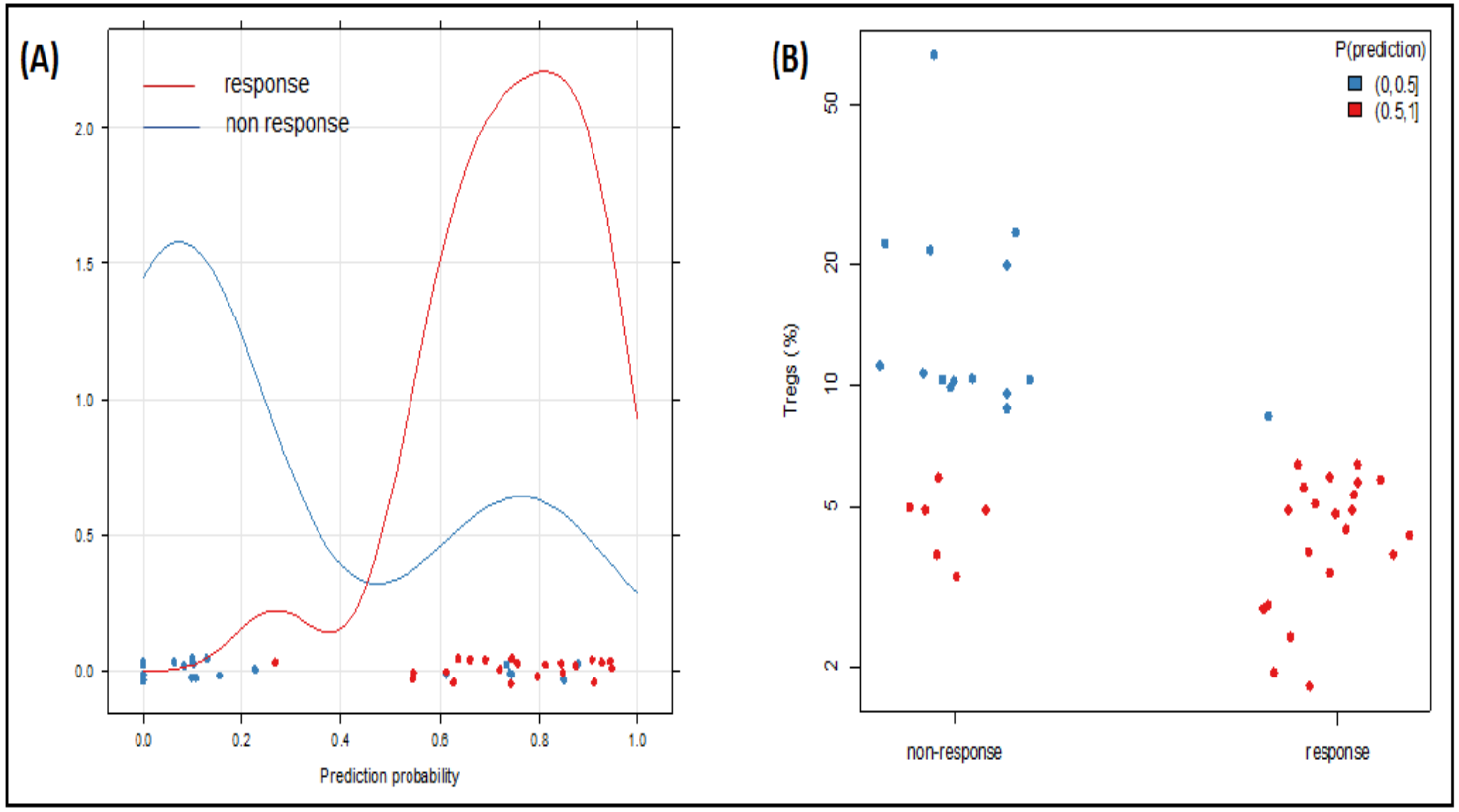
# Impact of tumor microenvironment

## High levels of circulating Tregs → ↓ Efficacy of TCEs



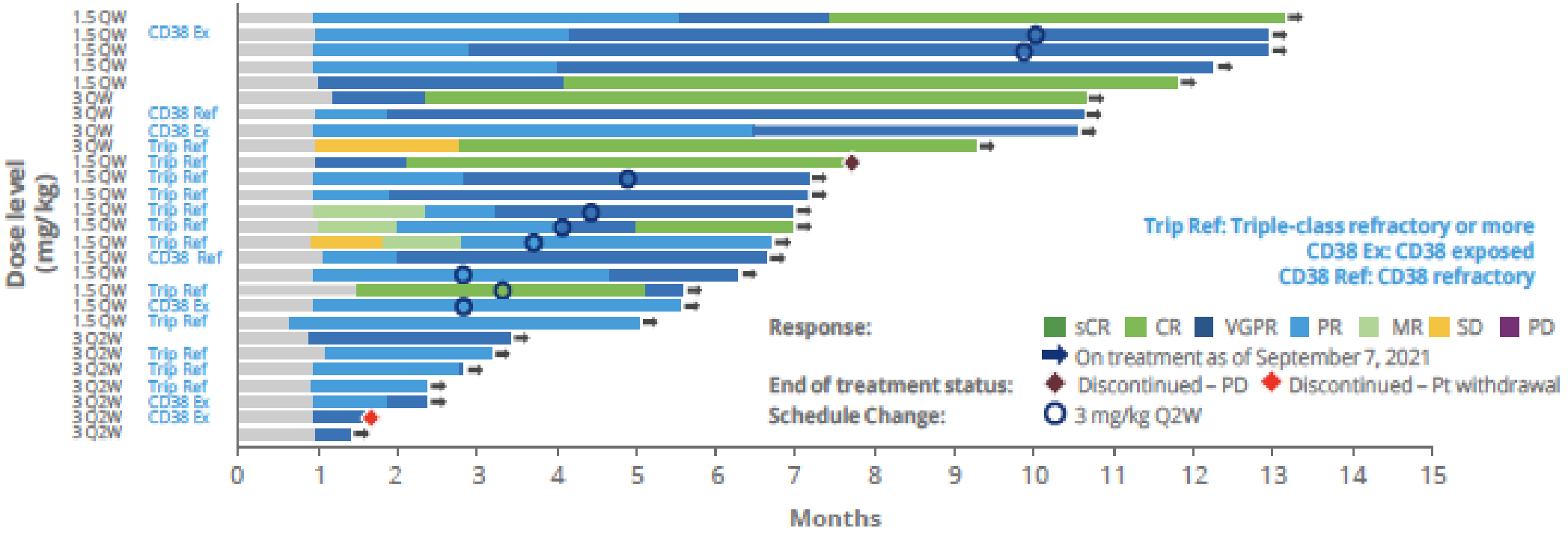

**Removal of Tregs may convert non-responders to responders**

**Disadvantage of CD3-binding bsTE: recruiting different types of T cells including Tregs**

Duell, J. et al., Leukemia 2017

# Subcutaneous Teclistamab in Combination with Daratumumab (TRIMM1) for the Treatment of Patients with r/r MM

Figure 1: Duration of response to tec + dara (n=27)




Addition of anti-CD38 Antibodies:
Depletion of regulatory cells (!?)
↑Response rate and ↑CR rate

Rodriguez-Otero P, et al. Blood 2021;138 (Suppl 1):1647.

# How to improve Therapy with BiAbs

- Long-term follow-up of trials with BisAb show long-lasting deep responses and no additional toxicity

- New formats of BisAb (high affinity binders to BCMA, low affinity binders to CD3, half-life extension) might improve efficacy and safety, esp. in BCMA mutants

- Short Duration of Treatment either fixed duration or treatment with extended treatment free intervals will allow to maintain/recover T cell fitness and reduce the risk of Target Antigen Loss !!

- Combination Therapy (IMiDs, CelMODs, ICPis, anti-CD38 MoAbs) to improve T cell function

- Targeting > 1 surface antigen on the Myeloma cell by combining 2 bispecific antibodies with different targets or trispecific antibodies, esp. In pts. with EMD

# Thanks to

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**Patients and family members**


**Funding Agencies**

imi innovative medicines initiative
T²EVOLVE
deutsche studiengruppe multiples myelom dsmm doing studies on multiple myeloma
EMN
Bundesministerium für Bildung und Forschung
European Commission
Wilhelm Sander-Stiftung fördert medizinische Forschung
DFG Deutsche Forschungsgemeinschaft
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.

# Thank you for your kind attention!

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