Novel Targets and Newer Drugs in MM

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Disclosures

Consultant: Astrazeneca, Janssen, Pfizer

Board/Founder: Dynamic Cell Therapies, C4 Therapeutics, Next RNA, Oncopep, Starton, Window, Predicta

Bench to Bedside Therapeutic Advances in Multiple Myeloma

Three major advances in MM: ASCT 1980-; Novel agents 2000-;Immune therapies 2020-

Proteasome inhibitors: bortezomib, carfilzomib, ixazomib; immunomodulatory drugs: thalidomide, lenalidomide, pomalidomide; HDAC inhibitor: panobinostat; monoclonal antibodies: elotuzumab, daratumumab, and isatuximab; nuclear transport inhibitor: selinexor; CAR T cell: idecel, ciltacel; bispecific T cell engagers: teclistamab, elranatamab, talquetamab

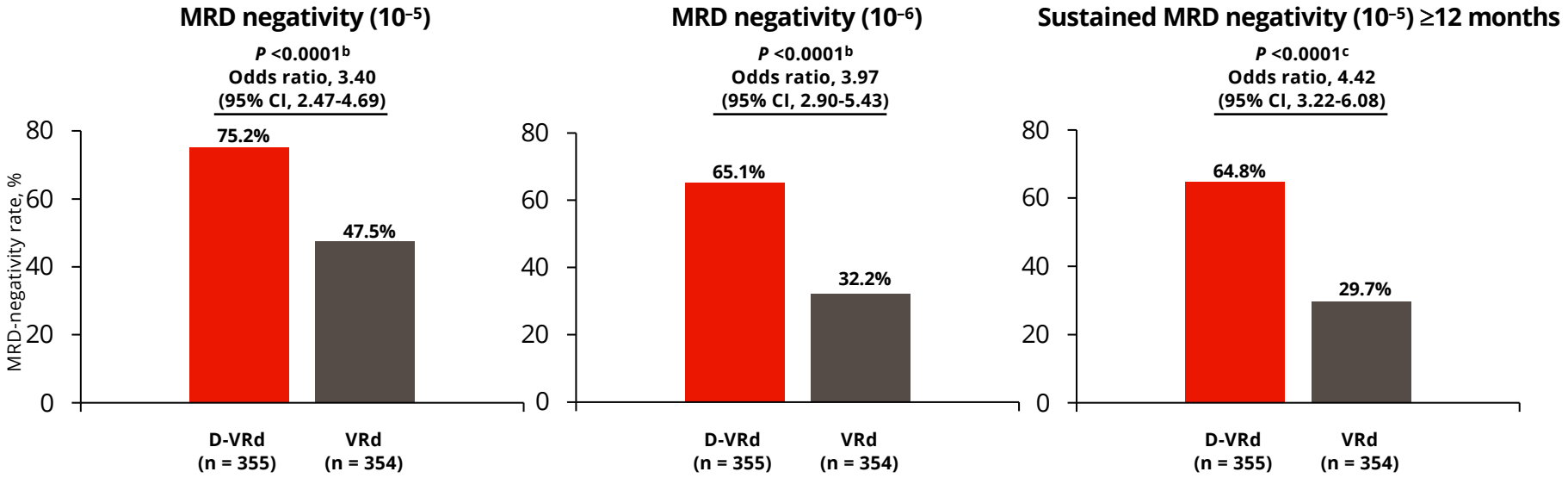
Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

Minimal residual disease negativity (MRD-) associated with prolonged PFS and OS in NDMM (transplant-eligible and -ineligible) and RRMM

34 FDA approvals (16 agents), median patient survival prolonged 3-4 fold, from 3 to at least 8-10 years, and MM is a chronic illness in many patients

All FDA approvals have been since Debates and Didactics in Hematology And Oncology Conference at Sea Island began!!

PERSEUS (Daratumumab-Lenalidomide Bortezomib Dex (Dara RVD) vs RVD, ASCT, DaraR vs R Maintenance): MRD-Negativity



- Deep and durable MRD negativity was achieved with D-VRd
- 64% (207/322) of patients receiving maintenance in the D-VRd group

Projected median PFS in SR MM 16 years

Sonneveld et al; NEJM 2024; 390:301-13

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone (IsaKRD) Induction in Patients with Newly Diagnosed Multiple Myeloma: Analysis of the MIDAS Trial

MIDAS IFM

MInimal residual Disease Adapted Strategy

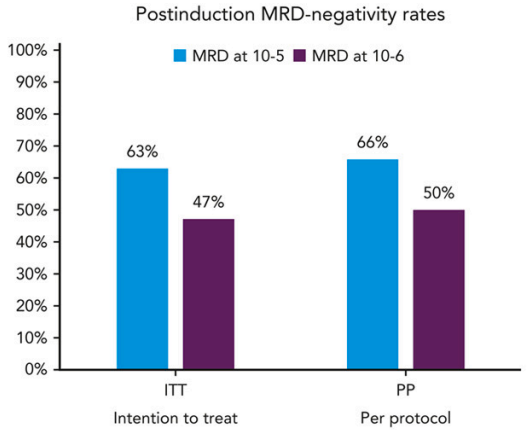
791 patients (pts) under 66 years
57% male
13% ISS III, 8% high-risk (LP score >1)

757 pts completed six 28-day cycles IsaKRD
5 pts dead
3 pts with progressive disease

761 pts did at least one stem cell harvest
Median of collected cells = 7×10^6 $CD34^+$/kg

Response rates after induction:

- 92% VGPR or better
- 65% CR/nCR



Conclusions: In patients with newly diagnosed multiple myeloma, 6 cycles of IsaKRD induce exceptionally high MRD-negativity rates. IsaKRD induction ensures successful stem cell collection with no new safety signals.

*Perrot et al. DOI: 10.1182/**blood**.2024026230*

blood Visual Abstract

Aurore Perrot A et al Blood 2025, in press

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Measurable Residual Disease-Guided Therapy in NDMM
Isatuximab Kyprolis Lenalidomide Dex Induction

499 MRD- (ASCT vs IKRD) 252 MRD+ (Tandem vs Single ASCT)

Variable	ASCT (N=242)	Isa-KRd (N=243)	Adjusted Relative Risk (95% CI)†	Tandem ASCT (N=124)	Single ASCT (N=109)
	no. of patients (%)			*no. of patients (%)*	
MRD-negative status before maintenance					
10^{-6} sensitivity: primary end point	208 (86)	205 (84)	1.02 (0.95–1.10)	40 (32)	44 (40)
10^{-5} sensitivity	228 (94)	225 (93)	1.02 (0.97–1.07)	76 (61)	73 (67)

Overall ASCT did not increase depth of MRD-
Rate of developing MRD- varied, ie, more gradual in t(11:14)

Perrot et al NEJM 2025, in press.

Teclistamab BCMA BiTE-Based Induction Transplant-Eligible NDMM Results

Tec-DR[a] and Tec-DVR[a] induction achieves MRD- (10^{-5}) in 100% of MRD-evaluable pts after C3 and maintained through C6

No TEAE-related discontinuations, no new safety signals compared with individual agents

Infections were common, 34.7% pts had grade 3/4 infections, no grade 5 events

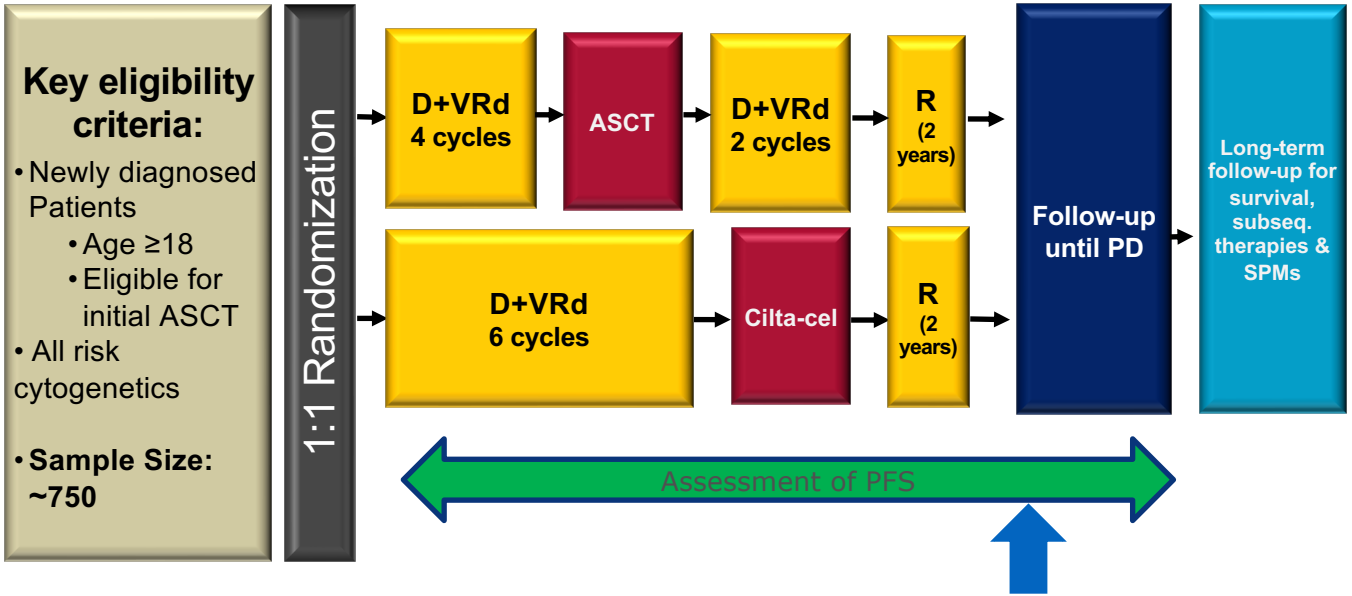
Infection prophylaxis, including Ig replacement, was adopted

Stem cell mobilization was feasible with Tec-D(V)R

Teclistamab with daratumumab-based induction in transplant-eligible NDMM demonstrates unprecedented early MRD-negativity rates

Rabb et al, ASH 2024

CARTITUDE 6: Randomized Phase 3 Trial of Ciltacel vs ASCT in Newly Diagnosed, Transplant Eligible Patients



Stratification factors:

a) ISS staging
b) Cytogenetics
c) Age

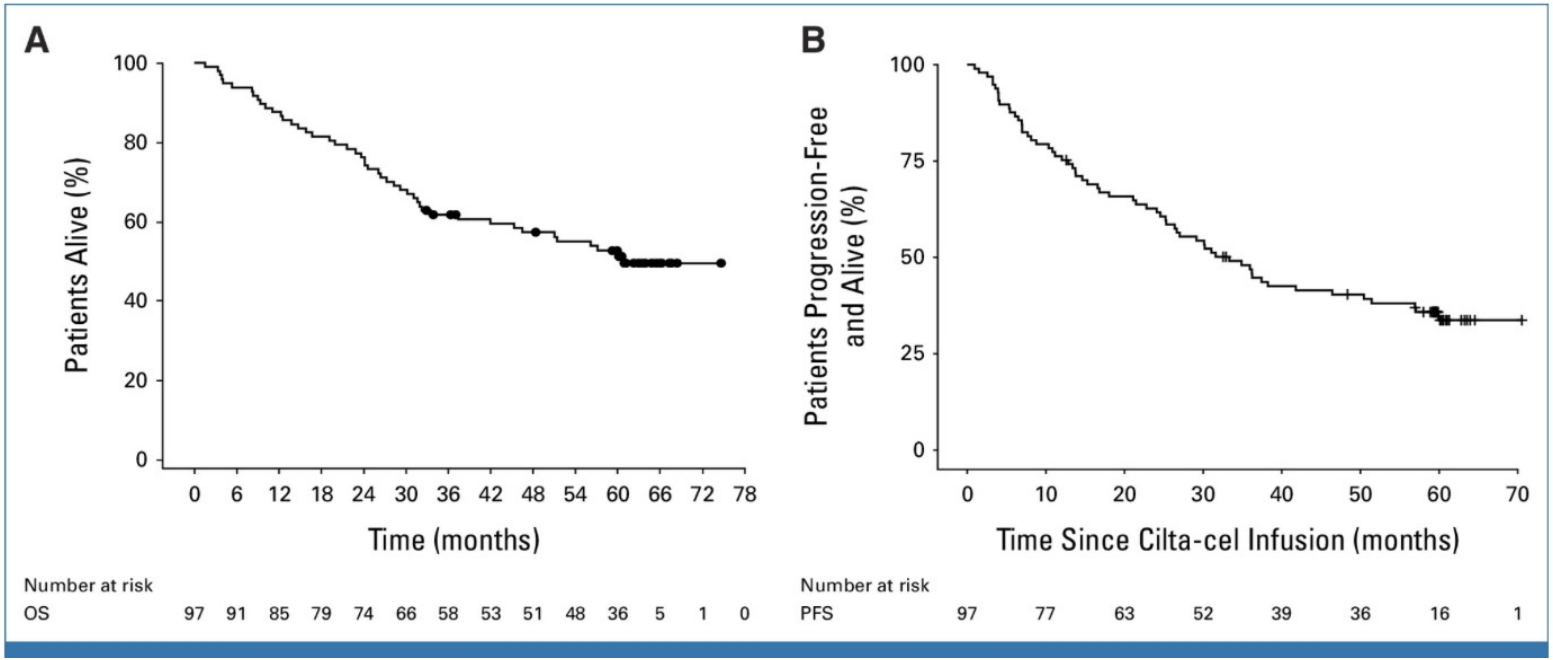
Dual Primary endpoints:
PFS and Sustained MRD neg CR

IMS Response Criteria in MM for the First Time Incudes Proposed Definition of Cure

Response Subcategory	Response Criteria
Sustained MRD negative	• Patients in complete remission • MRD negative in the bone marrow using 10-6 threshold, • At least 3 measurements 12 months apart between 1-5 years AND • MRD negative at year 5 (Sustained MRD negative for 5 years) AND • Negative by PET/CT confirmed minimum of one year apart including at year 5

Kumar et al November 2024

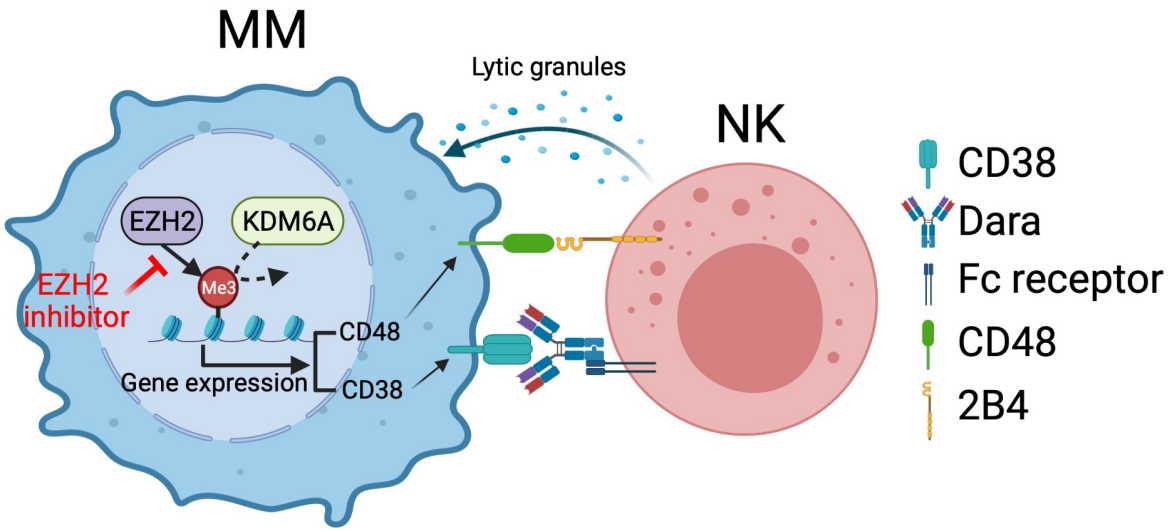
Cartitude 1 Ciltacel in RRMM (4 or more lines)
Median FU 60 months



32 (33%) pts progression-free and off therapy ≥5 years after cilta-cel

Jagannath S, et al J Clin Oncol. 2025, in press.

Genome-wide CRISPR-Cas9 Screen Identifies KDM6A as an Epigenetic Modulator of CD38/C48 Expression and CD38MoAb Sensitivity in MM



KDM6A inactivation downregulates CD38/CD48 expression via H3K27me3 of their promoters.

EZH2 inhibitor: enhances KDM6A; decreases H3K27me3 and upregulates CD38/CD48expression; as well as enhances NK cell activity and CD38MoAb-mediated ADCC

Due to CD48 upregulation of NK activity, EZH2 inhibitor may enhance ADCC triggered by other MoAbs as well.

Liu J et al. Nat Comm 2024; 15: 1367.

Mezigdomide (MEZI) Combination Therapies in RRMM

E3 Ligase Modulator with greater binding affinity and stability to cereblon triggering cytotoxicity even in pomalidomide-resistant MM

MEZI with dexamethasone In RRMM:

ORR: 50% in BCMA treated

MEZI with daratumumab (DARA) or elotuzumab (ELO) in RRMM:

ORR: MEZI DARA d 82.6%; MEZI E d 45.0%

EZH2, BET, and RAS-RAF-MEK-ERK pathways associated with disease progression and poor prognosis

ORR: MEZI TAZ (EZH2 inhibitor) 50.0% , MEZI BMS-986158 (BET inhibitor) 35.0%, MEZI TRAM (MEK inhibitor) 75.0%

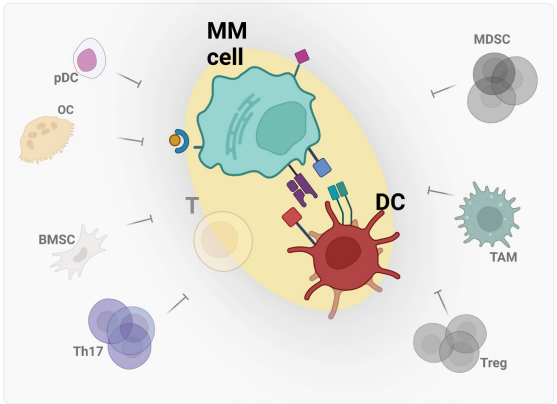
Most grade 3/4 TEAEs hematologic: neutropenia most common grade 3/4 TEAE, managed with G-CSF and dosing schedule adjustments

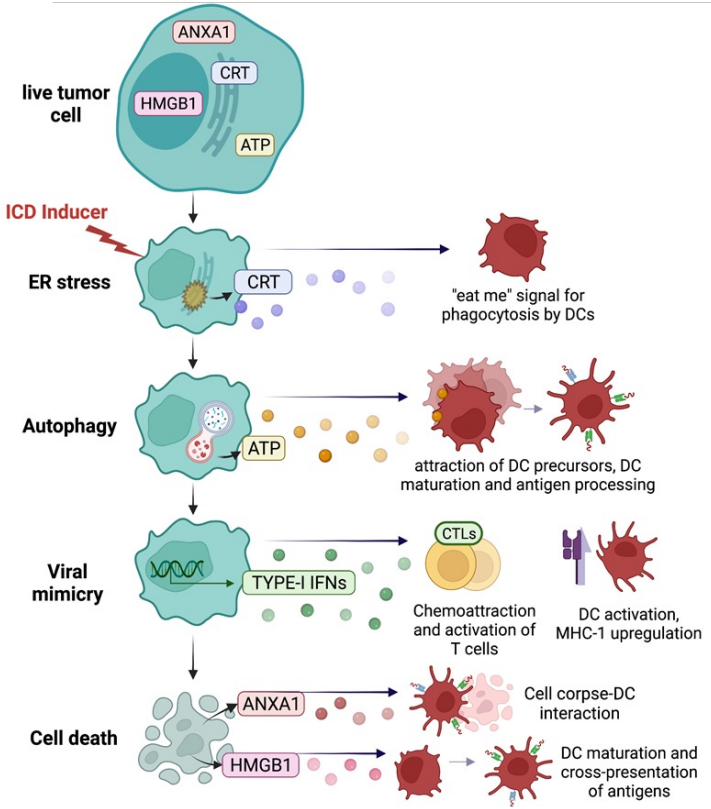
Richardson et al; N Engl J Med; 389; 2023:1009-22; Richardson et al ASH 2023; Costa et al ASH 2024

Bortezomib Triggers Immunogenic Cell Death in the Immunosuppressive MM Microenvironment

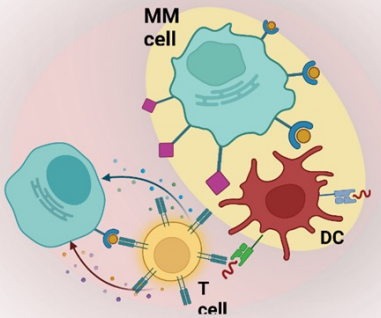
***Immunogenic cell death* (ICD)** → **Immune activation**

Immunosuppressive MM Microenviroment



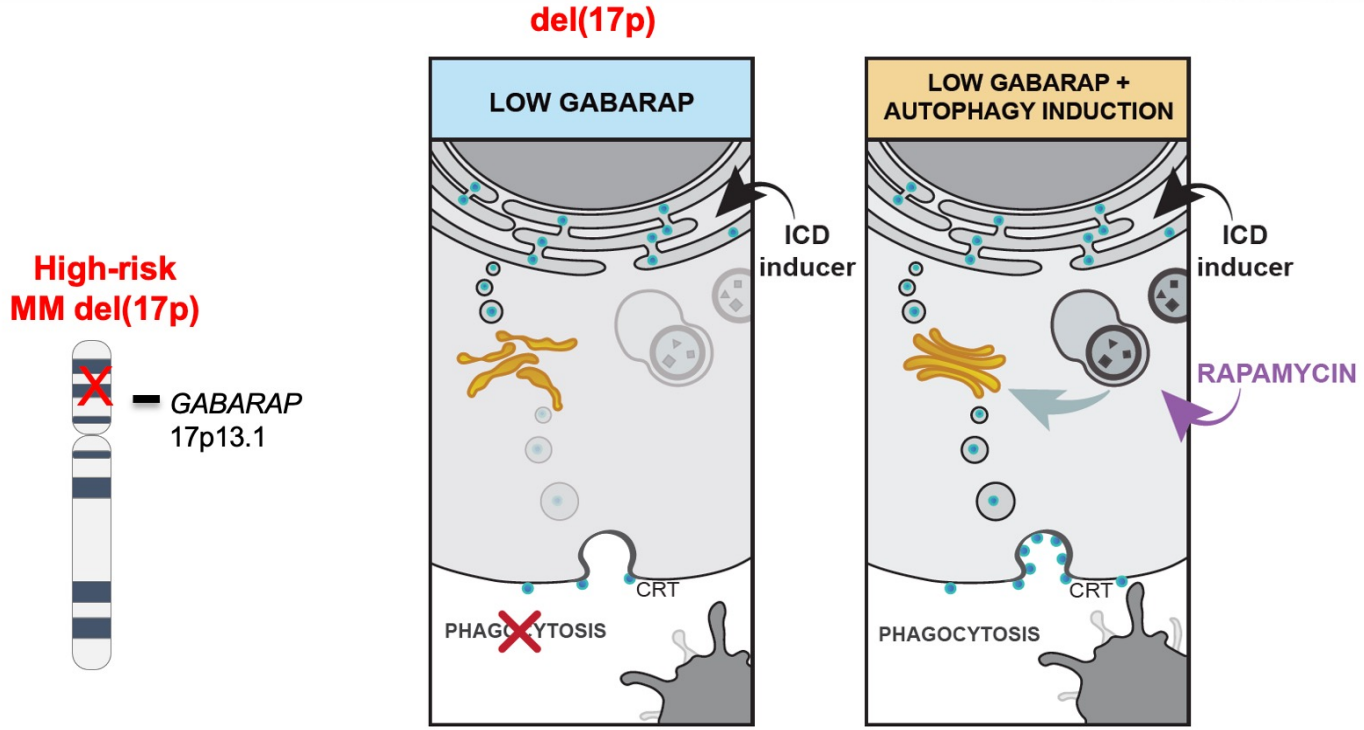


Immune activation



Johnstone M. et al Cells 2022
Gulla A, et al. Blood Cancer Discovery 2021; 2: 468-483.

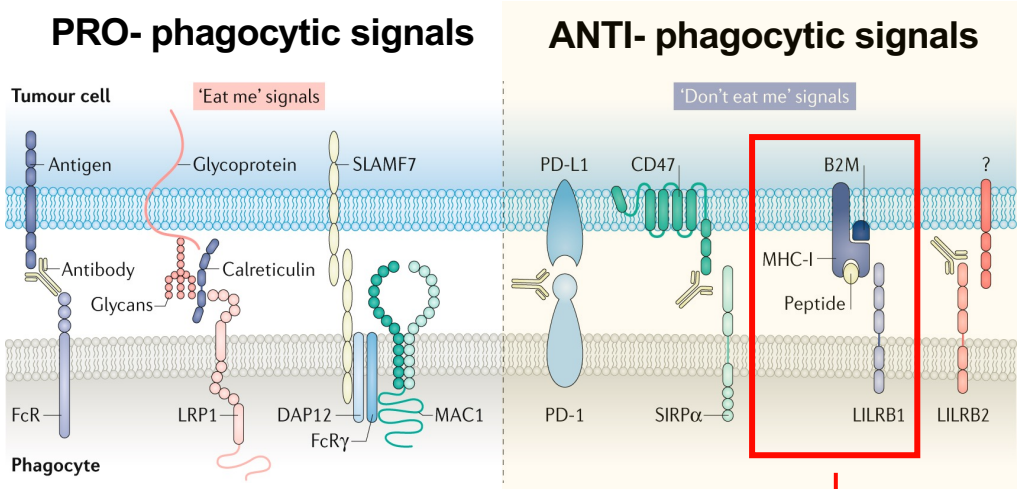
Triggering Autophagy (Rapamycin) with Immunogenic Cell Death (ICD) Inducer (Bortezomib) Induces ICD in *GABARAP*^{low} (del17p) High Risk MM



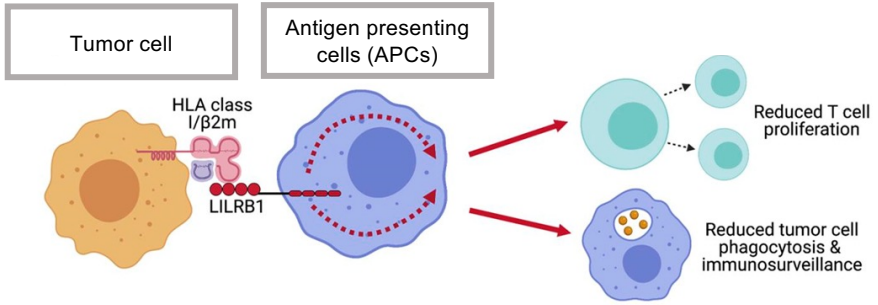
GABARAP encodes autophagy genes

Gulla et al Blood 2024: 143: 2612-26

Targeting Inhibitory Phagocytosis Checkpoints (LILRB1) to Restore Immunogenic Cell Death in MM



B2M/LILRB1 axis



GOAL

Inhibition of B2M/LILRB1 axis to increase immunogenic cell death

LILRB1 also checkpoint on T and NK cells; inhibition of B2M/LILRB1 axis to augment NK and T effector function

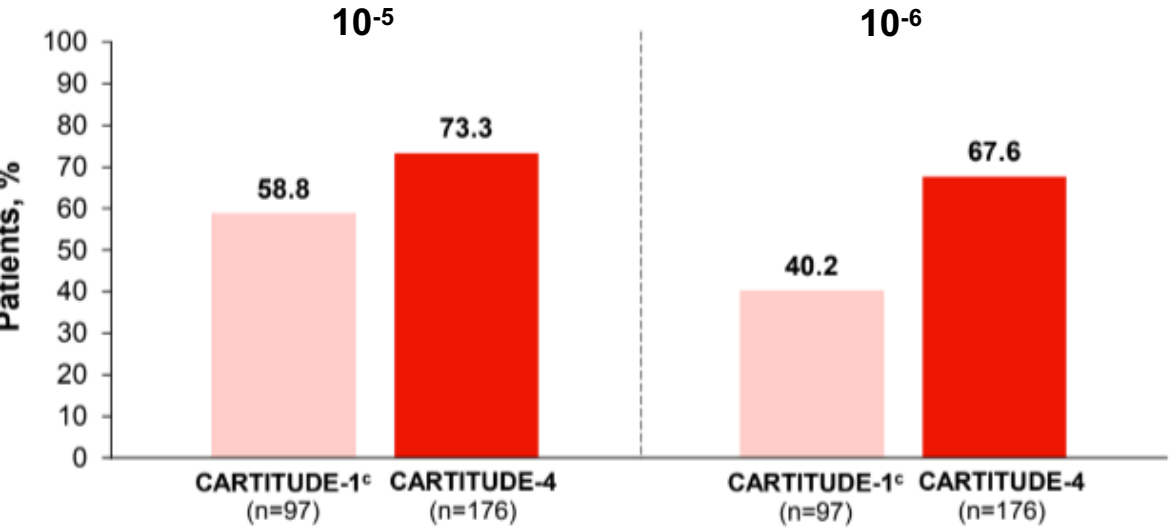
Gulla A et al

Please do not post

Ciltacel BCMA CAR T in RRMM

Cartitude 4 vs SOC: MRD- at 10–5 (89% vs 38% pts)
MRD- at 10–6 (86% vs 19%)
MRD- within 2 months

Higher rates of MRD- in CARTITUDE-4 vs CARTITUDE-1 (1-3 vs 4 or more lines therapy)



	CARTITUDE-1 (n=97)	CARTITUDE-4 (n=176)
30-month PFS rate, %	54.2	68.4
30-month OS rate, %	68.0	84.3

More patients achieved sustained (≥12 mo) MRD-negative ≥CR with cilta-cel vs SOC (52% vs10% pts; p<0.0001), with PFS (93.2%) and OS (97.3%) at 30 mos

San Miguel et al NEJM 2023; 389: 335-47; Popat et al, ASH 2024 .

Anitocabtagene Autoleucel BCMA CAR T for RRMM (iMMagine-1)

Small D-Domain construct facilitates high transduction efficiency and CAR positivity, with low total cell dose

D-Domain CARs stable and lack tonic signaling

D-Domain binder fast off-rate and high CAR surface expression, promoting tumor cell killing without prolonged inflammation

? Reduced neurotoxicity

At median follow-up 34 months:

- ORR 100%, CR 97%
- 93.1% MRD evaluable patients (n=54/58) MRD- (10^{-5} or lower)
- Median PFS for all pts 30.2 mo; for CR/sCR pts 34.3 mo
- **No delayed or non-ICANS neurotoxicities (Parkinsonism, cranial nerve palsies, GBS)**
- CRS 95% (47% $\geq$ grade 2), ICANS 18% (6% $\geq$ grade 2)

Bishop et al, ASH 2024

PHE885 BCMA CAR T: Rapid Production and Expansion in Vivo

- **MRD negativity rate[a]:**

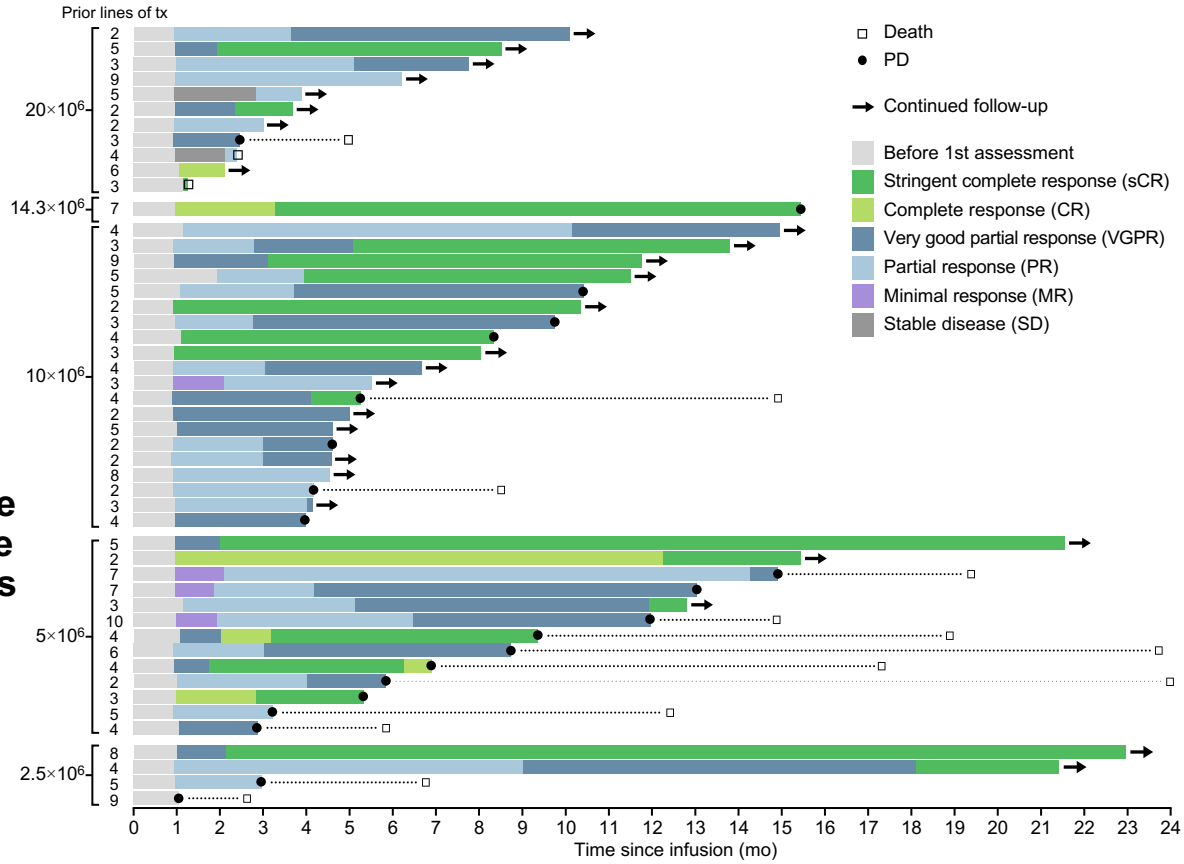
Dose	Month 3	Month 6
20×10⁶	4/5 (80%)	3/3 (100%)
14.3×10⁶	1/1 (100%)	1/1 (100%)
10×10⁶	7/13 (54%)	5/7 (71%)
5×10⁶	6/11 (55%)	5/7 (71%)
2.5×10⁶	0/2 (0%)	0/1 (0%)
All doses	18/32 (56%)	14/19 (74%)

100% ORR Median time to first response 0.95 (0.89-2.83) months and median time to best response 2.76 (0.92-18.1) months

Conversion to CR/sCR occurred as late as 18 months after infusion

In vivo expansion and persistence

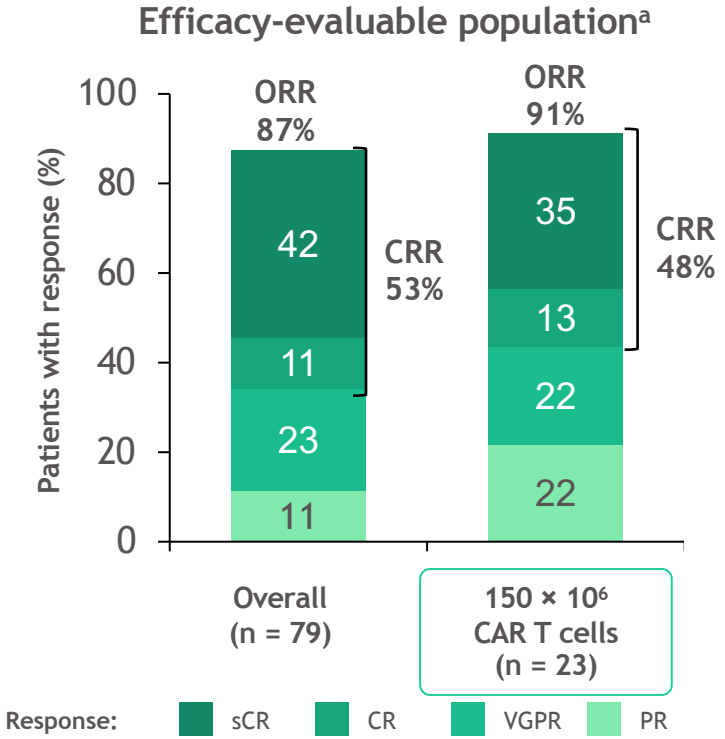
Median time of last detectable transgene 6 months



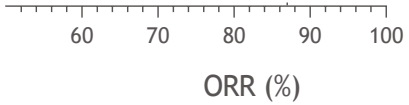
Sperling AS, et al. J Clin Oncol. 2023;41:8004

[a]MRD assessed by NGS with a sensitivity of 10^{-5} in all MRD-evaluable patients.

Arlocabtagene Autoleucel (BMS-986393) GPRC5D CAR T (Phase 1 Study)



Disease characteristic	n/N	ORR (%) (95% CI)
Triple class-refractory		
Yes	52/60	87 (75-94)
No	17/19	89 (67-99)
Extramedullary disease		
Yes	31/36	86 (71-95)
No	38/43	88 (75-96)
High-risk cytogenetics[b]		
Yes	26/31	84 (66-95)
No	43/48	90 (77-97)
Previous BCMA-targeted therapy		
Yes	**30/38**	**79 (63-90)**
No	**39/41**	**95 (84-99)**
Yes; refractory	**13/16**	**81 (54-96)**



Median DOR 18.0 mo

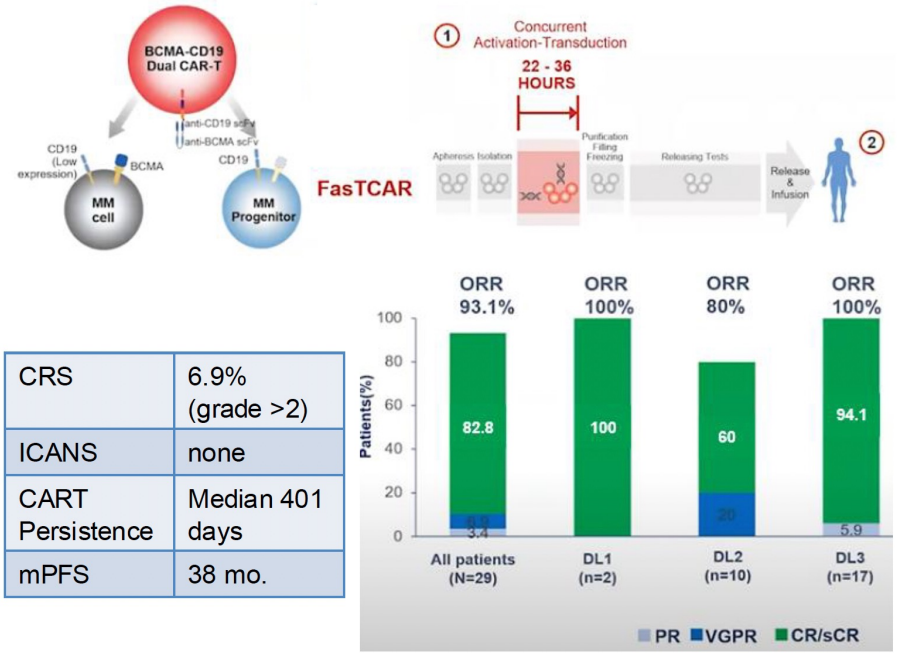
≥ CR: 85% (22/26) MRD-

Most skin, nail, oral on-target/off-tumor AEs resolve

Bal et al ASH 2024

Dual Targeting CAR T Cells

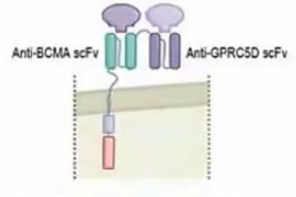
Dual-targeting BCMA-CD19 (Gracell): FasTCAR-T GC012F



CRS	6.9% (grade >2)
ICANS	none
CART Persistence	Median 401 days
mPFS	38 mo.

Du et al., ASCO 2023

BCMA/GPRC5D bispecific CAR-T Cells



N=21 pts.

ORR	91%
CR	75%
CRS ICANS	71% (only grade 1 or 2) 5% (only grade 1)
Nail/Skin Toxicities	Only grade 1
Median Follow-up	5.8 mo. 2 pts. progressed 1 pt. with a GPRC5D neg. MM

Zhou et al., Lancet Haematol 2024

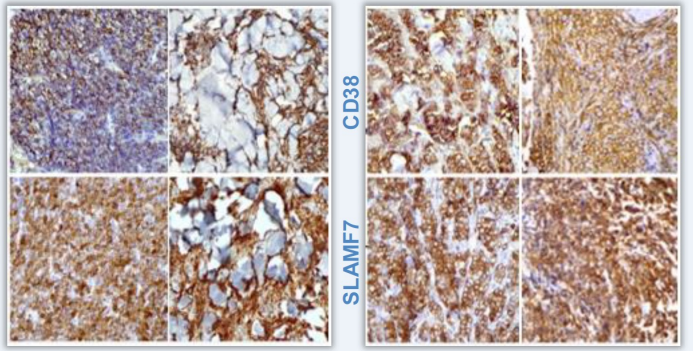
Novel Targets: CAR T Cells
CARAMBA-1: SLAMF7-directed CAR T Cells

Uniklinikum Würzburg

SLAMF7 is a strong CAR-T target in MM

- Sustained high level expression on MM/EMD,
- no interference from soluble SLAMF7

bone marrow extramed. lesion



CARAMBA-1 is a First-in-Human Phase I/IIa trial of SLAMF7 CAR-T therapy

Dose escalation is ongoing

- Safety: favorable safety signal, no DLTs
- Efficacy: SLAMF7 CAR-T engraftment, responses in heavily pretreated MM
- **But: SLAMF7 Expression on activated T Cells / CAR-T Cell fratricide**

→ 2nd generation SLAMF7 CAR-T Cells based-edited for SLAMF7 deletion

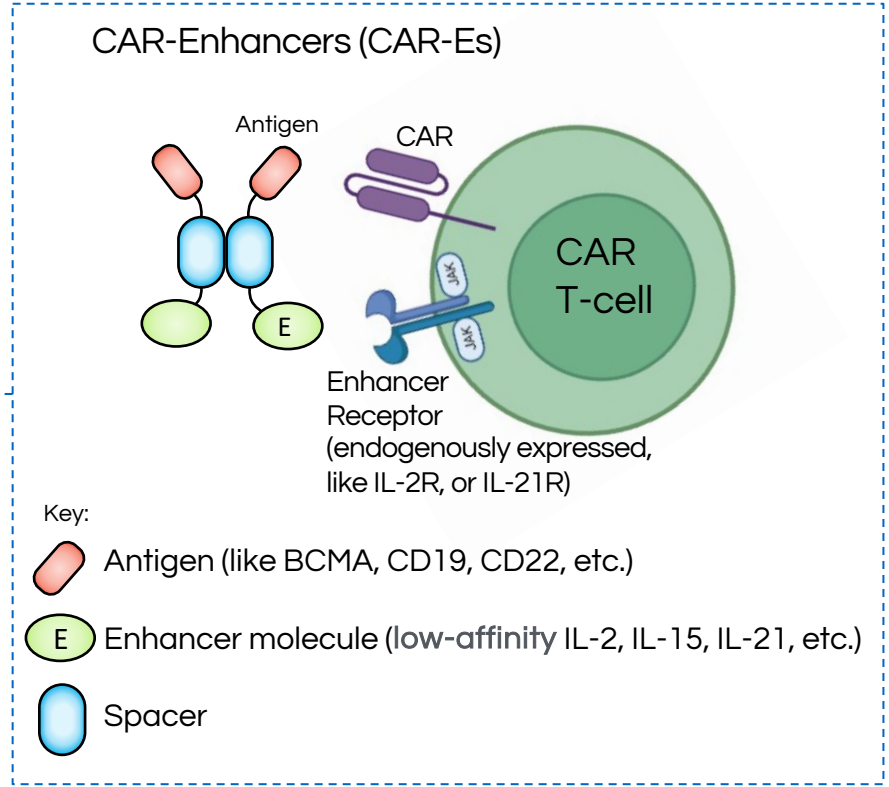
Also targets bone marrow fibroblasts and macrophages, NKT and T cell lymphoma

Einsele H et al, IMWG 2025

CAR-Enhancer (CAR-E) Molecules Selectively Target CAR T cells, Enhance Function and Drive Memory Cell Generation

The CAR-E platform:

- **Uses an off-the-shelf antigen to target the CAR molecule.**
- **Allows targeting any CAR T cells**
- **Uses a human self-protein to target CAR cells (no or low immunogenicity).**
- **Potential synergy between the CAR and Enhancer molecule may drive generation of memory CAR T cells**

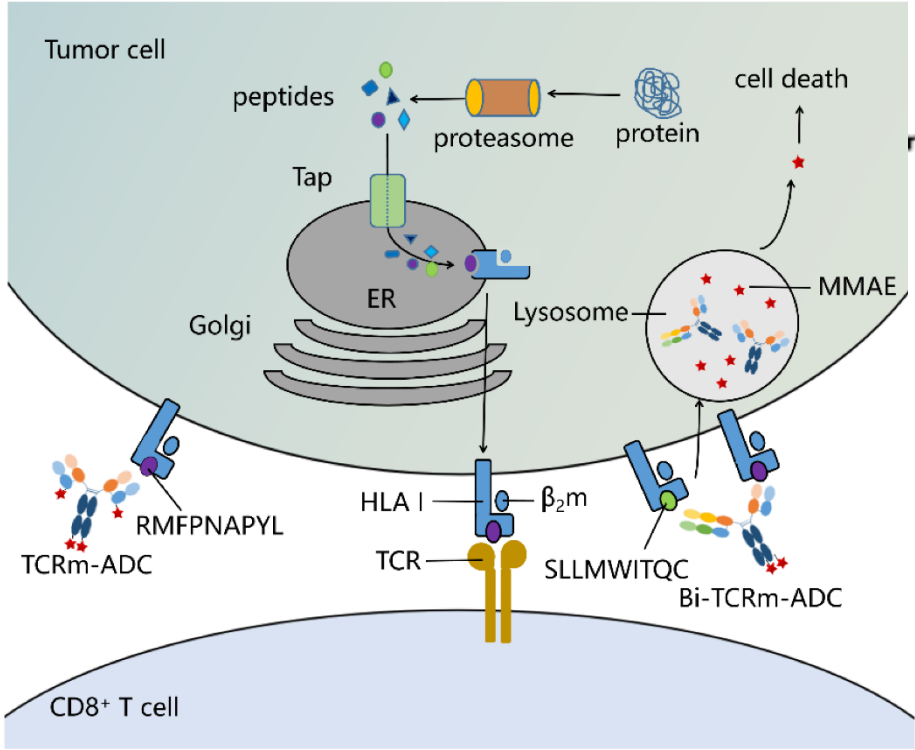


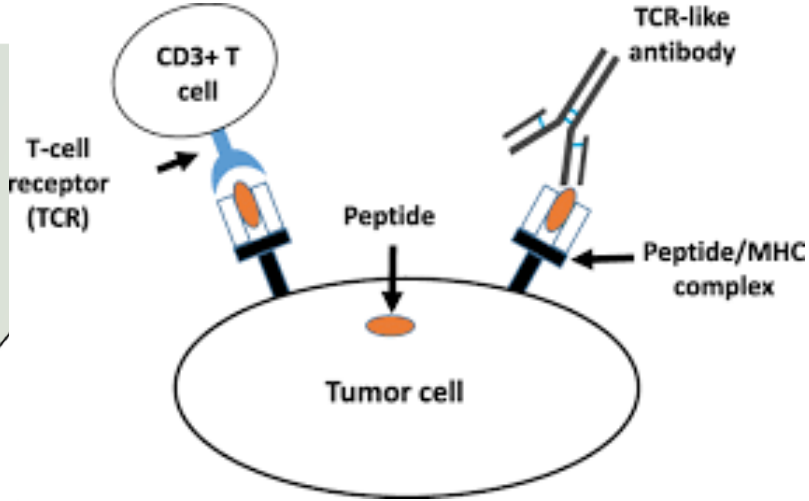
NB: CAR-E Administered Two Weeks Post CAR-T Infusion Leads to Complete Tumor Clearance and Functional Memory CAR T-Cell Generation

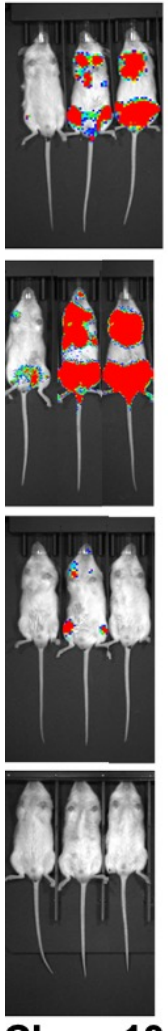
Dana-Farber Cancer Institute

Rakhshandehroo et al Nat Biotechnology 2024

TCR-Like Abs Targeting Intracellular Antigens (MZB1) in MM







Screen for TCR-like Ab Against MAB1 Peptide in HLA2+

Use as naked Ab, BiTE, ADC, or CAR T

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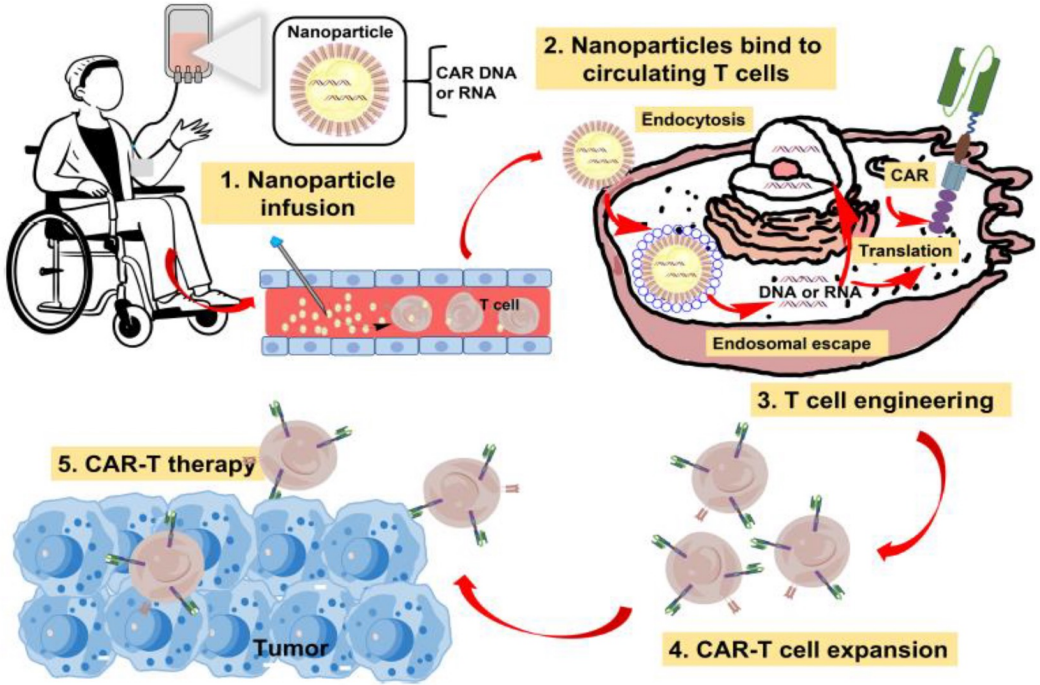
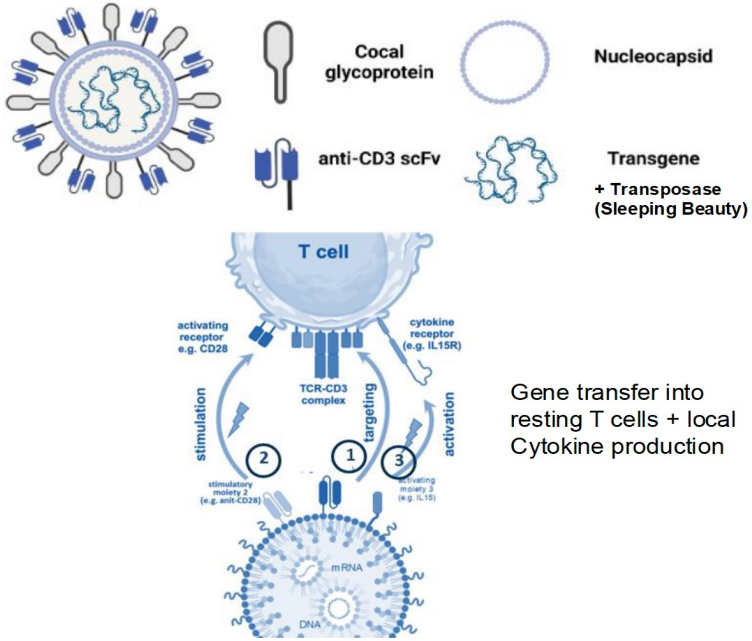
Munshi et al, 2025

In Vivo Generation of CAR T Cells

Process of in-situ CART-T therapy with nanoparticles in vivo



Qin, YT et al., Front. Immunol. 2023



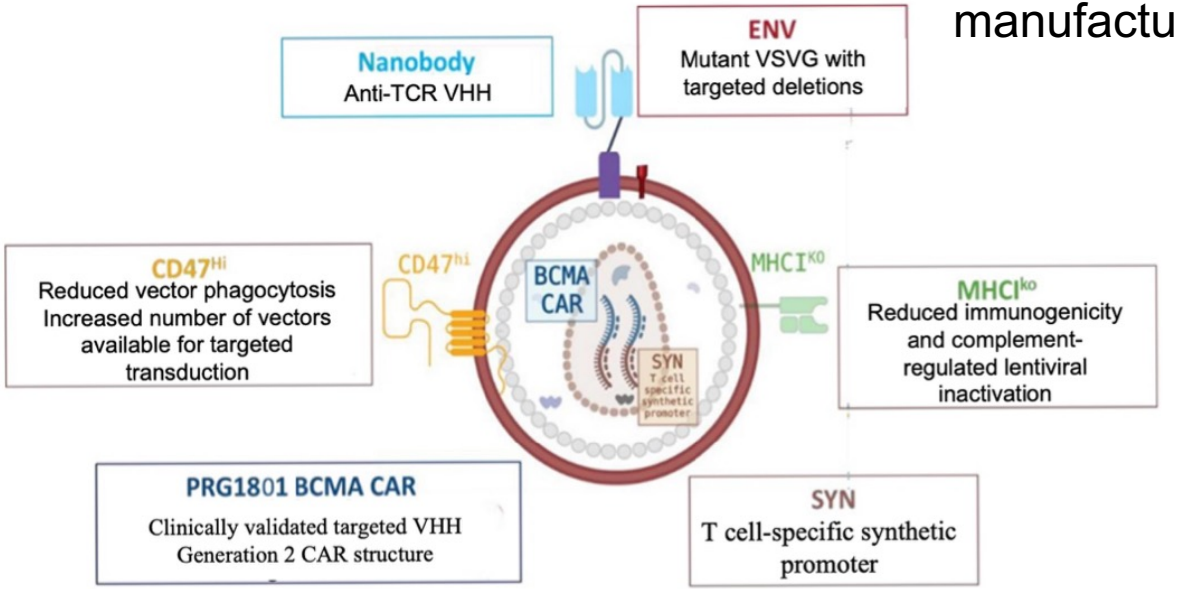
Gene transfer into resting T cells + local Cytokine production

Michels KR et al., J Immunother Cancer. 2023 Mar;11(3)

In Vivo CAR T in Multiple Myeloma

A

B



Delivers CAR to endogenous T cells in situ without need for apheresis, manufacturing or lymphocyte depletion

4 pts RRMM:

CRS 3 grade; 1 grade 1

ICANS 1 grade 1

Viral titer peaked at 12 h and undetected at 48h

CAR T detected at d4-8, peaked at d10-17 (also in BM, CSF, EMD)

At 2-3 mo 2 sCR, 2 PR

Xu J et al Lancet 2025, in press

Dual Targeting of BCMA and GPRC5D in RRMM

Goal: Decrease Tumor-Related (Loss/Mutation of Target) and Immune (Exhaustion) Resistance

Phase 1b Trial of Teclistamab + Talquetamab

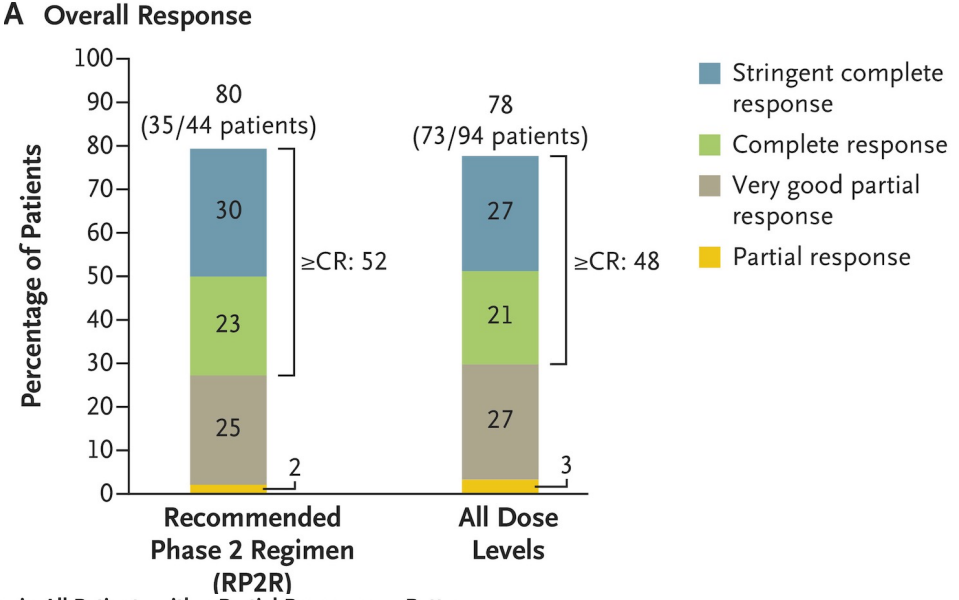
Safety consistent with each monotherapy

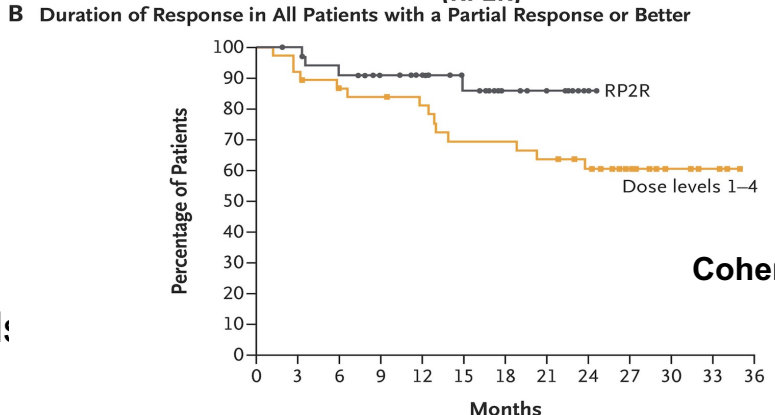
64% Grade 3 or 4 infections

78% ORR at all dose levels

80% ORR (61% EMD) at RP2D

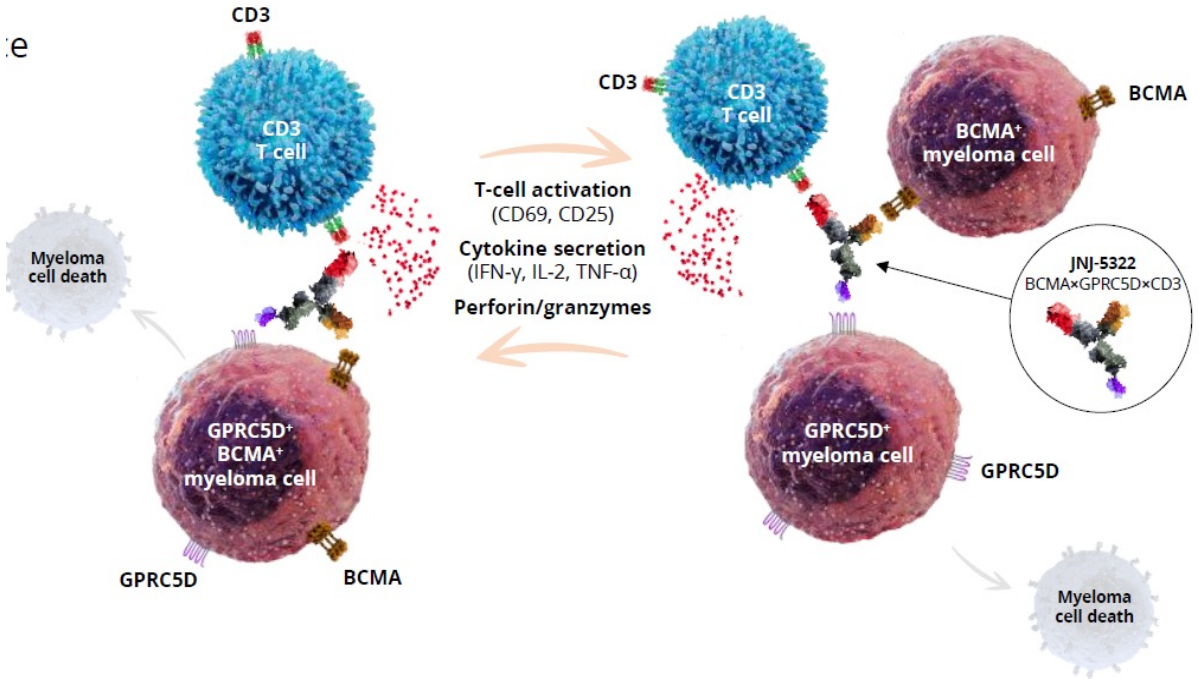
18 mo PFS: 86% at RP2D, 82% EMD, 77% all dose levels





Cohen et al NEJM 2025; 392: 138-49.

JNJ-79635322 BCMAxGPRC5DxCD3 Trispecific Antibody



Binds CD3 on T cells, BCMA and GPRC5D on MM cells

Binding avidity is enhanced by engagement of both Ags

May allow for less off-tumor avidity and/or lower doses, less off tumor, on target effects

May delay resistance due to mutation or loss of Ag

Pillarisetti et al. ASH 2023, Abs 456.

JNJ-5322 BCMA×GPRC5D×CD3 Trispecific T Cell Engager

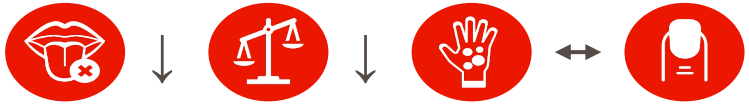
100 mg Q4W SC with 1 step-up dose selected as RP2D

- Dose escalation
- Dose and schedule optimization
- Step-up dose optimization

→ 100 mg Q4W SC (5 mg step-up dose)

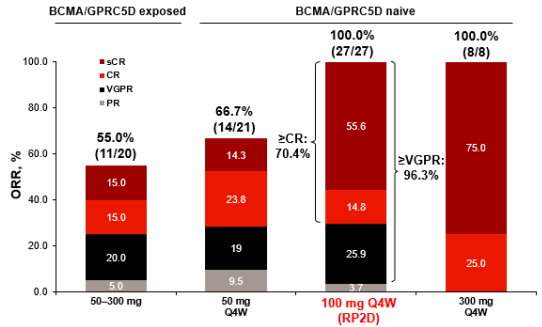
Improved or similar GPRC5D TEAEs

Taste ↓ Weight decrease ↓ Skin ↔ Nail

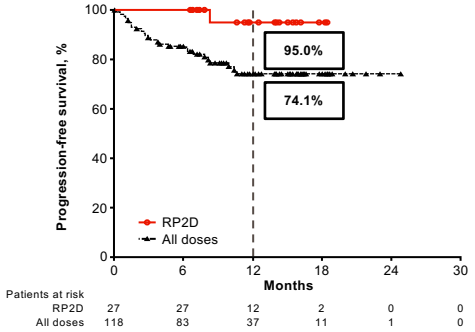


Low-grade GPRC5D TEAE profile

ORR 100% in patients naive to BCMA/GPRC5D at RP2D

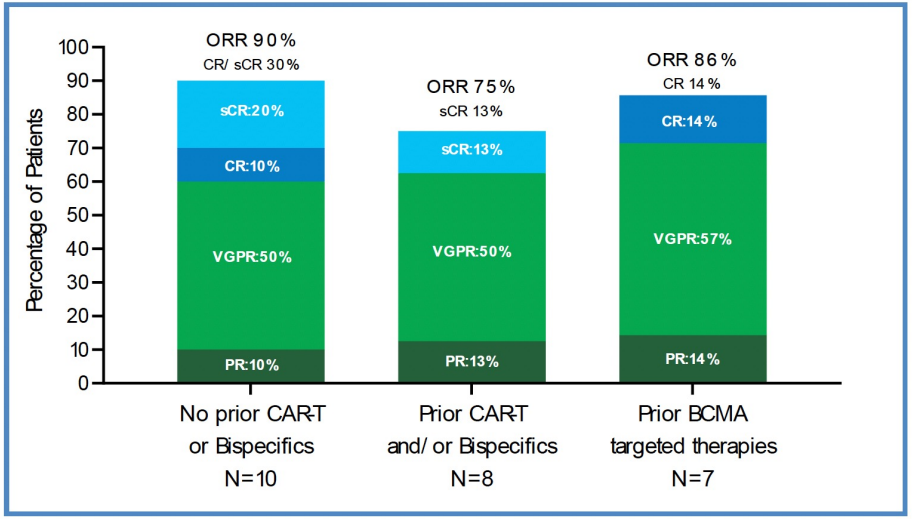


12-month PFS rate 95% in patients naive to BCMA/GPRC5D at RP2D



Presented by NWCJ van de Donk at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 30–June 3, 2025; Chicago, IL, USA & Virtual

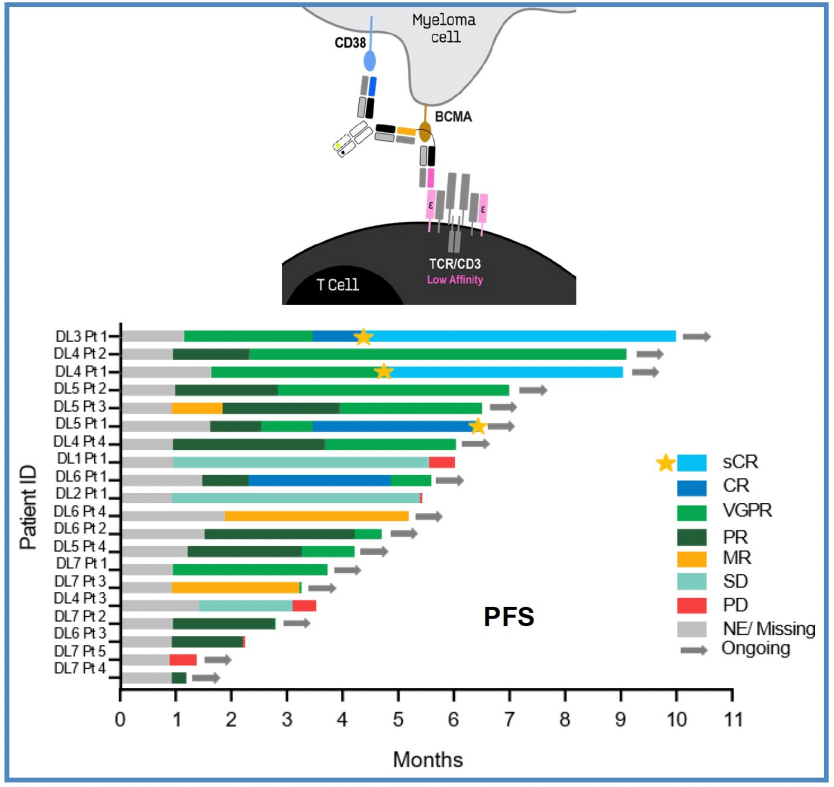
ISB (BCMAxCD38xCD3) Trispecific Antibody



Median follow up 6 months (range: 2-10)

No CRS grade >2

Infections grade > 2 15%



Quach, H., presented at EHA 2024

Cevostamab BiTE in RRMM

FcRH5 novel therapeutic target in MM

Cevostamab monotherapy manageable safety profile
- Most Gr 3–4 AEs reversible cytopenias
- Gr ≥3 infection rate 19.2%
- Majority of CRS Gr 1 (Gr 2 16.7%; no Gr 3) with TS dosing

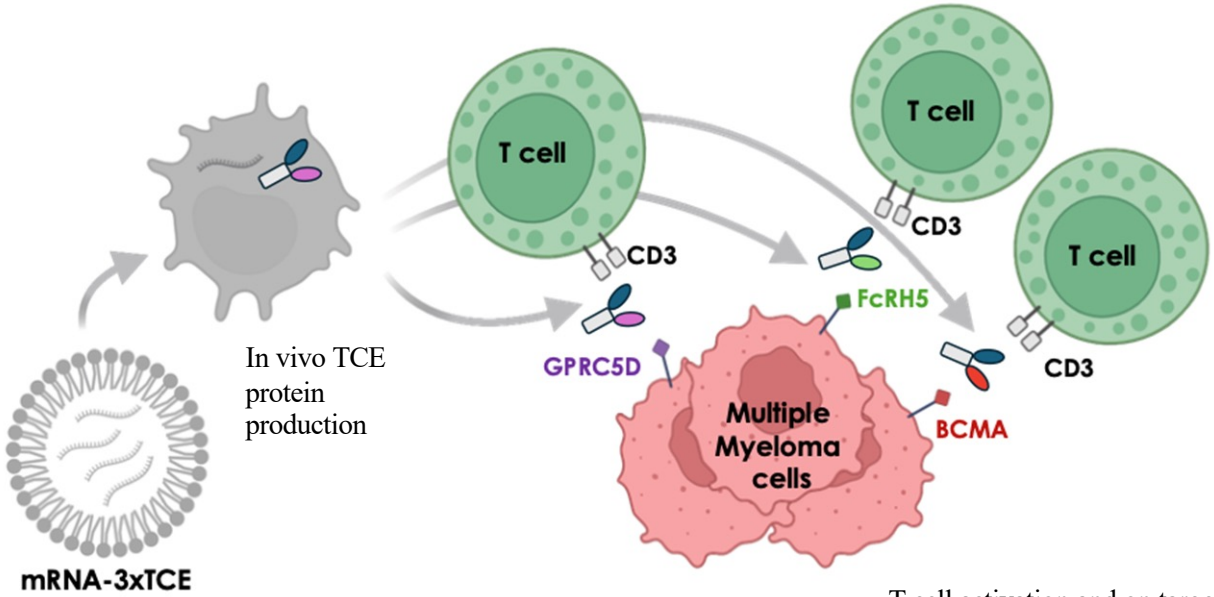
ORR 44.3% Cevostamab in RRMM, **60.6% BCMA -naïve patients**
Median DoR 10.4 mos; in ≥ VGPR mDoR 21.2 mos

Patients maintain response beyond the fixed 12-mo treatment

Dose of Q3W 160mg TD with C1 0.3/1.2/3.6/160mg TS for future single agent and combination studies

Richter et al, ASH 2024

Lipid Nanoparticle mRNAs (CD3, BCMA, GPRC5D, FcRH5) for In Vivo Production of Trispecific T Cell Engager



Garnaas et al. ASH 2024, Abs 4163.

Berdeja 6th Immune Effector Cell Therapies in Multiple Myeloma Workshop

Conclusions and Future Directions

Three eras of myeloma bench to bedside progress:

1980 and Ongoing-Stem cell transplant
2000 and Ongoing- Novel agents (IMiDs, Pis, CD38MoAb)
2020 and Ongoing-Immune therapies (CAR T, BiTEs)

MRD-CR now achievable In NDMM and RRMM

In Future:

Profiling the tumor and host will inform identify new targets for novel single agent and combination targeted and immune therapies.

Targeted and immune therapies including CAR T/BiTEs will be incorporated into earlier treatment of MM to achieve durable MRD- CR and restore memory anti-MM immunity, allowing patients to be disease-free and off all therapy.

2025 Robert A Kyle Lifetime Achievement Award

An individual whose body of work in the field of multiple myeloma has made significant advances in research, treatment, and care of myeloma patients.

Sagar Lonial, MD

A cherished long-term friend for me and many in our international myeloma family

Our family are dear friends

ASH 2021 was the start for Sagar in myeloma

Emory Sea Island Course for 25 years

Golf, Football-Superbowl

Anne and Bernard Gray Family Chair in Cancer

Have watched in awe his amazing success:

as a Dad

developing a world class Myeloma Center at Emory

becoming an international leader in myeloma translational research and care.

We are all the beneficiaries and very grateful.

Congratulations-the best is yet to come!!