Highlights from
IMS 20th meeting 2023

Paola Neri

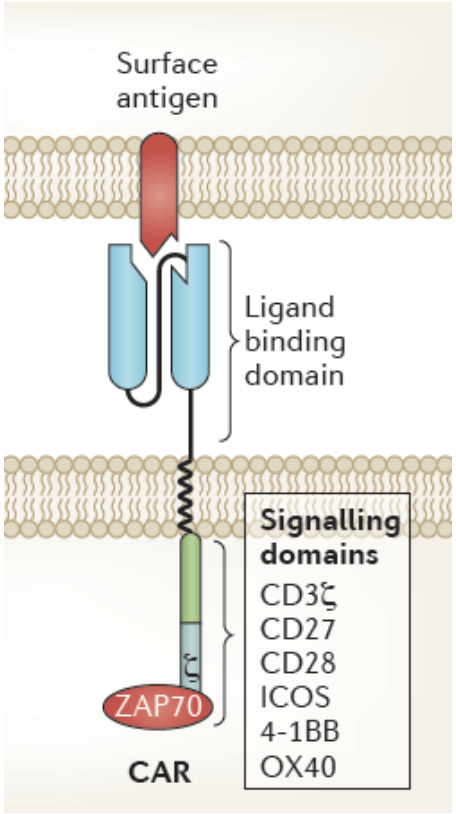
Fattori Predittivi della Risposta

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

Disclosures of Paola Neri

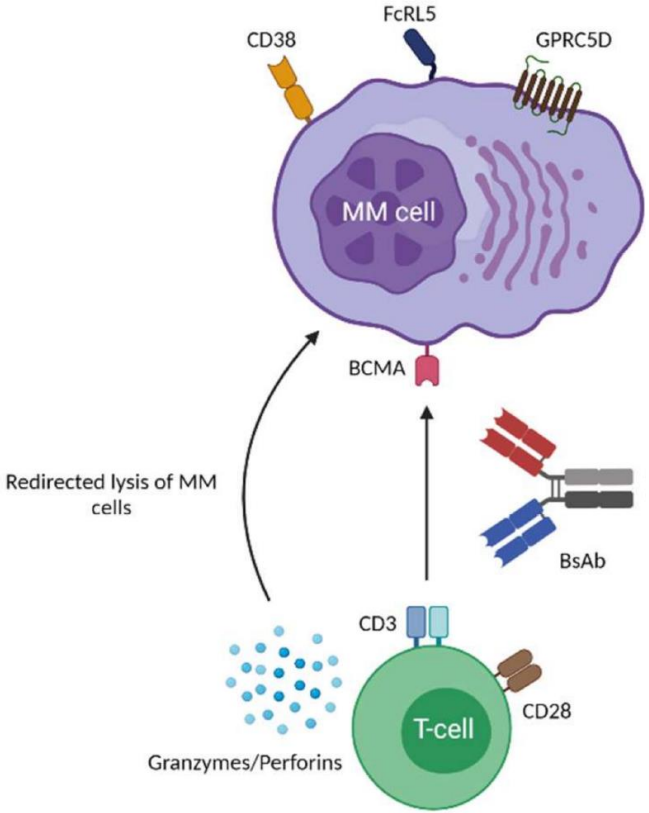
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sanofi			x			x	
Pfizer						x	
Janssen						x	
BMS			x			x	

Chimeric Antigen Receptor T cells (CART) and T cell engagers (TCE)



Fesnak A et al. Nat Rev Cancer 2016

BCMA
GPRC5D
FcRH5
CD38
SLAMF7
BCMA+TACI
BCMA+GPRC5D

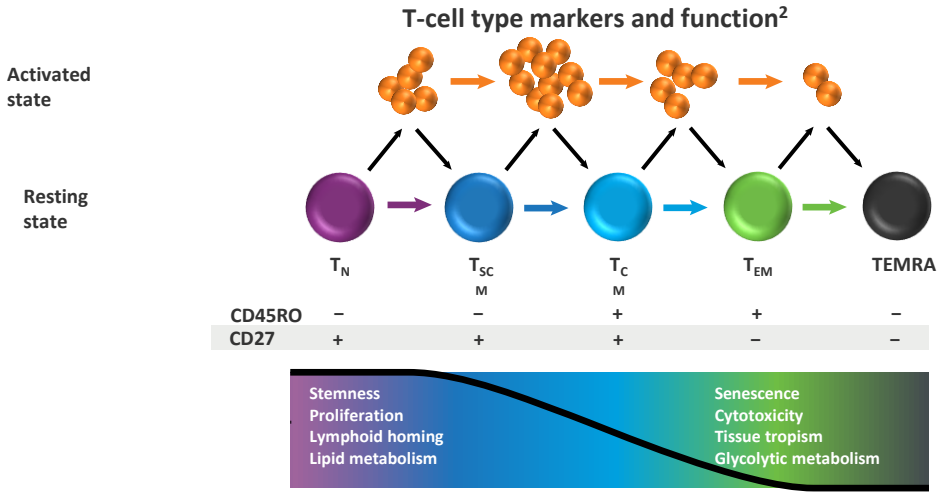


Hosny M et al, Journal of Clinical Medicine 2021

CAR-T and T cell engagers (TCE) have demonstrated unprecedented efficacy in RRMM patients.
However, the cellular and molecular predictors of response as well as the mediators of resistance remain elusive.

T-Cell Phenotypes as a Determinant of Clinical Activity of CAR-T

- As T cells differentiate, proliferation increases before decreasing as memory function and, subsequently, effector function increase.
- Preferential CAR+ CD8 T-cell expansion and enrichment of CAR+ T cells with memory phenotypes have been associated with enhanced CAR-T cell clinical activity[1].

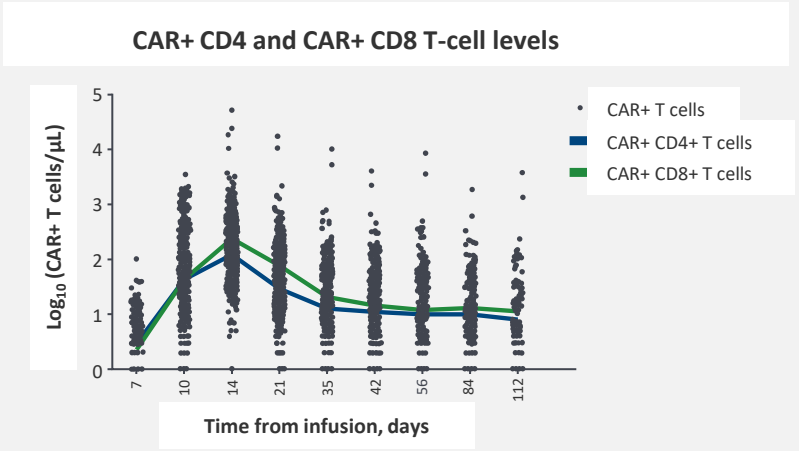


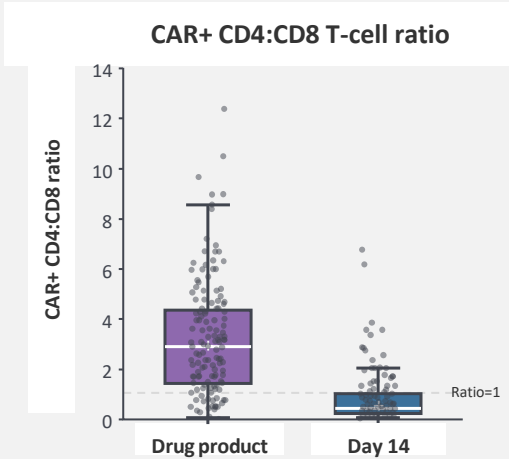
CAR, chimeric antigen receptor; T_{CM}, central memory T cell; T_{EM}, effector memory T cell; TEMRA, terminally differentiated T cell ;T_N, naive T cell; T_{SCM}, stem cell memory T cell.

1. Cohen AD et al, J Clin Invest 2019
2. Adapted from Springer Nature: Springer Nature, (2015). Harnessing Stem Cell-Like Memory T Cells for Adoptive Cell Transfer Therapy of Cancer. In: Ascierto, P., Stroncek, D., Wang, E. (eds) Developments in T Cell

CARTITUDE-4: Preferential Expansion of CAR+ CD8 T Cells Post Infusion

- Both CAR+ CD4 and CAR+ CD8 T cells expanded after infusion
- Consistent with CARTITUDE-1,[1] in CARTITUDE-4 CAR+ CD8 T cells expanded more than CAR+ CD4 T cells in blood
  - CAR+ CD4:CD8 T cells ratios were lower in blood at ~T_{max} than in drug product (P<0.0001)





Preferential CAR+ CD8 T-cell expansion has been suggested to be correlated with greater clinical activity[1]

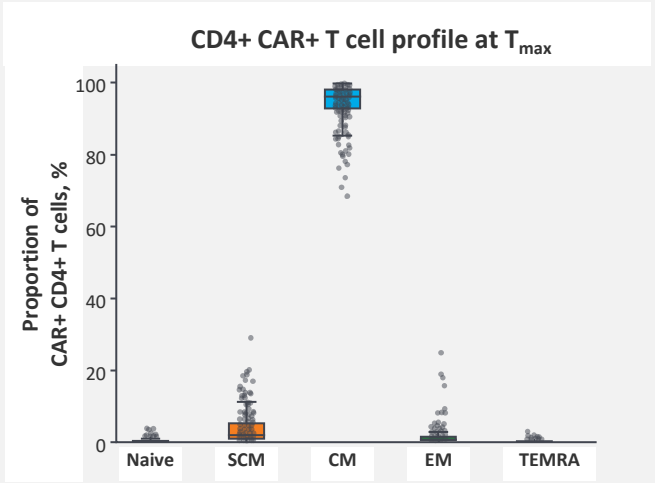
CAR, chimeric antigen receptor; T_{max}, time of peak expansion.

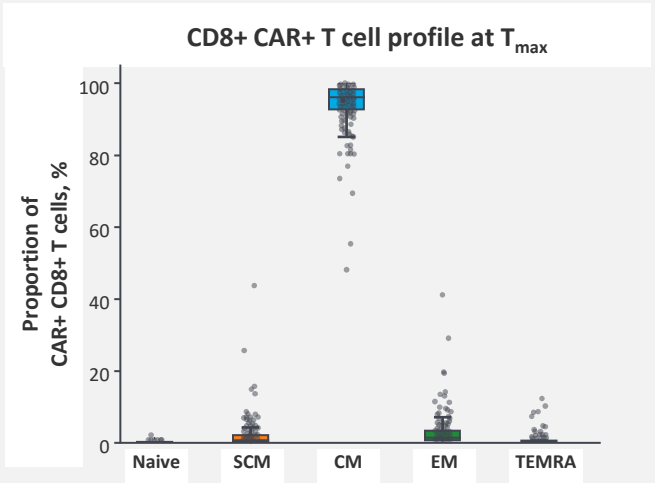
1. Zudaire E, et al. Presented at ASH; December 7–10, 2019; Orlando, FL.

Presented by C.F. de Larrea at the 20th International Myeloma Society (IMS) Annual Meeting and Exposition; September 27–30, 2023; Athens, Greece

CARTITUDE-4: CAR+ T Cells at Peak Expansion Primarily Have a Central Memory Phenotype

- T cells with a central memory phenotype were dominant in the CAR+ CD4+ and CD8+ compartments at T_{max}





Enrichment with T cells possessing memory phenotypes is suggested to enhance clinical responses and durations of response[1-3]

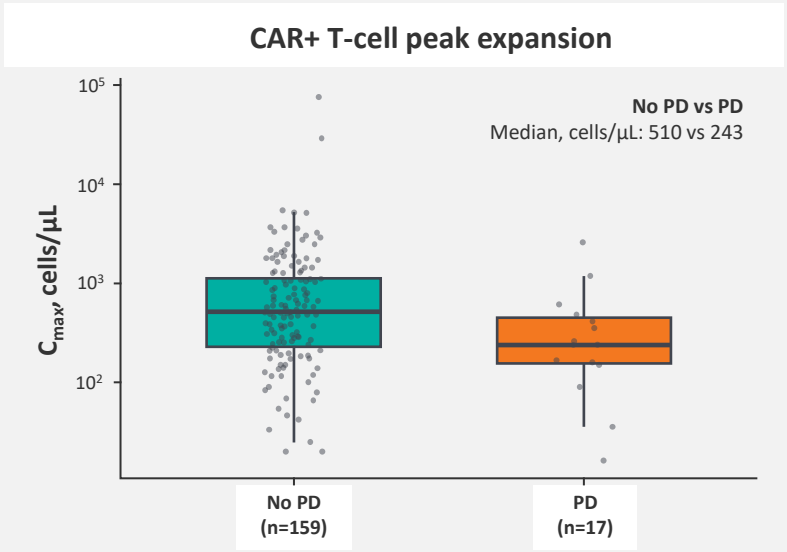
CAR, chimeric antigen receptor; CM, central memory; EM, effector memory; SCM, stem cell memory; TEMRA, terminally differentiated T cell; T_{max}, time of peak expansion.

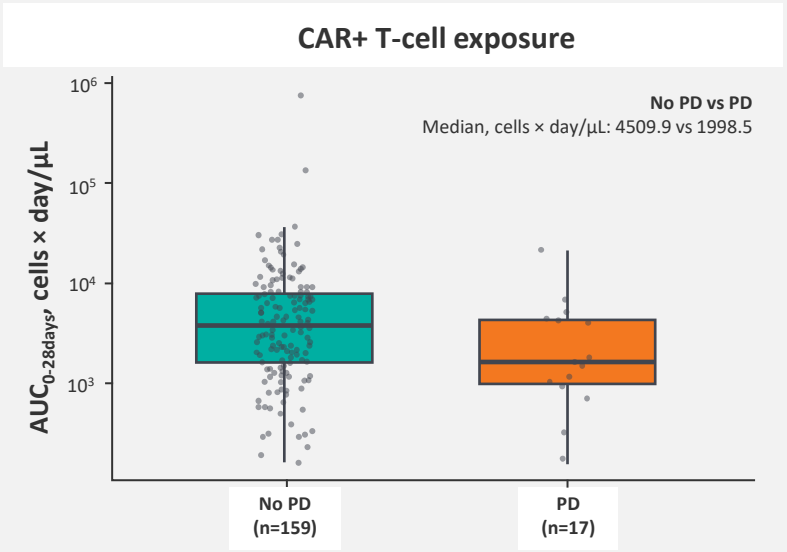
1. Zudaire E, et al. Presented at ASH; December 7–10, 2019; Orlando, FL. 2. Arcangeli S, et al. *J Clin Invest* 2022;132:e150807. 3. Terao T et al. *Transplant Cell Ther* 2023;29:573.e1-573.e8.

Presented by C.F. de Larrea at the 20th International Myeloma Society (IMS) Annual Meeting and Exposition; September 27–30, 2023; Athens, Greece

CARTITUDE-4: CAR-T Cell Expansion and Exposure Are Not Associated With Disease Progression

- CAR+ T-cell expansion (C_{max}) and exposure ($AUC_{0\text{-}d28}$) comparable in patients with progression vs those without

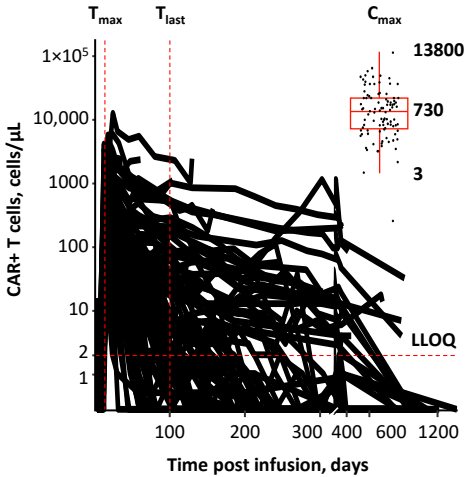


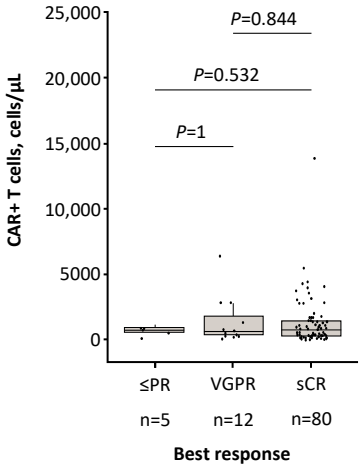


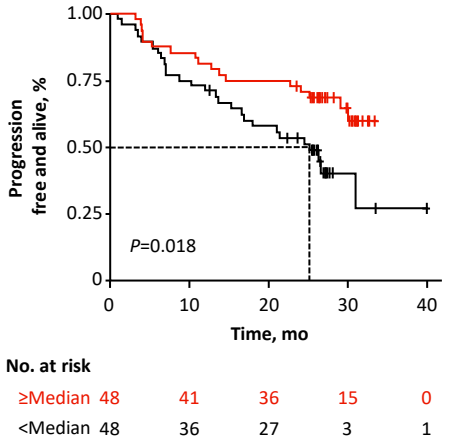
$AUC_{0\text{-}d28}$, area under the curve from day 0 to day 28 post infusion; CAR, chimeric antigen receptor; C_{max}, maximal concentration; PD, progressive disease.

Presented by C.F. de Larrea at the 20th International Myeloma Society (IMS) Annual Meeting and Exposition; September 27–30, 2023; Athens, Greece

Ciltacabtagene Autoleucel: Longer PFS Was Observed in Patients With a Higher Effector to Target Ratio (or CAR+ T cell to sBCMA Ratio)







Variable cilta-cel expansion and persistence[a]

Cilta-cel peak expansion (C_{max}) does not associate with best response[b]

Patients with higher effector to target ratio had significantly longer PFS[c]

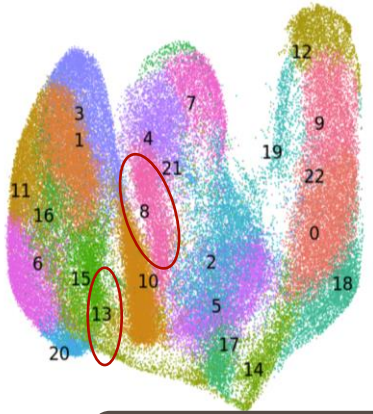
[a]C_{max} was 730 cells/µL (range, 3–13800), T_{max} was 14 days (range, 10–56), and T_{last} was 100 days (range, 20–912). [b]*P* value determined using Wilcoxon test. [c]To assess the significance of effector to target ratio, CAR+ T cells at C_{max} were normalized to baseline tumor burden utilizing sBCMA. Best response and PFS were assessed by independent review committee.

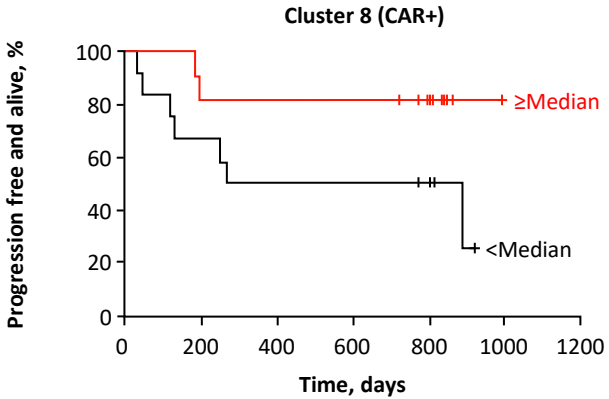
CAR, chimeric antigen receptor; C_{max}, maximum observed concentration of CAR+ T cells in blood; LLOQ, lower limit of quantification; PR, partial response; sBCMA, soluble BCMA; sCR, stringent complete response; T_{last}, actual sampling time (days post infusion) of last measurable concentration of CAR+ T cells; VGPR, very good PR.

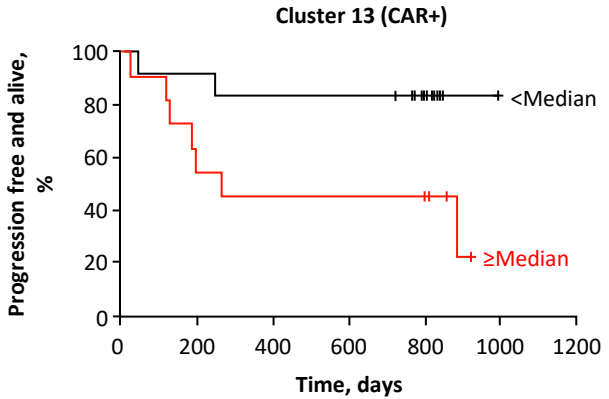
Montes de Oca R, ASH 2023, Abstract 2099

Ciltacabtagene Autoleucel Longer PFS Was Associated With a CAR+CD8+ Stem Cell–Like Phenotype in the Drug Product

Cluster	Hazard ratio	*P* value	Marker	Phenotype
8	**0.62**	**0.032**	CD8+TCF7+LEF1+CCR7+	CAR+CD8+ stem cell–like T cells with ability to proliferate into T_{cm} and T_{em}
13	**1.62**	**0.006**	CD4+FOXP3+	CAR+CD4+ Treg cell–like phenotype



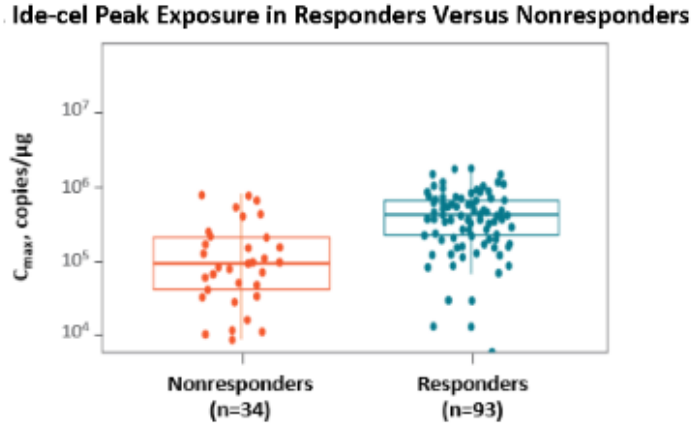


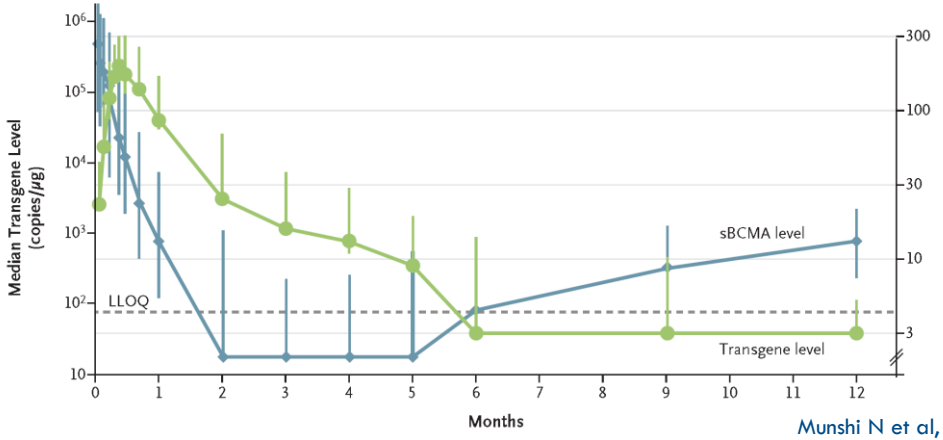


Longer PFS was directly associated with a CAR+CD8+ T-stem cell–like phenotype and inversely correlated with a CAR+CD4+ Treg cell–like phenotype in the drug product

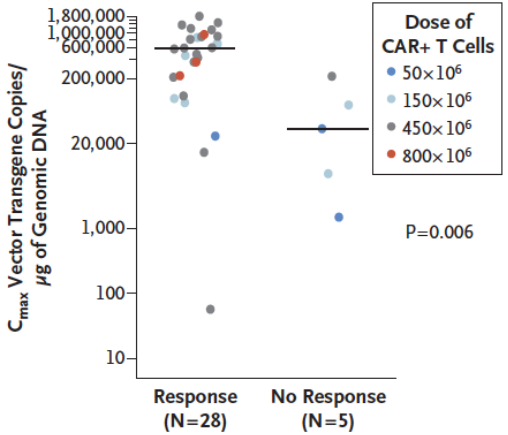
Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-seq) analysis of drug product. CAR, chimeric antigen receptor; PFS, progression-free survival; T_{cm}, central memory T cell; T_{em}, effector memory T cell.

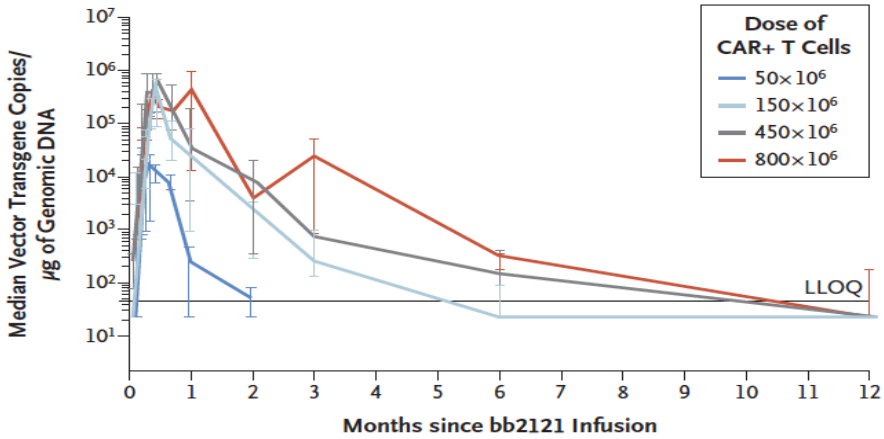
CAR T cells expansion (Cmax and AUC) correlate with clinical response with Ide-Cel





Munshi N et al, NEJM 2021



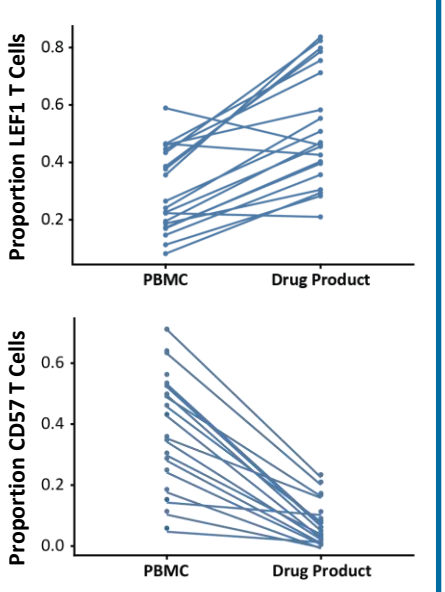


Raje N et al. N Engl J Med 2019

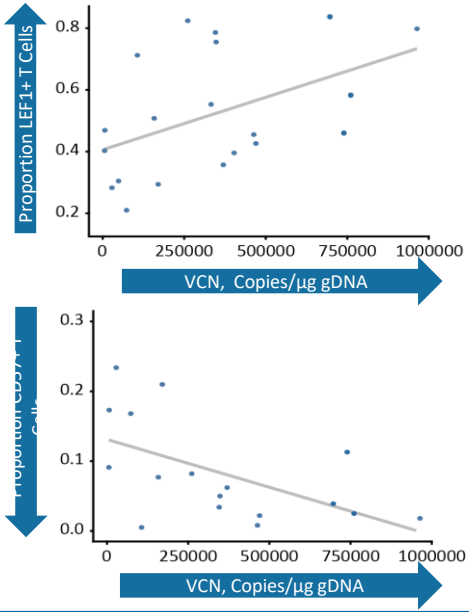
Enrichment for Memory-Like T Cells Is Associated With Robust CAR T Expansion and Less Progression by M6

- Patients with a higher proportion of memory-like T cells in bb21217 drug product have significantly better peak expansion.
- A higher proportion of memory-like T cells is associated with numerically less progression by M6.

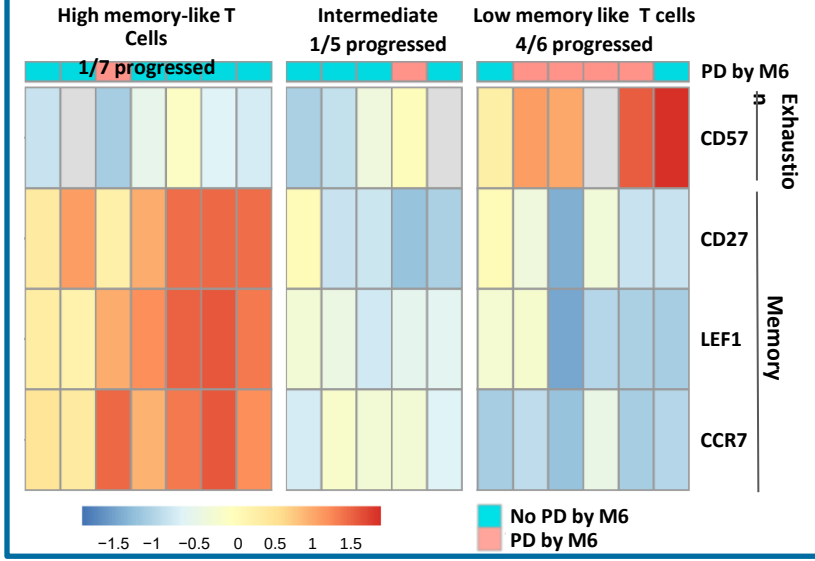
bb21217 Drug Product Enriched For Memory-Like T Cells



Memory-Like T Cells Associated With Peak CAR T Expansion



Memory-Like T Cells in Drug Product Associated With Less Progression at M6[a]



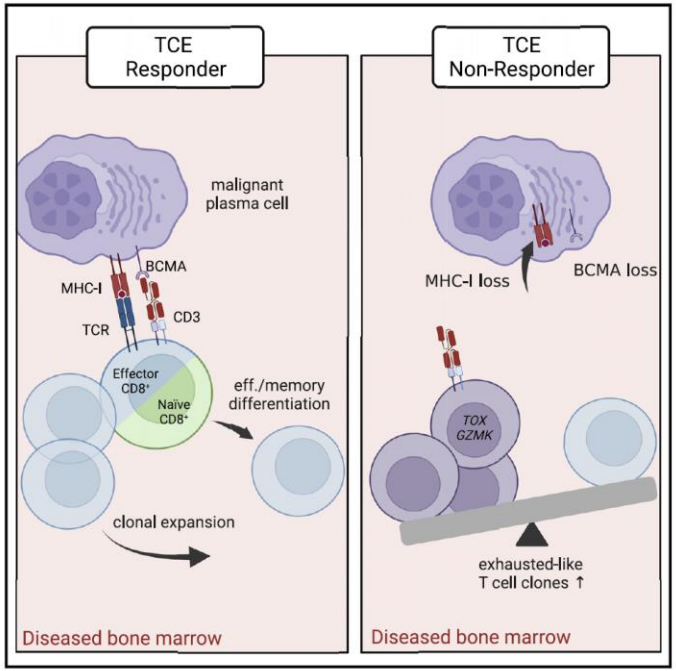
M6, month 6; PBMC, peripheral blood mononuclear cell in apheresis product; PD, progressive disease; VCN, vector copy number. [a]Responding patients with biomarker data who had either PD or a month 6 visit confirming absence of PD, 1 patient with continued stable disease at M6 included.

Adapted from Finney et al., ASGCT 2019

Cancer Cell

The pre-existing T cell landscape determines the response to bispecific T cell engagers in multiple myeloma patients

Graphical abstract



Authors

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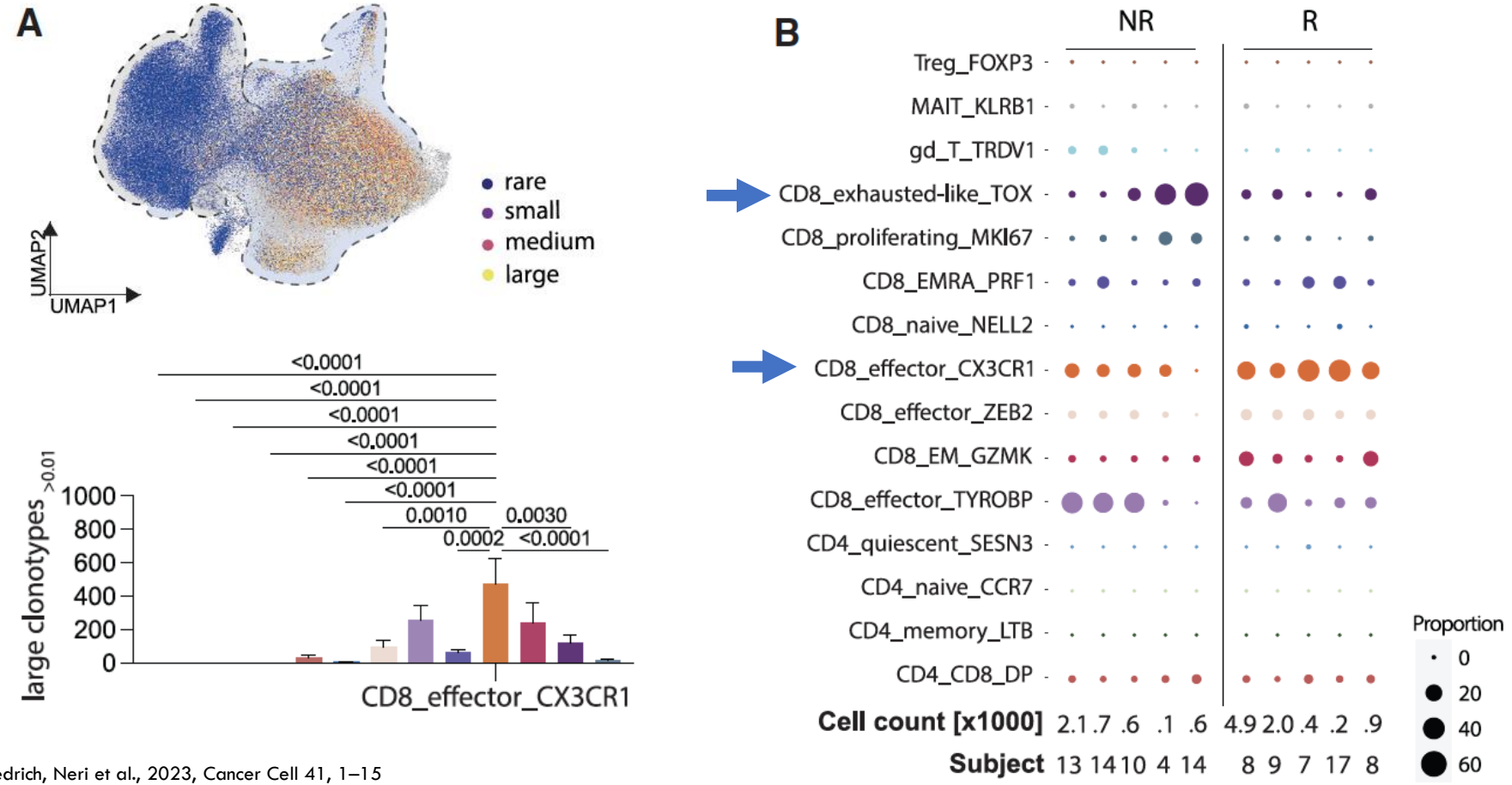
In brief

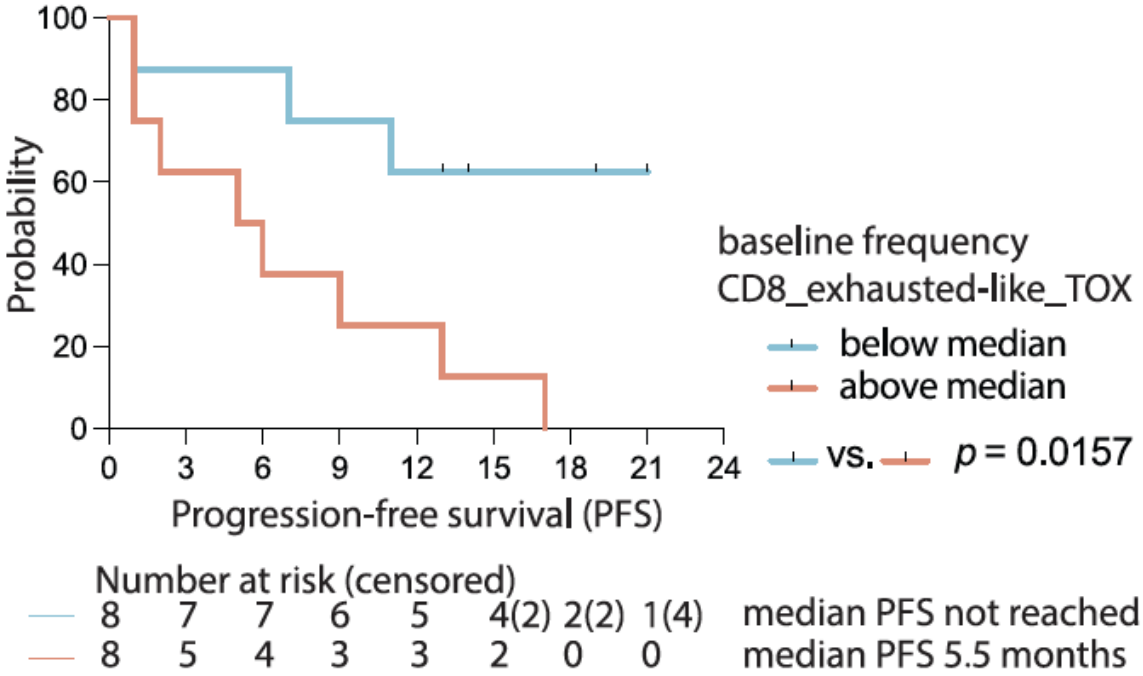
Bispecific T cell engagers (TCEs) have shown promise in the treatment of various cancers, but their mode of action in humans is elusive. Providing new insight into immunological mechanisms, Friedrich et al. identify how T cells in multiple myeloma patients respond to TCEs according to their cell state and link inter-individual differences in the immune repertoire to clinical response.

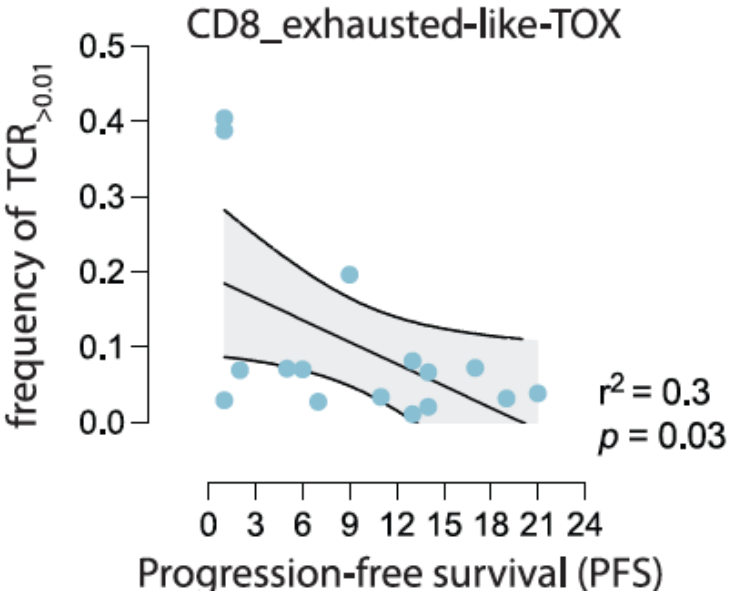
Abundance of exhausted-like T cell clones is associated with clinical response failure



Friedrich, Neri et al., 2023, Cancer Cell 41, 1–15

Proportion of pre-existing exhausted CD8+ clonotypes pre-therapy is significantly increased in BCMAxCD3 TCE non-responder patients

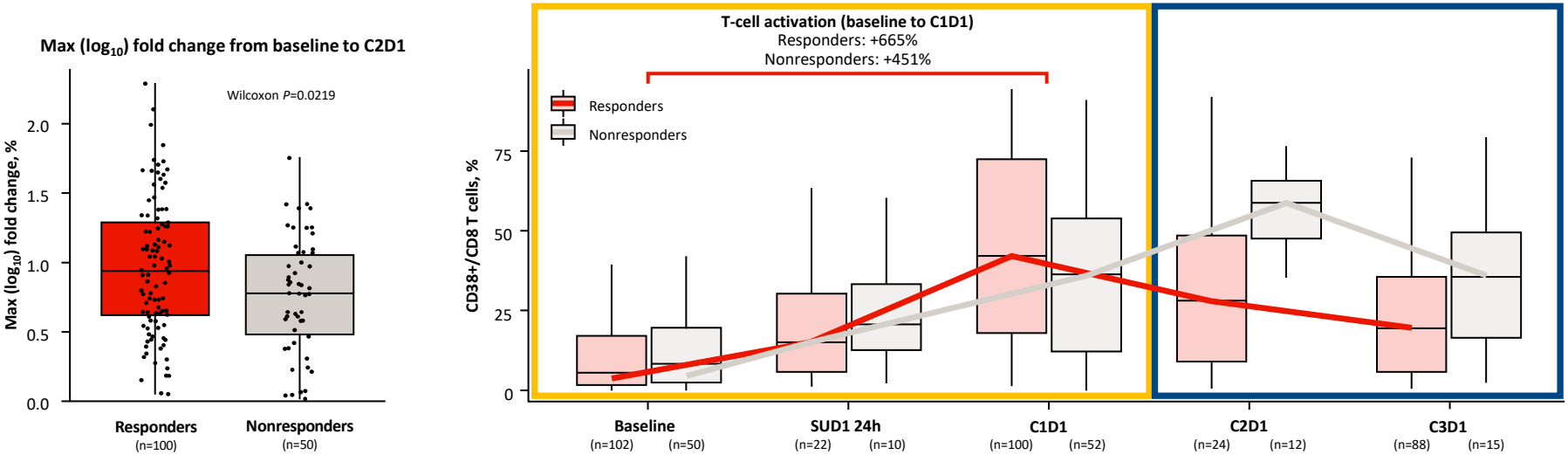




Friedrich, Neri et al., 2023, Cancer Cell 41, 1–15

Response Was Associated With Greater T-Cell Activation in the First Treatment Cycle Compared with Non responders

Greater early expression of CD38 on CD8 T cells in peripheral blood in responders

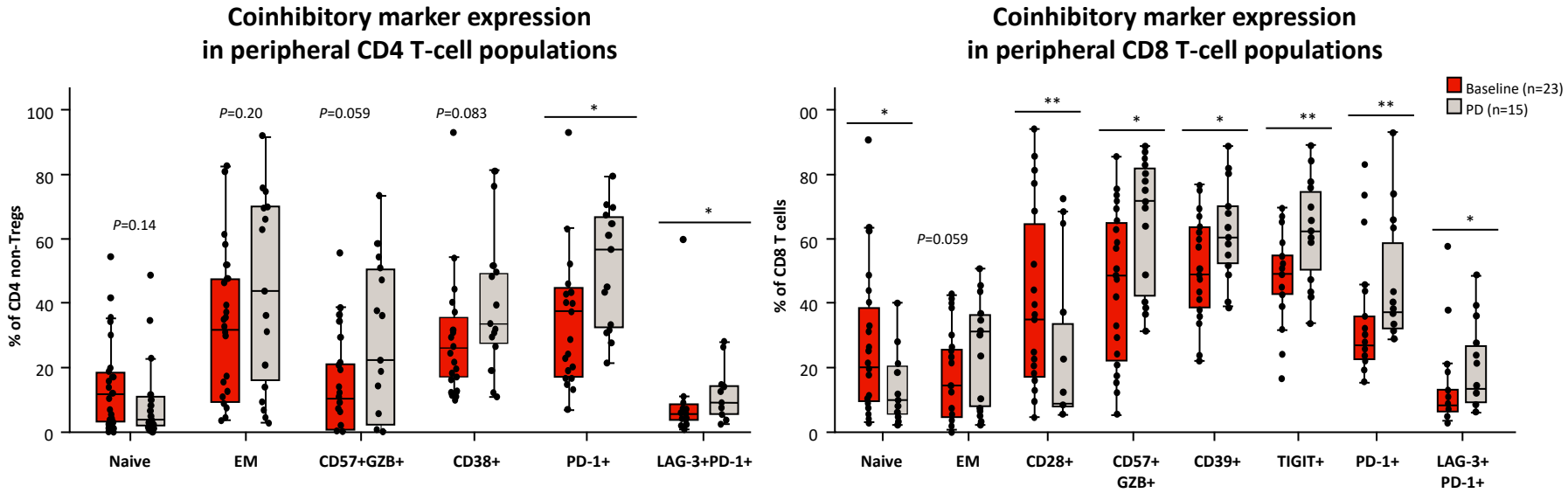


- Patients responding to teclistamab exhibited greater, transient T-cell activation early in the first treatment cycle, indicated by a greater maximum fold change in induction of CD38 on CD8 T cells in peripheral blood
- T-cell activation in responders was early, reaching peak CD38 induction on CD8 T cells at C1D1 (orange box), whereas, T-cell activation was delayed in non responders, reaching peak CD38 induction at C2D1 (blue box)

C, cycle; D, day; SUD1 24h, 24 hours after first step-up dose.

Vishwamitra D, ASH 2023, Abstract 0455

Relapse Was Associated With Higher Proportions of T Cells Expressing Exhaustion Markers, Checkpoints, at PD vs Baseline in the PB

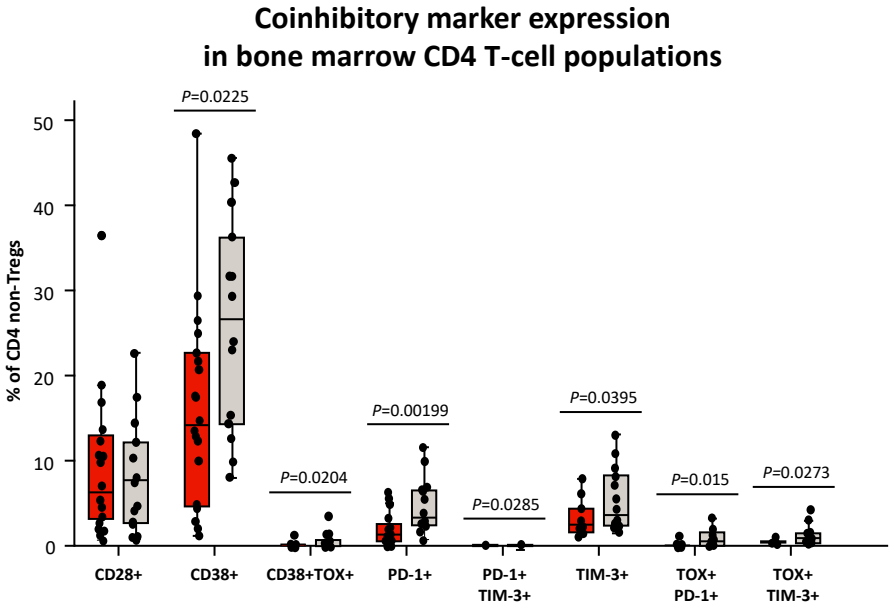


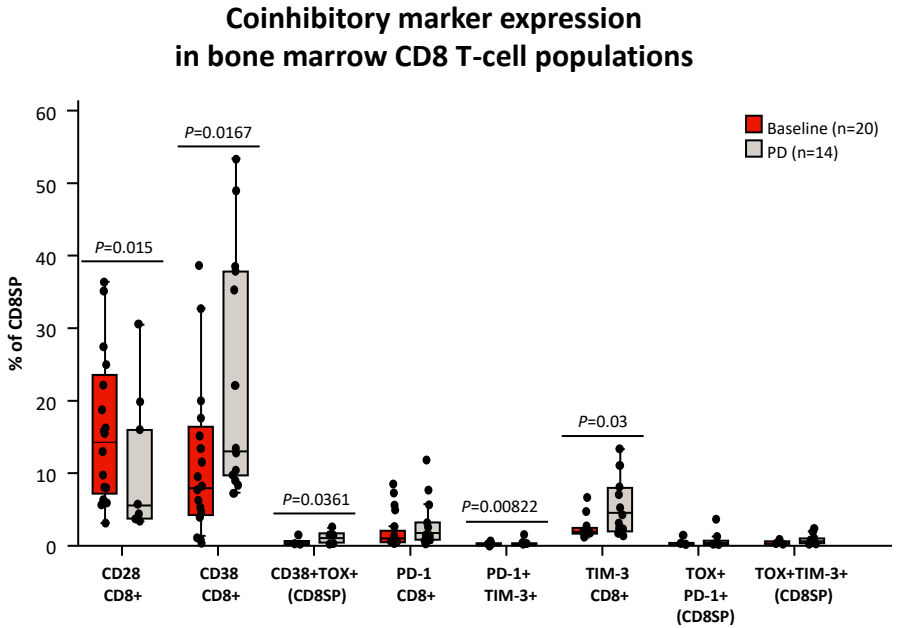
- CyTOF analysis in peripheral blood showed trends for lower frequencies of naive T cells and higher frequencies of differentiated EM CD4 and CD8 T-cell subsets at relapse vs baseline
- Significantly higher proportions of exhausted T cells at relapse were observed, indicated by increased frequencies of CD4 or CD8 T cells expression and co-expression PD-1, LAG-3, TIGIT, CD39, and CD57/GZB, as well as reduced frequencies of costimulatory CD28 and CD8 T cells

CyTOF analyses using unpaired Mann-Whitney U test for comparisons. *P<0.05. **P<0.01.
CyTOF, cytometry by time of flight; EM, effector memory; PD, progressive disease; Treg, regulatory T cell.

Vishwamitra D, ASH 2023, Abstract 0455

Relapse Was Associated With Higher Proportions of T Cells Expressing Exhaustion Markers, Checkpoints, at PD vs Baseline in the BM



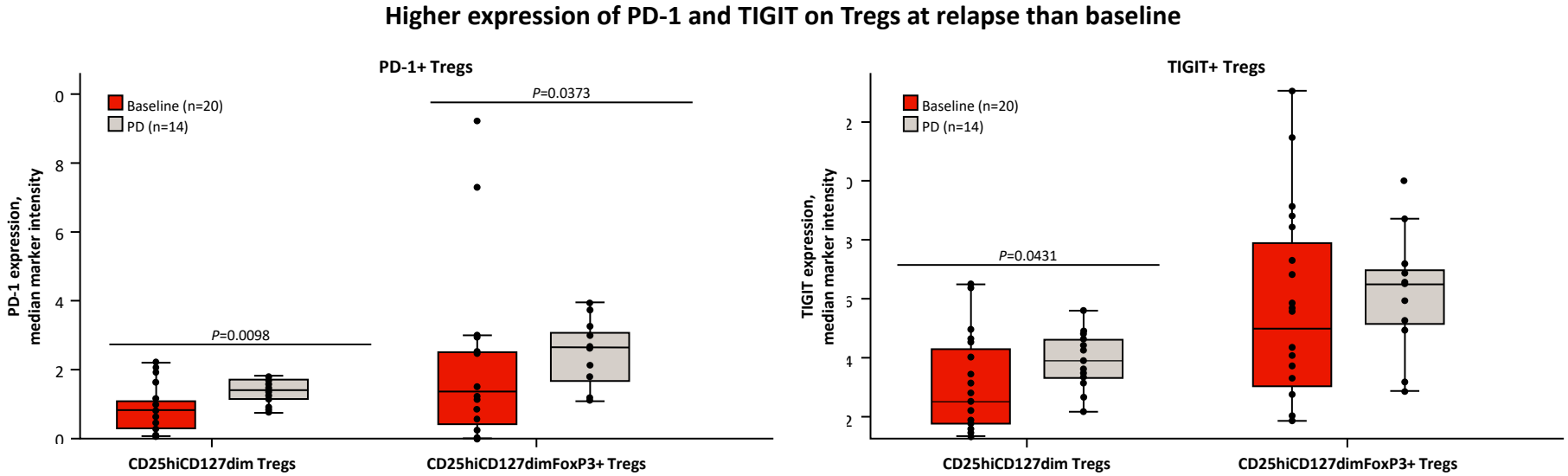


- CyTOF analysis in bone marrow showed that compared with baseline, patients who relapsed had lower CD28 expression on CD8 T cells and significantly higher proportions of CD4 and CD8 T cells expressing and co-expressing checkpoints as well as T-cell exhaustion markers

CyTOF analyses using unpaired Mann-Whitney U test for comparisons.
CyTOF, cytometry by time of flight; PD, progressive disease; Treg, regulatory T cell.

Vishwamitra D, ASH 2023, Abstract 0455

Relapse Was Associated With Higher Expression of Coinhibitory Receptors on Treg Populations at PD vs Baseline



- CyTOF analysis in bone marrow showed that expression of PD-1 and TIGIT, which contributes to immune suppressive potential, was significantly higher at PD compared with baseline across CD25hiCD127dim and/or CD25hiCD127dimFoxP3+ Tregs in patients who relapsed

PD, progressive disease; Treg, regulatory T cell.

Vishwamitra D, ASH 2023, Abstract 0455

Talquetamab (MonumenTAL-1): Greater T-cell Activation in Responders vs Non responders in Cycle 1

Longitudinal data

	QW		Q2W	
Parameter,[a] median (%)	**R**	**NR**	**R**	**NR**
CD38+/CD8+ T cells	8.41	0.64	7.32	0.79
LAG-3+/CD8+ T cells	5.63	0.56	6.12	0.57
PD-1+/CD8+ T cells	2.16	0.25	2.26	0.36
PD-1+LAG-3+/CD8+ T cells	9	0.77	11.5	0.78
PD-1+TIM-3+/CD8+ T cells	9.75	0.9	12.52	0.95
TIM-3+/CD8+ T cells	5.94	0.65	8.64	0.81

0.25 **Low** 12.5 **High**

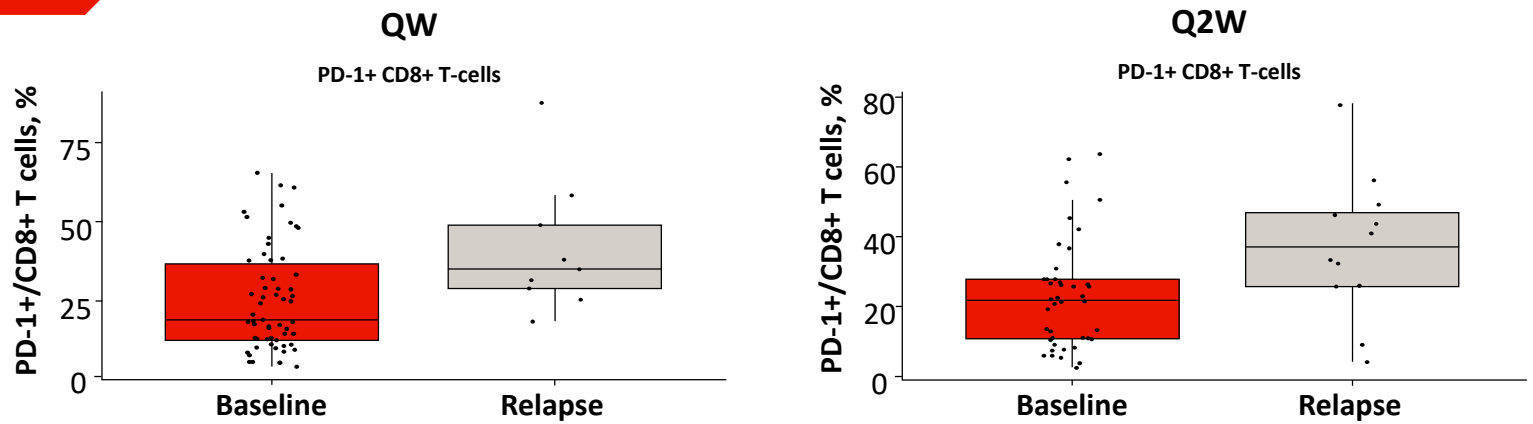
- Peak induction of expression of markers on CD8+ T cells in cycle 1 = activation

Max-fold change was measured at cycle 1 and corresponds with T-cell activation, indicated by maximum induction of markers at any point in cycle 1 relative to baseline.
[a]Evaluated using flow cytometry.
NR, nonresponders; Q2W, every other week; QW, weekly, R, responders

Vishwamitra D, ASH 2023, Abstract 1933

MonumenTAL-1: Exhausted T-cell Phenotype at Relapse

Relapse data

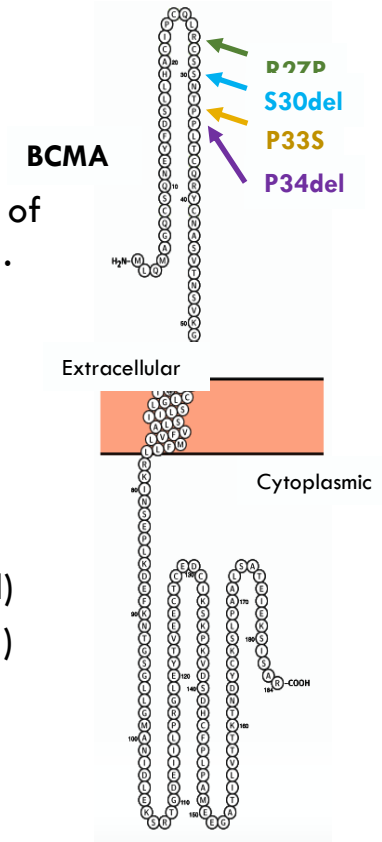


- Patients who relapsed had significantly higher frequencies of PD-1-expression CD8+ T cells compared with baseline across cohorts
- Across cohorts, higher frequencies of LAG-3-, TIM-3-, and PD-1/LAG-3-expressing CD8+ T cells and lower counts of CD3+ T cells were also observed in patients who relapsed compared with baseline (data not shown)

Q2W, every other week; QW, weekly

Vishwamitra D, ASH 2023, Abstract 1933

Antigen escape is a tumor intrinsic mechanism of resistance to targeted immunotherapies: BCMA



By combining bulk WGS and scCNV analysis in 18 RRMM patients we assessed the mechanisms of MM antigen escape to targeted immunotherapies and reported antigen drifting/loss in ~ 30%[1].

- 5 distinct genomic mechanisms leading to BCMA antigen escape:

Diploid 16p — Focal biallelic loss of *TNFRSF17*

Subclone (<1%) with *TNFRSF17* biallelic loss — Clonal *TNFRSF17* biallelic loss

Diploid 16p — 16p monoallelic loss + mut. *TNFRSF17* c.R27P point mutation

16p monoallelic loss + mut. *TNFRSF17* in-frame deletion (p.Ser30del)

16p monoallelic loss + mut. *TNFRSF17* in-frame deletion (p.Pro34del)

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Julius-Maximilians-
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Lee H et al. Nat Med. 2023;29:2295-2306

Antigen escape is a tumor intrinsic mechanism of resistance to targeted immunotherapies: GPRC5D

GPRC5D biallelic loss

- Post TCE:

Clonal convergence → 5 cases of MM relapse with biallelic genomic events on GPRC5D (biallelic deletions or monoallelic deletion and mutations) [1,2].

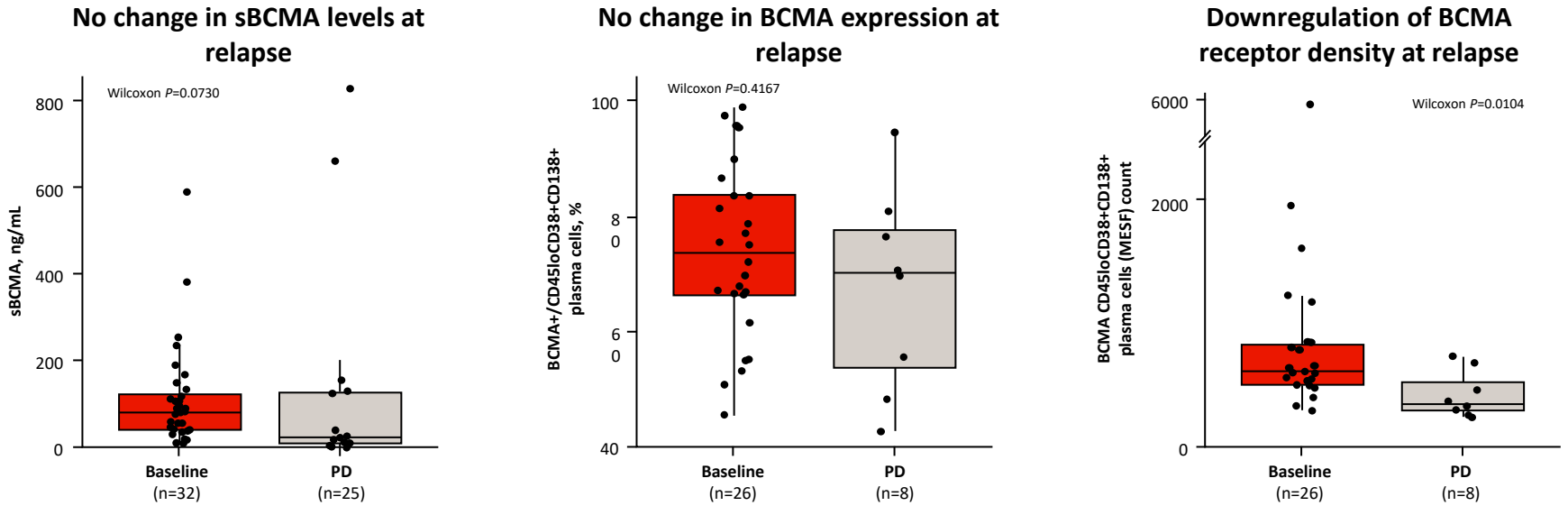
Epigenetic silencing: 2 patients with loss of chromatin accessibility at GPRC5D gene locus[2].

- Post anti-GPRC5D CAR T:

GPRC5D loss or reduction of surface antigen expression in 6/6 patients post anti-GPRC5D CAR T[3,4].

1. Lee H et al. Nat Med. 2023;29:2295-2306
2. Derrien J et al. Nat Cancer 2023; 4: 1536-1543
3. Mailankody S et al N Engl J Med 2022; 387:1196-1206
4. Mi X et al. N Engl J Med 2023; 389:1435-1437

Majestic 1: No change in BCMA Expression but Reduction of BCMA Receptor Density Was Observed at Relapse in Patients Initially Responding to Teclistamab

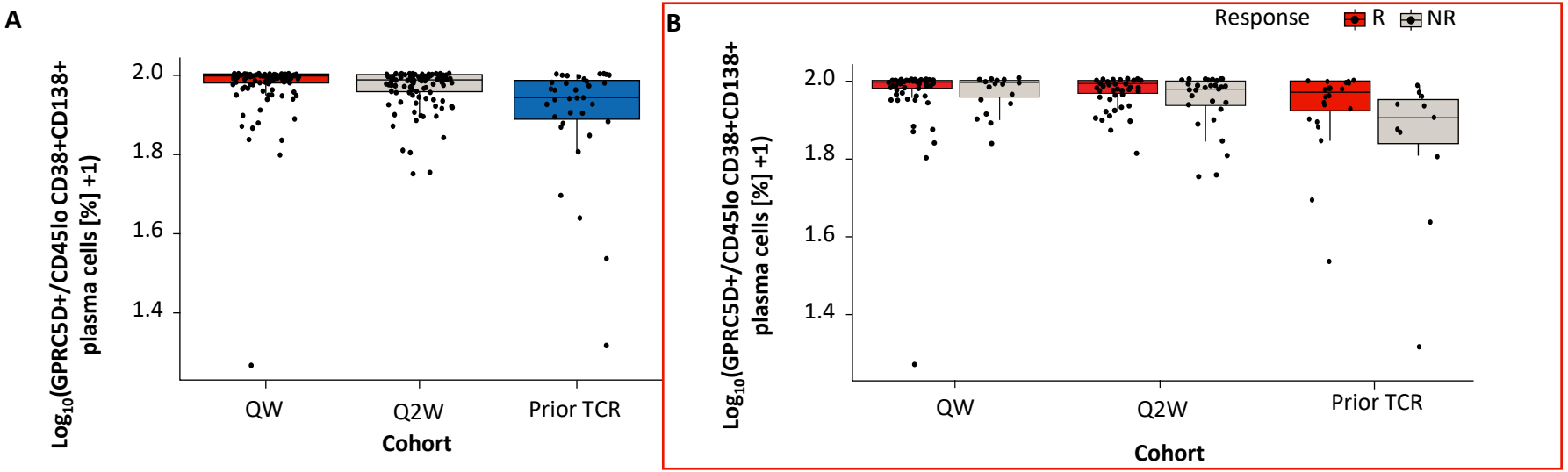


- Among patients who initially responded to teclistamab then progressed and had evaluable samples at either baseline or disease progression (PD; small n), there were no significant changes in sBCMA levels or frequency of BCMA+ plasma cells in bone marrow at PD relative to baseline; however, reduction in BCMA receptor density was observed at PD
  - Similar results were observed in patients with matched baseline and PD samples

BCMA, B-cell maturation antigen; MESF, molecules of equivalent soluble fluorochrome; PD, progressive disease; sBCMA, soluble BCMA.

Vishwamitra D, ASH 2023, Abstract 0455

MonumenTAL-5: High GPRC5D Expression at Baseline but No Correlation with Response

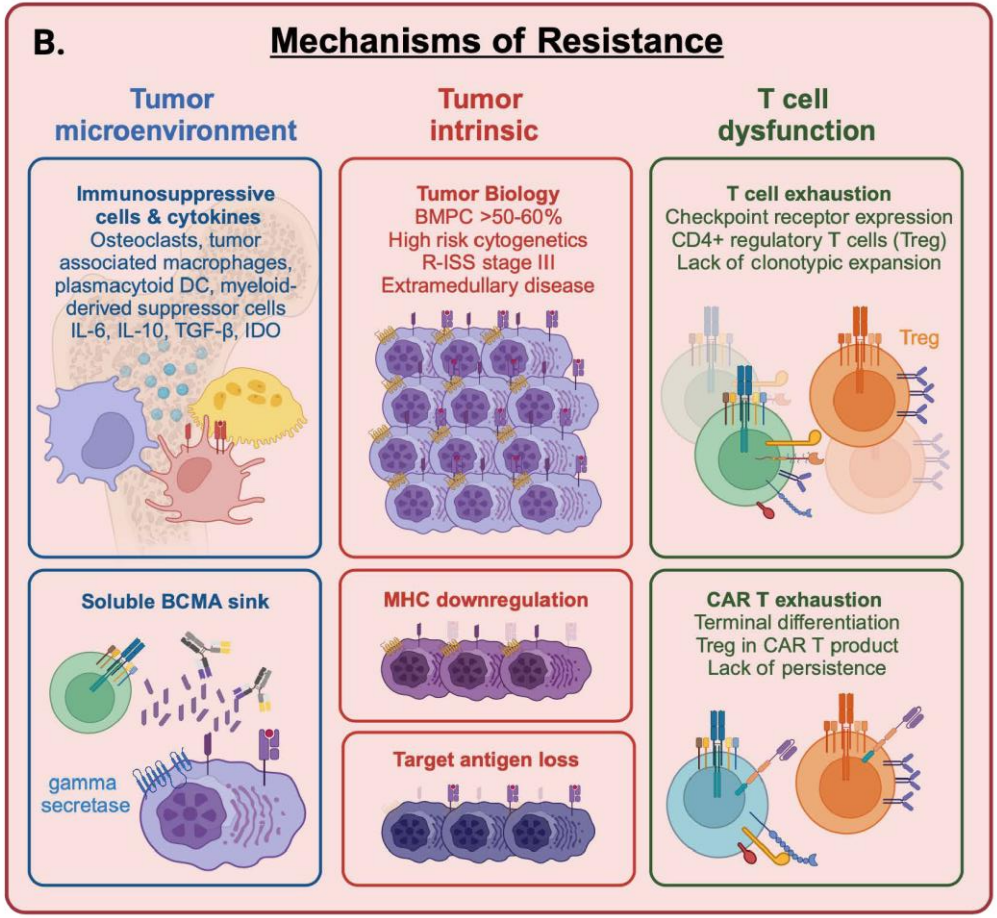


- GPRC5D was highly expressed on multiple myeloma cells in each cohort; generally, no correlations were observed between baseline GPRC5D expression and response
  - A trend of lower GPRC5D expression in non responders vs responders was observed in the prior TCR cohort
- Additional analyses showed that GPRC5D remained highly expressed at relapse in QW and Q2W cohorts, suggesting that downregulation of GPRC5D was not a mechanism at relapse (Supplement)

GPRC5D, G-protein-coupled receptor family C group 5 member D; NR, nonresponders; Q2W, every other week; QW, weekly; R, responders; TCR-T-cell redirection therapy

Vishwamitra D, ASH 2023, Abstract 1933

Summary



Lee H, Neri P et Bahlis N, Blood January 9, 2024

Immune fitness and T-cell function influence response to CAR-T and TCE

NR: Reduced population of T_{SCM}, T_{CM}

NR: Expansion of T reg and/or exhausted T cells T_{EX} ($CD57^+$, TOX^+, $CD28^-$, $PDCD1^+$, $TIGIT^+$, $LAG3^+$)

Antigen escape (biallelic loss, monoallelic loss coupled with extracellular domain mutations) is a mechanism of resistance (more frequent post TCE)

NR: Loss of MHC I surface protein expression on MM cells

Composition of myeloid/DC compartment (immuno-suppressive environment)

Primary resistance to T-cell based therapies

→ High serum soluble BCMA

→ High disease burden and EMD

Defining plasma cells genomic alterations coupled with the immune profiling will help to identify patients with the highest likelihood of respond to these therapies and individualize therapeutics.