CAR T Cell Therapy in Myeloma: Durability, Design and Path to Functional Cure

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Talk Outline

- Introduction: From Incurable to Potentially Curable
- Evidence for Durability with first generation CAR Ts
- Biomarkers & Predictors of Cure
- Next-Generation CAR T Design
- Pathway to increase the cure fraction

Survival Outcomes: A 60-Year Transformation

Survival in multiple myeloma has improved dramatically across treatment eras, driven by successive waves of therapeutic innovation. SEER data confirms a marked decline in MM-specific mortality from 2002 onward, correlating with novel agent approvals — patients diagnosed in the 2000s have dramatically better outcomes than those diagnosed in the 1990s.

~2

1960s–70s

Alkylating agents only — Median OS (years)

~4–5

1990s (ASCT Era)

Autologous stem cell transplant — Median OS (years)

~5–7

2000s (Novel Agents)

IMiDs + Proteasome Inhibitors — Median OS (years)

~8–10

2010s (Triplets + mAbs)

Monoclonal antibody combinations — Median OS
Median OS (years)

~61 mo

2020s (CAR-T + Bispecifics)

Median OS in RRMM (cilta-cel, CARTITUDE-1); 1/3 of
1/3 of patients progression-free at ≥5 years;
'functional cure'

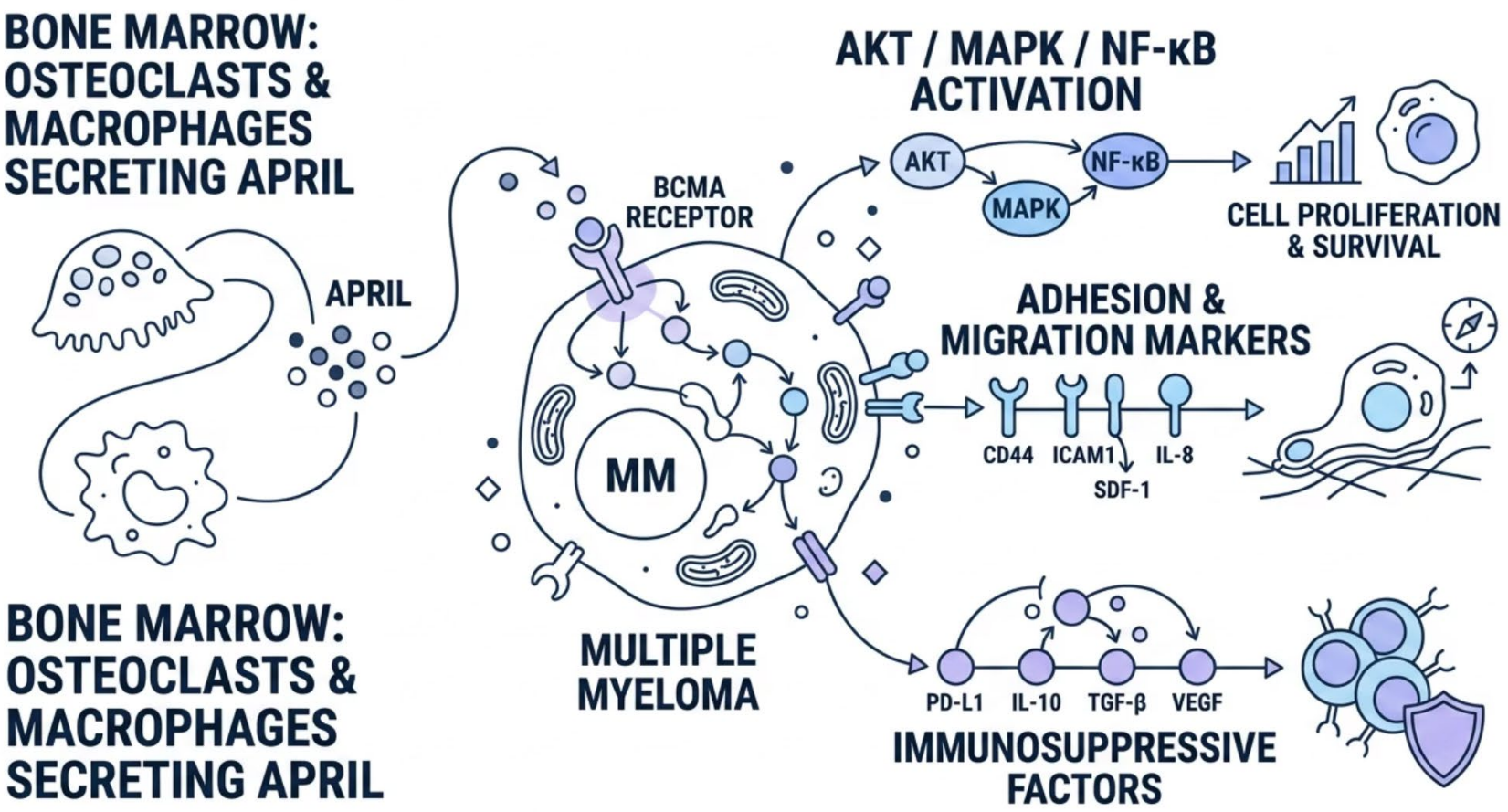
Kumar SK et al. Blood. 2008;111(5):2516–2520.

Voorhees PM et al. J Clin Oncol. 2025.

SEER Cancer Statistics. National Cancer Institute. seer.cancer.gov.

BCMA Signaling in the Bone Marrow Microenvironment

APRIL/BCMA Pathway Drives MM Proliferation, Survival and Immunosuppression



BCMA overexpression
>6 fold increase in BCMA mRNA/protein in engineered MM cells

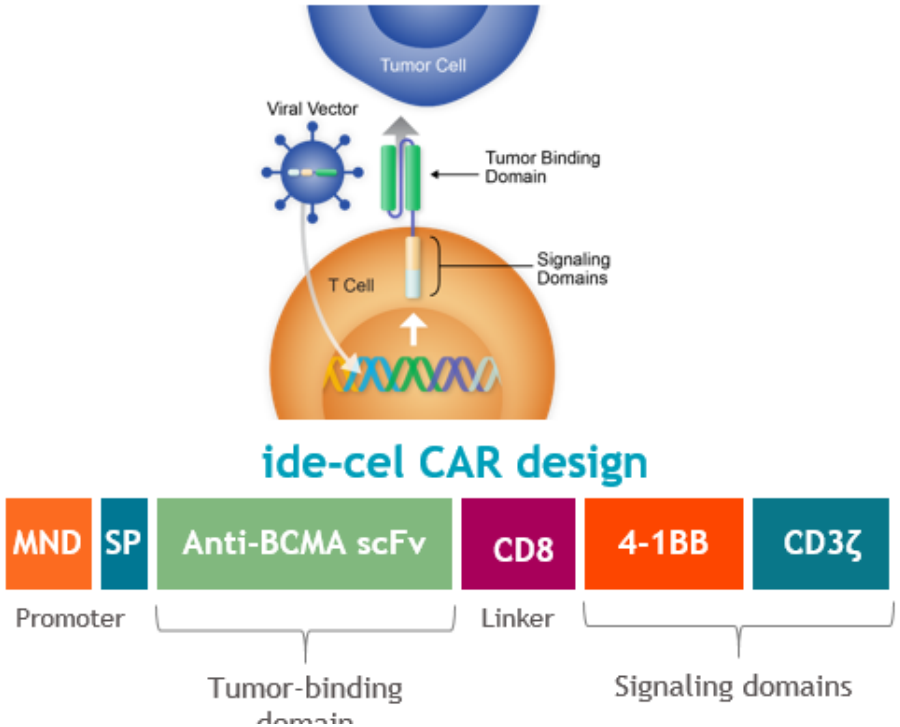
Accelerated Tumor Growth
R-BCMA tumors grew significantly faster vs controls

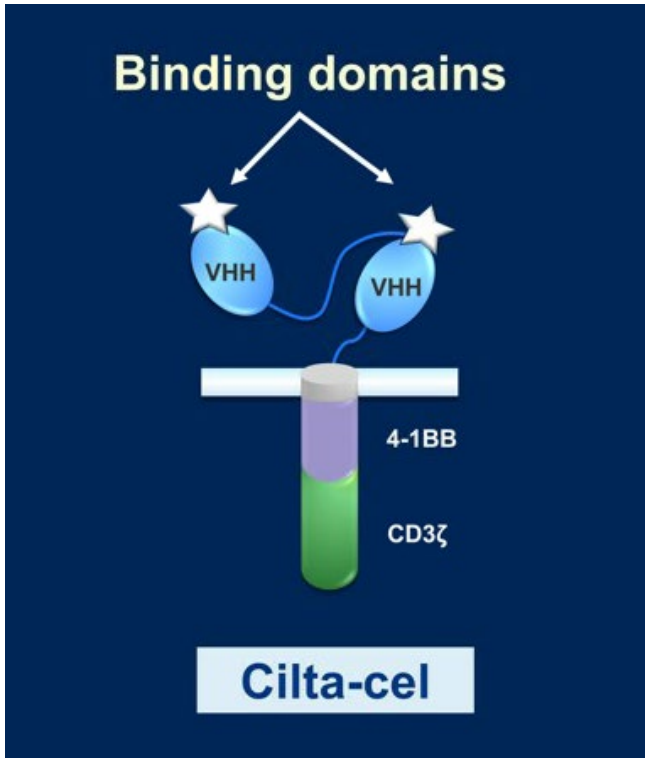
Immunosuppressive Program
Upregulates PD-L1, IL-10, TGF-B, and VEGF, enabling immune evasion

Bone marrow crosstalk
Induces CCL3/CCL4, CD44, ICAM1, and SDF-1 – reinforcing a pro-tumor BM feedback loop.

Tai YT, Acharya C, An G, et al. Blood 2016;127(25):3225-3236

FDA Approved CAR T in Myeloma

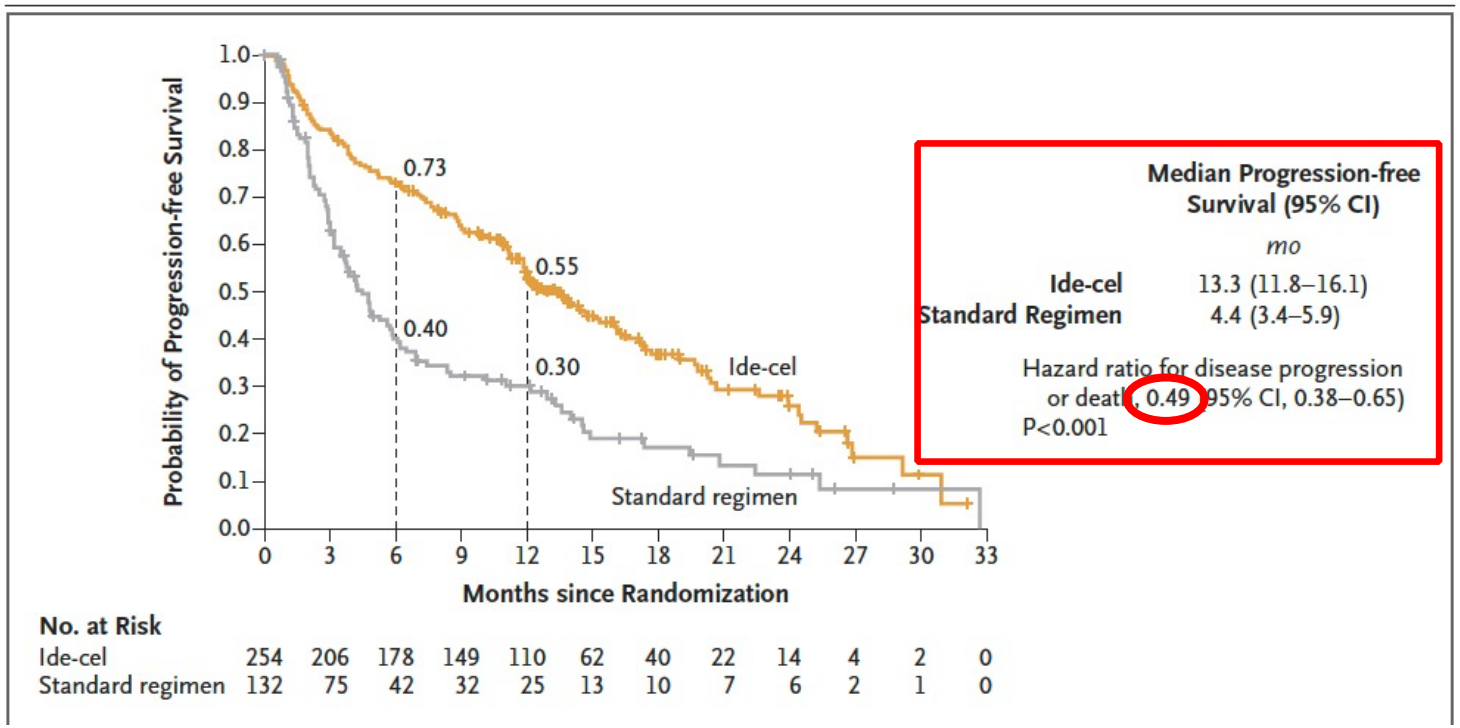




Idecabtagene vicleucel (Ide-cel)

- Phase 2 KarMMa study: patients with median 6 prior LOT, ORR , median PFS
- KarMMa 3 (first phase 3 CAR T study in RRMM):

- Triple class exposed, CD38 refractory
  - **lines 3-5**
  - vs DPD/DVD//KD/EPD/IRD
  - >95% refractory to CD38



Rodriguez-Otero P, et al. NEJM 2023

KarMMa-3 Subgroup Analysis: Summary of Key Data in Older Older Patients (≥70 yr) With RRMM

Ide-cel demonstrated consistent efficacy and tolerability in patients aged ≥70 years with relapsed/refractory multiple myeloma, with outcomes numerically comparable to or exceeding those in younger patients.

Efficacy

- ORR: 81.6% (ide-cel) vs 48.1% (standard regimens), P=0.0037
- Median PFS: 18.9 months (ide-cel) vs 5.7 months (standard regimens), P=0.0012 — a 3.3-fold improvement
- Median OS: Not reached with ide-cel (vs 39.5 months in <70 yr cohort)

Safety

- No new safety signals in ≥70 yr patients
- CRS rate: 6.4% (ide-cel ≥70 yr) — low and comparable to younger patients (4.5%)
- iiNT rate: 6.4% (ide-cel ≥70 yr) vs 2.2% (<70 yr)
- Infection rate: 25.5% (ide-cel ≥70 yr) — consistent with overall trial population

Quality of Life & Context

- Greater and more durable improvements in improvements in global health status/QoL status/QoL with ide-cel vs standard regimens regimens in older patients
- Older enrollees had more favorable baseline characteristics (lower high-risk cytogenetics: 32.7% vs 44.4%; lower triple-class refractory: 55.1% vs 66.8%)
- High crossover rate (67%) from standard regimens to ide-cel may confound OS interpretation

Ailawadhi S, et al. Tandem Meetings 2026 [Presentation #28667]

Real-World Evidence: Ide-cel in Older Patients

Multiple real-world datasets corroborate KarMMa-3 findings, demonstrating that older age does not reduce ide-cel efficacy, while highlighting the need for vigilant toxicity vigilant toxicity monitoring—particularly for ICANS.

CIBMTR Registry (US; May 2021–Jun 2023) 2023)

- No difference in ORR or CR rates at 6 months by age by age
- 6-mo PFS: 68.3% (≥70 yr) vs 60.4% (<70 yr); multivariable HR 0.62 favoring older patients
- Higher ICANS risk: 37.1% vs 24.2% (HR 2.25); higher CRS ≥2 risk (HR 1.67)
- Frail patients: higher ICANS/infections, but no difference in response, PFS, or OS at 6 months

US Myeloma CAR-T Consortium (SOC ide-cel) ide-cel)

- Median age 64; 75% would not have met KarMMa KarMMa eligibility criteria; 31% aged ≥70 in updated updated 2025 cohort
- Median PFS 8.5 months; OS 12.5 months (median follow-up 6.1 months)
- On multivariable analysis, **younger age was associated with inferior PFS**—older age was not a disadvantage

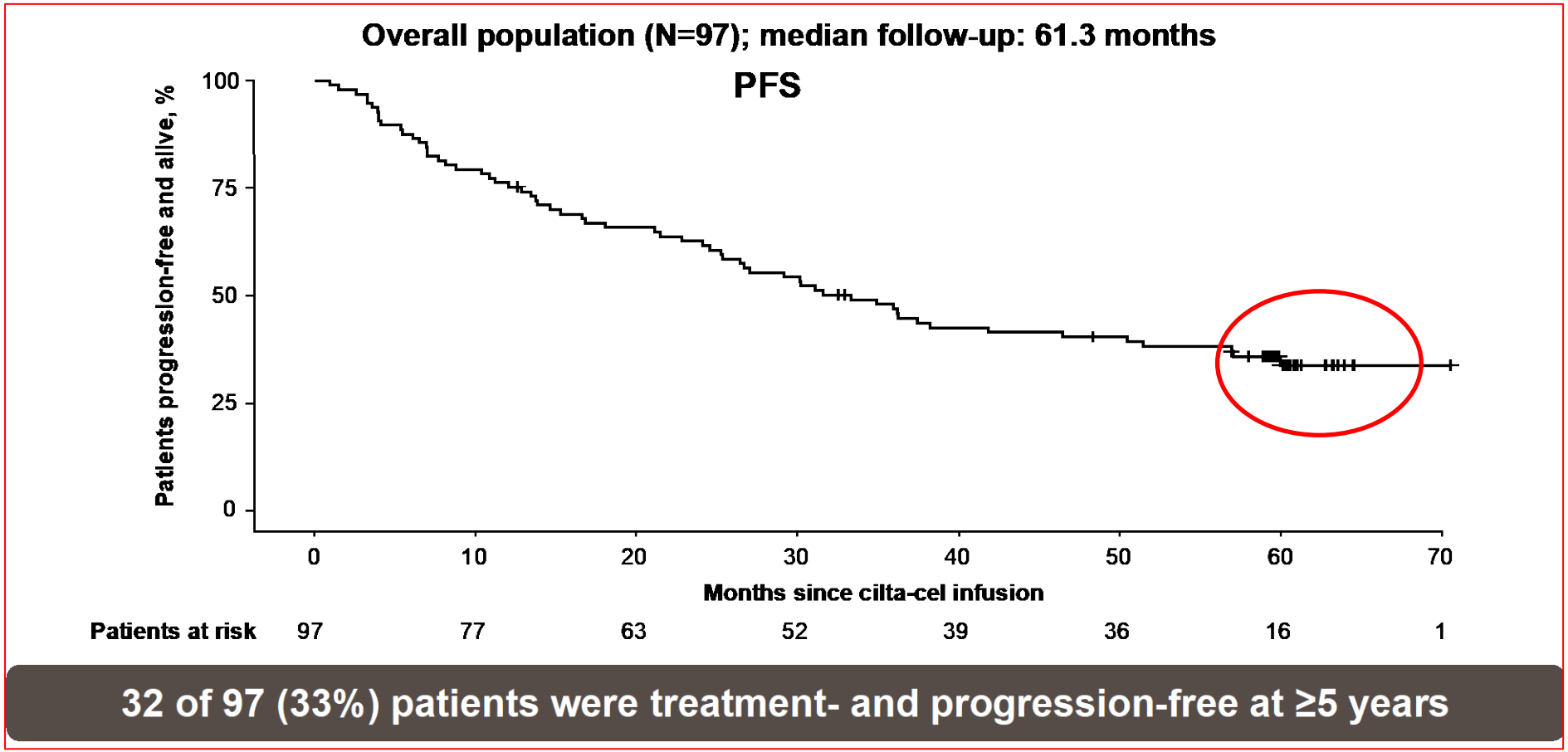
Kalariya et al. (Older Patients ≥65 yr; n=75/156)

- Median age 69 (range 65–83); 66.7% frail; 77.3% KarMMa-ineligible
- Best ORR 86.7%; median PFS 9.1 months; median OS 26.5 months
- Grade ≥3 CRS 1%; grade ≥3 ICANS 4%
- Frailty/geriatric features did not confer inferior efficacy or survival vs younger cohort

Synthesis: Across real-world datasets, older age (≥65/≥70) does not reduce ide-cel efficacy. The main age-related signal is higher ICANS risk (and sometimes higher CRS ≥2 sometimes higher CRS ≥2 risk), supporting careful toxicity monitoring rather than age-based exclusion.

CARTITUDE-1 Long-Term Remission (Ciltacel): One Third of Patients Were Progression-Free for ≥5 Years

- 97 patients, mFU 33.4 mo
- Median 6 LOT
- 42% penta-refractory
- 88% triple class refractory
- 99% refractory to last line
- ORR 97.9%
- sCR 82.5%
- mPFS 34.9 mo
- mOS not reached
  62.9% alive at 3 yrs



Lin Y, et al. ASCO 2023

Voorhees P, et al. ASCO 2025

Defining Cure in Multiple Myeloma

International Myeloma Society Cure Summit: Proposed Operational Definition

> Patients achieving sustained MRD negativity (10^{-6} sensitivity) who remain off all anti-myeloma therapy for ≥5 years may be considered cured. — IMS Cure Summit, February 2026

Effective therapy of finite duration

No evidence of disease (MRD negativity at 10^{-6} sensitivity)

No relapse after stopping therapy

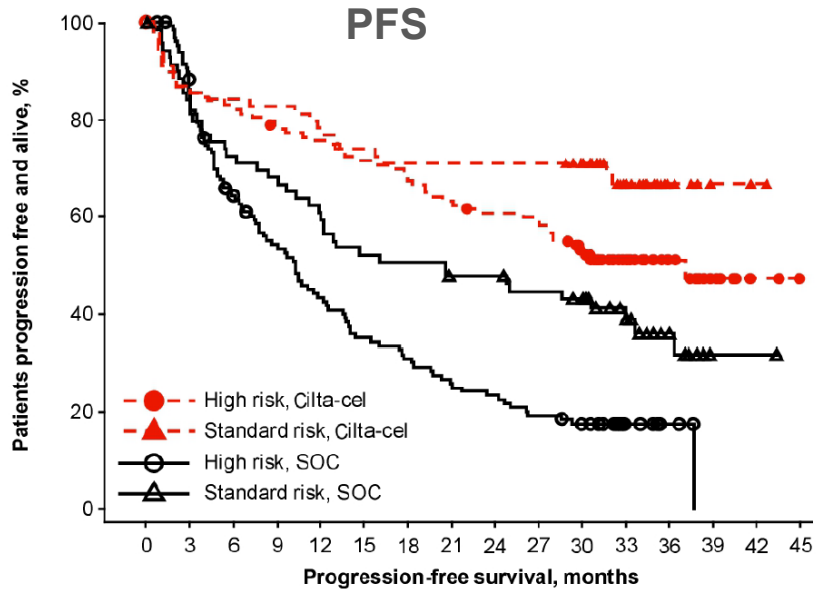
Surrogate Endpoints Under Evaluation

- MRD negativity (10^{-6} (10^{-6} sensitivity)
- Immune Reconstitution
- Time off therapy (≥5 years)
- MGUS-like reversion under study

BCMA-directed immunotherapies, including CAR T-cell therapy and bispecific antibodies, represent the most promising platforms for achieving durable, treatment-free remission.

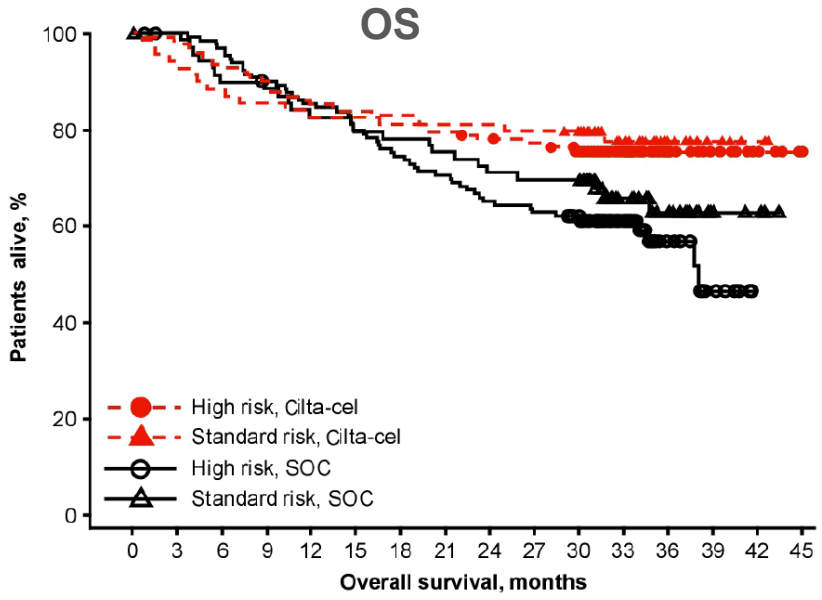
IMS Myeloma Cure Summit: Definitions, Metrics, and Milestones. February 20–21, 2026. International Myeloma Society. Reported by MMRF, March 2026.

CARTITUDE-4 subgroup analysis



Patients at risk

High risk, SOC	132	111	79	65	52	42	37	31	28	23	20	7	3	0	0	0
High risk, Cilta-cel	123	106	102	96	92	87	84	76	73	70	55	31	14	7	2	0
Standard risk, SOC	70	58	50	47	41	36	35	32	32	29	27	18	9	1	1	0
Standard risk, Cilta-cel	69	59	58	57	53	51	49	49	49	49	46	27	9	2	1	0



Patients at risk

High risk, SOC	132	130	126	116	110	103	96	91	84	81	75	38	14	6	0	0
High risk, Cilta-cel	123	121	115	111	105	103	102	98	95	93	83	50	23	14	5	0
Standard risk, SOC	70	69	62	61	57	55	54	52	49	48	48	29	18	5	3	0
Standard risk, Cilta-cel	69	65	61	59	57	57	56	56	56	55	52	35	13	5	2	0

PFS	Cilta-cel	SOC
High risk, months (95% CI)	**37.1 (26.7–NE)**	10.3 (7.6–12.6)
Standard risk, months (95% CI)	**NR (NE–NE)**	20.6 (11.2–33.6)

OS	Cilta-cel	SOC
High risk, months (95% CI)	**NR (NE–NE)**	38.0 (34.0–NE)
Standard risk, months (95% CI)	**NR (NE–NE)**	NR (34.7–NE)

The median follow-up was 33.6 months (range, 0.1–45.0).
NR, not reached; SOC, standard of care.

Sidana S, et al. ASCO 2025

CARTITUDE-1 Long-Term Remission (Ciltacel): Baseline Demographics and Disease Characteristics Were Generally Comparable Between Patients With or Without PD Within 5 years

	≥5 years progression free (n=32)	PD within 5 years (n=46)	*P*-value[a]
Age, median (range), years	60.0 (43–78)	61.5 (47–77)	0.515
Prior LOT, median (range)	6.5 (3–14)	5.0 (3–18)	0.058
Triple-class[b] refractory, n (%)	29 (90.6)	39 (84.8)	0.513
Penta-drug[c] refractory, n (%)	15 (46.9)	15 (32.6)	0.241
High-risk cytogenetics,[d] n/N (%)	**7/30 (23.3)[e]**	**12/45 (26.7)**	**0.793**
Extramedullary plasmacytomas, n (%)	**4 (12.5)[f]**	**6 (13.0)**	**1.000**
Bone marrow plasma cells, median (range), %	5.0 (0.8–80.0)	24.0 (0.0–95.0)	0.053
High baseline tumor burden,[g] n (%)	**2 (6.3)**	**8 (17.4)**	**0.184**
Soluble BCMA, median (range), µg/L	36.0 (3.7–864.6)	58.5 (3.8–1342.9)	0.117
Time from start of last LOT to progression on that line, median (range), months	**3.98 (0.7–48.6)[h]**	**3.89 (0.7–21.5)[i]**	

Patients with high-risk cytogenetics and extramedullary plasmacytomas were equally likely to be progression-free. Of note, the percentage of patients with high tumor burden was numerically lower among patients who were progression-free

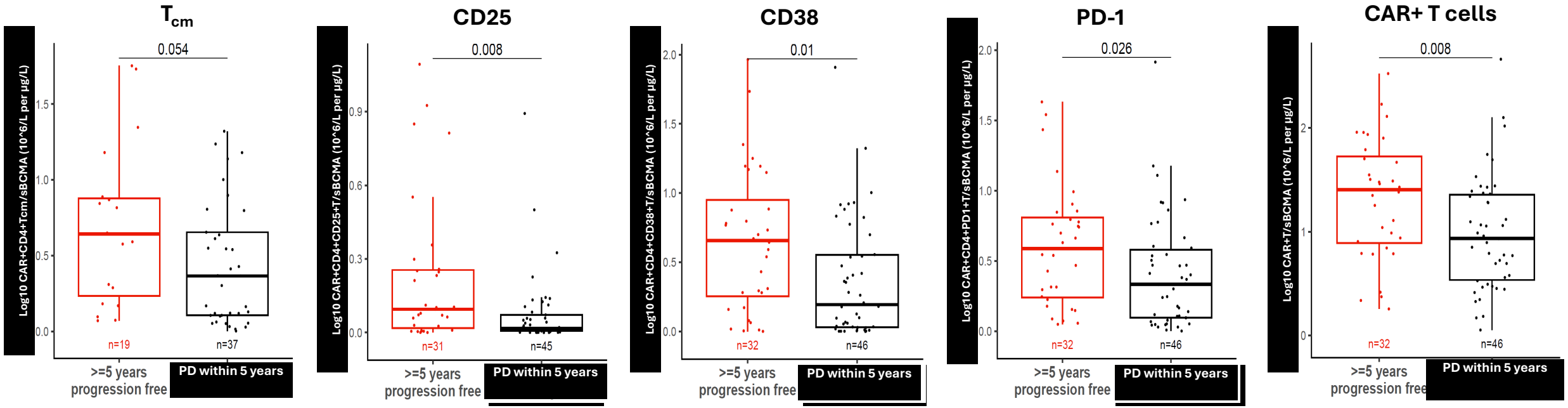
[a]P values were calculated by Fisher's test for categorical variables and Wilcoxon test for numerical variables for descriptive purposes without multiplicity adjustments. [b]≥1 PI, ≥IMiD, and 1 anti-CD38 antibody. [c]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody. [d]Either del17p, t(14;16), or t(4;14). [e]4 patients had del17p, 2 had t(14;16), and the remaining 1 patient had a double hit of del17p and t(14;14). [f]Extramedullary disease denotes soft tissue plasmacytoma that was not contiguous with bone. [g]Low tumor burden defined as meeting all following parameters (as applicable): bone marrow % plasma cell <50%, serum M-protein <3 g/dL, serum FLC <3000 mg/L; high tumor burden defined as meeting any of the following parameters: bone marrow % plasma cell ≥80%, serum M-protein ≥5 g/dL, serum FLC ≥5000 mg/L; intermediate tumor burden did not fit either criteria of high or low tumor burden. [h]n=29. [i]n=42. cilta-cel, ciltacabtagene autoleucel; EMD, extramedullary disease; IMiD, immunomodulatory drug; LOT, line of therapy; PD, progressive disease; PI, proteasome inhibitor.

Voorhees P, et al. ASCO 2025

CARTITUDE-1 Long-Term Remission: Long-Term Disease Control is Associated With Activated T cell Phenotypes and Higher E:T Ratio After Infusion

Post-infusion E:T ratio[a]

CAR+ CD4+ T cells[b]



Long-term disease control was significantly associated with higher CAR+ CD4+ T cells with a central memory phenotype and positive for CD25, CD38, and PD-1 activation markers as well as higher overall E:T ratio

[a]E:T ratio was defined as maximal CAR-positive T-cell levels normalized by pre-infusion serum soluble BCMA levels. [b]Similar results were observed for CAR+ CD8+ T cells. [c]Two-sided nominal p-values, unadjusted for multiplicity, were provided for descriptive purposes. These analyses were exploratory in nature and utilized for hypothesis generation.

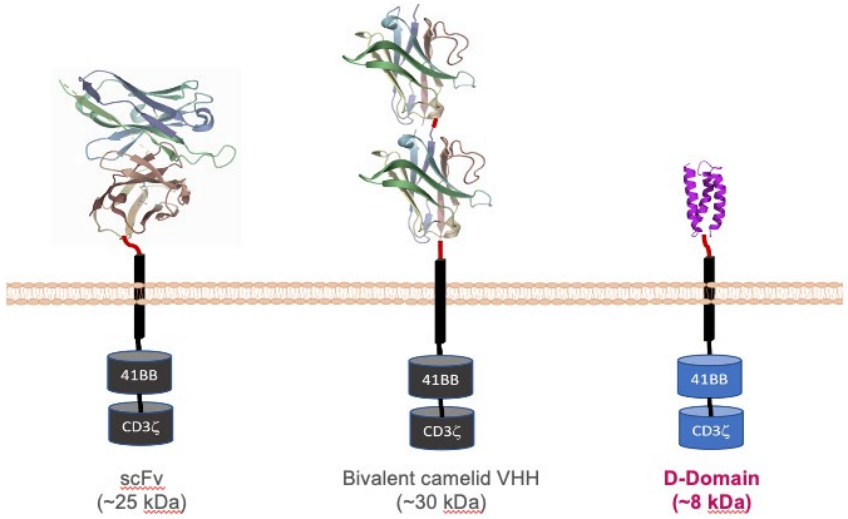
CAR, chimeric antigen receptor; E:T, effector to target; PD, progressive disease; T_{cm}, central memory T cells.

Voorhees P, et al. ASCO 2025

Unique Toxicity Profile

- Significant hypogammaglobulinemia
- Delayed neurotoxicity
  - Movement and Neurocognitive Treatment-emergent adverse events (MNT)
  - Cranial nerve palsies (CNP)
- Enterocolitis (IEC-EC)

Anitocel, IMMagine 1 Study

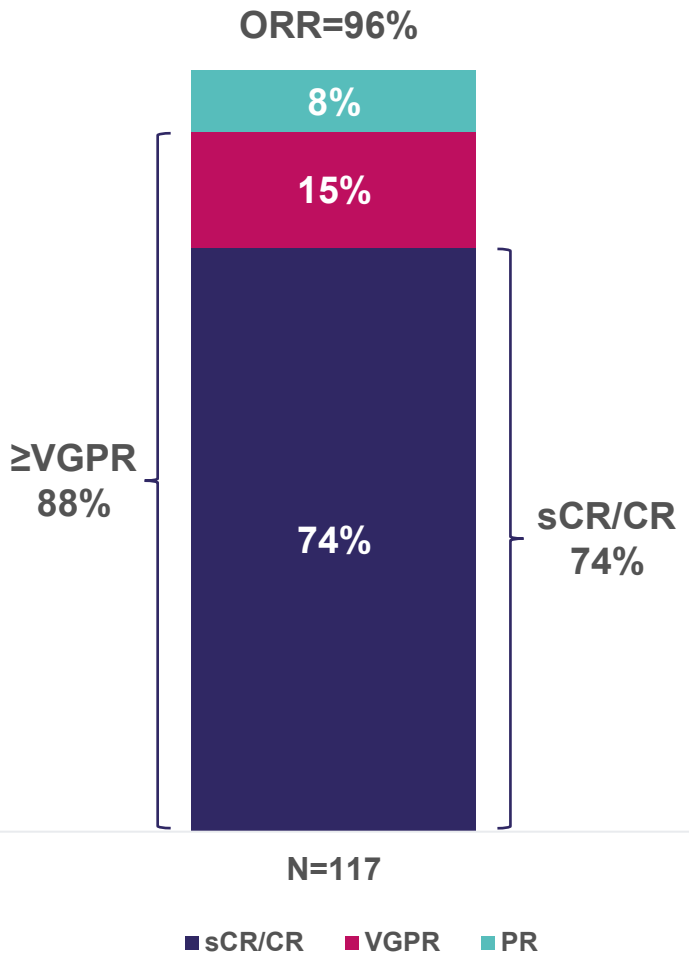


D-Domain Attributes

Non-antibody derived synthetic protein::

- Small size of construct facilitates high transduction efficiency
- Lack tonic signaling
- Fast off rate and high CAR surface expression

Efficacy Evaluable Patients, N=117



N=117	PFS Rate (%) (95% CI)	OS Rate (%) (95% CI)
6-Month	93.1 (86.7, 96.5)	95.7 (90.0, 98.2)
12-Month	82.1 (73.6, 88.1)	94.0 (87.8, 97.1)
18-Month	67.4 (55.4, 76.8)	88.0 (78.8, 93.4)
24-Month	61.7 (48.0, 72.8)	83.0 (70.7, 90.5)

MRD Negativity at 10^{-5} Sensitivity Level	
Overall MRD negativity, % (n/N)	95% (91/96)
Median time to MRD negativity, months (min – max)	1.0 (0.9 – 6.4)
MRD negativity sustained for ≥ 6 months, % (n/N)	83% (54/65)
MRD Negativity at 10^{-6} Sensitivity Level	
Overall MRD negativity, % (n/N)	78% (68/87)

Patel K, et al. ASH 2026

Novel Targets: GPRC5D

Arlocabtagene Autoleucel (Arlocel) (BMS-986393) | Phase 1 CC-95266-MM-001 (NCT04674813)

Why GPRC5D?

Target Biology

- Orphan G protein-coupled receptor (class C, group 5, member D)
- Highly expressed on malignant plasma cells; little to no expression on non-plasma immune cells
- Limited expression elsewhere — favorable therapeutic window

Complementary to BCMA

- Independent of BCMA expression — active in BCMA-refractory/post-BCMA BCMA patients
- No cross-resistance with BCMA-directed therapies (ide-cel, cilta-cel, belantamab)
- Validated clinically by talquetamab (approved bispecific, Talvey) — ORR 73%,
- CR 35%

Rationale for CAR T Over Bispecific

- Single infusion vs continuous weekly/biweekly dosing with talquetamab talquetamab
- Potential for deeper, more durable responses
- Avoids cumulative infection risk and treatment burden of bispecific antibodies

Phase 1 Results

≥3 Prior Lines	1–3 Prior Lines
87%	94%
ORR (all doses, n=79; ASH 2024)	ORR (IMS 2025)
53%	65%
CR rate (all doses; ASH 2024)	sCR rate (IMS 2025)
91%	23%
ORR at RP2D (150×10^6 cells, n=23; ASH 2024)	VGPR rate (IMS 2025)
18.0 months	24.3 months
Median duration of response (95% CI: 13.3–23.0; ASH 2024)	Median PFS (95% CI: 12.5–NR; IMS 2025)
90%	96%
12-month OS rate (ASH 2024)	ORR at RP2D in 1–3 prior lines (ASH 2024)
18.3 months	18.2 months
Median PFS (ASH 2024)	Median follow-up (IMS 2025)

Key patient characteristics: 42% del(17p), 36% extramedullary plasmacytomas, 46% prior BCMA-targeted therapy. Responses observed regardless of high-risk cytogenetics or prior BCMA exposure. FDA RMAT designation granted.

GPRC5D-related toxicities: dysgeusia, nail/skin changes (class effect shared with talquetamab).
CRS predominantly grade 1/2. Rare cerebellar events reported with GPRC5D CAR T — requires monitoring.

Development Pipeline

Phase 1 (CC-95266-MM-001)
≥3L RRMM — ongoing long-term follow-up (IMS 2025)

QUINTESSENTIAL (Phase 2)
Triple/quad-class exposed RRMM — data expected 2026

QUINTESSENTIAL-2 (Phase 3)
1–3L lenalidomide-refractory RRMM vs SoC — enrolling (NCT06615479)

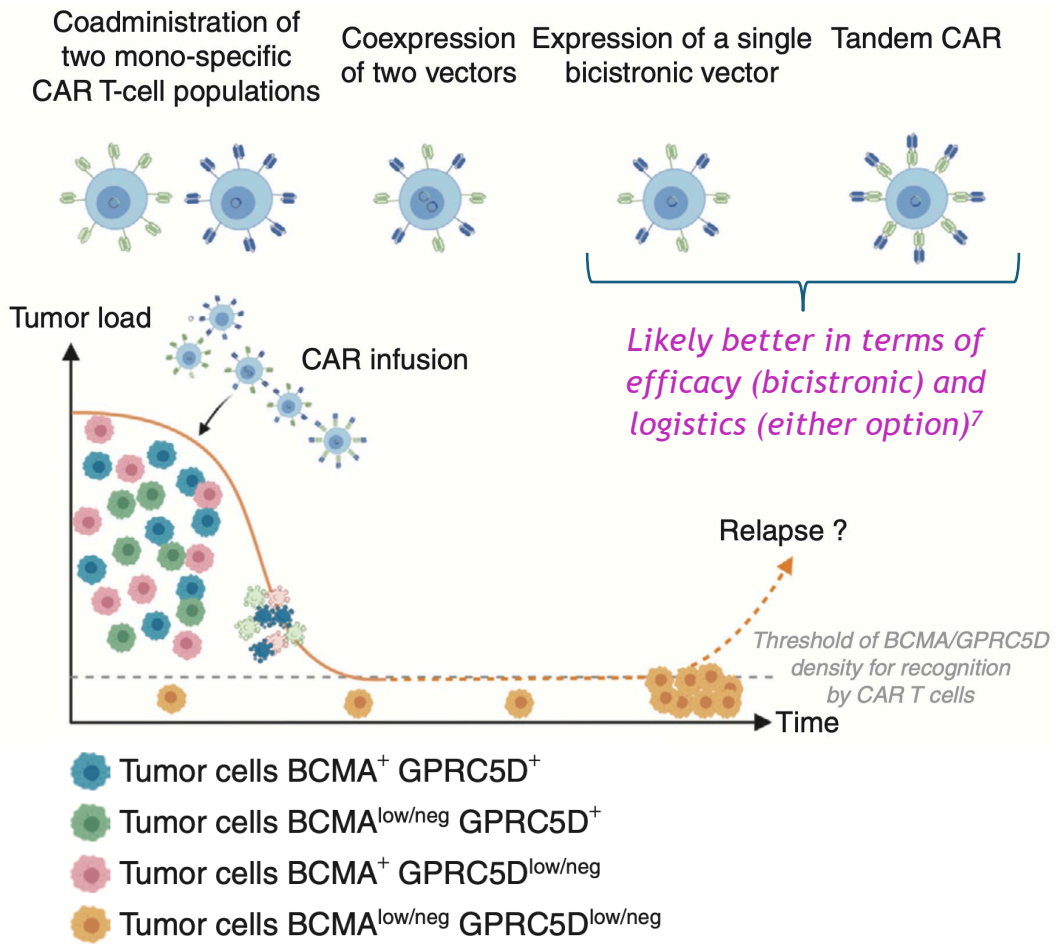
Bal S, et al. ASH 2024 (Abstracts 922 & 2069); Berdeja JG, et al. IMS 2025 (PA-076); Pelosci A. CancerNetwork, Sept 2025

Dual Targeting

Which targets should you combine?

- BCMA & CD19 targeting[1,2]
- BCMA & CS1 targeting[3,4]
- BCMA & GPRC5D targeting[5-7]

How do you combine the targets?



BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; GPRC5D, G protein-coupled receptor class C group 5 member D.

1. Du J, et al. Presented at ASCO; June 2-6, 2023; Chicago, IL, USA. Abstract #8005. 2. Garfall AL et al, Blood Cancer Discov. 2023 Mar 1;4(2):118-133. 3. Zah E et al. Nat Commun. 2020 May 8;11(1):2283. 4. Li C et al, Leukemia. 2024 Jan;38(1):149-159. 5. Zhou D et al. Lancet Haematol. 2024 Oct;11(10):e751-e760. 6. Yao H et al. J Hematol Oncol. 2025 May 19;18(1):56. 7. Fernández de Larrea C et al. Blood Cancer Discov. 2020 Jul 6;1(2):146–154

Picture credit: Simon S et al. Blood Cancer Discov. 2020 Aug 3;1(2):130–133.

AZD0120: CD19 & BCMA

Dual-Target Mechanism

AZD0120 simultaneously targets **BCMA** and **CD19** and **CD19** — delivering a potent, two-pronged pronged attack against myeloma cells and potentially eliminating disease-sustaining clonogenic precursors.

FasTCAR Platform

Engineered on the proprietary **FasTCAR rapid rapid manufacturing platform**, enabling unprecedented speed from apheresis to patient patient infusion without sacrificing cell quality. quality.

DURGA-1 (AZD0120)

BCMA× CD19 | Phase 1b/2 | ASH 2025

23

Evaluable patients

2 dose levels

4

Median prior lines

Range 3–7; 69% tripleclass refractory

96%

ORR

78.3%

CR/sCR

94%

MRD–

<10^{-5} at 1 month

28

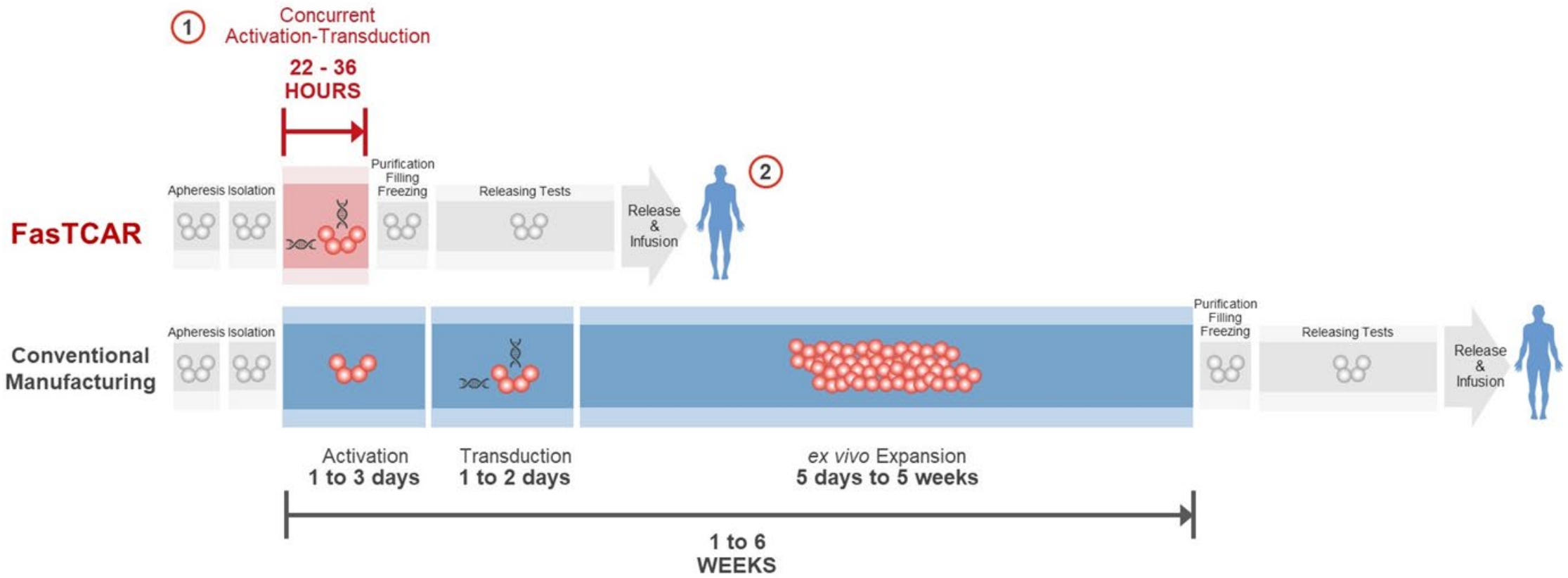
Days to response

Median

- ORR in prior BCMA CAR-Texposed (n=5): 100%
- CRS: 62% (all grade 1-2); no ICANS at DL1; no grade ≥3 CRS
- No deaths, no DLTs, no delayed neurotoxicity
- Median follow-up: 3.9 months

Richard S, et al. Blood 2025

FasTCAR Platform: Next-Day Manufacturing



1. FasTCAR transforms the three primary production steps—activation, transduction and expansion—into a single "concurrent activation-transduction" step.

2. With minimized *ex vivo* culture time, FasTCAR-T cells are younger and shows enhanced proliferation and tumor clearance activities in preclinical studies, making possible the lower cell dosage and eliminating the need for *ex vivo* expansion. Expansion happens in patient body, an optimal condition.

Qiang, et al. ASCO 2023

Allogeneic CAR T: CB-011

How It Works

Step 1: Donor T-Cell Harvest

- Healthy allogeneic donor T cells collected
- No patient-specific manufacturing required
- Product available off-the-shelf immediately

Step 2: CRISPR Genome Editing (chRDNA technology)

- TRAC locus knocked out → removes TCR → prevents graft-versus-host disease (GvHD)
- B2M knocked out → removes HLA class I surface expression → evades host T-cell rejection

Step 3: Immune Cloaking — Dual NK + T-Cell Evasion

- B2M–HLA-E fusion transgene inserted at the B2M locus
- HLA-E presents a "don't kill me" inhibitory signal to host NK cells via NKG2A receptor
- First allogeneic CAR T with dual evasion of both host T cells AND NK cells

Step 4: Anti-BCMA CAR Insertion & Infusion

- Anti-BCMA CAR construct inserted — targets BCMA on myeloma plasma cells
- Single infusion after standard lymphodepletion
- No bridging therapy; median time from enrollment to infusion: 1 day
- Potential for 50–100 patient doses per manufacturing batch

FDA granted Regenerative Medicine Advanced Therapy (RMAT) designation to CB-011 — March 2026. Dose expansion (Part B) ongoing; updated data expected 2026.

CaMMouflage Phase 1 Results

Efficacy

92%
ORR
BCMA-naïve, RDE, n=12

75%
≥CR rate
BCMA-naïve cohort at RDE

91%
MRD negativity
10^{-5}, n=11

58%
Remaining ≥VGPR
at ≥6 months (7/12)

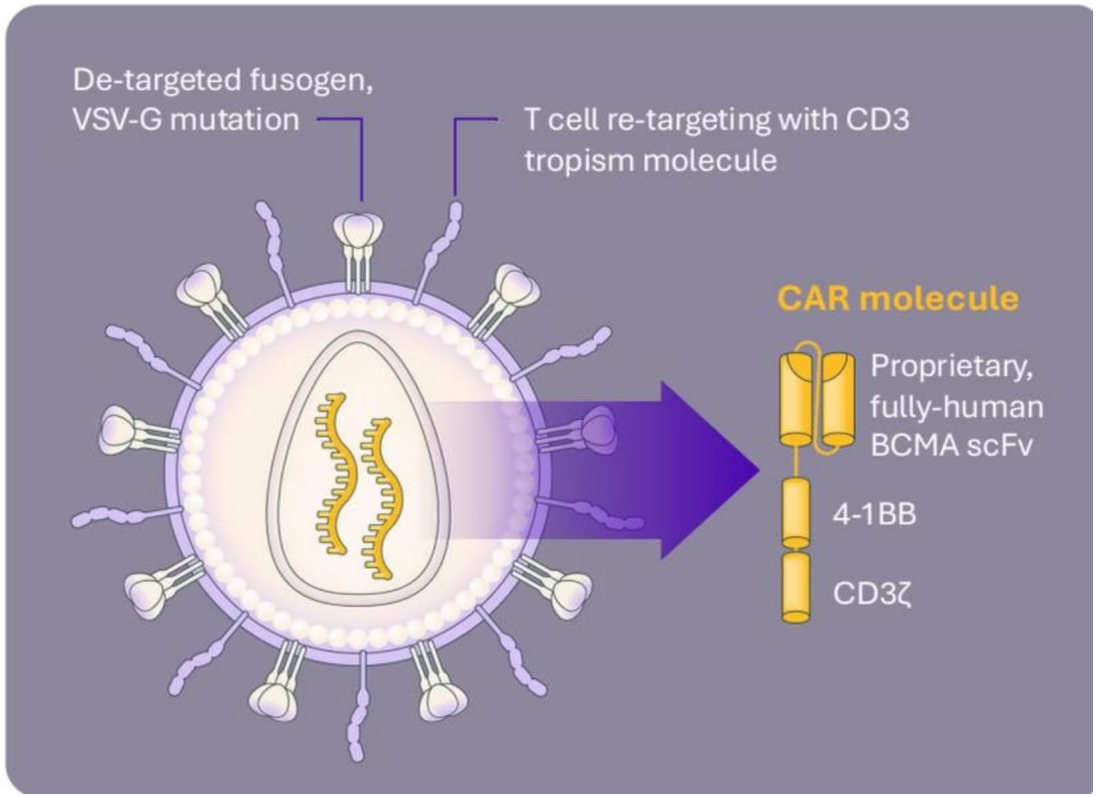
Tolerability

21%
CRS rate
all grade ≤2, across all cohorts

0%
GvHD
no ICANS, no enterocolitis, no parkinsonism

Rossi A, et al. CaMMouflage Phase 1, ASTCT 2026

KLN-1010: A Modified LVV Generating Anti-BCMA CAR-T Cells *In Vivo*



Envelope-Modified LVV LVV

Replication-incompetent, self-inactivating lentiviral vector for safe delivery.

De-targeted VSV-G Fusogen

Avoids delivery to LDL-expressing cells while maintaining high transduction efficiency.

Precise T-Cell Re-targeting

CD3 scFv avoids liver uptake and drug sinks, directing the vector specifically to T cells.

Anti-BCMA CAR

Selected for high activity against BCMA-positive tumors; features proprietary proprietary fully-human BCMA scFv, 4-1BB, and CD3ζ CD3ζ domains.

Ho J, et al. LBA. ASH 2025

Baseline Characteristics of Initial 4 Patients

Patient	Dose Level	Age/Sex	MM Subtype	High-Risk Cytogenetics	Prior Lines	Prior ASCT	Refractoriness
1	DL1 (2×10^7 IU/kg)	72 / Male	IgG lambda	del17p, +1q	4	Y	PI, IMiD, α-CD38
2	DL1 (2×10^7 IU/kg)	62 / Female	IgG lambda	del17p, t(4;14), del1p32	3	Y	IMiD, α-CD38
3	DL1 (2×10^7 IU/kg)	61 / Female	IgG lambda	t(4;14)	3	Y	PI, IMiD, α-CD38
4	DL-1 (6×10^6 IU/kg)	70 / Male	IgM kappa	del17p, +1q	5	Y	PI, IMiD, α-CD38

All patients had prior autologous stem cell transplant and were triple-class refractory. BMPC ranged from <5% to 60% at baseline.

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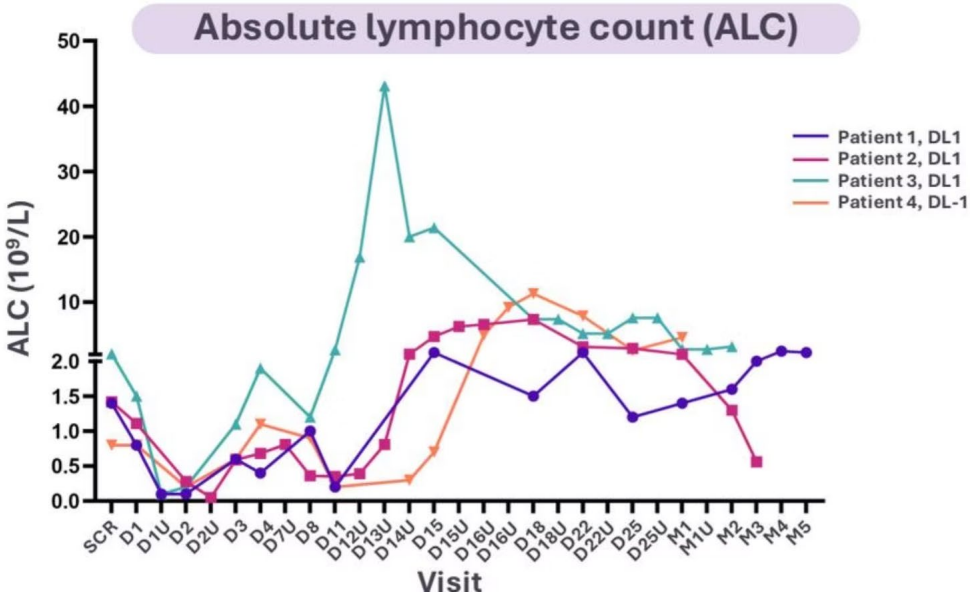
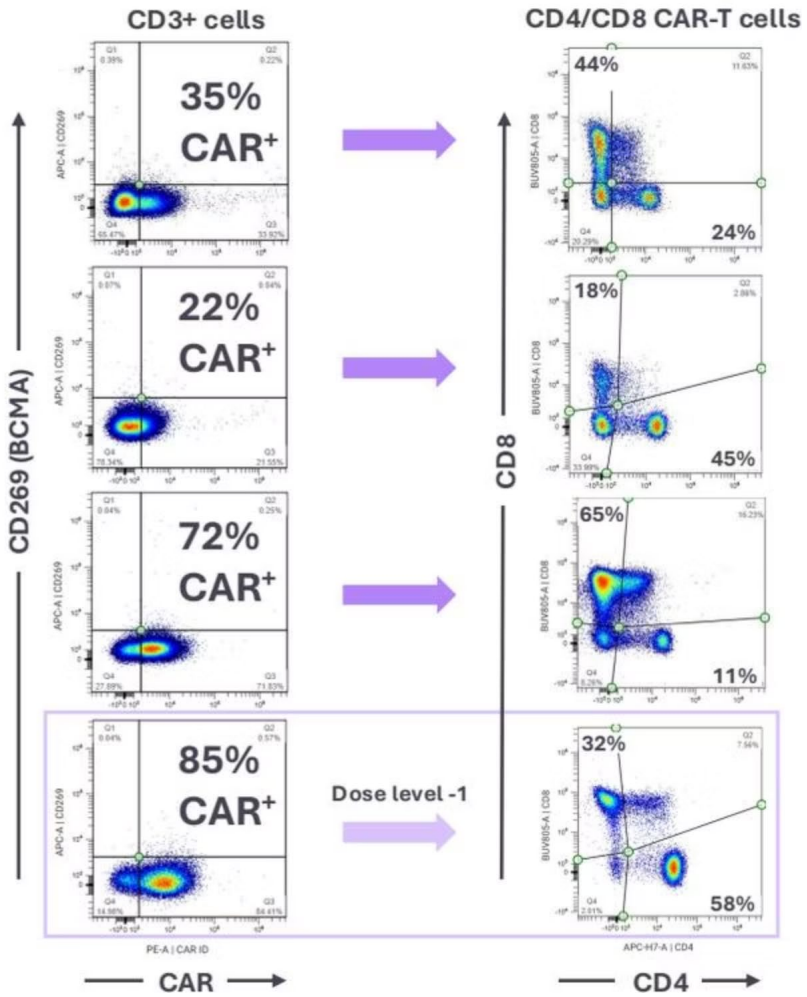
CAR-T Expansion Without Lymphodepleting Chemotherapy

Absolute Lymphocyte Count (ALC)



Dexamethasone administered to patients 3 and 4. No clinical sequelae related to lymphocytosis.

Blood CAR-T Cells at Day 15



CAR+ fractions of CD3+ cells at Day 15: **35%**, **22%**, **72%** (DL1 patients) and **85%** (DL-1 patient), with mixed CD4/CD8 phenotypes across all patients.

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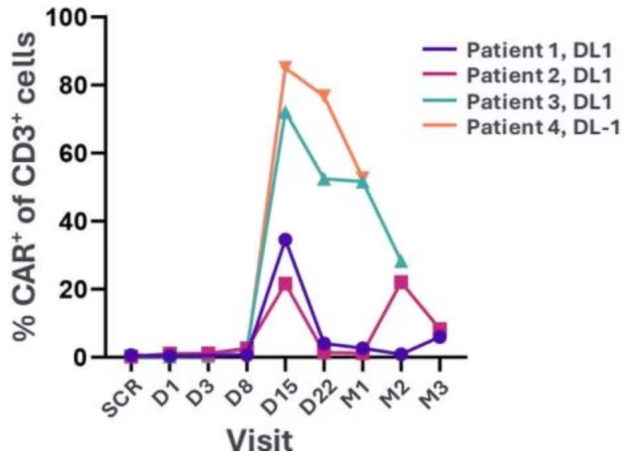
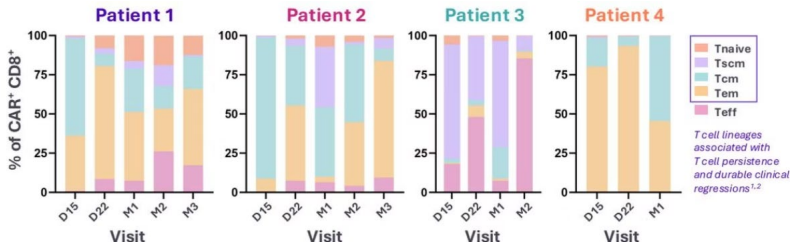
Persistent Memory CAR-T Cells and Expansion Commensurate with Approved Therapies

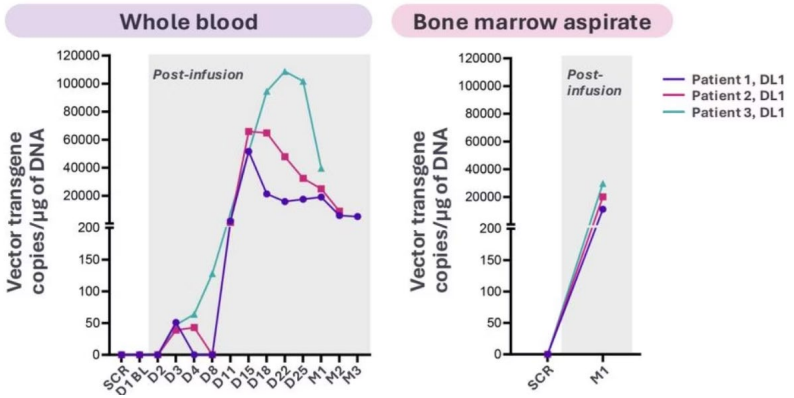
% CAR+ of CD3+ Cells Over Time



Circulating BCMA CAR-T Cell Phenotypes



Vector Transgene Copies vs. Approved *Ex Vivo* CAR-T



51,647

Patient 1 Cmax

Vector copies/µg DNA

65,873

Patient 2 Cmax

Vector copies/µg DNA

108,730

Patient 3 Cmax

Vector copies/µg DNA

Cmax in line with approved *ex vivo* CAR-T (CARTITUDE-1 median: 47,806; CARTITUDE-4 median: CARTITUDE-4 median: 34,891). Persistence observed in both blood and bone marrow. Memory marrow. Memory T-cell phenotypes (Tscm, Tcm) are associated with durable clinical regressions.

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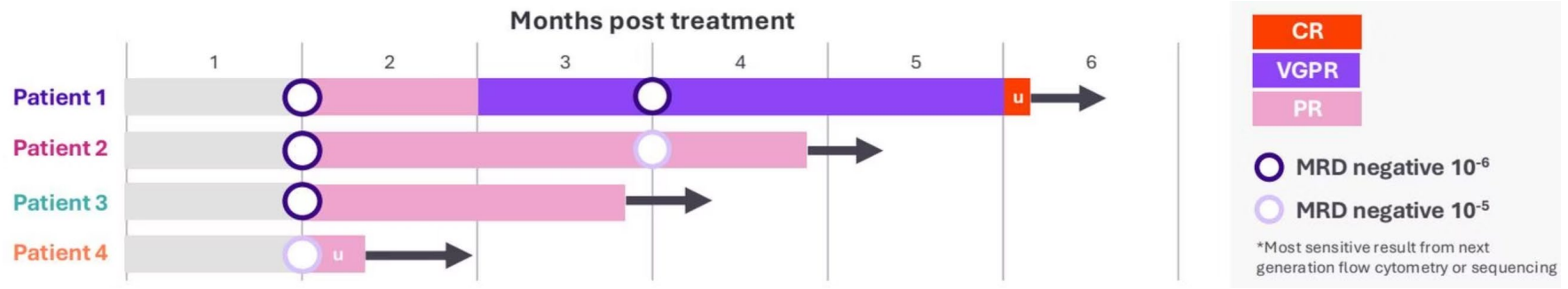
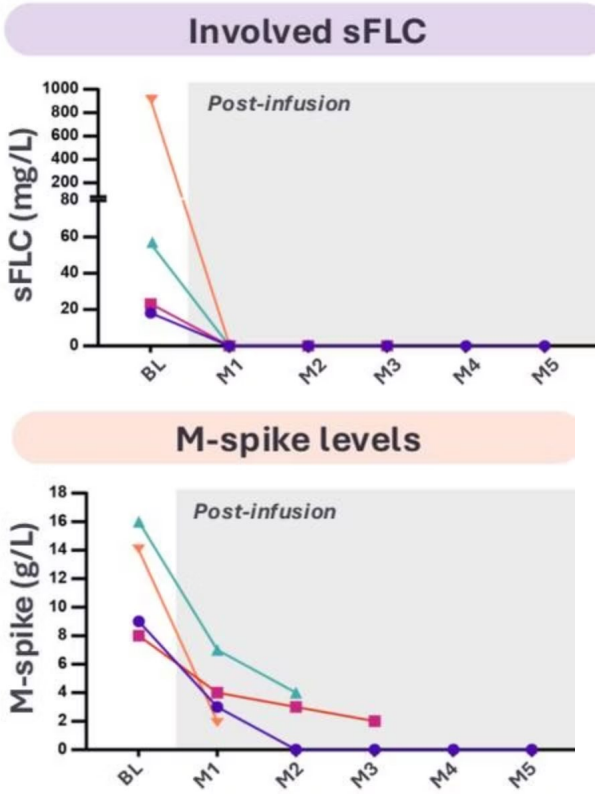
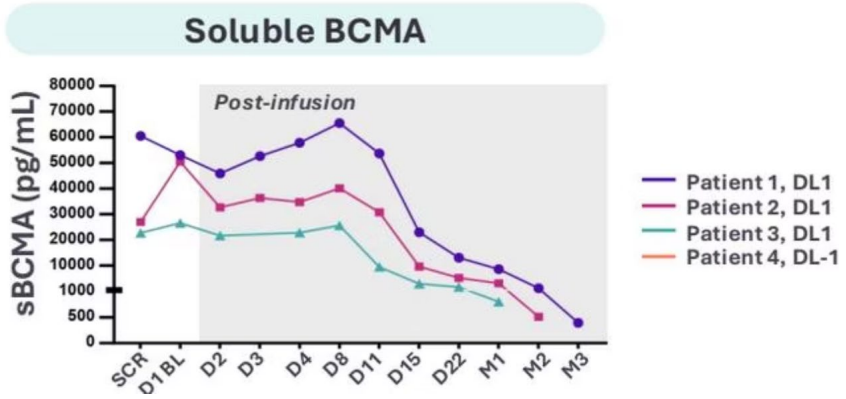
Deep, Ongoing MRD-Negative Responses Across All 4 Patients



Involved sFLC & M-Spike



Soluble BCMA



All patients achieved MRD negativity (10^{-5} or 10^{-6} sensitivity). Patient 1 achieved CR CR deepening over 6 months. sFLC, M-spike, and soluble BCMA all declined sharply post- sharply post-infusion and remained suppressed through month 5.

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Take Home Messages

Current Approved CAR T: Right Drug, Right Patient

- Ide-cel (KarMMa-3): preferred in older/frailer patients — favorable tolerability, manageable CRS/iiNT, sustained QoL improvement vs standard regimens
- Cilta-cel (CARTITUDE-1/4): deepest responses, 33% of patients progression-free ≥5 yr — first evidence of potential functional cure from a single infusion

Earlier Is Better — and Predictors Matter

- Moving CAR T earlier in the treatment sequence drives deeper, more durable responses
- Key predictors of ≥5-yr PFS: lower tumor burden, higher naïve T-cell fraction in drug product, favorable T:N ratio, sustained MRD negativity (10^{-5}–10^{-6})
- Patient selection and optimal sequencing (before bispecific exposure) are critical to maximizing cure potential

Expanding Beyond BCMA: New Targets on the Horizon

- GPRC5D and FcRH5 emerging as potent alternative/combination targets, including post-BCMA failure
- Dual targeting (BCMA+CD19, e.g. AZD012; GPRC5D+BCMA): addresses clonal escape via B-cell reservoir
- Multi-antigen strategies may overcome antigen loss, a key resistance mechanism

Next-Generation CAR T Design: In Vivo, Allogeneic & Beyond

- Allogeneic/off-the-shelf (CB-011): immediate availability, no bridging, no GvHD — democratizing access
- In vivo CAR T (lipid nanoparticle delivery): eliminates ex vivo manufacturing entirely — potential for rapid, scalable, low-cost delivery
- Armored CARs, logic-gated constructs, and T-cell engineering (TSCM enrichment) to enhance persistence and reduce exhaustion

Toward a Majority Cure Fraction — Including High-Risk Disease

- Expanding the cure fraction beyond the current ~33% requires earlier use, better patient selection, and next-gen design
- High-risk populations remain the greatest unmet need: plasma cell leukemia (PCL), extramedullary disease (EMD), high-risk cytogenetics (del17p, t(4;14), gain1q), and functional high-risk disease
- The convergence of optimized CAR T design, earlier intervention, and combination strategies offers a realistic path to majority cure and transformed outcomes across all risk groups

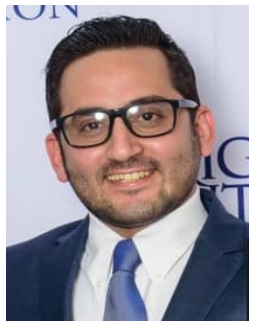
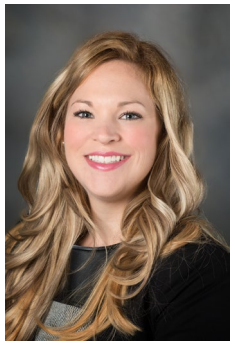
Thank You







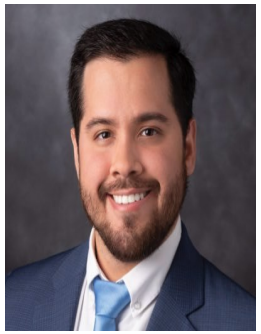






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