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# CAR T vs bispecifics: how to manage toxicity and sequencing

*Experience from multiple myeloma*

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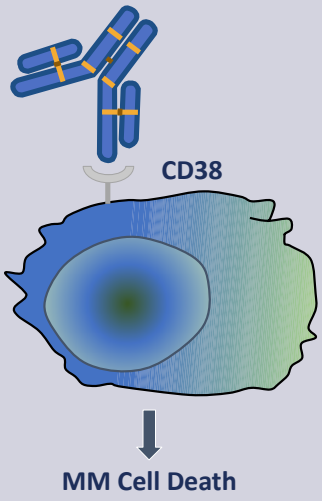
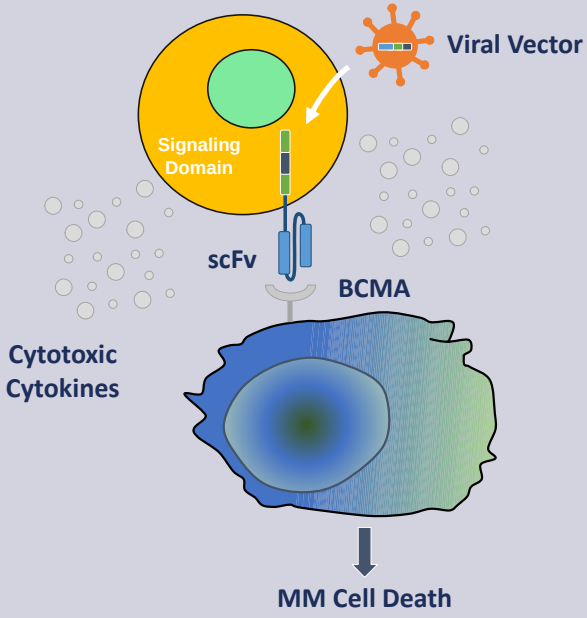
# Exploiting the immune system for anti-MM treatment

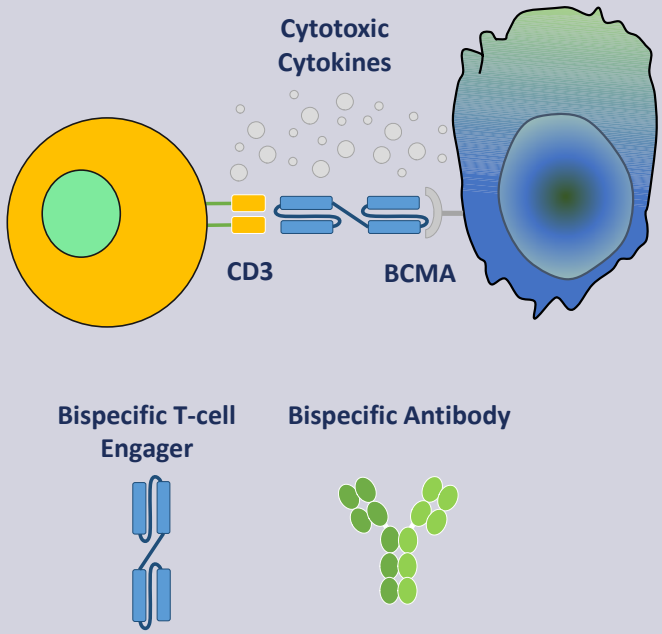
## Monoclonal Abs




## CAR T-Cells




## Bispecific Antibodies or T-Cell Engagers




CAR, chimeric antigen receptor; BCMA, B cell maturation antigen; CD, cluster of differentiation; MM, multiple myeloma; scFv, single chain fragment variable.

Yu B, et al. J Hematol Oncol. 2020;13(1):125.

# Immunotherapeutic targets in multiple myeloma

| | MM cells | Shedding | Other BM cells | Other organs |
|---|---|---|---|---|
| CD38 | ++++ | - | ++ | +++ |
| BCMA | +++ | + | - | (+) |
| SLAMF7/CS1 | +++ | - | + | - |
| FCRL5 | +++ | + | + | - |
| GPRC5D | +++ | - | - | + |

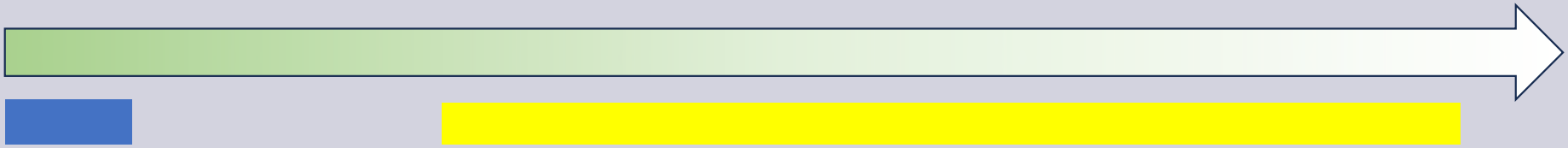
BCMA, B cell maturation antigen; BM, bone marrow; CD, cluster of differentiation; CS1, CD2 subunit 1;
FCRL5, Fc receptor-like 5; GPRC5D, G-protein coupled receptor family C group 5 member D;
MM, multiple myeloma; SLAMF7, signaling lymphocytic activation molecule family member 7.

| | ABBV-383 (Abbvie) | REG5458 (Regeneron) | Alnuctamab (BMS) | Elranatamab (Pfizer) | Teclistamab (Janssen) | Talquetamab (Janssen) | Cevostomab (Roche) |
|---|---|---|---|---|---|---|---|
| |  |  |  |  |  |  |  |
| **Administration** | **IV, Q3W<br>No step up** | **IV, weekly<br>Step-up** | **SQ, weekly<br>Step-up** | **SQ, weekly<br>Step-up** | **SQ, weekly<br>Step-up** | **SQ, weekly<br>Step-up** | **IV, Q3W<br>Step-up** |
| **Nr of prior lines** | **4-5 (3-15)** | **6** | | **5 (2-14)** | **5 (2-14)** | **5 (2-17)** | **6 (2-11)** |
| **ORR** | **58-61%** | **75% at highest dose** | **53% (all patients)<br>56% at highest dose** | **64%** | **63%** | **74%** | **Pre-Toci 54,8%** |
| **CRS** | **72-83% (Gr3; 0-2%)** | **48% (Gr3; 0,6%)** | **53% (GR3; 0%)** | **87% > 67%** | **71% (Gr3; 0,6%)** | **79% (Gr3; 2%)** | **Pre-treatment with Tociluzumab 35%** |
| **Infections** | **43-50%,<br>grade 3/4: 22%** | **52%<br>grade 3/4: 22%** | **34%<br>grade 3/4: 9%** | **66%<br>grade 3/4: 35%** | **63%;<br>grade 3/4: 35.2%** | **57%<br>grade 3/4: 16,8%** | **50%<br>grade 3/4: 25%** |
| **Unique toxicities** | | | **Neuropathy 6%** | **Neuropathy** | **Hypogamma 72%** | **Skin, nail, Dysgeusia** | **Neurotoxicity 14%** |
| **Reference** | Lee, ASCO 2023 | Lesokhin, Nat Med, 2023 | Wong, ASH 2022 | Bahlis, Nat Med,2023 | Moreau, NEJM 2022 | Chari, NEJM 2023 | Trudell, ASH 2022 |

| BCMA | GPRC5D | FCRH5 |
|---|---|---|

Cross trial comparisons cannot be inferred.
CRS, cytokine release syndrome; gr, grade; IV, intravenous; ORR, overall response rate; Q3W, every 3 weeks; SQ, subcutaneous.

# Complications

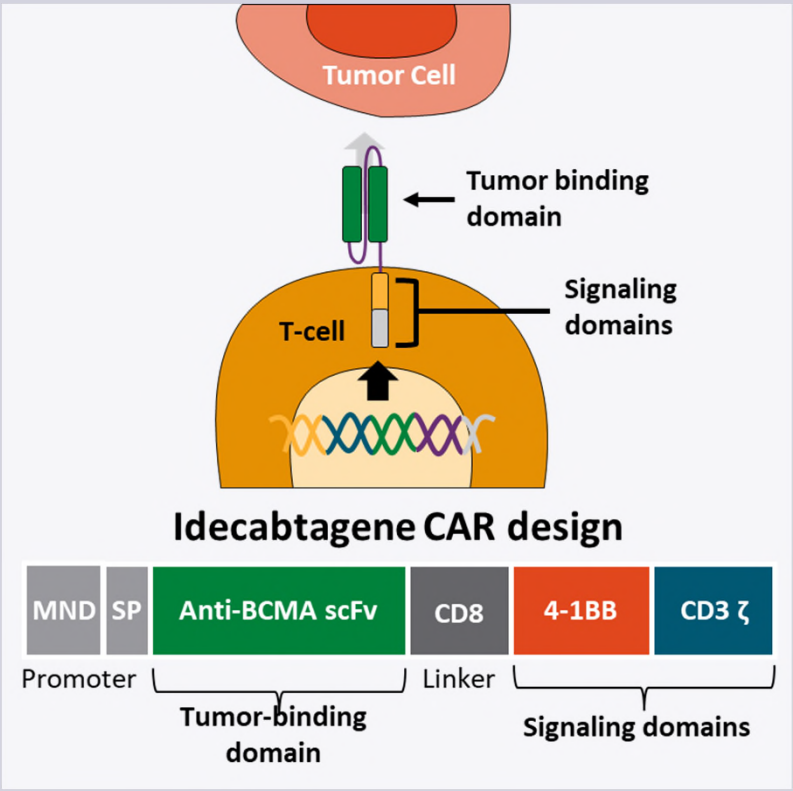


**CRS**

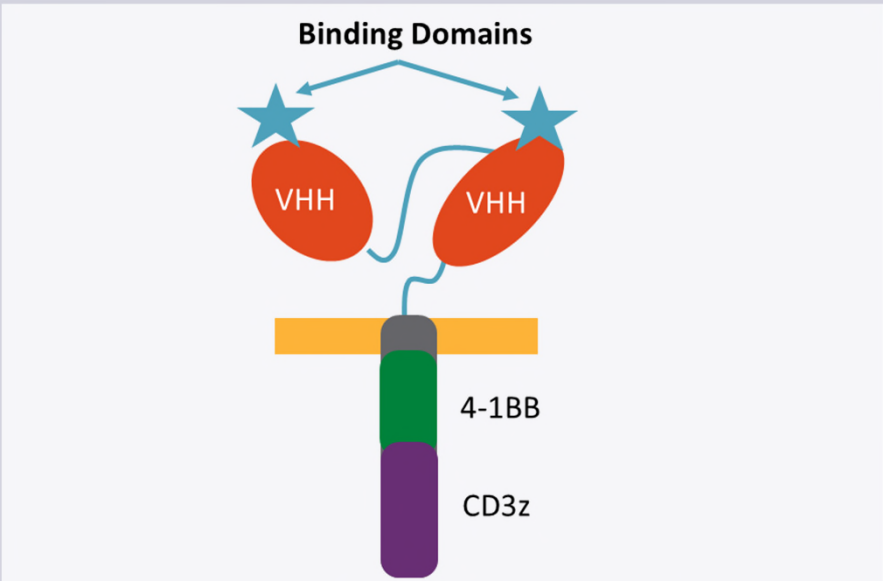
**Neurologic toxicities and ICANS**

**infection**

## KarMMa:
## idecabtagene vicleucel (ide-cel)




## CARTITUDE:
## ciltacabtagene autoleucel (cilta-cel)




- Contains 2 BCMA-targeting single-chain antibody designed confer avidity
- Identical to the CAR construct used in the LEGEND-2 study

Munshi NC, et al. NEJM. 2021;384:705-16.

CAR, chimeric antigen receptor; BCMA: B-cell Mature Antigen, VHH: variable domains of heavy-chain antibodies, scFv : single-chain variable fragment

Berdeja JG, et al. Lancet. 2021;398:314-24.

# Baseline characteristics: KarMMa (ide-cel) and CARTITUDE-1 (cilta-cel)

| Characteristic | Ide-cel | Cilta-cel |
|---|---|---|
| Median age, years (range) | 61 (33-78) | 61 (56-68) |
| Extramedullary disease, n (%) | 50 (39) | 13 (13) |
| R-ISS stage III, n (%) | 21 (16) | NA |
| ISS stage III, n (%) | NA | 14 (14) |
| Number of prior lines, n (range) | 6 (3-16) | 6 (4-8) |
| Triple-refractory disease, n (%) | 108 (84) | 85 (88) |

Cross trial comparisons cannot be inferred.
NA, not assessed; R-ISS, Revised International Staging System.

Munshi NC, et al. NEJM. 2021;384:705-16.
Berdeja JG, et al. Lancet. 2021;398:314-24.

# Efficacy and safety: KarMMa (ide-cel) and CARTITUDE-1 (cilta-cel)

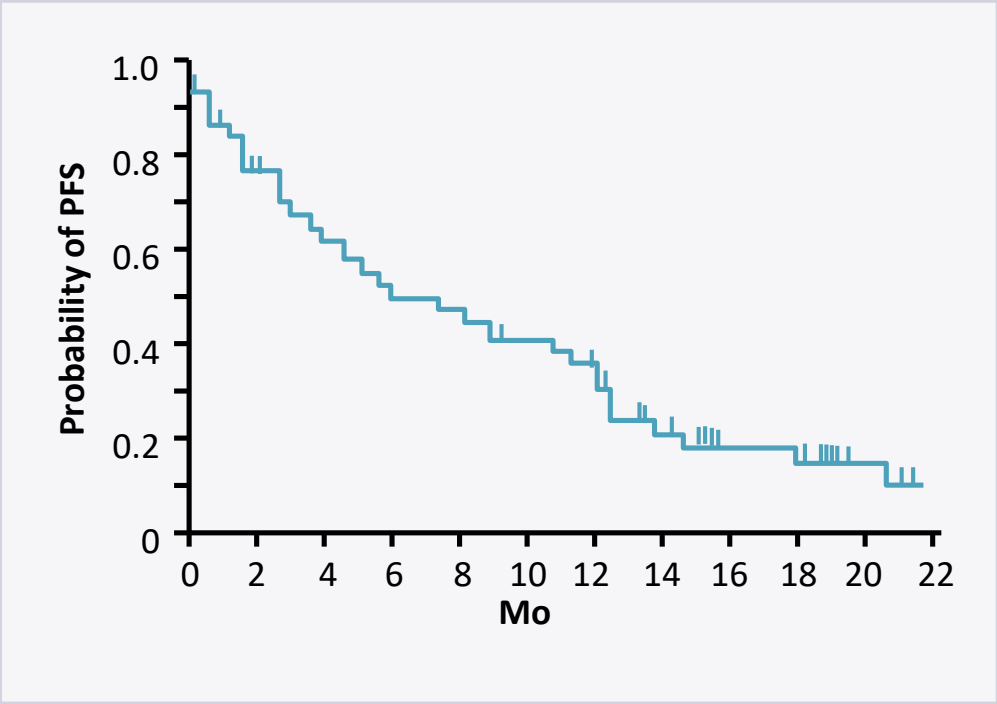
| Efficacy | Ide-cel | Cilta-cel |
|---|---|---|
| Overall response rate, % | 73 | 98 |
| Complete response rate, % | 33 | 82 |
| DoR, months | 10,7 | NR |
| Median PFS, months | 8,8 | 34,9 |
| Median follow-up, months | 13 | 33,4 |

| Safety | Ide-cel | Cilta-cel |
|---|---|---|
| CRS, any grade, % | 84 | 95 |
| CRS grade 3 or higher, % | 5 | 5 |
| Neurotoxicity, any grade, % | 18 | 21 |
| Neurotoxicity, grade 3 or higher, % | 3 | 12 |

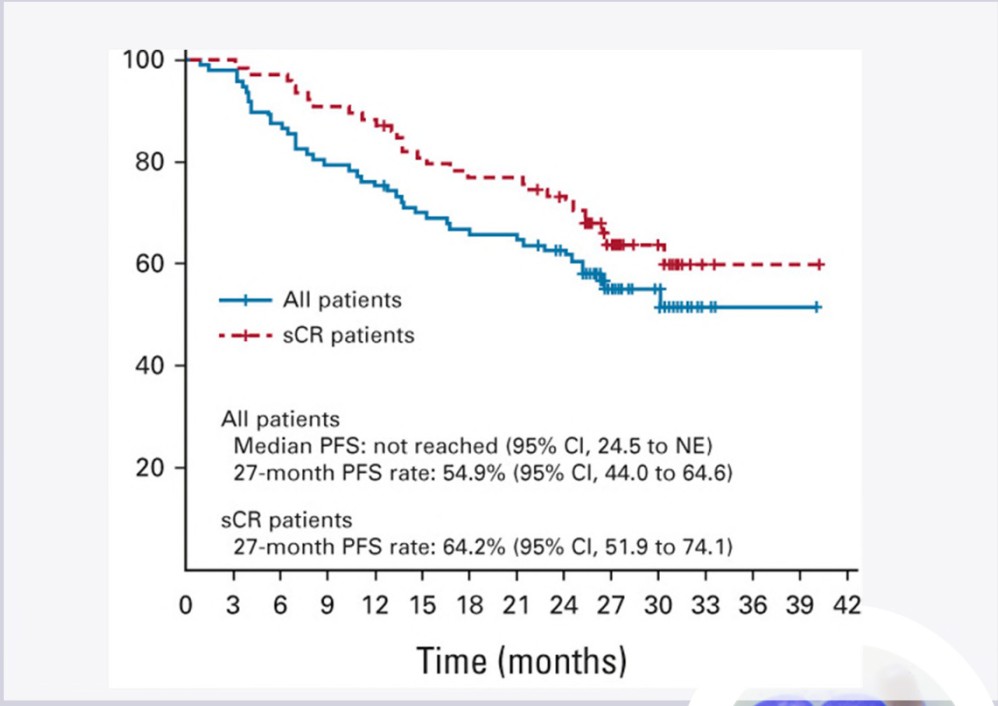
Cross trial comparisons cannot be inferred.
CRS, cytokine release syndrome; DoR, duration of response; NR, not reached; PFS, progression-free survival.

Munshi NC, et al. NEJM. 2021;384:705-16.
Berdeja JG, et al. Lancet. 2021;398:314-24.

# EMA-approved BCMA CART for myeloma




Median PFS
ide-cel: 8.8 months




Median PFS
cilta-cel: 34.9 months

Cross trial comparisons cannot be inferred.
BCMA, B cell maturation antigen; CART, chimeric antigen receptor T cell therapy; EMA, European Medicines Agency; Mo, months; PFS, progression-free survival.

Munshi NC, et al. NEJM. 2021;384:705-16.
Berdeja JG, et al. Lancet. 2021;398:314-24.
Lin Y, et al. JCO 41, 2023 (suppl 16; abstr 8009).

# Factors impacting tumor response

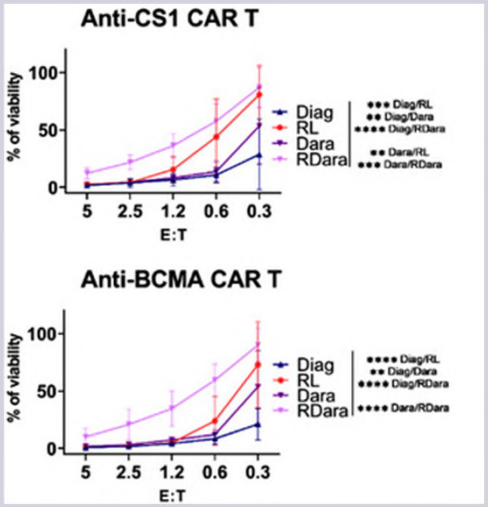
# Factors impacting tumor response

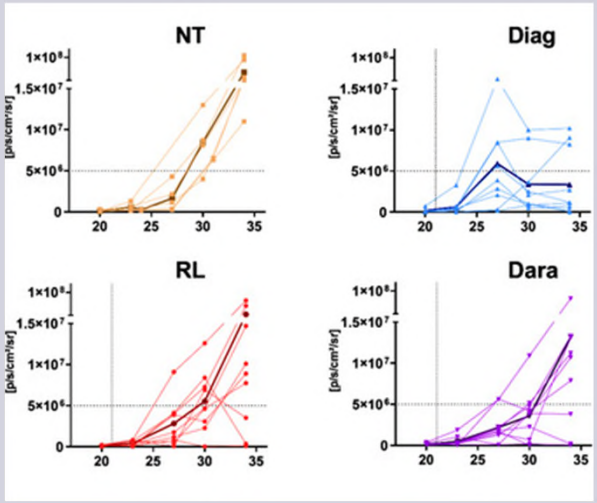
Impact of immune counts and T-cell fitness

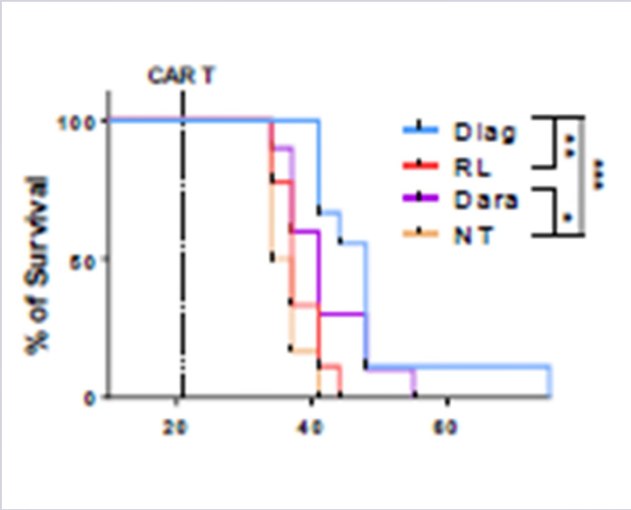
Antigen loss
Antigen downregulation
Mutations in epitope

Tumor characteristics at baseline

# Impact of immune counts and T-cell fitness

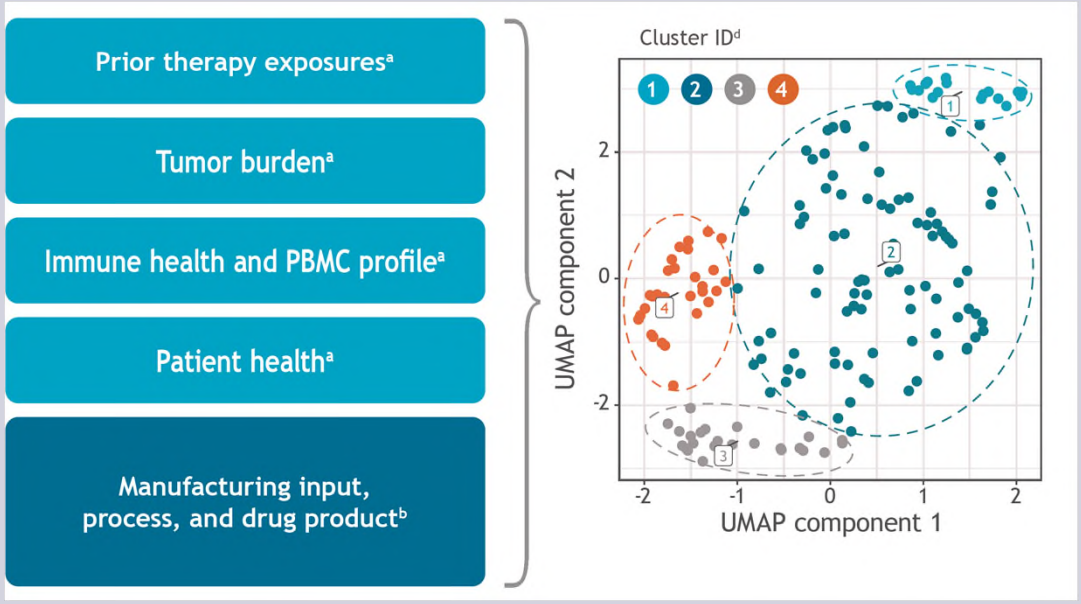



Abecassis A et al, EJHaem. 2022; 3(3): 970–4.

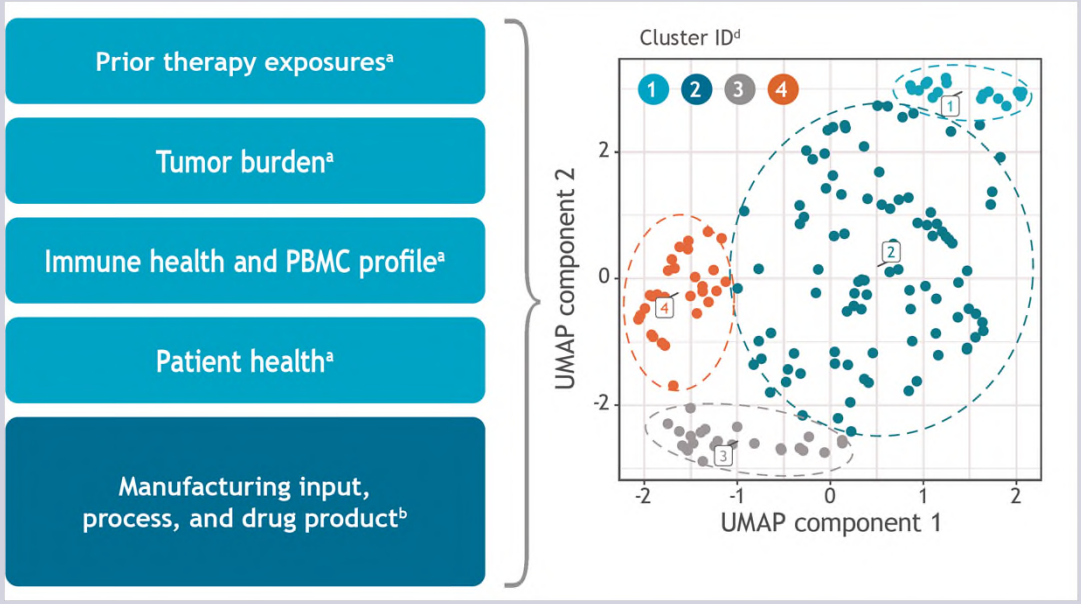
# Impact of immune counts and T-cell fitness




| Feature | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 |
|---|---|---|---|---|
| | Least favorable | | | Most favorable |
| Prior therapies | Recent alkylator, PI, TI ↑ Prior regimens | Recent alkylator, PI, TI | Recent alkylator, PI ↓ Prior regimens | Distant alkylator, PI, TI |
| Tumor burden | ↑ sBCMA/ M-protein | ↑ sBCMA/ M-protein ↑ LDH | ↓ sBCMA/ M-protein | ↓ sBCMA/ M-protein |
| Immune profile | ↓ ALC ↑ Mono:Leuk | ↑ ALC ↑ Mono:Leuk | ↓ ALC ↓ Mono:Leuk | ↑ ALC ↓ Mono:Leuk |
| Patient fitness | ↓ Albumin ↓ Creatinine clearance | ↓ Creatinine clearance | ↑ Creatinine clearance | ↑ Albumin ↓ Creatinine clearance |
| Drug product | ↓ CD3/CAR% ↓ VCN | ↓ CD3/CAR% | ↑ CD3/CAR% | ↑ CD3/CAR% ↑ VCN |
| Efficacy | mPFS: 3 mo CRR: 18% | mPFS: 7.9 mo CRR: 32% | mPFS: 11.7 mo CRR: 50% | mPFS: 14.5 mo CRR: 61% |

Rytlewski J, et al. Poster presentation at EHA 2022. P866.

# Impact of immune counts and T-cell fitness

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| Tumor burden | ↑ sBCMA/ M-protein | ↑ sBCMA/ M-protein ↑ LDH | ↓ sBCMA/ M-protein | ↓ sBCMA/ M-protein |
| Immune profile | ↓ ALC ↑ Mono:Leuk | ↑ ALC ↑ Mono:Leuk | ↓ ALC ↓ Mono:Leuk | ↑ ALC ↓ Mono:Leuk |
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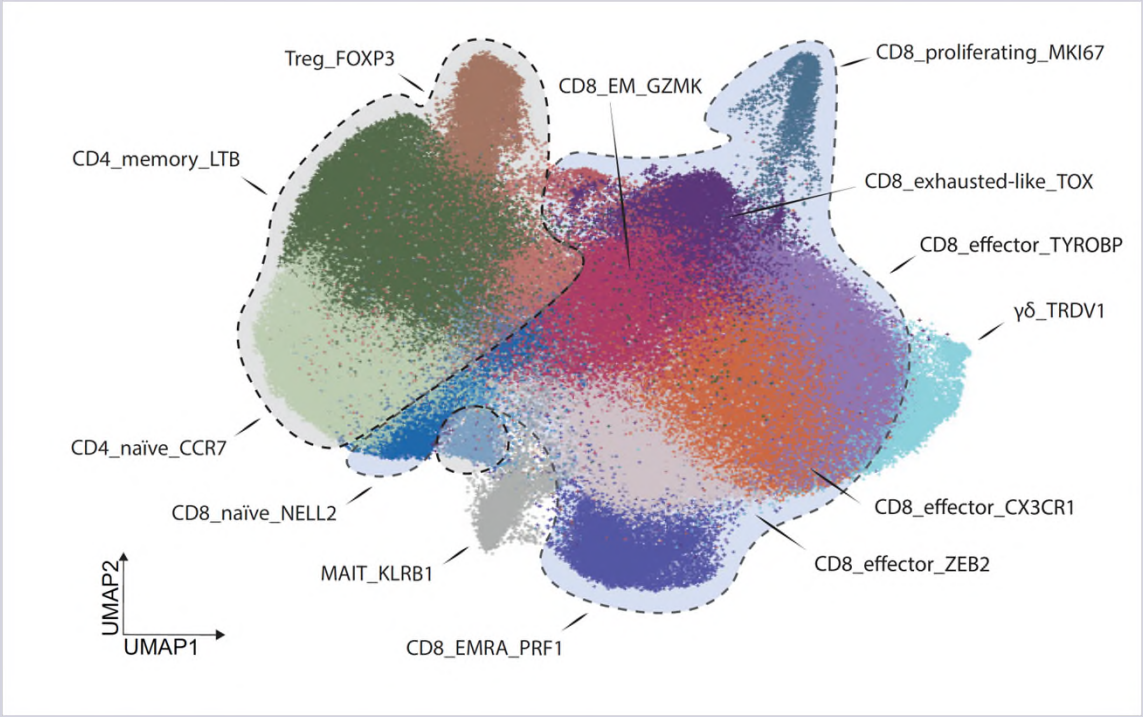
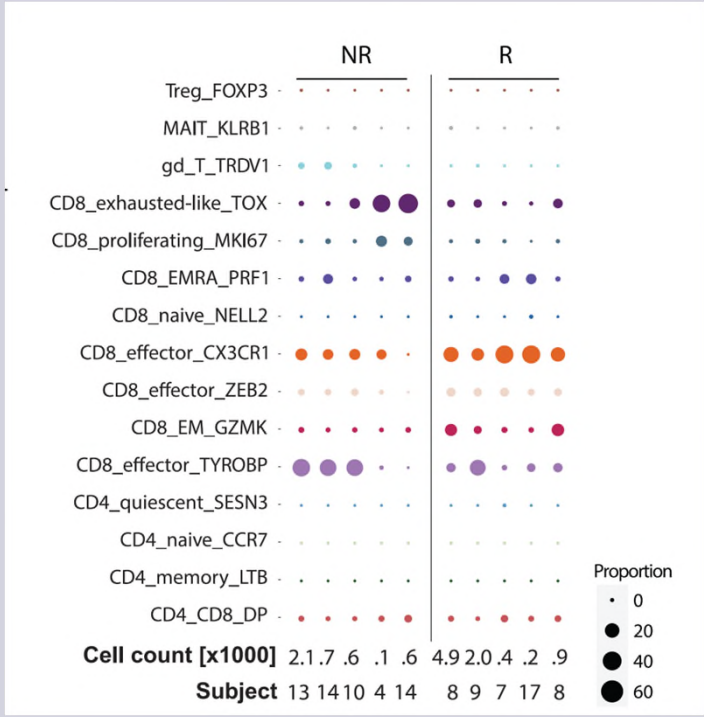
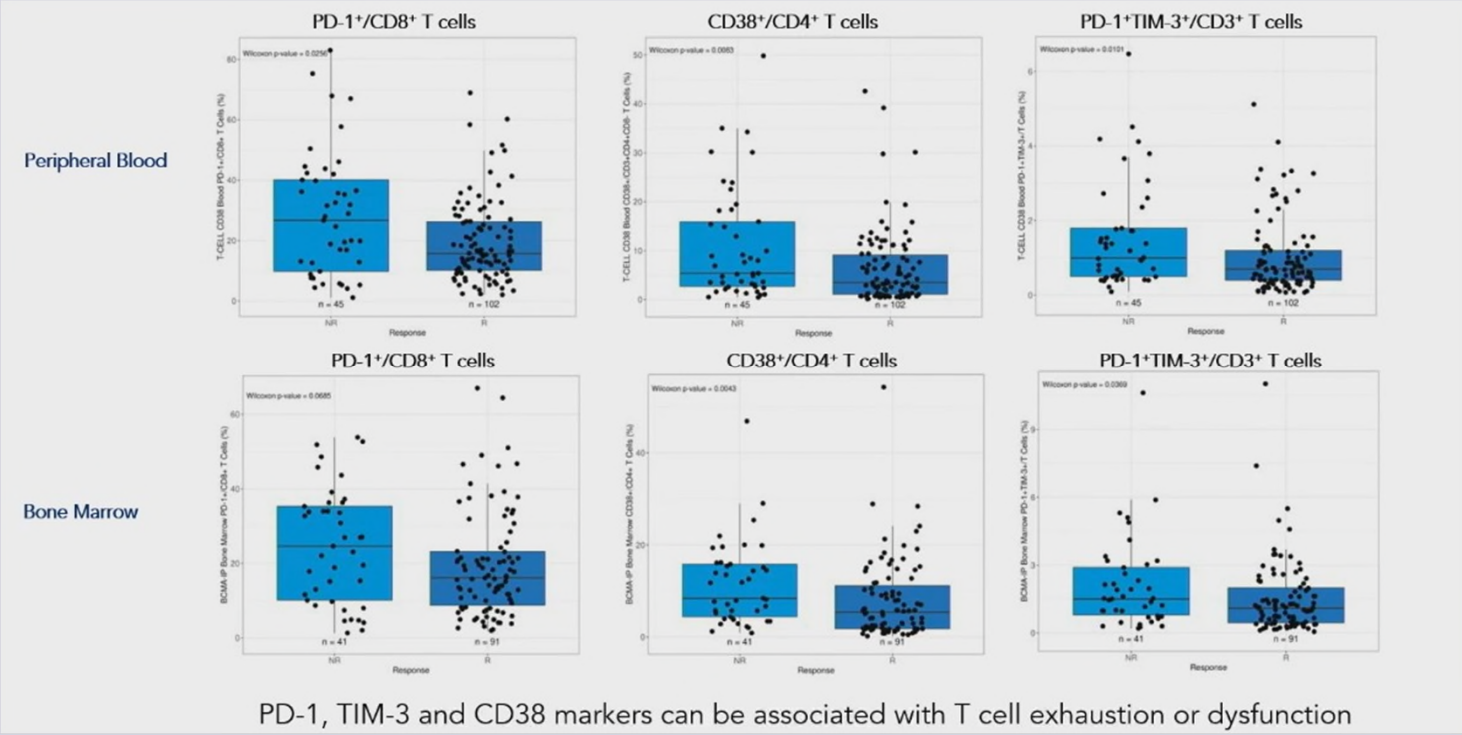



Friedrich MJ, et al. Cancer Cell. 2023;41(4):711-725.e6.

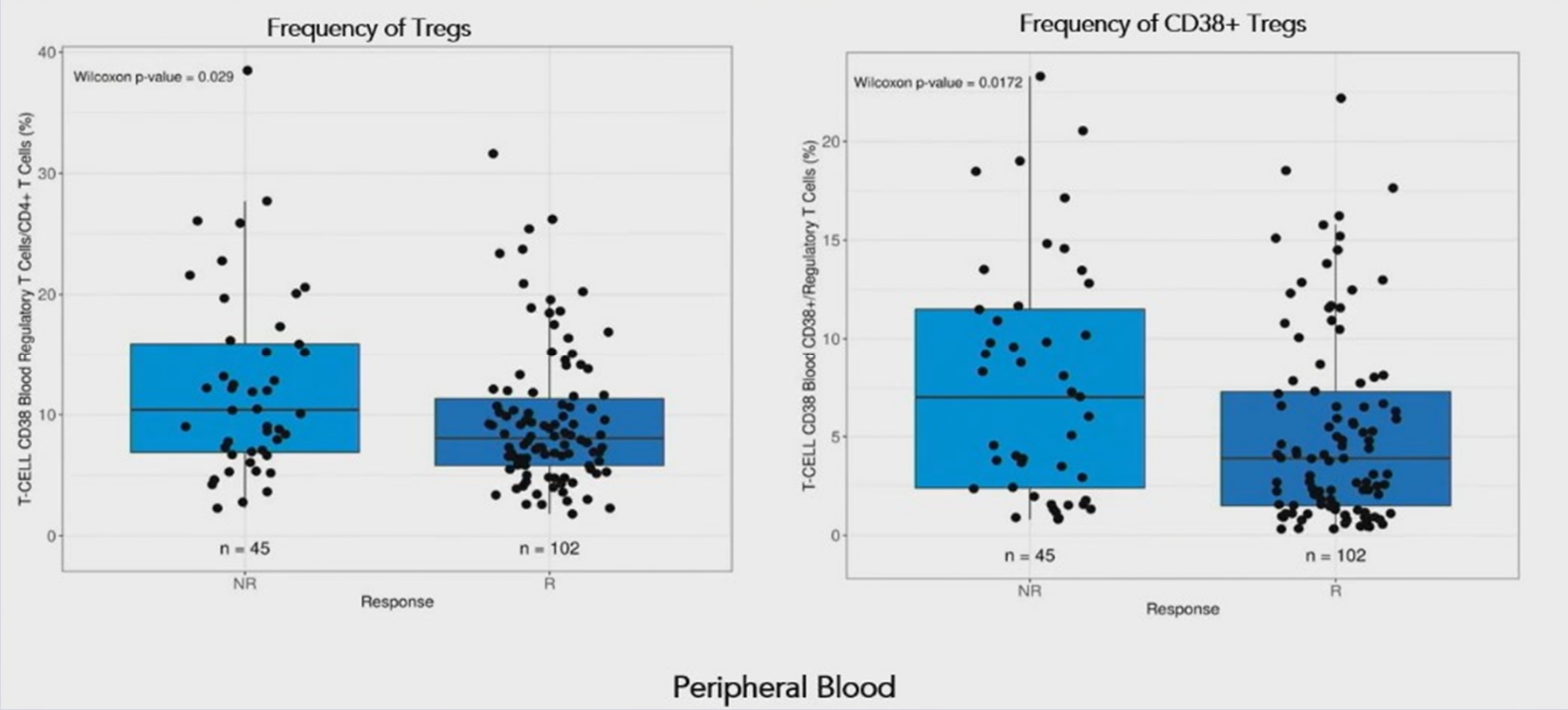
# Impact of immune counts and T-cell fitness




PD-1, TIM-3 and CD38 markers can be associated with T cell exhaustion or dysfunction

Cortes-Selva J, et al. Oral presentation at ASH 2022. Blood. 140(Suppl_1):241-3.

# Impact of immune counts and T-cell fitness




Cortes-Selva J, et al. Oral presentation at ASH 2022. Blood. 140(Suppl_1):241-3.

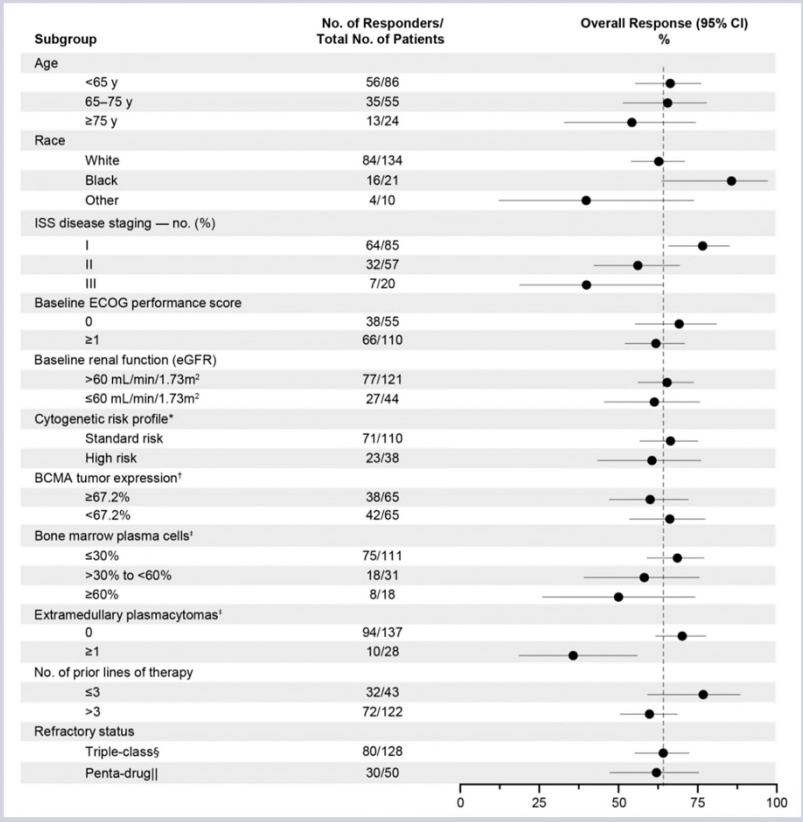
# Tumor characteristics

~ 30% of patients do not respond to anti-BCMA bispecifics

- High disease burden:
  - Increased bone marrow plasma cells
  - ISS stage III
- Extramedullary disease (EMD)
- High risk cytogenetics
- Prior treatment with bispecifics?

# Tumor characteristics

## MajesTEC-1 (teclistamab)

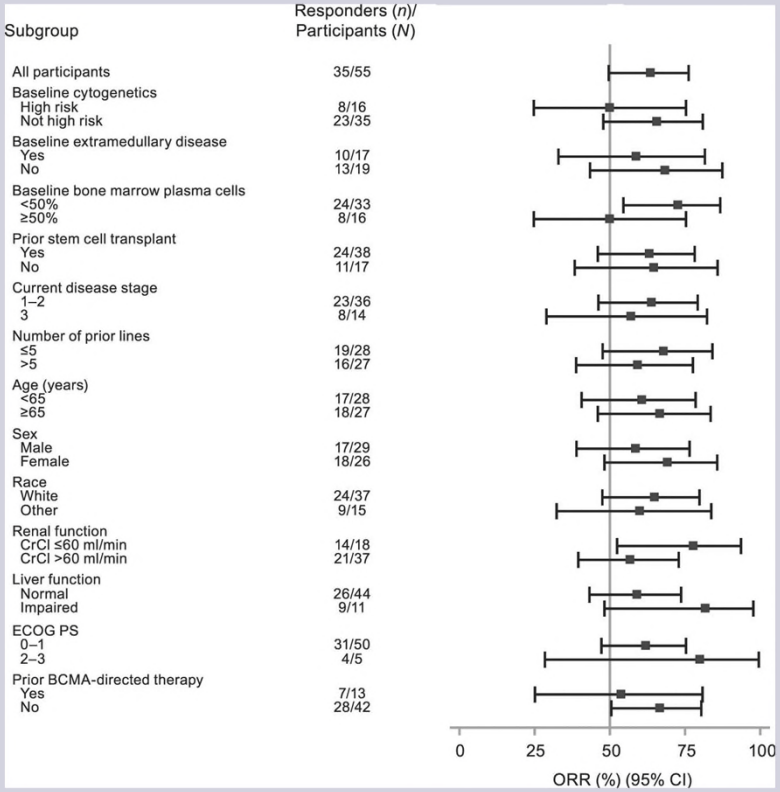


| Subgroup | No. of Responders/ Total No. of Patients |
|---|---|
| Age | |
| <65 y | 56/86 |
| 65–75 y | 35/55 |
| ≥75 y | 13/24 |
| Race | |
| White | 84/134 |
| Black | 16/21 |
| Other | 4/10 |
| ISS disease staging — no. (%) | |
| I | 64/85 |
| II | 32/57 |
| III | 7/20 |
| Baseline ECOG performance score | |
| 0 | 38/55 |
| ≥1 | 66/110 |
| Baseline renal function (eGFR) | |
| >60 mL/min/1.73m² | 77/121 |
| ≤60 mL/min/1.73m² | 27/44 |
| Cytogenetic risk profile* | |
| Standard risk | 71/110 |
| High risk | 23/38 |
| BCMA tumor expression† | |
| ≥67.2% | 38/65 |
| <67.2% | 42/65 |
| Bone marrow plasma cells‡ | |
| ≤30% | 75/111 |
| >30% to <60% | 18/31 |
| ≥60% | 8/18 |
| Extramedullary plasmacytomas‡ | |
| 0 | 94/137 |
| ≥1 | 10/28 |
| No. of prior lines of therapy | |
| ≤3 | 32/43 |
| >3 | 72/122 |
| Refractory status | |
| Triple-class§ | 80/128 |
| Penta-drug‖ | 30/50 |



Moreau P, et al. N Engl J Med. 2022;387(6):495-505.

## MagnetisMM-1 (elranatamab)

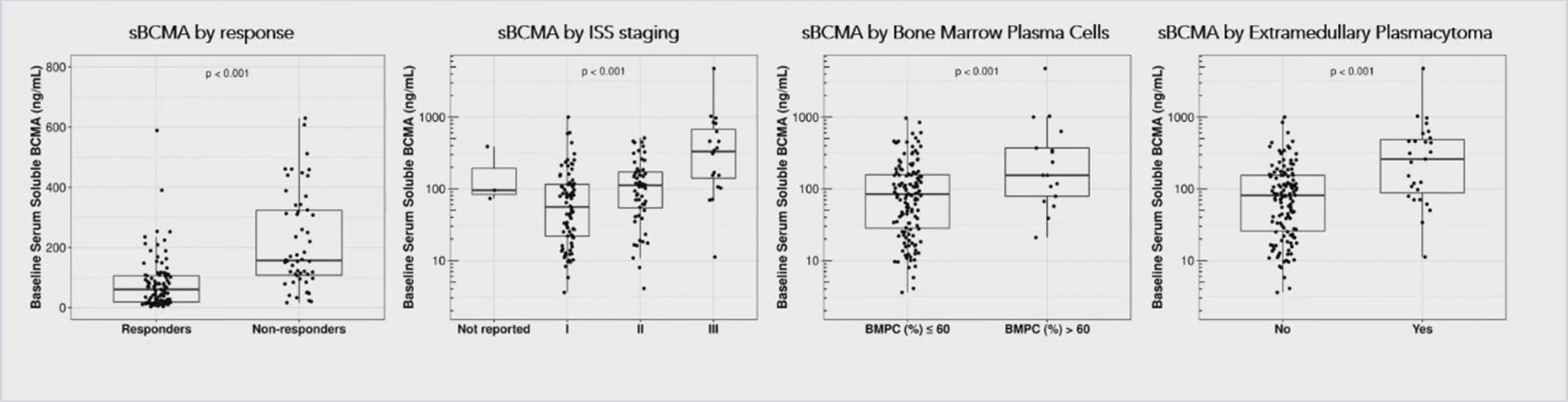


| Subgroup | Responders (*n*)/ Participants (*N*) |
|---|---|
| All participants | 35/55 |
| Baseline cytogenetics | |
| High risk | 8/16 |
| Not high risk | 23/35 |
| Baseline extramedullary disease | |
| Yes | 10/17 |
| No | 13/19 |
| Baseline bone marrow plasma cells | |
| <50% | 24/33 |
| ≥50% | 8/16 |
| Prior stem cell transplant | |
| Yes | 24/38 |
| No | 11/17 |
| Current disease stage | |
| 1–2 | 23/36 |
| 3 | 8/14 |
| Number of prior lines | |
| ≤5 | 19/28 |
| >5 | 16/27 |
| Age (years) | |
| <65 | 17/28 |
| ≥65 | 18/27 |
| Sex | |
| Male | 17/29 |
| Female | 18/26 |
| Race | |
| White | 24/37 |
| Other | 9/15 |
| Renal function | |
| CrCl ≤60 ml/min | 14/18 |
| CrCl >60 ml/min | 21/37 |
| Liver function | |
| Normal | 26/44 |
| Impaired | 9/11 |
| ECOG PS | |
| 0–1 | 31/50 |
| 2–3 | 4/5 |
| Prior BCMA-directed therapy | |
| Yes | 7/13 |
| No | 28/42 |



Bahlis NJ, et al. Nat Med. 2023;29(10):2570-2576.

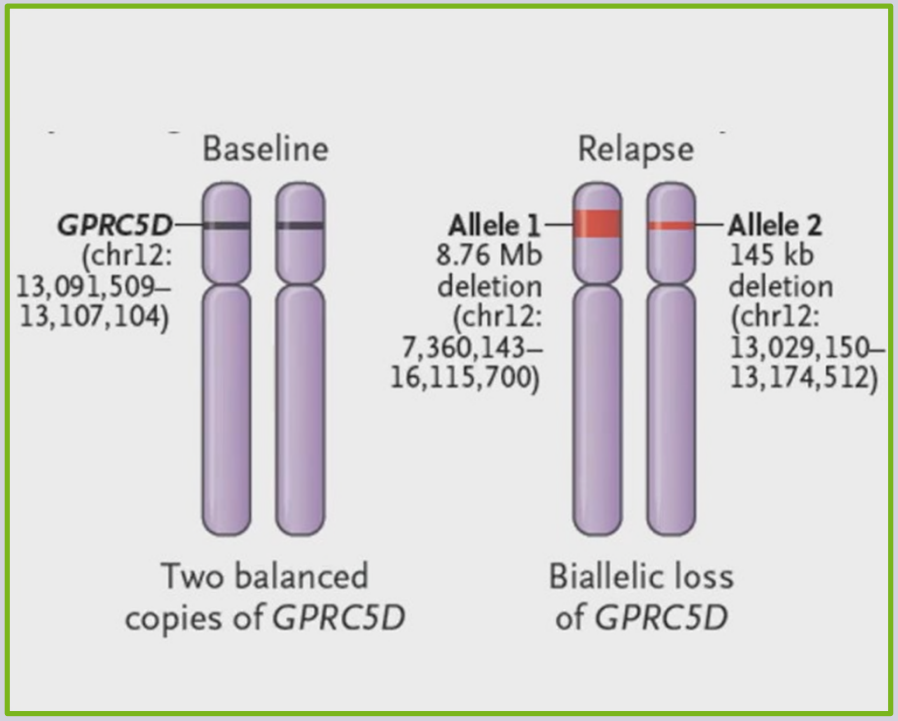
# Tumor characteristics




Cortes-Selva J, et al. Oral presentation at ASH 2022. Blood. 140(Suppl_1):241-3.

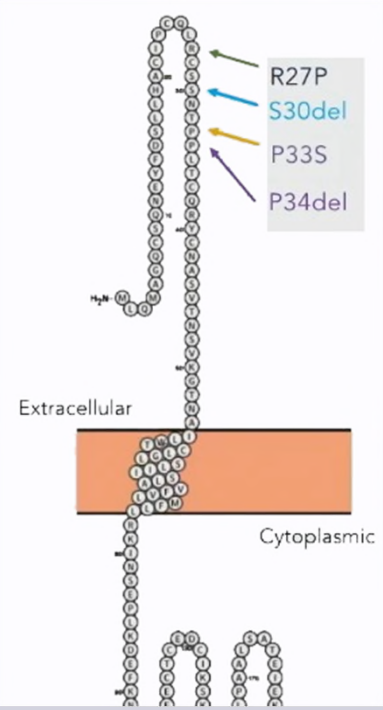
Antigen loss
Antigen downregulation
Mutations in epitope

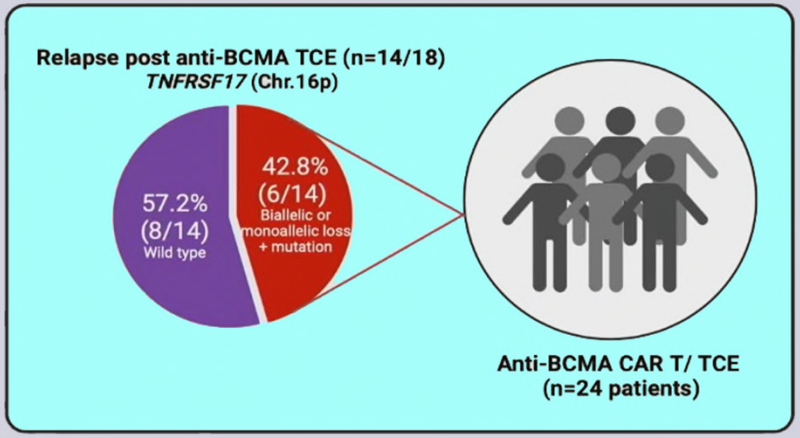

Da Via MC, et al. Nat Med. 2021




Mi X, et al. N Engl J Med. 2023

## Antigen loss
## Antigen downregulation
## Mutations in epitope



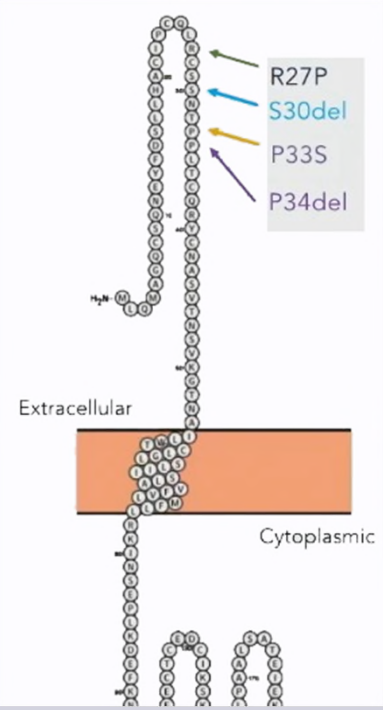

1) TNFRSF17 missense mutations
- p.Arg27Pro (n=1)
- p.Pro33Ser (germline mutation, n=1)

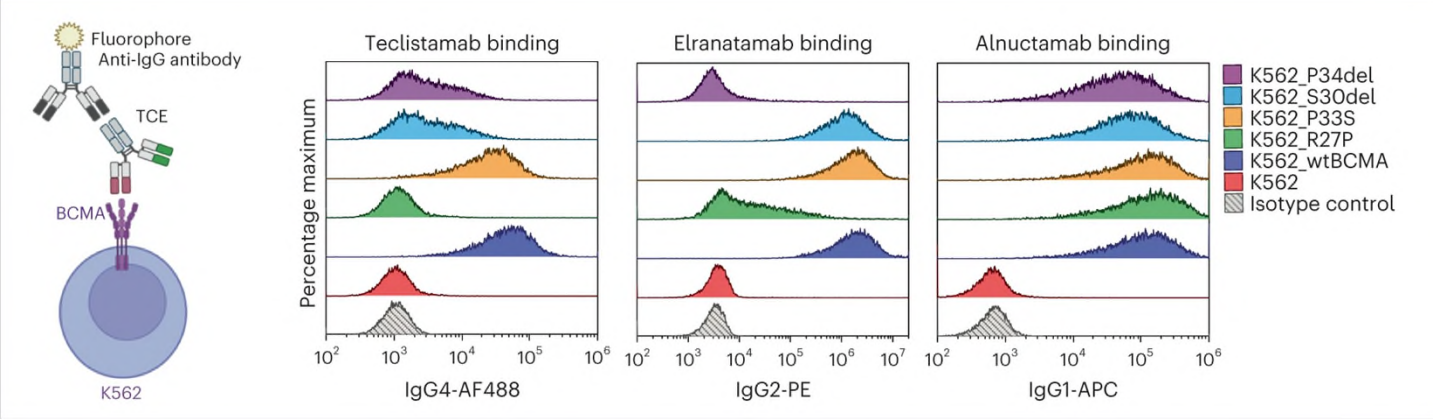
2) TNFRSF17 in-frame deletions
- p.Pro34del (n =3)
- p.Ser30del (n=2)

3) TNFRSF17 biallelic deletion (n=1)

Lee H, et al. Nat Med. 2023 29(9):2295-2306.

## Antigen loss
## Antigen downregulation
## Mutations in epitope




Lee H, et al. Nat Med. 2023 29(9):2295-2306.

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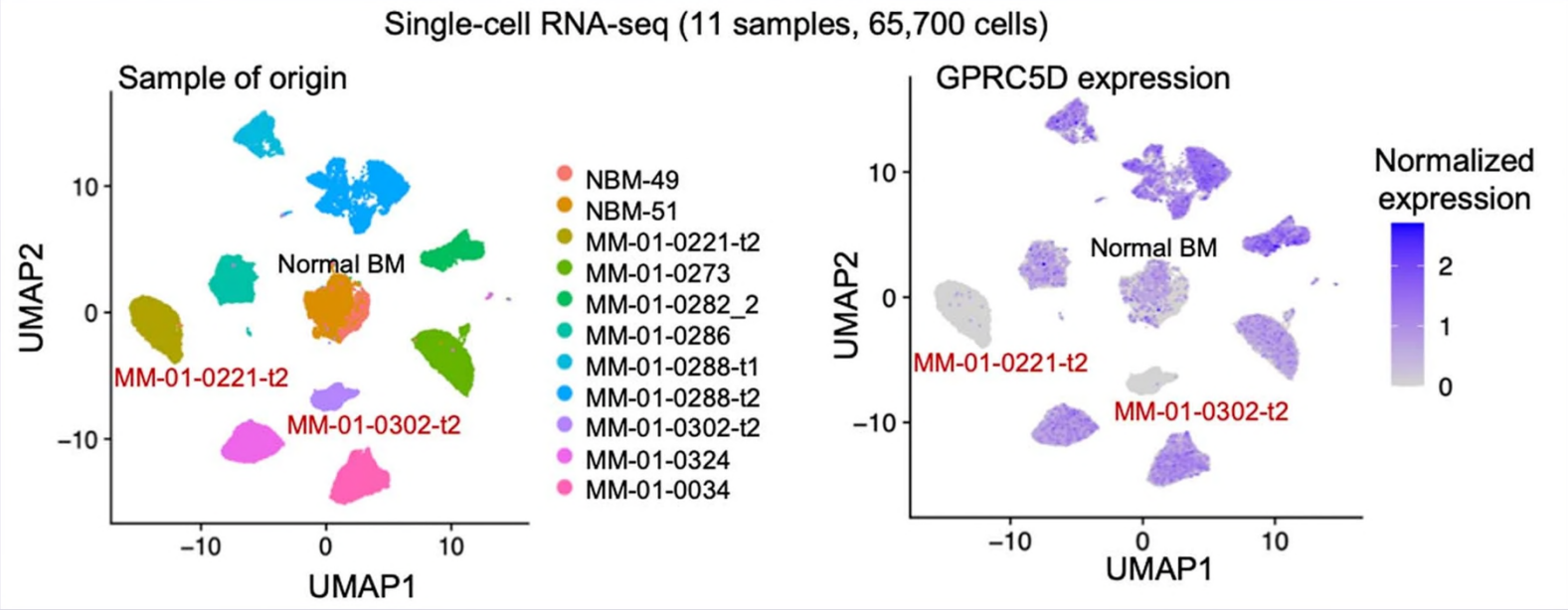


Derrien J, et al. Nat Cancer. 2023 Nov;4(11):1536-1543.

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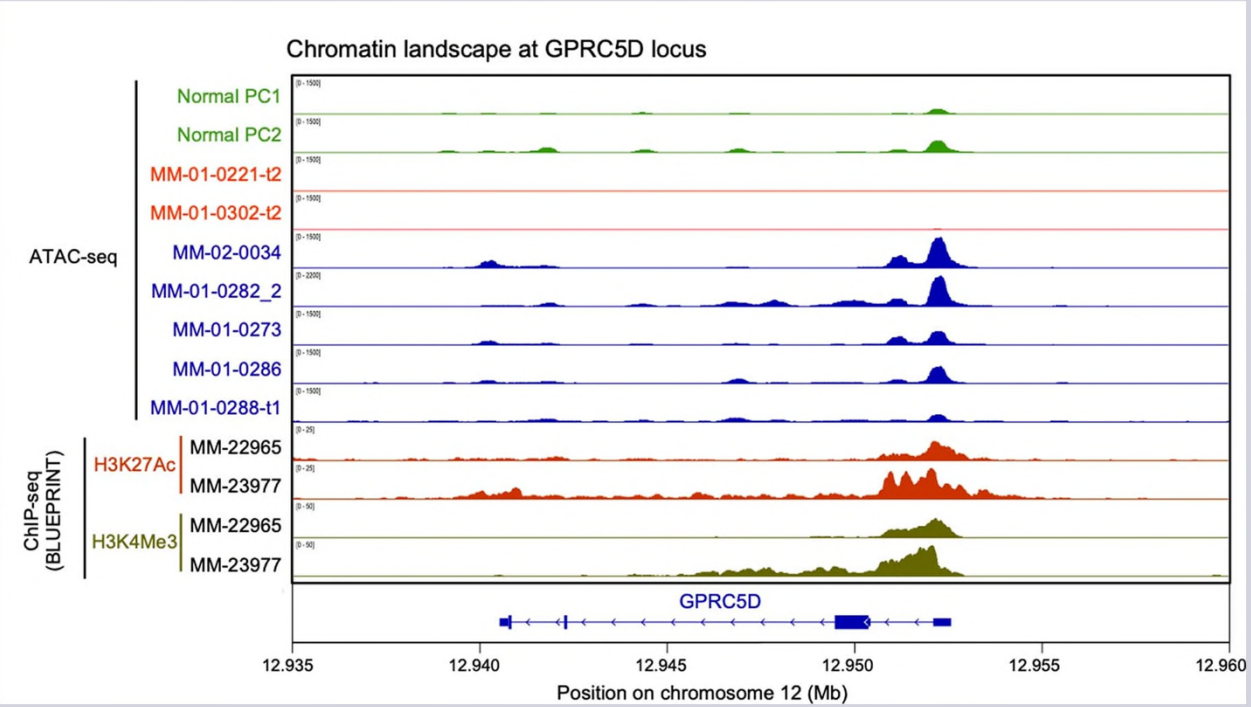


Derrien J, et al. Nat Cancer. 2023 Nov;4(11):1536-1543.

# Advantages and disadvantages of CAR-T and bispecifics

| | CAR-T | Bispecifics |
|---|---|---|
| **Avantages** | Strong and rapid anti-tumor effects.<br>Efficient in different subgroups<br>Autologous or allogeneic products | Off the shelf available<br>Good anti-tumor control<br>Favorable safety profile |
| **Disadvantages** | Delay in production<br>Side effects<br>Costs +++ | Continuous treatment<br>Costs ++ |

Kegyes D, et al. J Hematol Oncol. 2022;15(1):78.

# Conclusions

Wave of new immunotherapeutic agents in multiple myeloma.

Selection of patients for either CAR-T or bispecific antibodies.

Understanding and follow-up of resistance mechanisms may guide for future therapies.

Treatments remain expensive, hampering access for patients.