CAR T-Cell and Bispecific Antibody Therapies in Multiple Myeloma

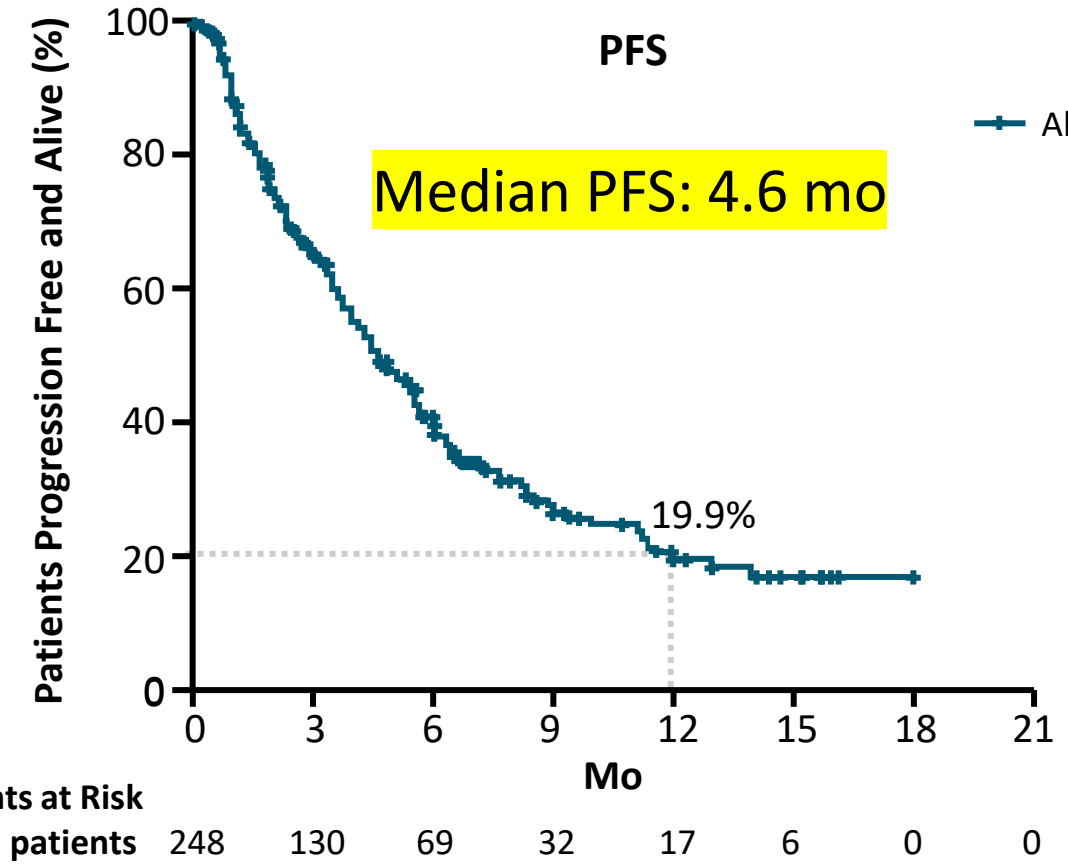
Dr Noa Lavi November 2025

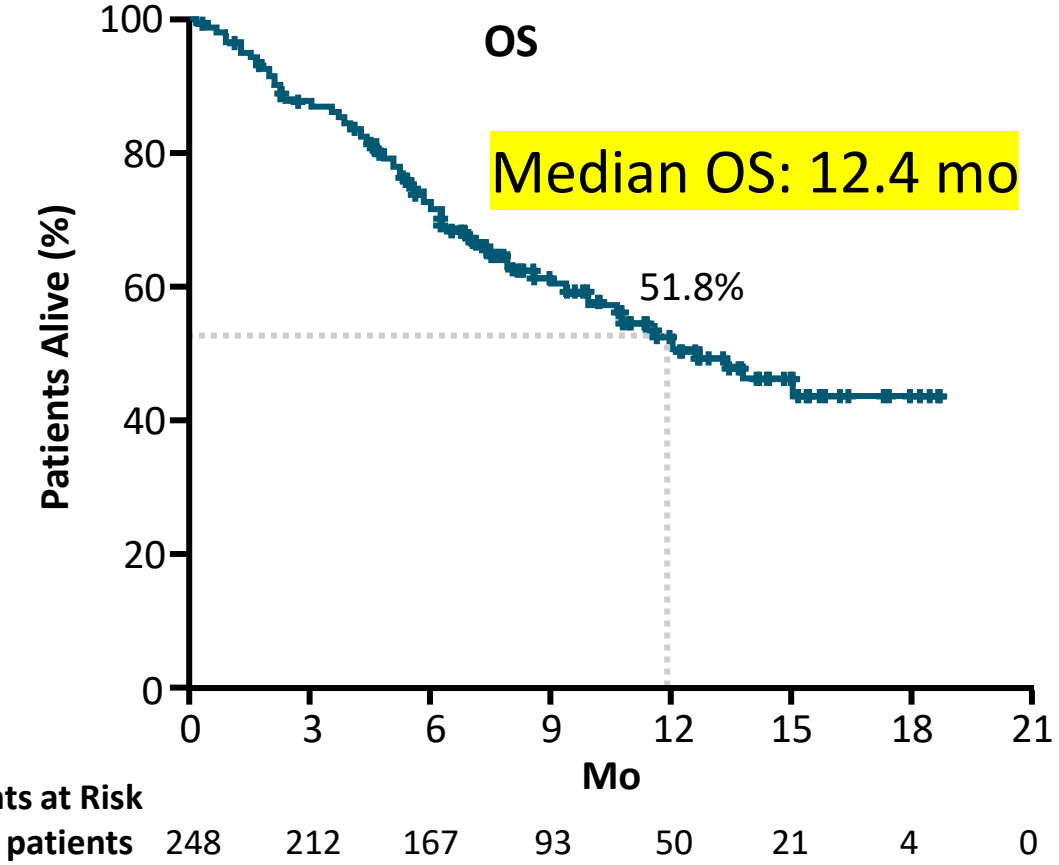
*חלק מהשקופיות במצגת זאת נלקחו מאתר: וחלק מהשקופיות נלקחו ממצגת של פרופ' יעל כהן

AGENDA

- **Immunotherapy in Multiple Myeloma**
- **CAR T-Cell Therapies in R/R MM**
  - Ide-Cel & Cilta-cel in RRMM
  - Bridging Therapy
  - Other Novel CAR T-Cell Approaches
- **Bispecific Antibodies** in R/R MM, Combination Regimens
- **Adverse Events** associated With CAR-T and Bispecific Abs
- **Sequencing** Immunotherapies in R/R MM
- **Resistance** to BisAbs & CART
- **Conclusions**

LocoMMotion Trial of Real-life SoC: Outcomes in All Patients With Triple-Class Exposed MM

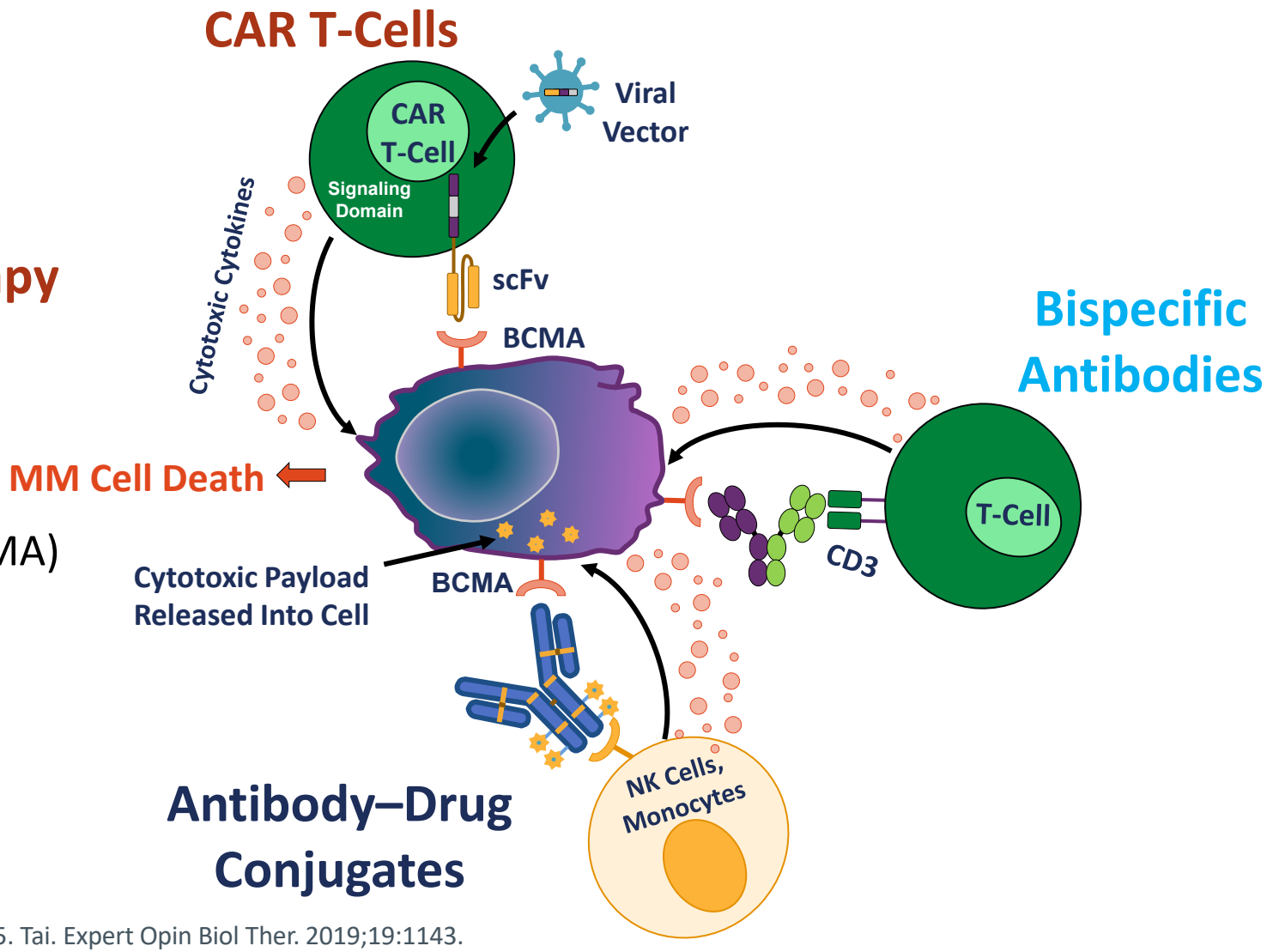




Mateos. Leukemia. 2022;36:1371.

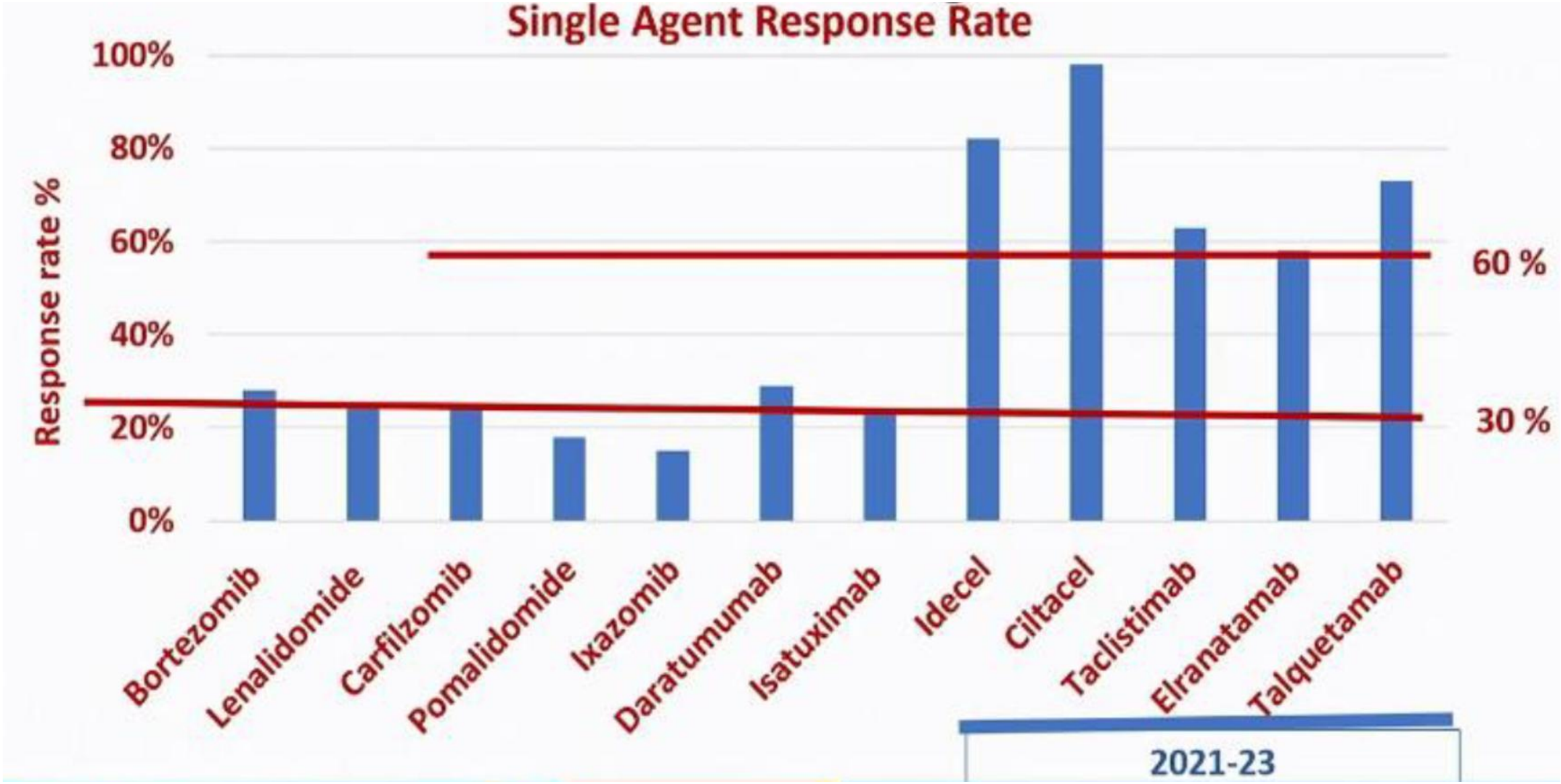
Immunotherapy in Multiple Myeloma

- **Antibody–drug conjugate**
  - Belantamab mafodotin-blmf
- **BCMA-directed CAR T-cell therapy**
  - Idecabtagene vicleucel
  - Ciltacabtagene autoleucel
- **Bispecific antibodies**
  - Teclistamab and elranatamab (BCMA)
  - Talquetamab (GPRC5D and CD3)
  - Linvoseltamab (BCMA and CD3)
- **Naked antibodies**

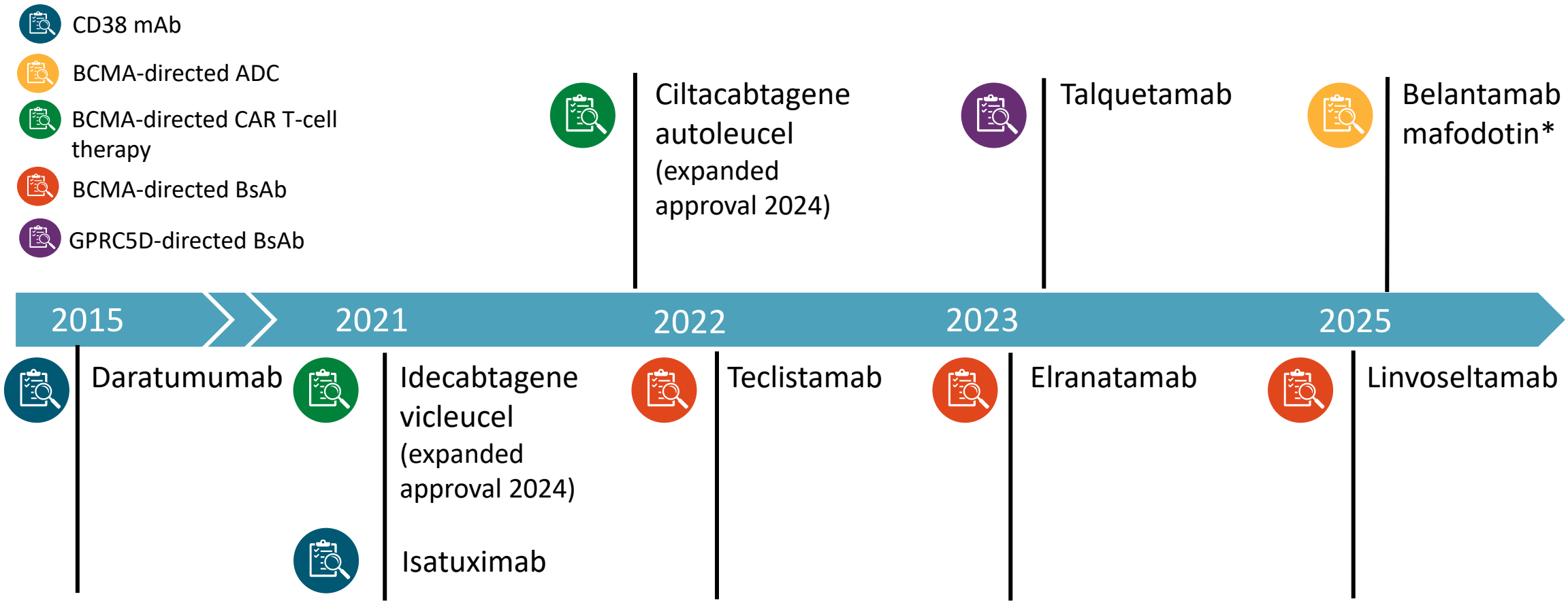


Cho. Front Immunol. 2018;9:1821. Su. J Hematol Oncol. 2021;14:115. Tai. Expert Opin Biol Ther. 2019;19:1143.

Immunotherapy is a different League! Tremendous Progress



Novel Therapies in MM- FDA APPROVAL



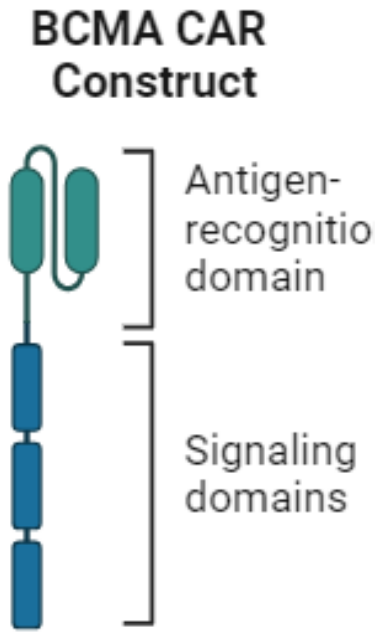
*Belantamab mafodotin monotherapy was voluntarily withdrawn in November 2022 but regained FDA approval in October 2025 for use in combination with bortezomib and dexamethasone.

Ciltacabtagene autoleucel PI. Belantamab mafodotin PI. Daratumumab PI.
Elranatamab PI. Isatuximab PI. Idecabtagene vicleucel PI. Teclistamab PI. Talquetamab PI. Linvoseltamab PI. Belantamab mafodotin PI.

CAR T-Cell Therapies in R/R MM

FDA Approved CAR T-Cell Therapies for R/R MM

Parameter	Idecabtagene Vicleucel	Ciltacabtagene Autoleucel
CAR type	BCMA/CD137 (4-1BB)/CD3ζ	**2-BCMA binding domains**/CD137 (4-1BB)/CD3ζ
Costimulatory domain	4-1BB	
Vector	Lentiviral	
Lymphodepletion	IV cyclophosphamide IV 300 mg/m^2 + fludarabine 30 mg/m^2 QD x 3 days	
Pivotal trials	KarMMa and KarMMa-3	CARTITUDE-1 and CARTITUDE-4
Median time from leukapheresis to delivery	35 days	32 days



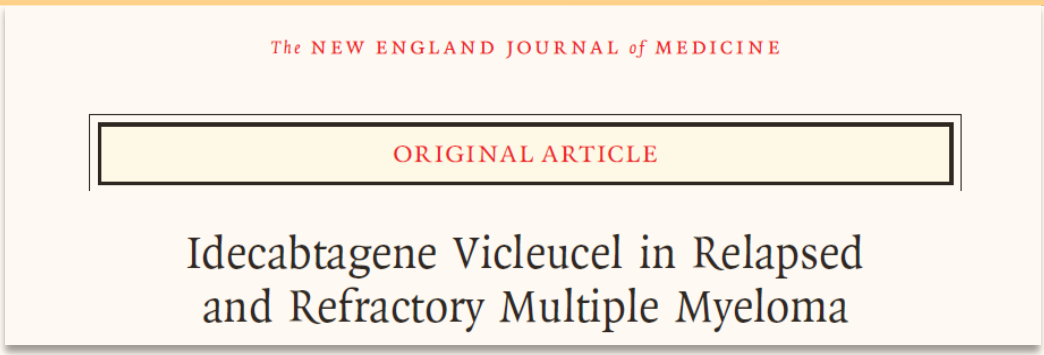
Initial approvals: patients with **R/R MM after ≥4 prior LoT, including an IMiD, PI, and CD38 mAb**

Expanded indications granted (April 2024):

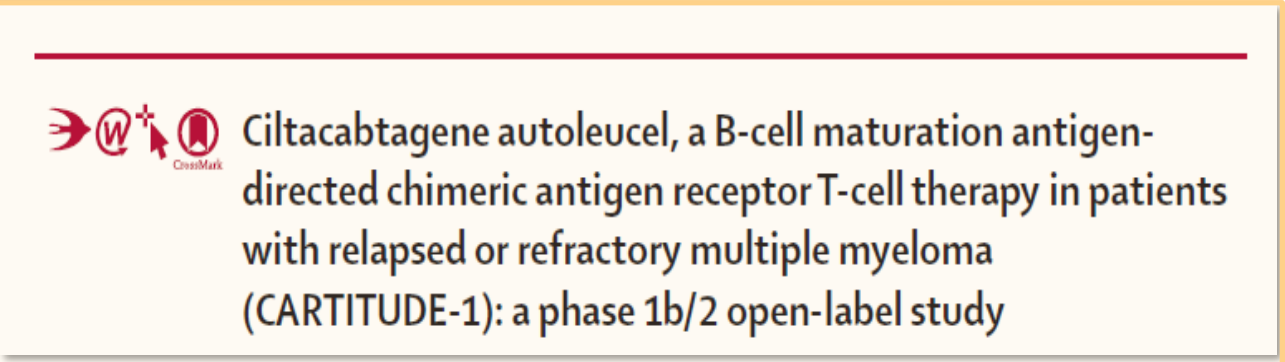
ide-cel after ≥2 prior LoT including an IMiD, PI, and CD38 mAb and

cilta-cel after 1+ prior LoT including a PI and IMiD and refractory to Len

Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Abebe. Front Immunol. 2022



Munshi NC et al. **N Engl J Med 2021;384:705-16.**



Berdeja JG et al ***Lancet*** **2021; 398: 314–24**

Ide-Cel & Cilta-cel Phase 1b/2 in RRMM

- **Karmma (ide-cel)**
- **Cartitude-1 (cilta-cel)**

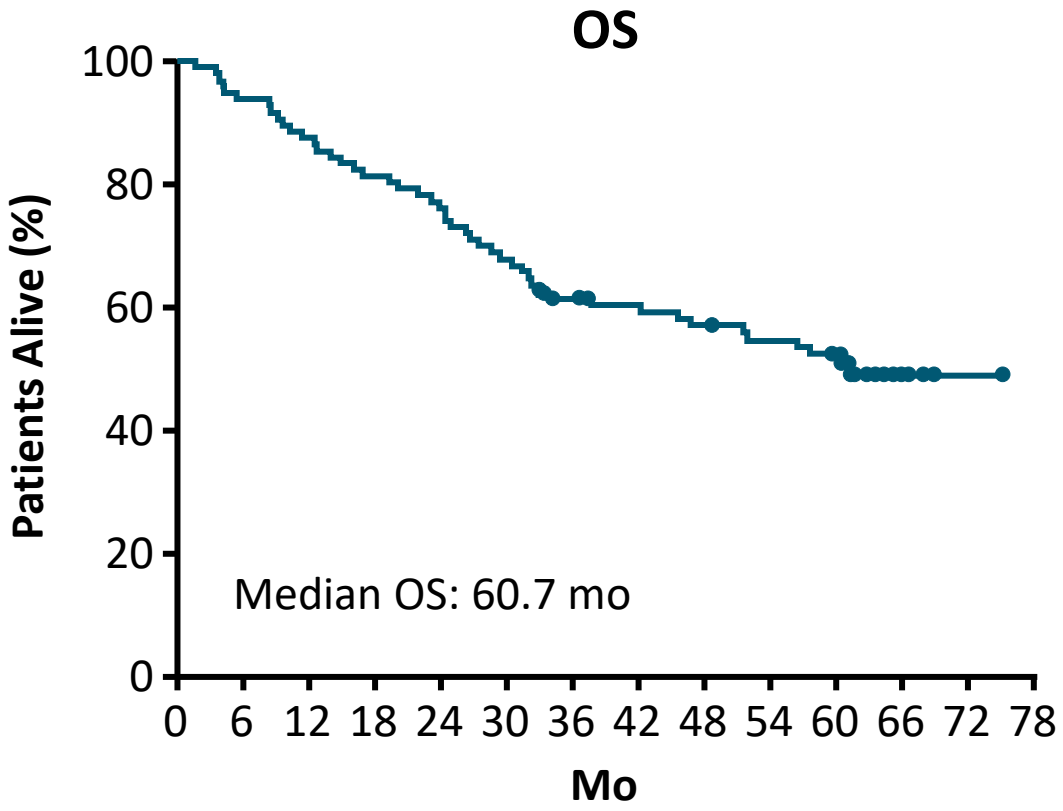
	KarMMA (Ide-Cel) n=128	Cartitude-1 (Cilta-Cel) n=97
Population	≥3 prior regimens Triple class exposed Refractory to last LoT	≥3 prior regimens or double refractory Triple class exposed Progressive disease (IMWG)
Endpoints	**Primary**: ORR **Secondary**: CR rate	**Primary**: safety & dose confirmation, ORR **Secondary**: PFS, OS, MRDneg (10^{-5})
Dose	**150 – 450 x 10^6**	**0·75 × 10^6** CAR-positive viable T cells/kg
Median Age (range)	61 (33-78)	61 (33-78)
EMD	39%	13.4%
High tumor burden	51%	21.9%
HR Cyto	35%	23.7%
Bridging Tx	88%	75%
Prior LoT (Median)	6	6
Triple refractory	84%	87.6%
Penta refractory	26%	42.3%

Efficacy

	KarMMA (Ide-Cell) n=128	Cartitude-1 (Cilta-Cell) n=97
ORR	**73%** **81%** in 450M dose	**97.9%**
CR rate	**33%** **39%** in 450M dose	**82.5%**
MRD negativity	26%	**34%**
DoR (Median, months)	**10.7** **11.3** at 450M dose; **19** in pts with CR	**33.9**
PFS (Median, months)	**8.8** [95%CI 5.6-11.6] **12.1** at 450M dose **20.2** at pts with CR	**34.9 mo** [95%CI 25.2-NE] Not reached in CR pts
OS (Median, months)	***24.8** [95%CI 31.2 – 19.9] **78%** at 12 months	Not reached 62% at **3 years**

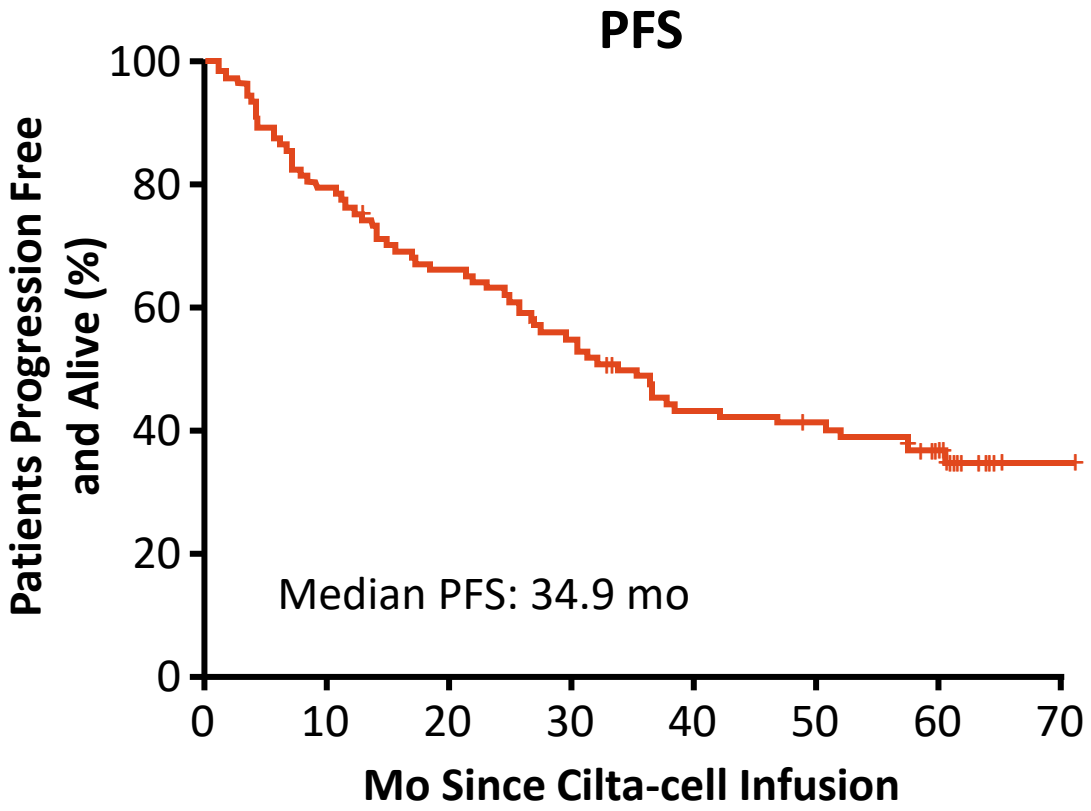
CARTITUDE-1 Cilta-cel in R/R MM: Long-term Survival Outcomes (≥5 Yr)

Median follow-up: 61.3 mo



Patients at Risk, n

OS	97	91	85	79	74	66	58	53	51	48	36	5	1	0



Patients at Risk, n

PFS	97	77	63	52	39	36	16	1

1/3 remain alive and progression-free for ≥5 years

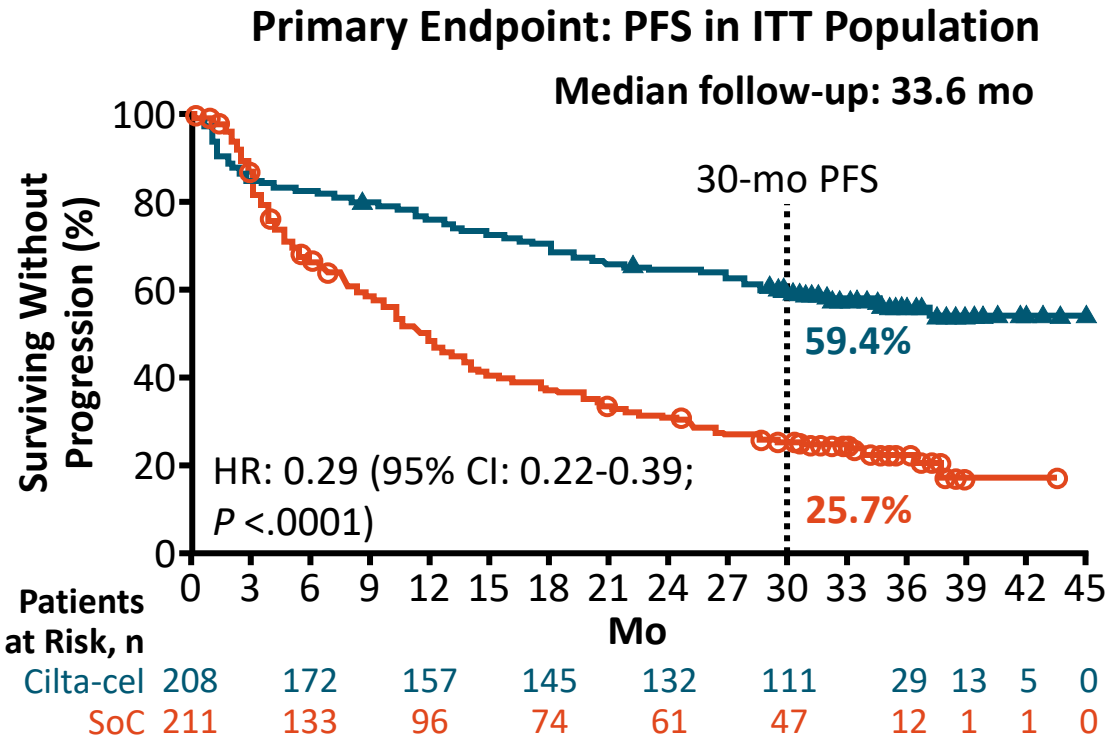
Jagannath. JCO. 2025

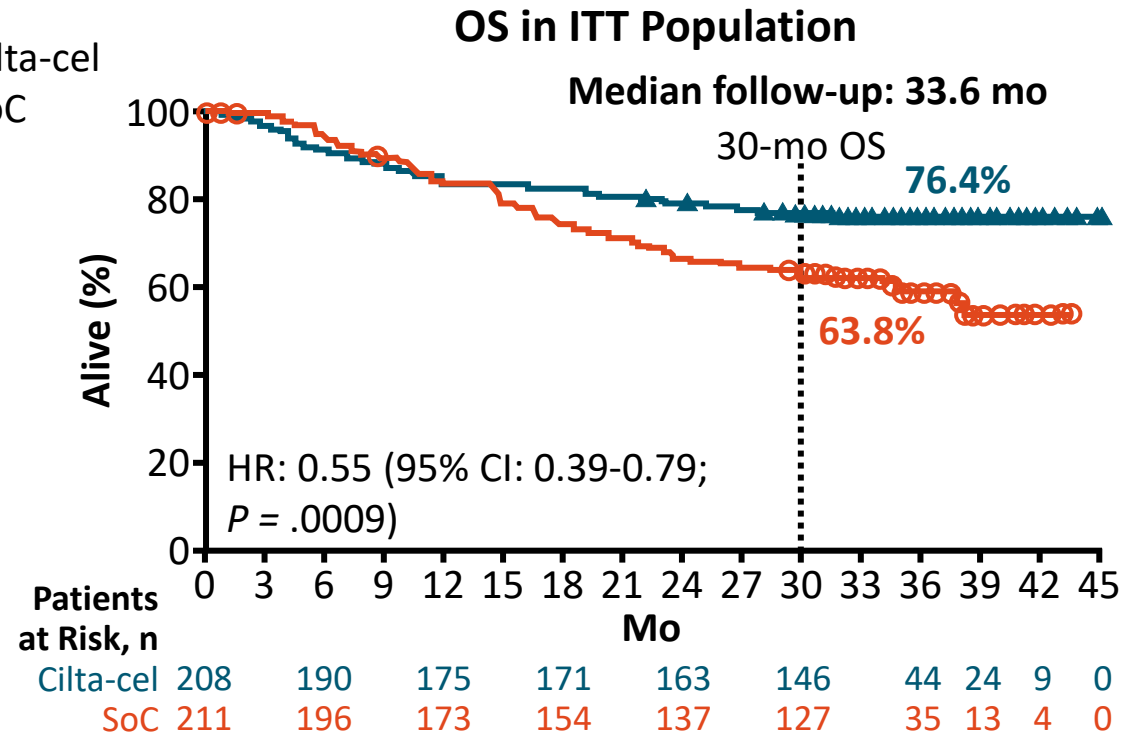
Ide-Cel & Cilta-cel Phase 3 RCT in RRMM

- **Karmma-4 (ide-cel)**
- **Cartitude-4 (cilta-cel)**

	KarMMA-3 (Ide-Cell) n=254	Cartitude-4 (Cilta-Cell) n=208
Population	2–4 previous regimens, Triple Class exposed, Refractory to last LoT	1–3 prior LOT (including PI + IMiD), Len refractory
Comparator arm	DPd, DVd, IRd, Kd, or Epd n = 132	PVd or DPd n=211
Endpoints	**1º**: PFS (ITT population by IRC); **2º**: ORR (by IRC), OS, CRR by IRC, Safety	**1º**: PFS **2º**: CR, ORR, MRD negativity, OS, Safety, PROs
Age (Median)	63 (30-81)	61.5 (27–78)
EMD	24%	21.2%
High tumor burden	28%	20.4%
HR Cyto	42%	59.4%
Prior LoT	Median: 3 (2–4)	2-3 LoT: 67.3%
Triple refractory	65%	14.4%
Penta refractory	6%	6.7% (exposed)

CARTITUDE-4 (Update): PFS and OS After 34 Mo of Follow-up



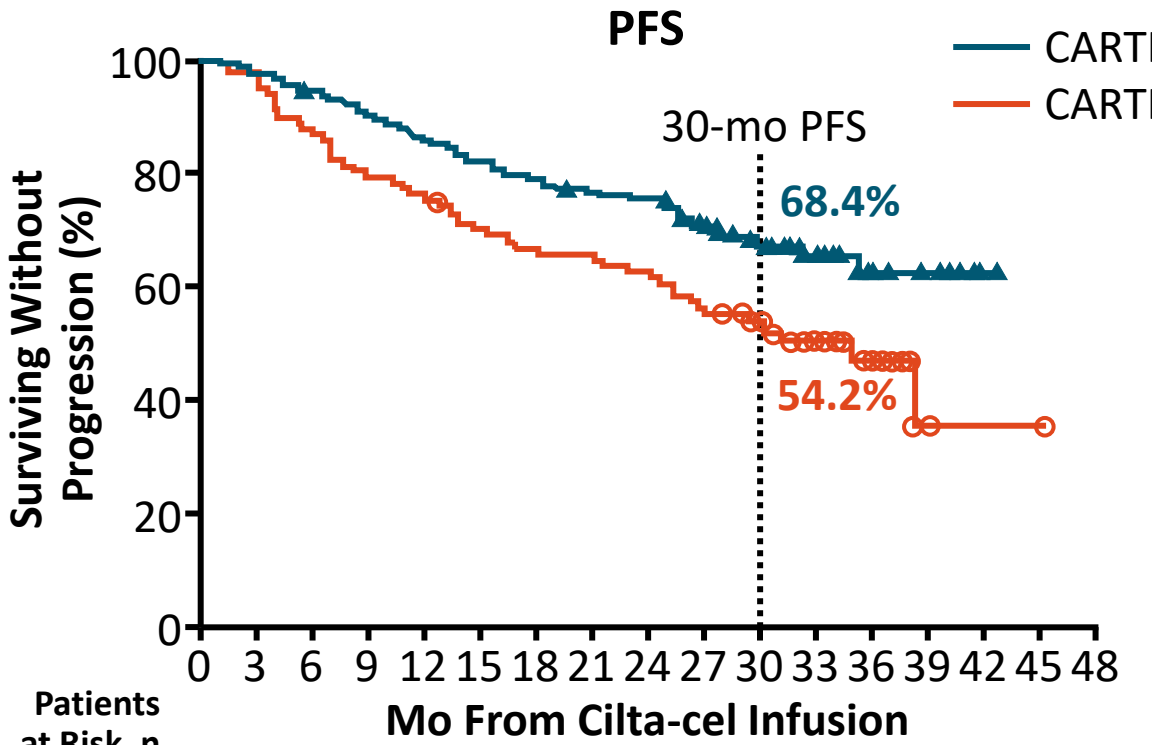


- Reduction in the risk of progression or death with cilta-cel across all prespecified subgroups regardless of prior lines of tx, ISS staging, presence/absence of soft tissue plasmacytomas, tumor burden status, cytogenetic risk at baseline, tx refractory status, prior exposure to daratumumab ± bortezomib

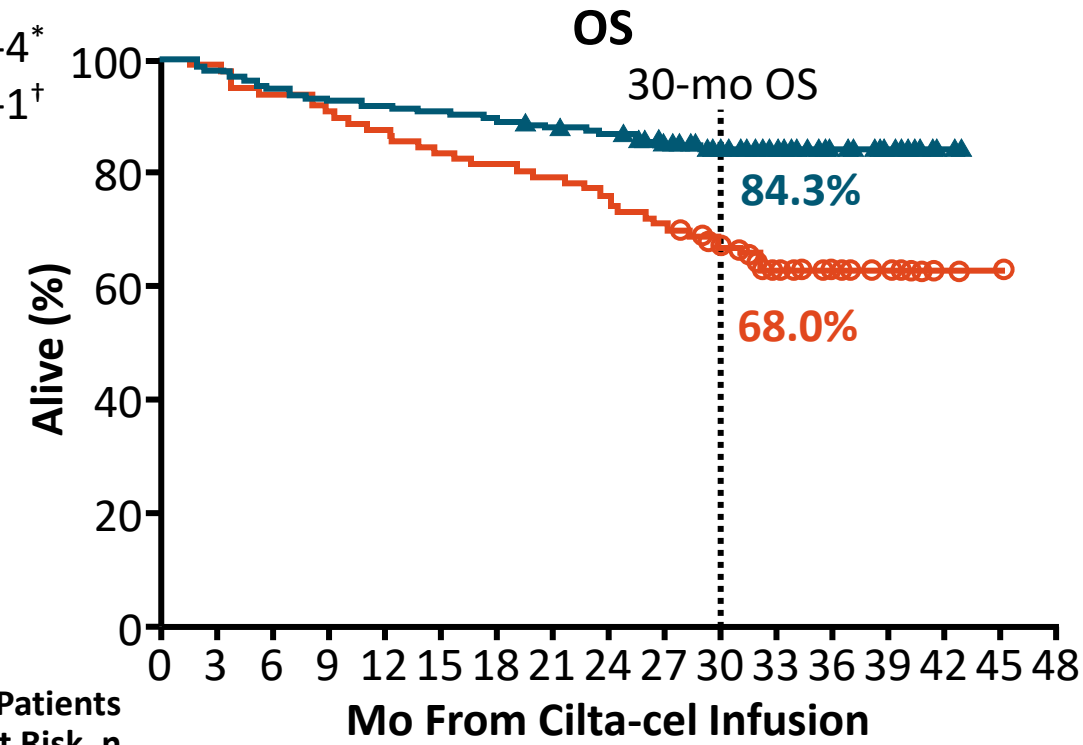
- Reduction in risk of death with cilta-cel across most prespecified subgroups except ISS stage III, which had 12 patients in the cilta-cel arm and 14 patients in the SoC arm

Mateos. IMS 2024. Abstr OA-65.

CARTITUDE-4 vs CARTITUDE-1 Phase Ib/II Trial of Cilta-Cel: PFS and OS in As-Treated Patient Population



Patients at Risk, n													
CARTITUDE-4 (1-3 prior LOT)	176	165	150	138	131	61	37	12	8	1	0	0	
CARTITUDE-1 (≥3 prior LOT)	97	85	74	64	60	44	25	13	2	1	1	0	



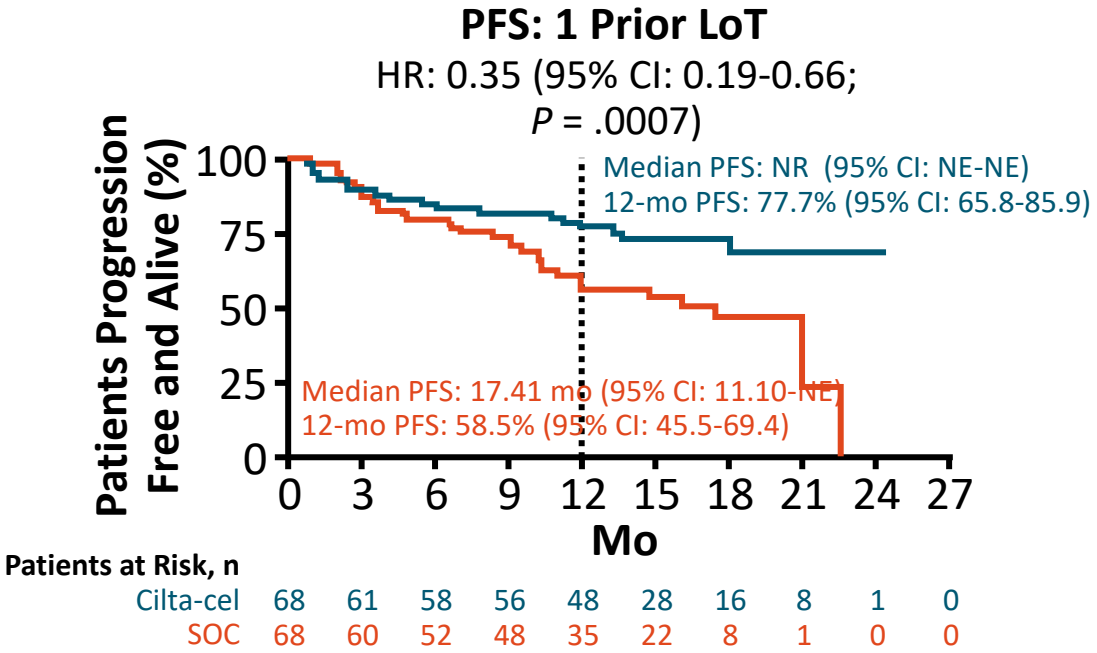
Patients at Risk, n													
CARTITUDE-4 (1-3 prior LOT)	176	167	162	158	151	83	53	20	12	2	0	0	
CARTITUDE-1 (≥3 prior LOT)	97	91	85	79	74	59	33	19	10	2	1	0	

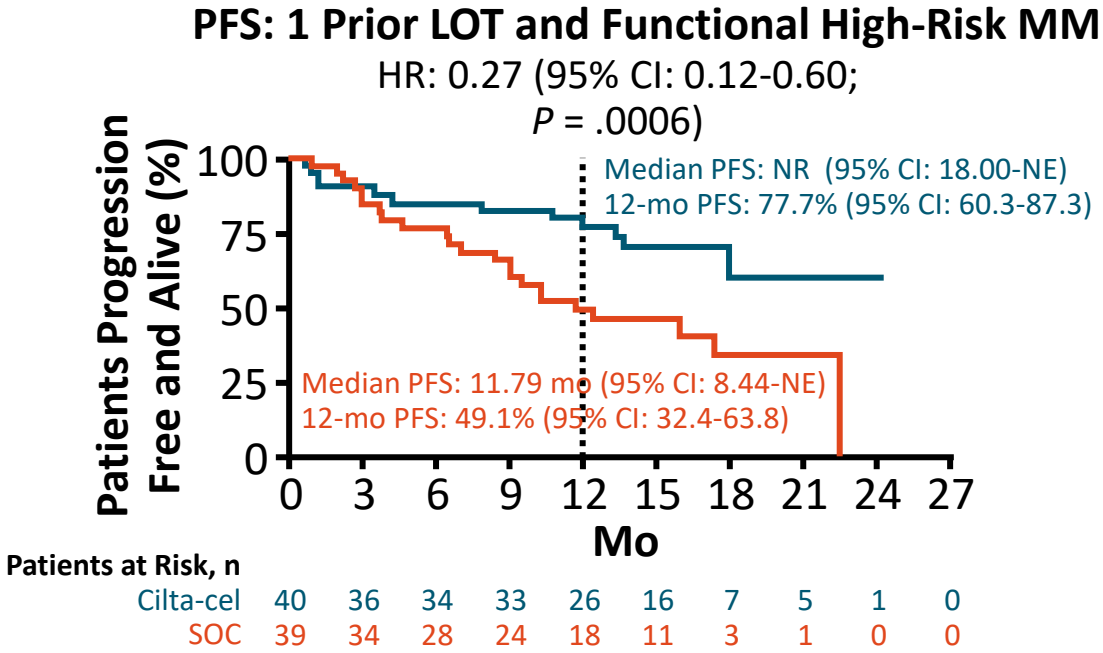
*Re-baselined to start at time of cilta-cel infusion for those who received cilta-cel on study, with a median f/u of 30.5 mo. †Median f/u: 33.4 mo.

- Use of cilta-cel in earlier lines of therapy demonstrated numerically higher OS and PFS rates

Mateos. IMS 2024. Abstr OA-65. Lin. ASCO 2023. Abstr 8009.

CARTITUDE-4 (Patients With Functional High-Risk MM): PFS, Response, and MRD Negativity

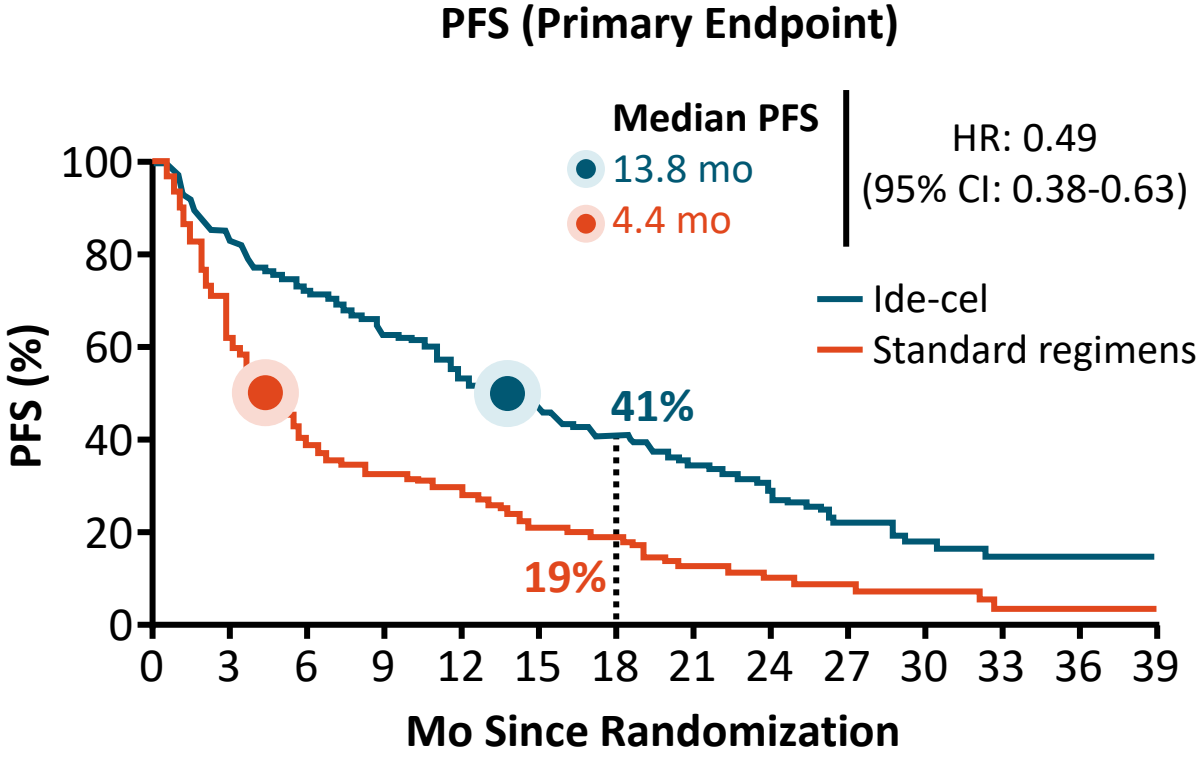




Response, %	Received Cilta-cel After 1 Prior LoT (n = 61)	Received Cilta-cel After 1 Prior LoT and Have Functional High-Risk MM (n = 35)
ORR	90	88
≥CR	71	68
MRD negativity (10^{-5})	63	65

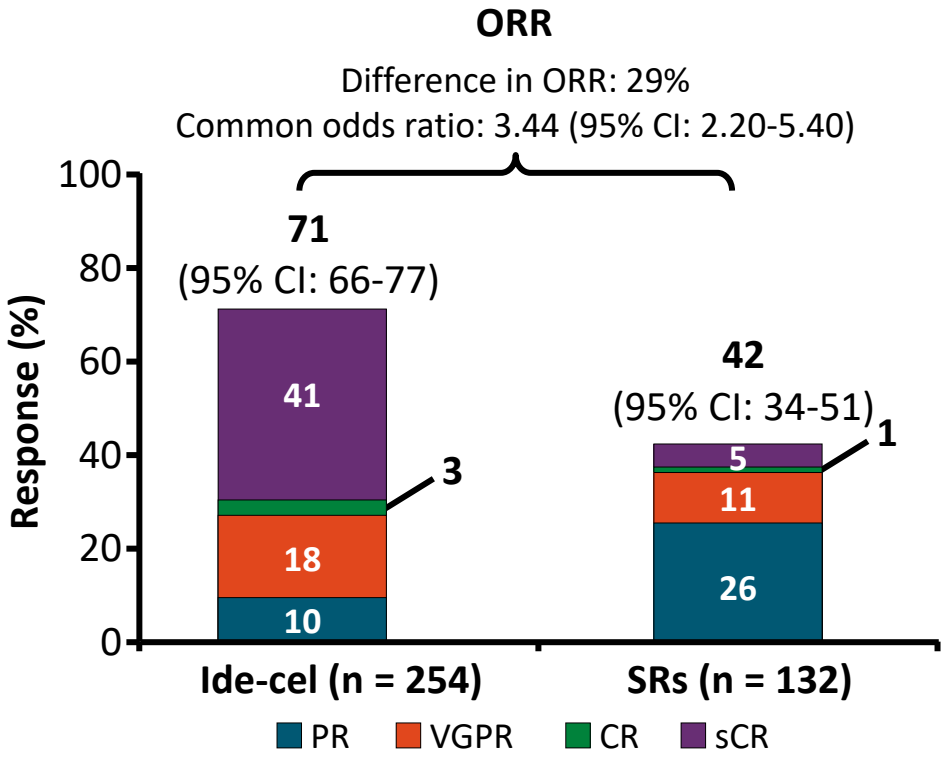
Weisel. EHA 2024. Abstr P959.

KarMMa-3: PFS and Response



Patients at Risk, n

Ide-cel	254	206	177	153	131	111	94	77	54	25	14	7	7	2
SRs	132	76	43	34	31	21	18	12	9	6	5	3	2	1



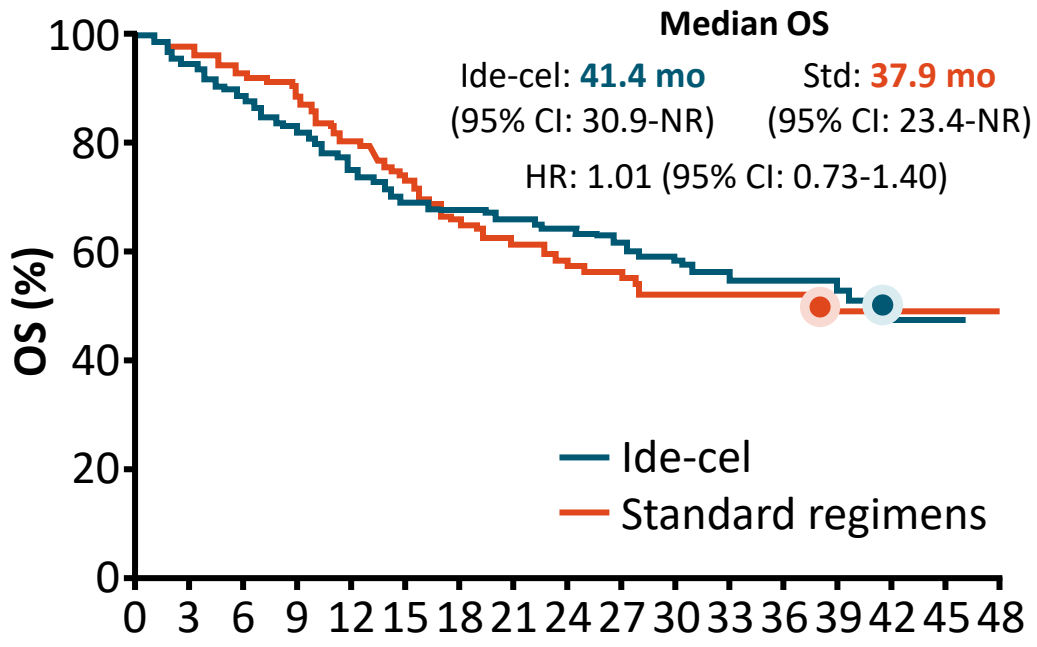
DoR	Ide-cel (n = 254)	SoC (n = 132)
Median DoR, mo (95% CI)	16.6 (12.1-19.6)	9.7 (5.5-16.1)

Median follow-up: 30.9 mo

Ailawadhi. Blood. 2024;144:2389.

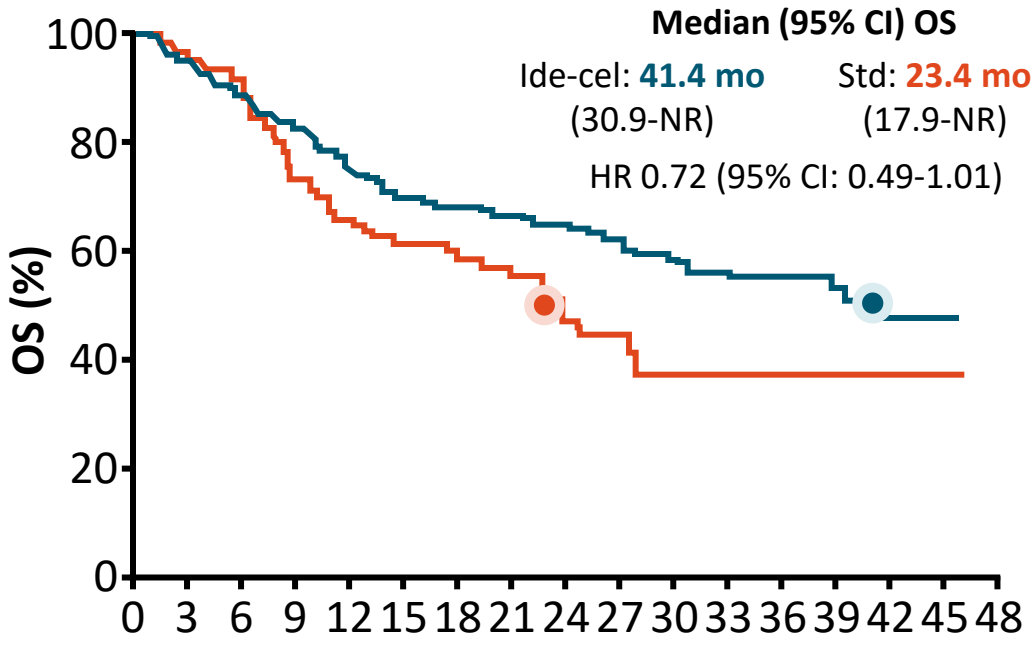
KarMMa-3: OS

OS in the ITT Population



Patients at Risk, n													
Ide-cel	254	223	190	169	143	75	48	44	30	13	4	0
Standard regimens	132	120	103	81	59	32	24	18	11	4	3	0

Severity OS Analysis Adjusted for Crossover



Patients at Risk, n													
Ide-cel	254	223	190	169	143	75	48	44	30	13	4	0
Standard regimens	132	118	67	42	21	9	8	4	2	1	1	0

- 56% of patients in the SoC arm crossed over to receive ide-cel

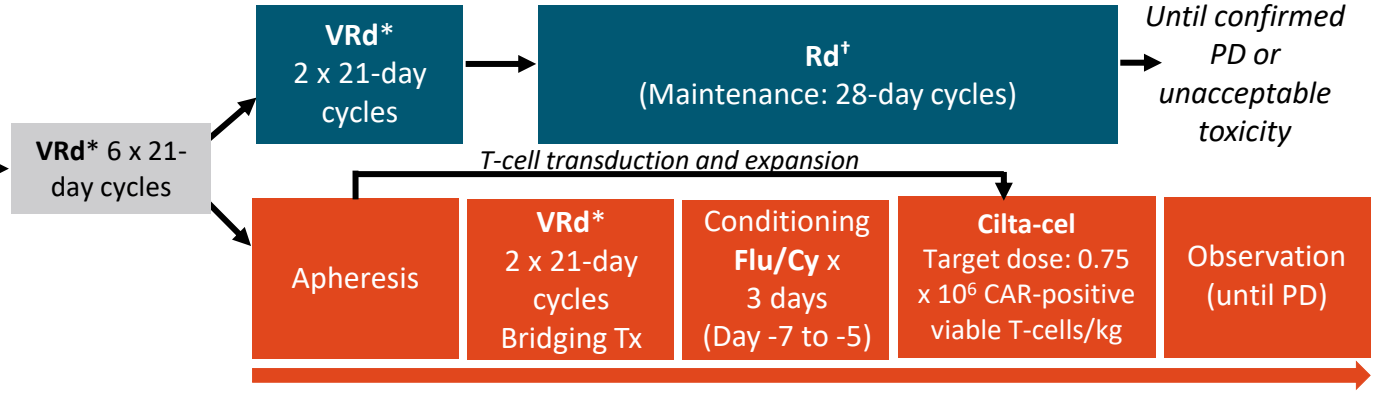
Median follow-up: 30.9 mo

Ailawadhi. Blood. 2024;144:2389.

Phase III CARTITUDE-5 and CARTITUDE-6 Trials

CARTITUDE-5

Patients with NDMM and documented diagnosis of MM; measurable disease at screening; ECOG PS 0/1; not considered for HDCT with ASCT; clinical laboratory values that meet criteria (N = 743)

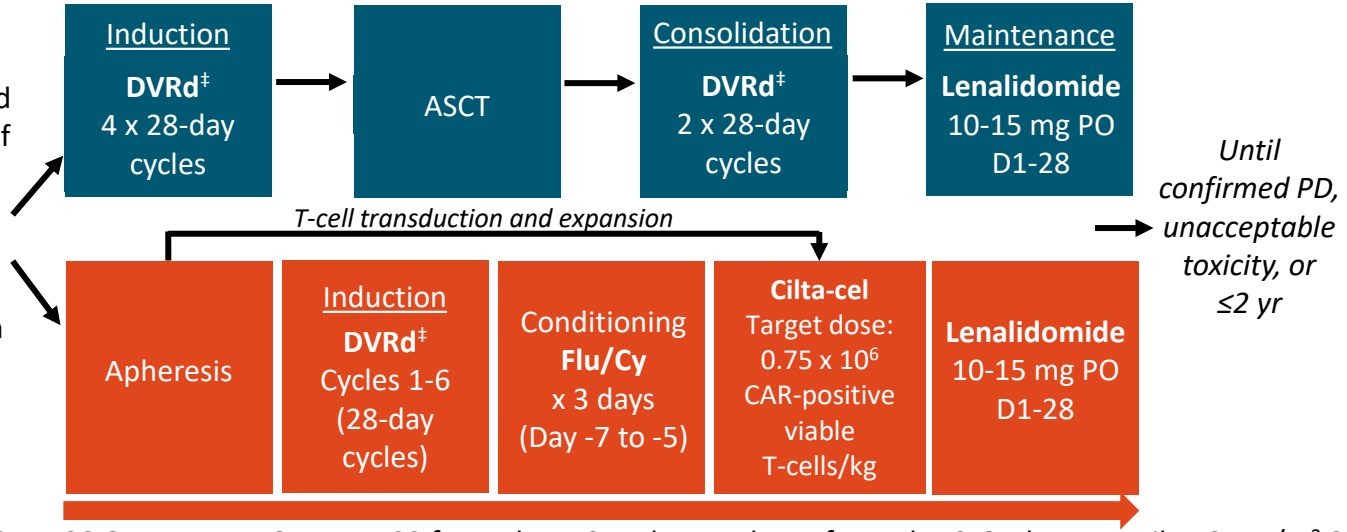


- **Primary endpoint:** PFS
- **Key secondary endpoints:** sustained MRD-negative CR, MRD-negative CR at 9 mo, overall MRD-negative CR, OS, ≥ CR, TTNT, PFS2, safety

*Bortezomib 1.3 mg/m^2 SC D1, D4, D8, D11 + lenalidomide 25 mg PO D1-14 + dexamethasone 20 mg PO D1, D2, D4, D5, D8, D9, D11, D12. †Lenalidomide 25 mg PO D1-21 + Dexamethasone 40 mg PO D1, D8, D15, D22.

CARTITUDE-6

Patients with NDMM and documented diagnosis of MM + intended HDT/ASCT; measurable disease at screening; ECOG PS 0/1; clinical laboratory values within prespecified range (target N = 750)



- **Coprimary endpoints:** PFS, sustained MRD-negative CR
- **Key secondary endpoints:** overall response, ≥ CR, MRD-negative CR, time to subsequent antimyeloma tx, PFS2, OS, HRQoL, safety

‡Daratumumab 1800 mg SC QW on D1, D8, D15, D22 for cycles 1-2 and D1 and D15 for cycles 3-6 + bortezomib 1.3 mg/m^2 SC D1, D4, D8, D11 for cycles 1-6 + lenalidomide 25 mg PO D1-21 for cycles 1-6 + dexamethasone 40 mg PO QW on D1, D8, D15, D22 for cycles 1-6.

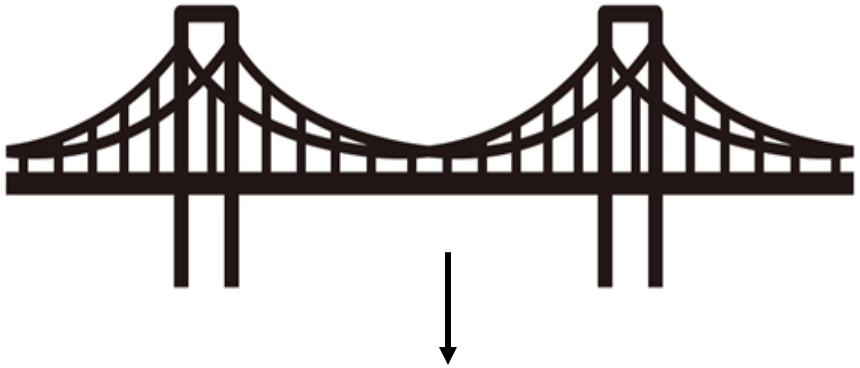
NCT04923893. NCT05257083.

Holding Therapy, Bridging Therapy, and Lymphodepletion Chemotherapy in MM

Holding therapy

- Definition: before apheresis
- **Goal:** control disease without jeopardizing feasibility of CAR T therapy
- Not standardized
- Often used: PIs, IMiDs, anti-CD38 mAbs, dex
- Avoid alkylators, bendamustine, polychemotherapy, TCEs

Apheresis



CAR T-Cell Infusion

Lymphodepletion CT

- Standardized
- Timed with CAR T-cell infusion
- **Goal:** induce extreme lymphopenia and corresponding cytokine milieu
- Fludarabine + cyclophosphamide
- Limited data for bendamustine
- Dose adjustment/drug choice influenced by renal function

Bridging therapy

- Definition: after apheresis, waiting for CAR T-cell therapy
- **Goal:** avoid clinical deterioration, reduce disease burden
- Not standardized
- Often used: PIs, IMiDs, anti-CD38 mAbs, dex
- Acceptable: alkylators, bendamustine, polychemotherapy, TCEs

Adapted from Costa. Leukemia. 2025;39:543.

Effective Bridging: Critical for CAR T-Cell Therapy

- Nonresponse to bridging can lead to:
  - Increased immune-mediated toxicity (parkinsonism)
  - High nonrelapse mortality
  - Decreased CAR T efficacy

Effective bridging is essential to get patients to CAR T and can mitigate the risk of toxicity

Sidana. Blood. 2025;146:167. Sidana. Blood. 2025;145:85. Hansen. JCO. 2023;41:2087. Gagelmann. JCO. 2024;42:1665. Rejeski. ASH 2024. Abstr 912.

Real-world Cilta-cel Outcomes: Impact of Bridging Response

- Analysis of >700 patients with MM receiving cilta-cel (MM RWD Consortium)
- Nonresponders to bridging had 10× higher risk of parkinsonism (5% vs 0.5% in responders; overall 2.9% incidence)
- Nonresponse or no bridging also linked to higher nonrelapse mortality
- Takeaway: **CAR T infusion may be best delayed until a bridging response (≥ PR) is achieved**

Surbhi Sidana, MD. Unpublished data US MM Immunotherapy Consortium. Data submitted ASH 2025.

What Bridging Therapy to Use

Highly effective anti-MM therapy that a patient is not refractory to

Holding: Before Apheresis

- Avoid drugs that can impact T-cell health (bendamustine, bispecific antibodies)
- Avoid drugs that have same target as CAR T therapy (BCMA-directed therapy)

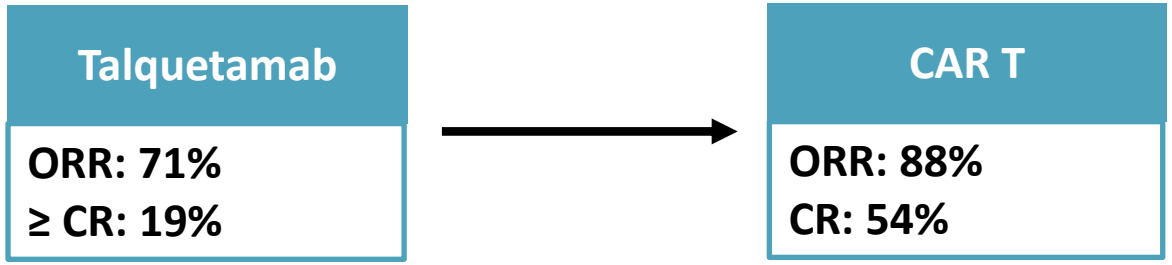
Bridging: After Apheresis

- Avoid drugs that have same target as CAR T therapy (BCMA-directed therapy)
- If possible, avoid drugs that can cause significant toxicity
- 1-2 cycles; longer if needed, or change regimen if not responding

Talquetamab: Effective Bridging Option for Late Relapse

Heavily pretreated population (N = 134):

- n = 119 with CAR T infusion (cilta-cel; n = 98)
- n = 19 patients received talquetamab as holding therapy
- Median prior LoT: 5
- High-risk cytogenetics: 44%
- EMD: 41%
- Median talquetamab exposure: 23 days



Dhakal. Blood. 2025;[Epub].

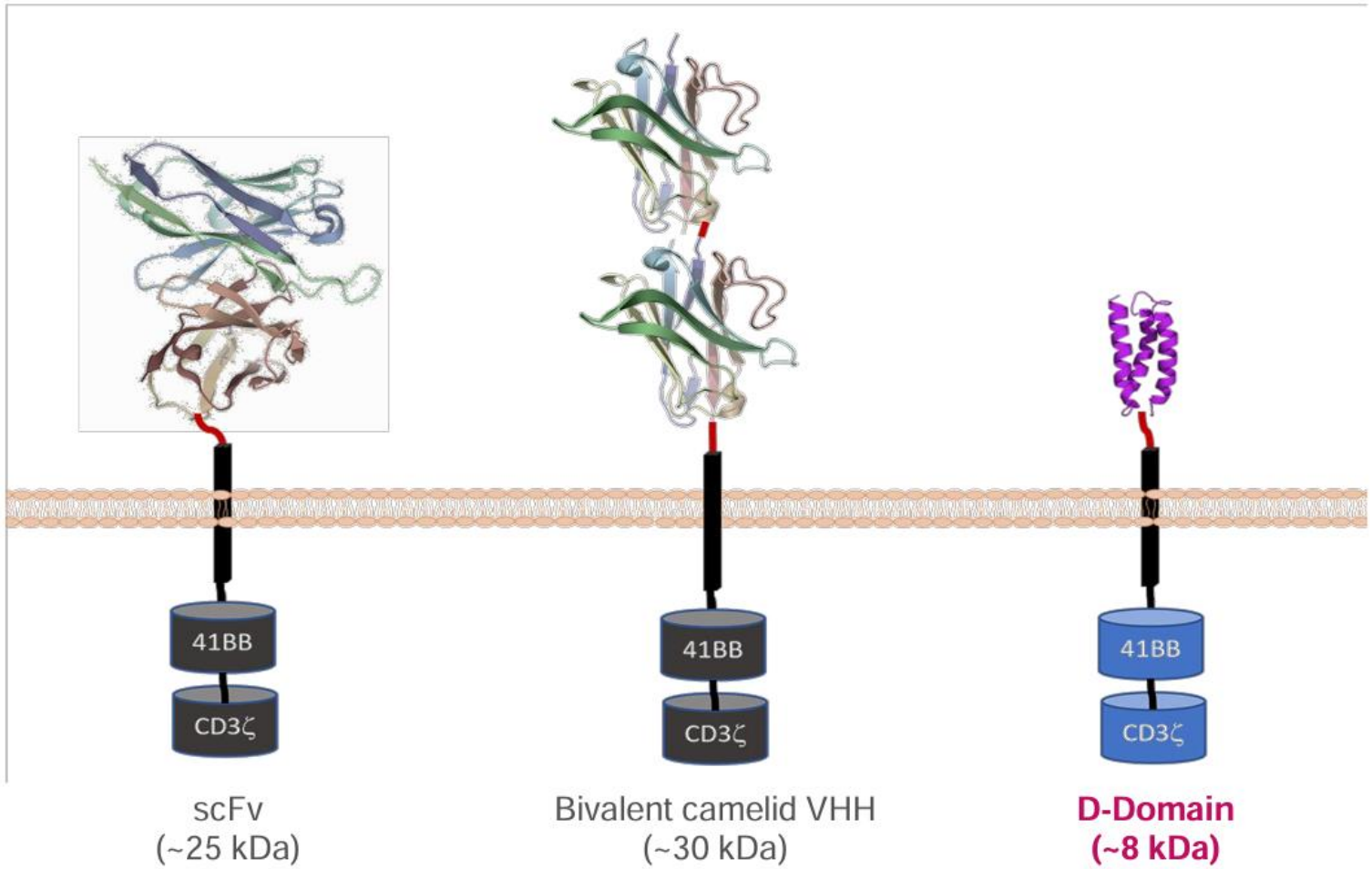
Practical Aspects of Bridging Therapy

- Use most effective therapy, depending on early vs late relapse, prior exposure
- Avoid alkylating agents like bendamustine and bispecific antibodies prior to apheresis (holding therapy): can adversely impact CAR T manufacturing
- Radiation to EMD sites is highly effective
- Timing of CAR T infusion is important: infuse after effective bridging (≥ PR) to reduce severe toxicity
- Minimize treatment-free intervals between different segments
- 2-wk washout (3 wk for talquetamab) from bridging to CAR T, but can be shorter

Other Novel CAR T-Cell Approaches

Anitocabtagene autoleucel (anito-cel/CART-ddBCMA)

Autologous BCMA-directed CAR T-cell therapy using a novel, D-Domain binder[1,2]



scFv
(~25 kDa)

Bivalent camelid VHH
(~30 kDa)

D-Domain
(~8 kDa)

D-Domain Attributes:
Non-Antibody Derived Synthetic Protein[1,2]

Size

Small D-Domain construct facilitates high transduction efficiency and CAR positivity[2-4] resulting in a low total cell dose

Structure & Stability

D-Domain CARs are stable and lack tonic signaling[4,6] due to the rapid folding, lack of disulfide bonds, and hydrophobic core[5,6] of the D-Domain

Binding

The D-Domain binder has a fast off-rate[4] and high CAR surface expression[4]. This combination may allow optimal tumor cell killing without prolonged inflammation

[1]Rotte, et al. Immuno-Oncology Insights 2022; 3(1), 13–24; [2]Frigault, et al. Blood Adv. 2023; 7(5):768-777; [3]Cante-Barrett, et al. BMC Res. Notes 2016; 9:13; [4]Buonato, et al. Mol. Cancer Ther. 2022; 21(7):1171-1183; [5]Zhu, et al. Proc. Nat. Acad. Sci. 2003; 100(26): 15486-15491; [6]Qin, et al. Mol. Ther. 2019; 27(7): 1262-1274.

iMMagine-1: Conclusions A Phase II Trial of Anito-cel in R/R MM:

- **Anito-cel utilizes a novel, synthetic, compact and stable D-Domain binder**
  - D-Domain facilitates high transduction efficiency, CAR positivity, and CAR density on the T-cell surface and has a fast off-rate

- **Anito-cel demonstrated deep and durable efficacy at a median follow-up of 9.5 months**
  - ORR was 97% and sCR/CR rate was 62%, per IMWG criteria
  - 93.1% of MRD evaluable patients (n=54/58) were MRD negative at 10^{-5} or lower
  - Median PFS and OS not reached; 12-month PFS rate was 78.5% and OS rate was 96.5%

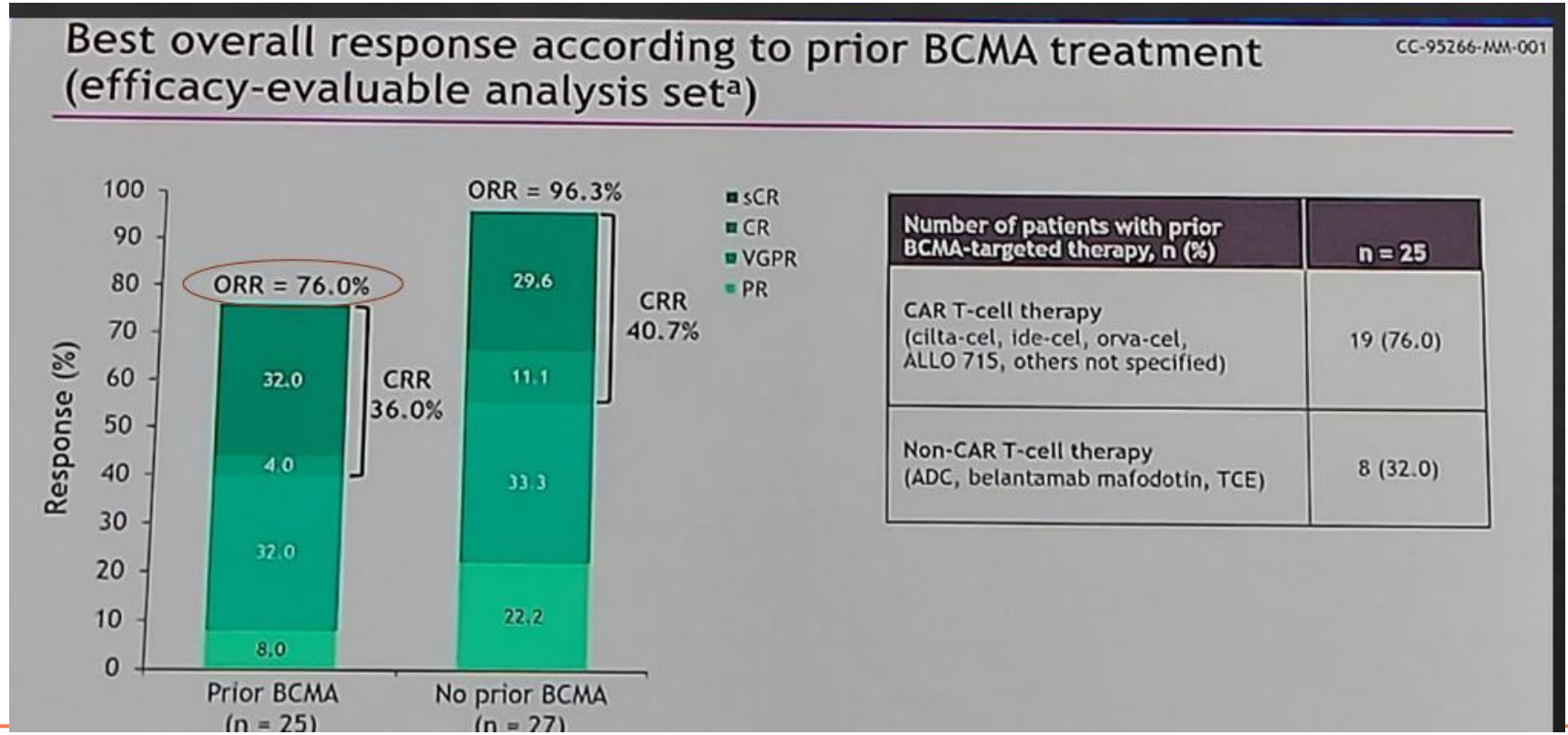
- **The anito-cel safety profile is predictable and manageable**
  - No delayed or non-ICANS neurotoxicities to date, including no Parkinsonism, no cranial nerve palsies, and no Guillain-Barré syndrome reported across clinical trials
  - 86% of patients did not have CRS or had a max Grade 1 CRS
  - 91% of patients did not have ICANS

- **More than 150 patients dosed across the anito-cel programs for RRMM**

Anito-cel demonstrated deep, durable responses in 4L+ RRMM with a manageable safety profile, including no delayed or non-ICANS neurotoxicities

BMS-986393 (CC-95266), a G protein-coupled receptor class C group 5 member D (GPRC5D)-targeted CAR T-cell therapy for relapsed/refractory multiple myeloma: results from a phase 1 study

Susan Bal,[1] Jesus Berdeja,[2] Myo Htut,[3] M. Hakan Kocoglu,[4] Tara Gregory,[5] Larry D. Anderson, Jr,[6] Adriana Rossi,[7] Daniel Egan,[8] Luciano J. Costa,[1] Lisa M. Kelly,[9] Safiyyah Ziyad,[9] Hongxiang Hu,[9] Yanping Chen,[9] Allison J. Kaeding,[9] Michael R. Burgess,[9]



Dual-Targeting CAR Constructs

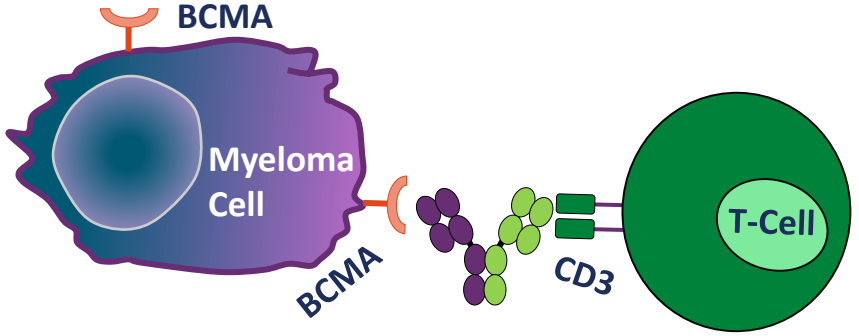
- Dual-targeting CAR constructs may overcome resistance mechanisms to single target CAR constructs, and this may lead to improved outcomes[1,2]
  - AZD0120 (GC012F): a BCMA/CD19 dual targeting CAR T-cell therapy under investigation in R/R MM
  - BMS-986453: a CAR-T-cell therapy that targets both BCMA and GPRC5D

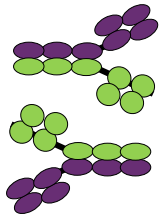
1. Saeed. Curr Tissue Microenviron Rep. 2025;[Epub].
2. Du. Blood. 2023;142:1022. 3. NCT05850234. 4. NCT06153251.

Bispecific Antibodies in R/R MM

Bispecific Therapy Options for Multiple Myeloma

- "Off-the-shelf" immunotherapy with multiple binding domains
  - Target different tumor antigens like BCMA, GPRC5D, FcRH5
  - Also binds to immune cell targets, including CD3 (T-cell)
    - Teclistamab*: CD3 x BCMA
    - Elranatamab*: CD3 x BCMA
    - Talquetamab*: CD3 x GPRC5D
    - Cevostamab: CD3 x FcRH5
    - Linvoseltamab*: CD3 x BCMA
    - Etentamig: CD3 x BCMA





*FDA approved for treating adults with R/R MM after ≥4 prior lines of therapy, including a PI, IMiD, and anti-CD38 mAb.

- Variable administration: SC or IV options with required step-up dosing

Elranatamab-bcmm PI. Teclistamab-cqyv PI. Talquetamab-tgvs PI. van de Donk. Lancet. 2023;402:142.

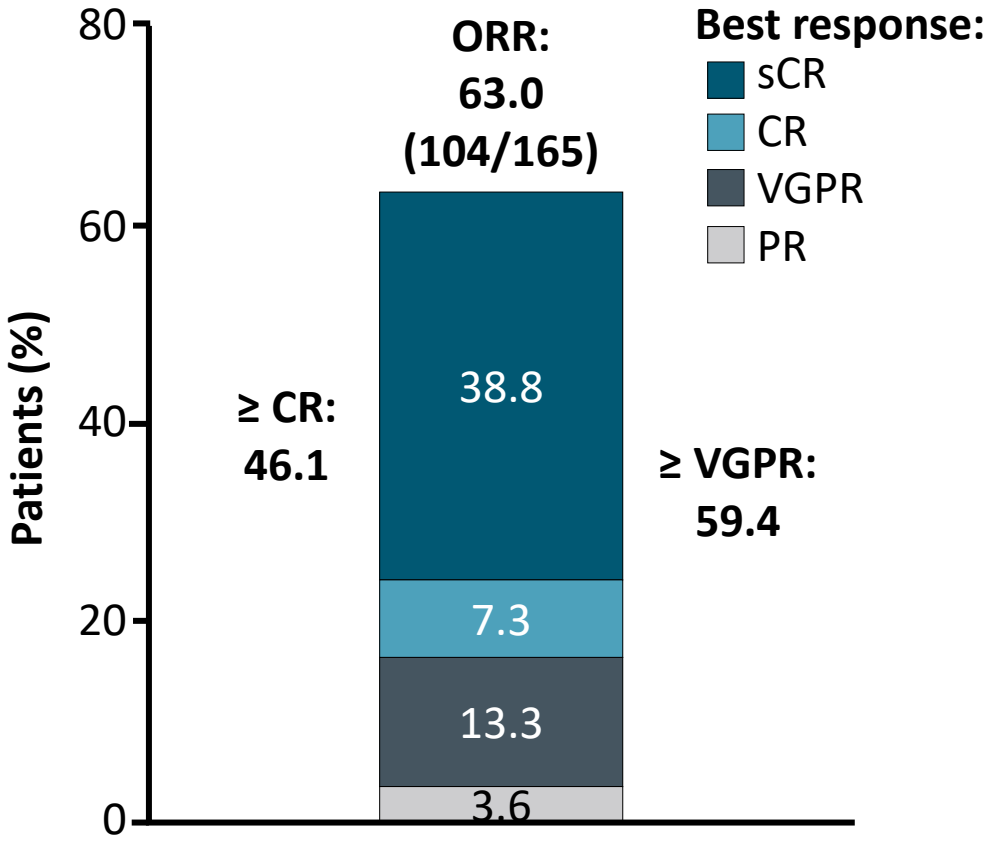
Efficacy of Bispecific Antibodies in R/R MM

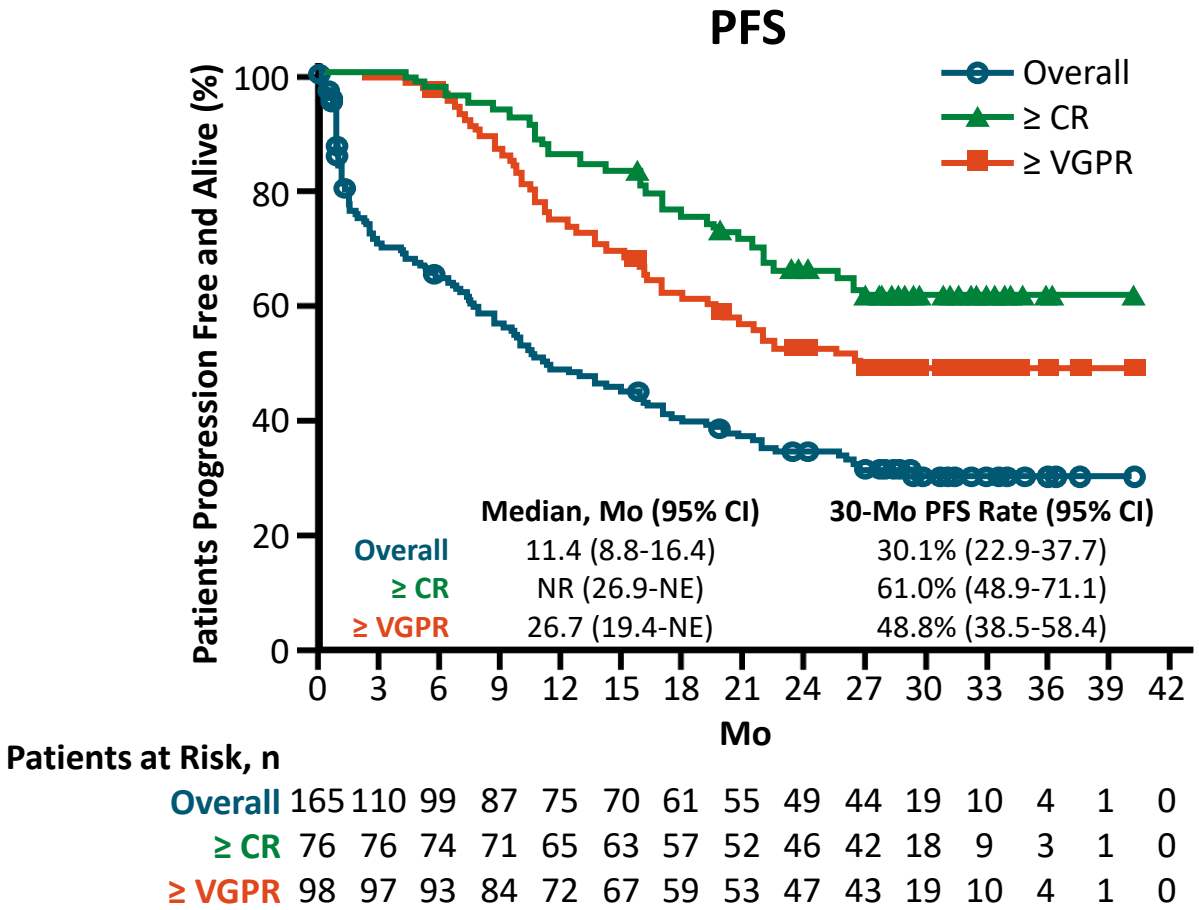
Target	Agents	Trial	ORR, %	mDOR, mo	mPFS, mo
BCMA	Elranatamab	MagnetisMM-3	61	NR	17.2
	Teclistamab	MajesTEC-1	63	24.0	11.4
	Linvoseltamab	LINKER-MM1	70	29.4	NR
GPRC5D	Talquetamab	MonumenTAL-1 QWK	74	9.5	7.5
		MonumenTAL-1 Q2WK	73	17.5	11.2

High response rates and durable responses

Garfall. ASCO 2024. Abstr 7540. Popat. IMS 2024. Abstr P-067. Prince. ASH 2024. Abstr 4738. Rasche. EHA 2024. Abstr P915.
Ye. IMS 2024. Abstr P-098. Chari. Lancet Haematol. 2025;12:e269. Lentzsch. EHA 2024. Abstr S212 Bumma. JCO. 2024;42:2702.

Phase I/II MajesTEC-1: Teclistamab in R/R MM





Patients at Risk, n

Overall	165	110	99	87	75	70	61	55	49	44	19	10	4	1	0
≥ CR	76	76	74	71	65	63	57	52	46	42	18	9	3	1	0
≥ VGPR	98	97	93	84	72	67	59	53	47	43	19	10	4	1	0

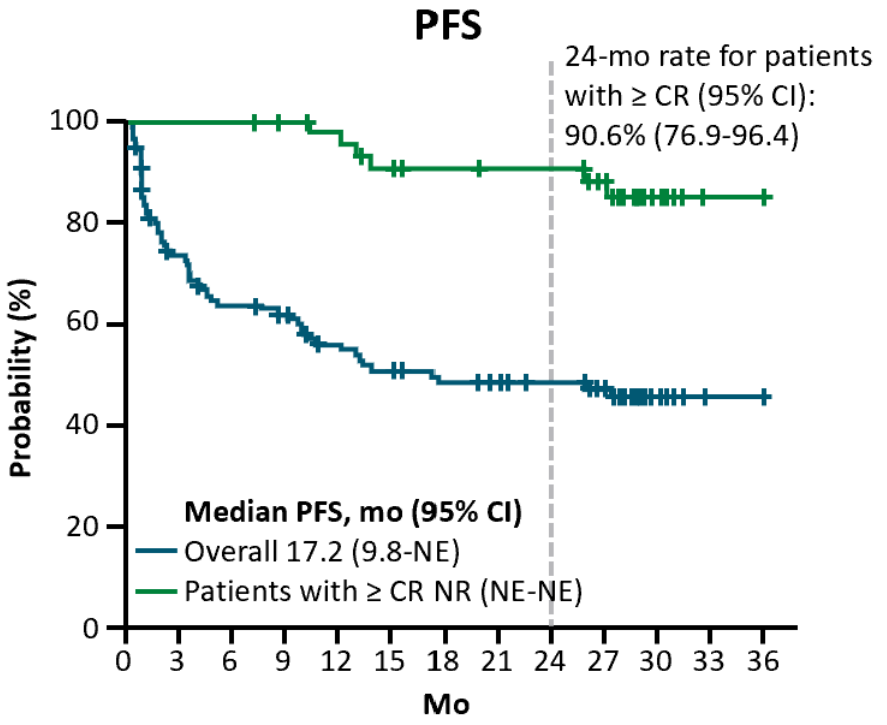
Moreau. NEJM. 2022;387:495. van de Donk. ASCO 2023. Abstr 8011. Garfall. ASCO 2024. Abstr 7540.

Phase II MagnetisMM-3: Elranatamab for BCMA-Directed Therapy-Naive R/R MM (Cohort A)

- Patients with MM refractory to ≥1 lines of therapy (median 5), including an IMiD, PI, and anti-CD38 mAb
  - 97% triple-class refractory , 25% HR cytogenetics
  - 32% EMD

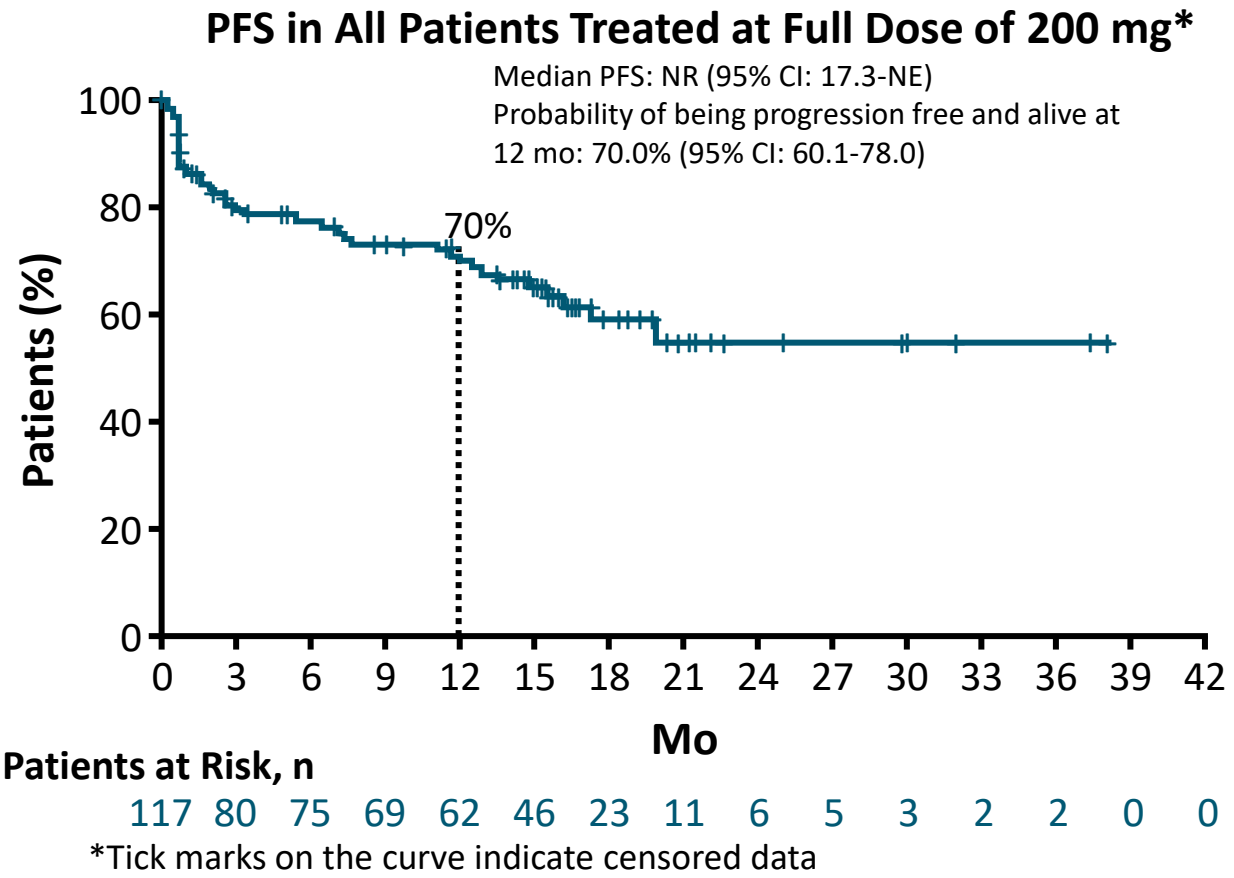
Response	N = 125
ORR, n (%)	**75 (61.0)**
▪ ≥ CR	46 (37.4)
▪ VGPR	23 (18.7)
▪ PR	6 (4.9)
Median DoR, mo	NE
▪ 2-yr DoR, % (95% CI)	66.9 (54.4-76.7)
Median DoR if:	
▪ ≥ VGPR	NE
▪ ≥ CR	NE

Median follow-up: 28.4 mo

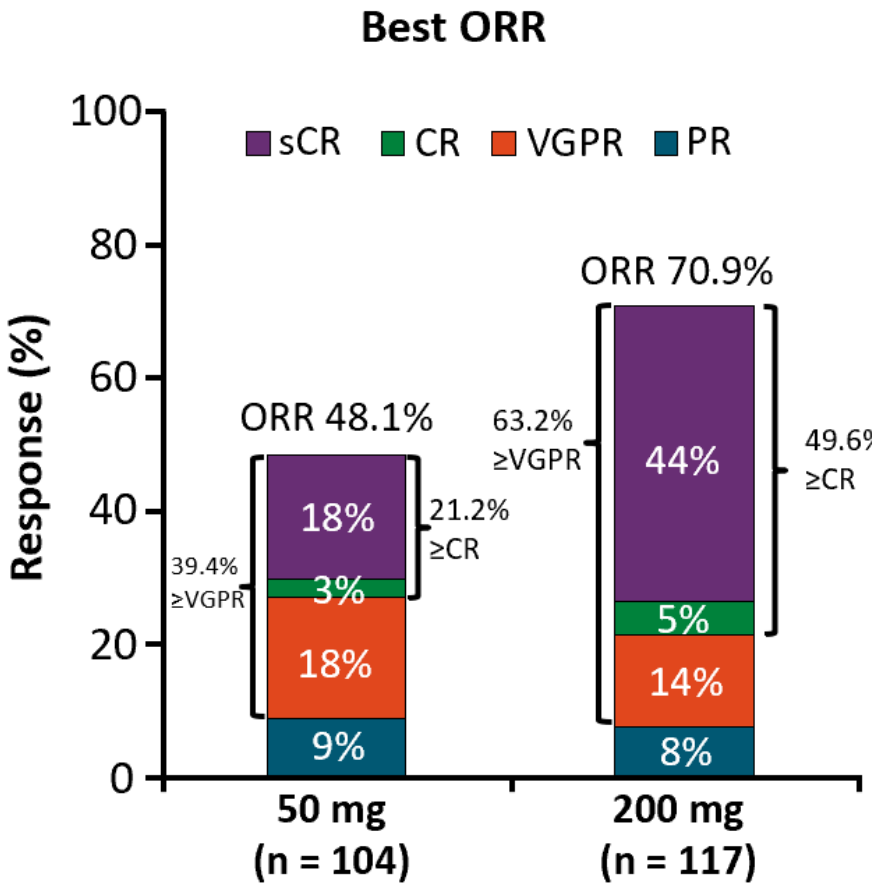


Lesokhin. Nat Med. 2023;29:2259. Mohty. EHA 2024. P932. Prince. ASH 2024. Abstr 4738

LINKER-MM1: Phase I/II First-in-Human Trial of Linvoseltamab for R/R MM



*Tick marks on the curve indicate censored data



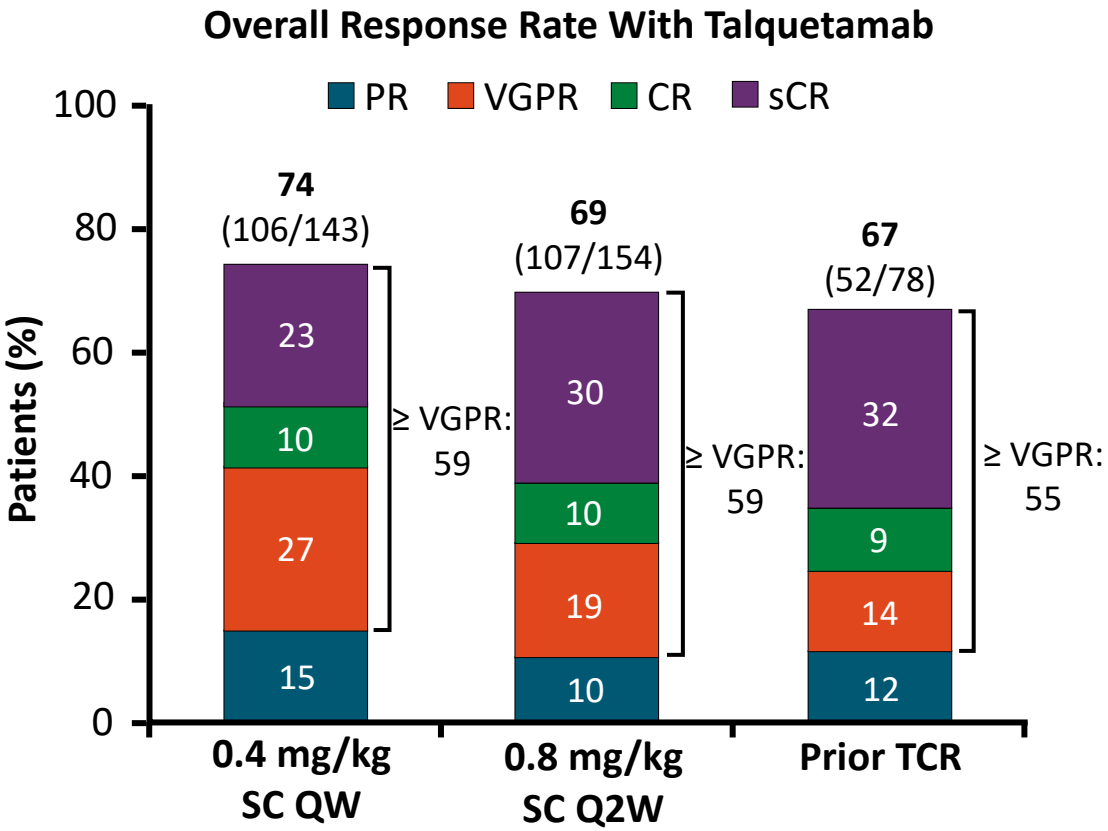
On July 2, 2025, the FDA granted accelerated approval to linvoseltamab for adults with R/R MM after ≥4 prior LoTs, including a PI, IMiD, and anti-CD38 mAb

Bumma. JCO. 2024;42:2702.

Phase II MonumenTAL-1: Talquetamab in R/R MM

- Patients with R/R MM after ≥3 lines of therapy (median 5-6), including an IMiD, PI, anti-CD38 mAb
  - 71%-85% triple-class refractory
  - ~30% HR cytogenetics; 23-32% with EMD

Outcome	0.4 mg/kg QW (n = 143)	0.8 mg/kg Q2W (n = 154)	Prior T-Cell Redirection Tx (n = 78)
Median f/u, mo	29.8	23.4	20.5
Median DoR, mo (95% CI)	9.5 (6.7-13.4)	17.5 (12.5-NE)	N/A
Median PFS, mo (95% CI)	7.5 (5.7-9.4)	11.2 (8.4-14.6)	7.7 (4.1-14.5)
24-mo OS, %	60.6	67.1	57.3



In post hoc analyses, ORR was 72% in patients receiving previous CAR-T therapy and 58 in patients receiving previous bispecific antibody therapy

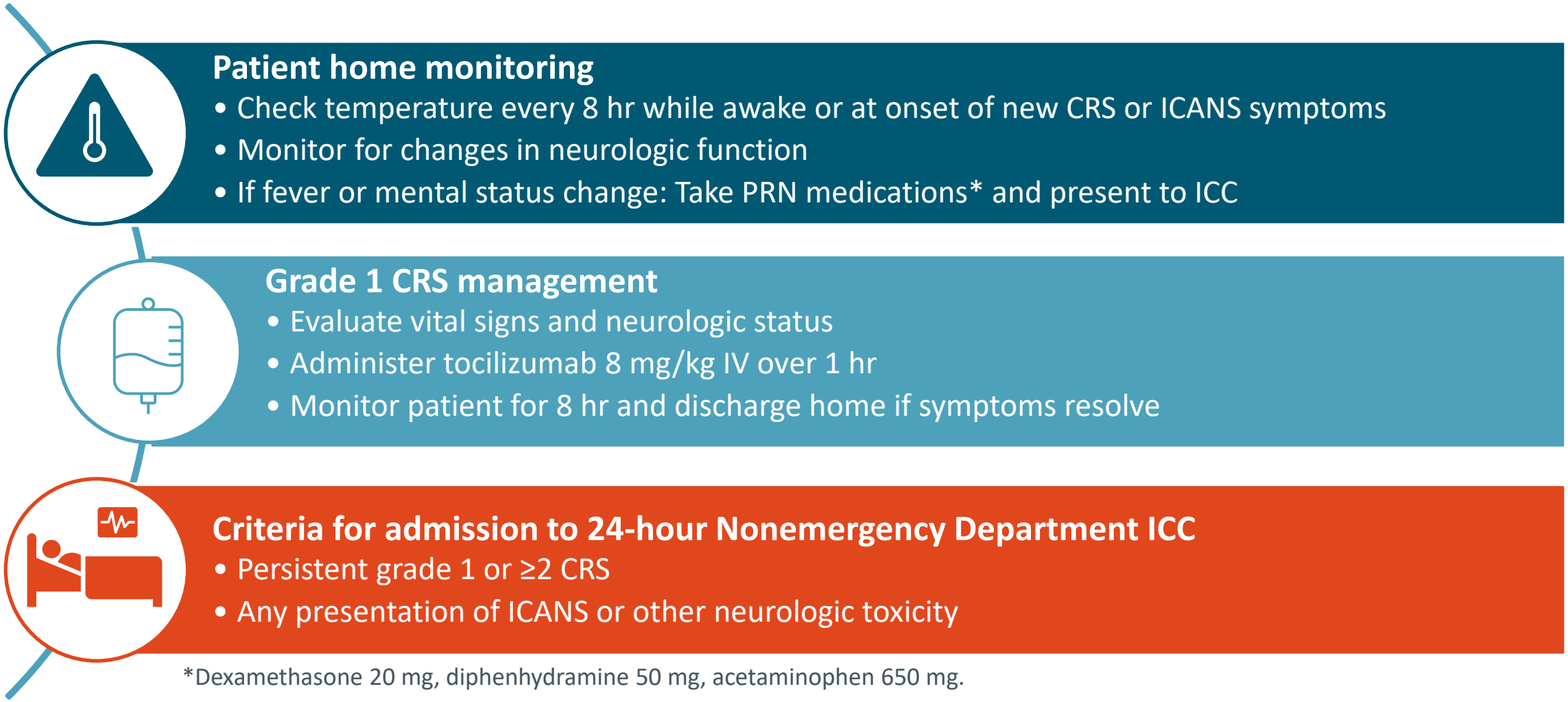
Chari. NEJM. 2022;387:2232. Schinke. ASCO 2023. Abstr 8036. Rasche. EHA 2024. Abstr P915. Chari. Lancet Haematol. 2025;12:e269.

Bispecific Antibody Administration and Dosing: RRMM

	Teclistamab	Talquetamab		Elranatamab	Linvoseltamab
Target	BCMAxCD3	GPRC5DxCD3		BCMAxCD3	BCMAxCD3
Administration	SC	SC		SC	IV
Step-up dosing schedule	▪ D1: 0.06 mg/kg (SUD1) ▪ D4: 0.3 mg/kg (SUD2) ▪ D7: 1.5 mg/kg (1st full)	*Weekly* D1: 0.01 mg/kg (SUD1) D4: 0.06 mg/kg (SUD2) D7: 0.4 mg/kg (1st full)	*Q2W* D1: 0.01 mg/kg (SUD1) D4: 0.06 mg/kg (SUD2) D7: 0.4 mg/kg (SUD3) D10: 0.8 mg/kg (1st full)	D1: 12 mg (SUD1) D4: 32 mg (SUD2) D8: 76 mg (1st full)	D1: 5 mg (SUD1) D8: 25 mg (SUD2) D15: 200 mg (1st full)
Subsequent doses	▪ 1.5 mg/kg weekly ▪ For those w/ ≥ CR for ≥6 mo, can switch to Q2W	▪ 0.4 mg/kg weekly	▪ 0.8 mg/kg Q2W	▪ 76 mg weekly for 24 wk ▪ After Wk 24+, those w/ ≥ PR for ≥2 mo, can switch to Q2W	▪ 200 mg weekly through Wk 13 ▪ For Wk 14+, switch to Q2W ▪ For those w/ ≥ VGPR at Wk 24+ can switch to Q4W
Duration	Until PD or unacceptable toxicity	Until PD or unacceptable toxicity		Until PD or unacceptable toxicity	Until PD or unacceptable toxicity

Teclistamab-cqyv PI. Talquetamab-tgvs PI. Elranatamab-bcmm PI. Linvoseltamab-gcpt PI.

Outpatient Model for Administration of Bispecific Antibodies: AE Management

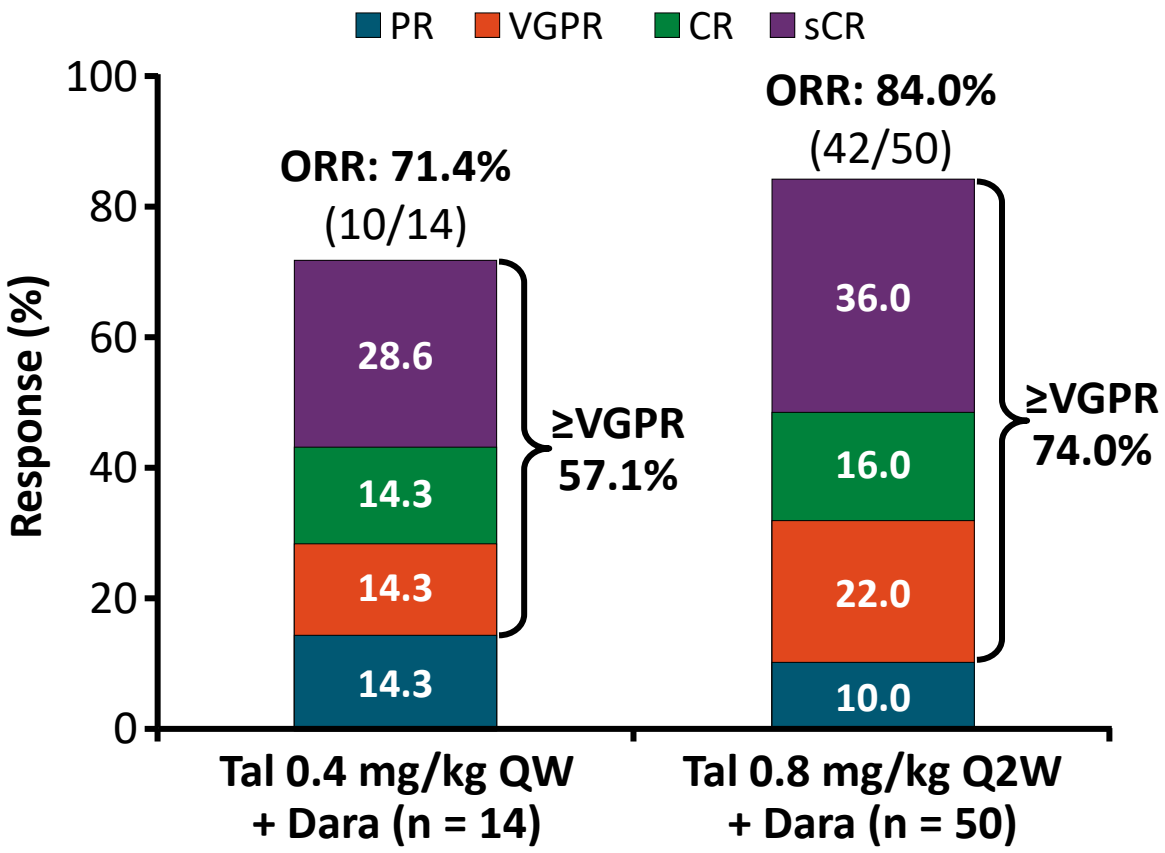


*Dexamethasone 20 mg, diphenhydramine 50 mg, acetaminophen 650 mg.

Scott. IMS 2024. Abstr NSO-06. Scott. Clinical Lymphoma, Myeloma and Leukemia. 2025; 25: 656.

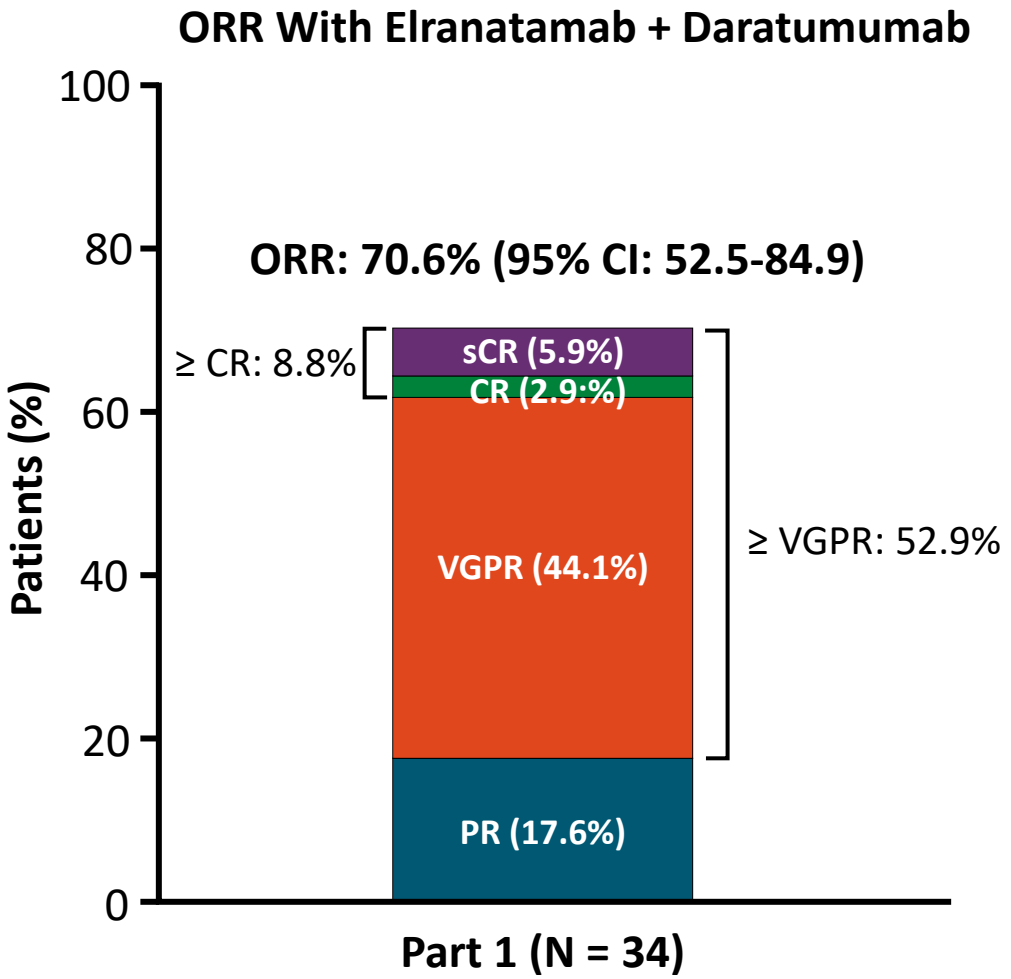
Bispecific Antibody-Based Combination Regimens in MM

TRIMM-2 (Talquetamab + Daratumumab Cohort)



Dholaria. JCO. 2023;41. Abstr 8003.

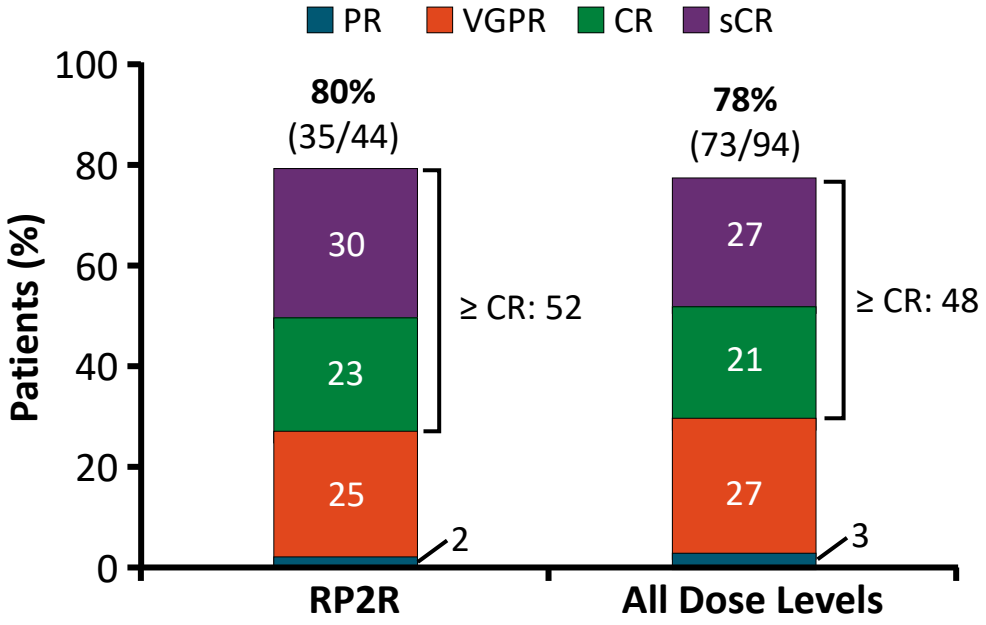
Phase III MagnetisMM-5: Elranatamab + Daratumumab in RRMM



NCT05020236. Grosicki. ASH 2023. Abstr 1921.

RedirectTT-1: Teclistamab + Talquetamab in RRMM

Median prior LoT: 4 (1-11); EMD: 36%; HR cytogenetics in 41%



Median f/u: 20.3 mo (range: 0.5-37.1)

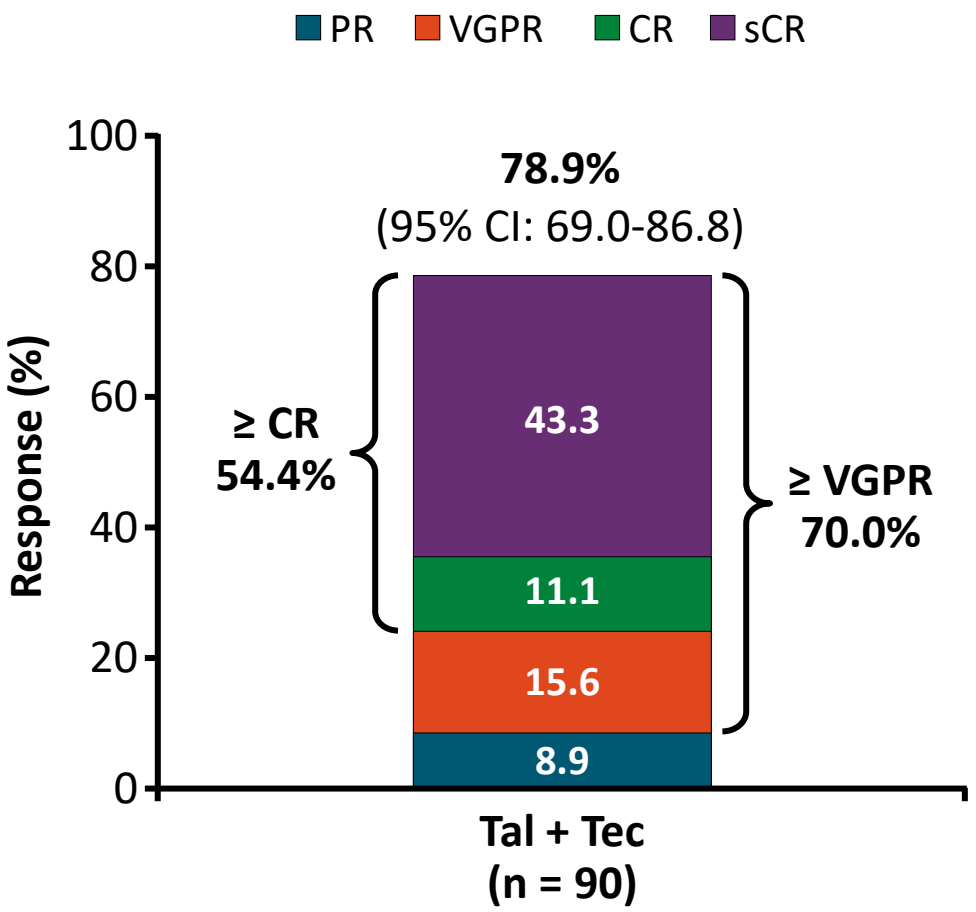
	RP2R* (N = 44)	All Dose Levels (N = 94)
Median f/u, mo (range)	18.2 (0.7-27.0)	20.3 (0.5-37.1)
Median time to first response, mo (range)	1.4 (0.3-5.1)	1.8 (0.3-7.7)
12-mo DoR, % (95% CI)	91 (75-97)	86 (75-92)
18-mo DoR, % (95% CI)	86 (66-95)	77 (64-85)
12-mo PFS, % (95% CI)	74 (57-84)	71 (60-79)
18-mo PFS, % (95% CI)	70 (52-82)	62 (51-72)

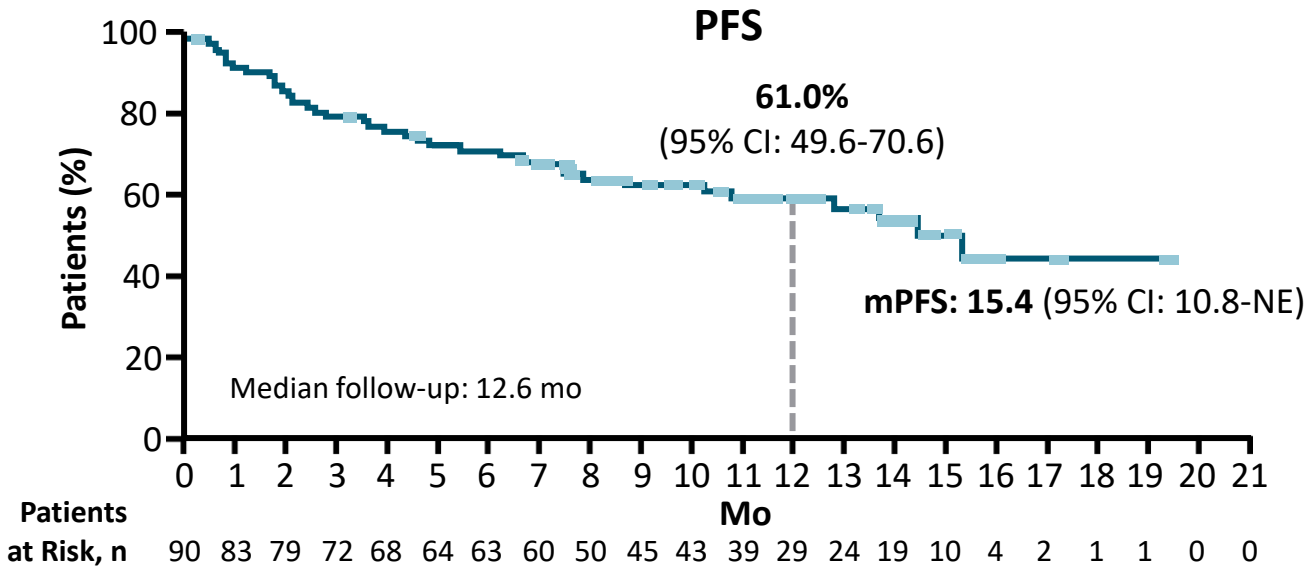
*Teclistamab 3.0 mg/kg Q2W + talquetamab 0.8 mg/kg Q2W.

Mateos. EHA 2023. Abstr S190. NCT04586426. Cohen. NEJM. 2025;392:138.

RedirectTT-1: Patients With True EMD Response and PFS

Teclistamab + Talquetamab in R/R MM





Median PFS among patients with triple-class exposed R/R MM with EMD:

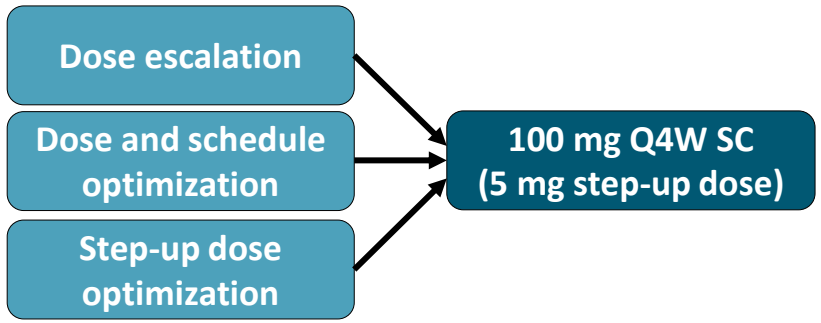
- Approved bispecific antibodies including talquetamab and teclistamab: <6 mo

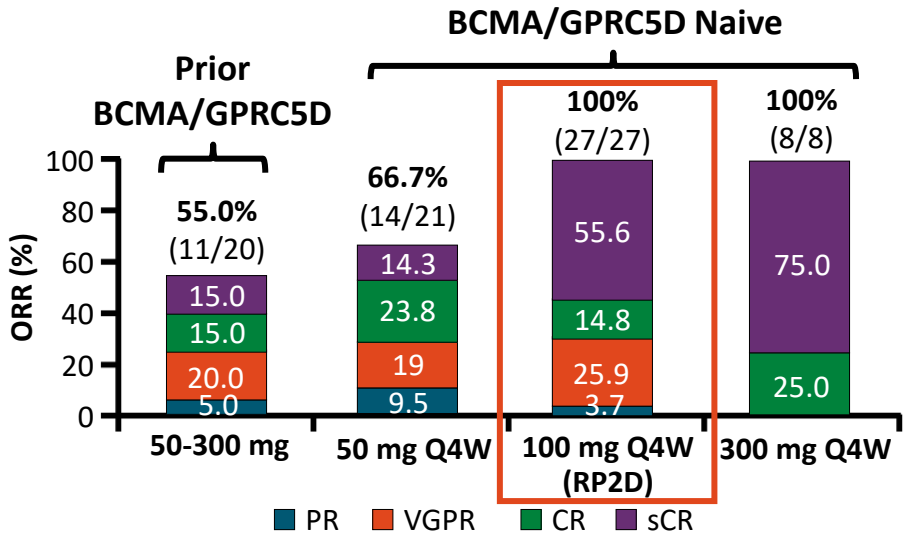
Kumar. EHA 2025. Abstr LB4001. Moreau. Clin Lymphoma Myeloma Leuk. 2025;25:646. Ho. Curr Oncol. 2025;32:182.

Next Generation of Targeted Immunotherapies: BCMA x GPRC5D x CD3 Trispecific Antibody

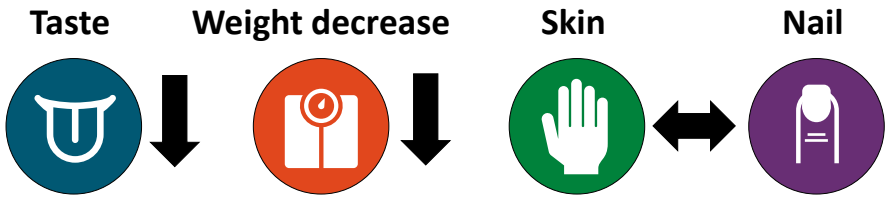
JNJ-5322 is a trispecific antibody targeting BCMA x GPRC5D x CD3 in MM cells

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





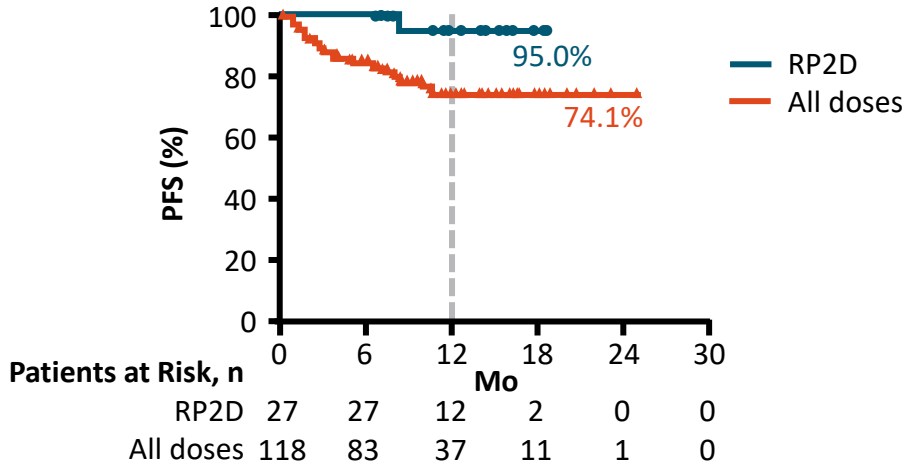
Improved or similar GPRC5D TEAEs



Low-grade GPRC5D TEAE profile

CRS with prophylactic tocilizumab: 20%, all grade 1

PFS Patients Naive to BCMA/GPRC5D



van de Donk. ASCO 2025. Abstr7505.

Adverse Events Associated With CAR T-Cell Therapies and Bispecific Abs

Acute Toxicities: CAR T-Cell Therapy and Bispecific Antibodies

Acute Toxicities
▪ Cytokine-release syndrome
▪ Cytopenias
▪ Immune effector cell–associated neurotoxicity syndrome
▪ Immune effector cell associated HLH-like syndrome
▪ Infections

Generally managed by treatment center

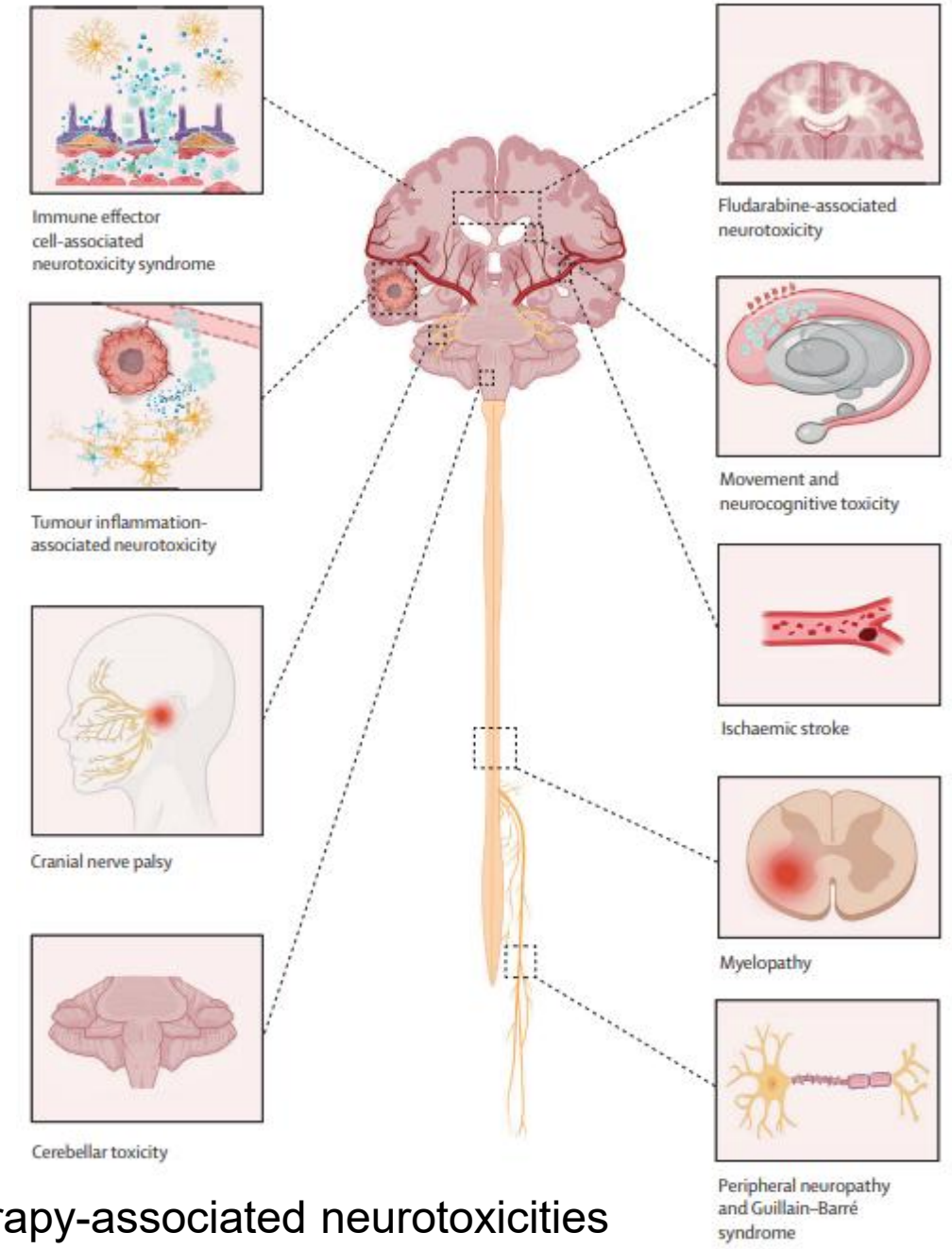
Management of Acute Toxicities	
CRS	Tocilizumab, corticosteroids, anakinra
Neurotoxicity (ie, ICANs)	Seizure prophylaxis, corticosteroids, anakinra, siltuximab, cyclophosphamide
IEC-HS	Anakinra, steroids, ruxolitinib, etoposide, emapalumab
Cytopenias	Growth factors (after CRS resolved), antimicrobial prophylaxis, transfusion support

Hines. Transplant Cell Ther. 2023;29:438.e1. Jain. Blood. 2023;141:2430. NCCN. Clinical practice guidelines in oncology management of immunotherapy-related toxicities. v1.2025. Maus. J Immunother Cancer. 2020;8:e001511. Tallantyre. J Neurol. 2021;268:1544.

Delayed Incidence of Toxicities

Patient education is very important regarding the delayed incidence of toxicities

- Delayed incidence of adverse events may occur
  - Infections
  - Hypogammaglobulinemia
  - Cytopenias
  - Neurologic events
  - Secondary cancers



CAR T-cell therapy-associated neurotoxicities

Class Effect: Incidence of Infection With Bispecific Antibodies in MM

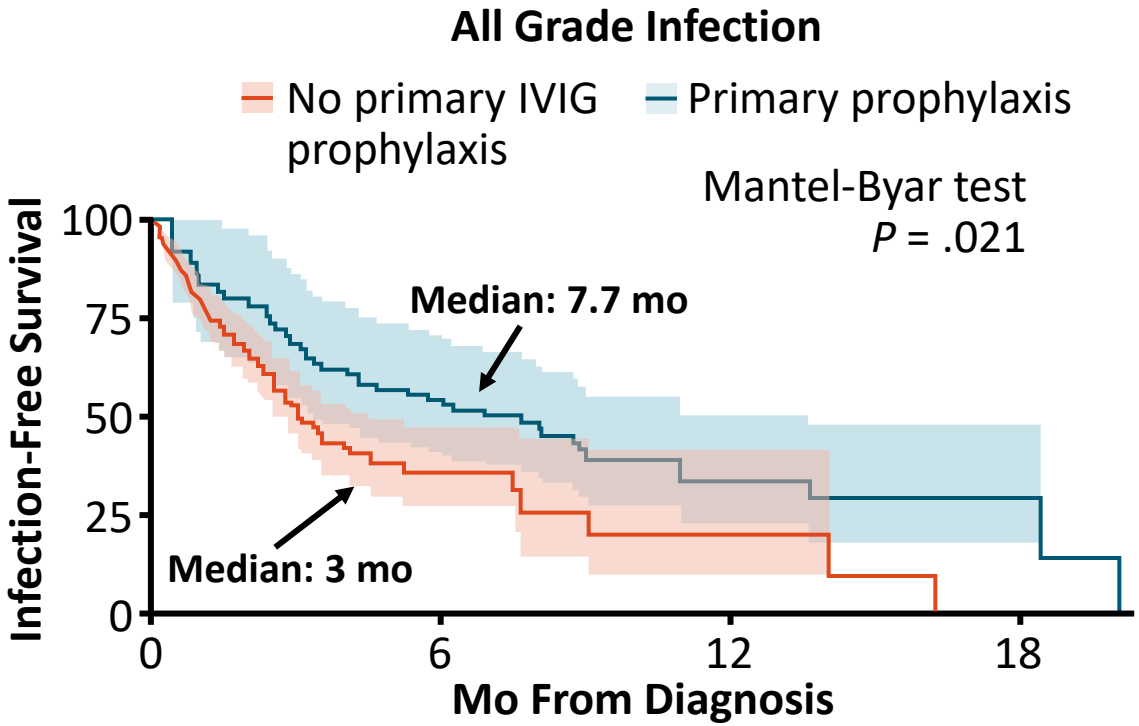
Target	Agents	Trial	Any Grade Infections, %	Grade ≥3 Infections, %
BCMA-directed	Elranatamab	MagnetisMM-3	70	40
	Linvoseltamab	LINKER-MM1	74	36
	Teclistamab	MajesTEC-1	76	45
GPRC5D-directed	Talquetamab	MonumenTAL-1	59*	20*

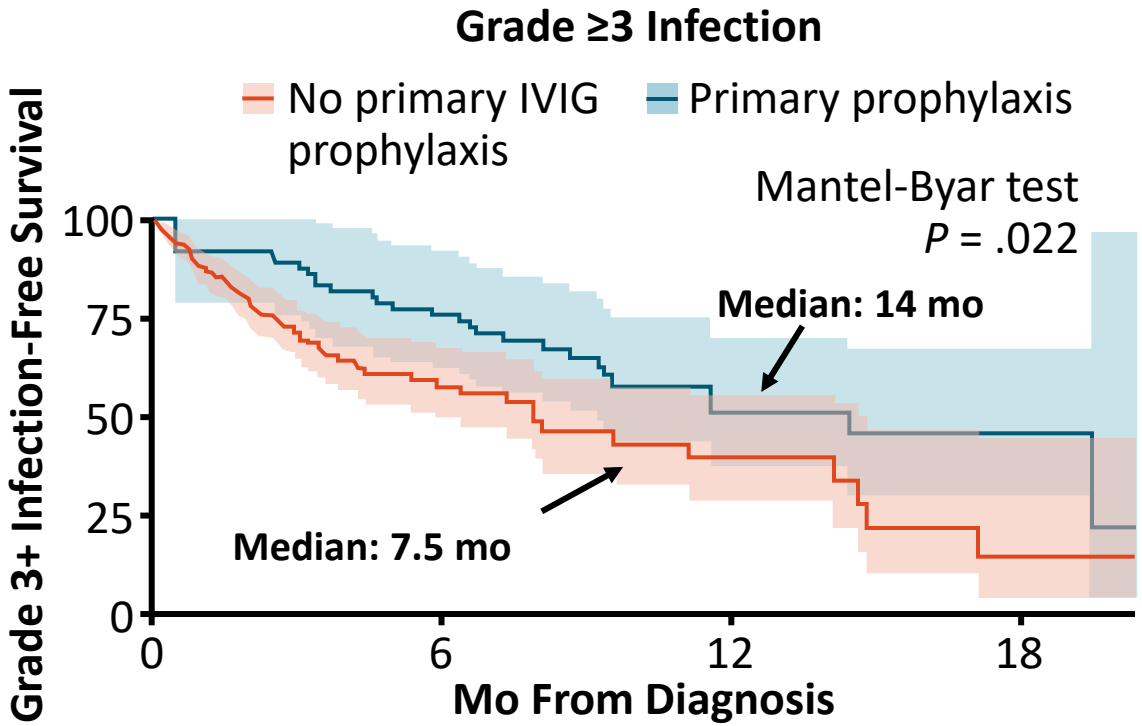
***Talquetamab dose 0.4 mg/kg weekly.**

Patients remain susceptible to infections throughout the duration of bispecific antibody therapy, particularly those receiving BCMA-directed agents

Moreau. N Engl J Med. 2022;387:495. Teclistamab PI. Lesokhin. Nat Med. 2023;29:2259. Elranatamab PI. Chari. N Engl J Med. 2022;387:2232. Talquetamab PI. Bumma. J Clin Oncol. 2024;42:2702. Linvoseltamab PI. Bangolo. Cancers (Basel). 2025;17:282.

Effect of IVIG Prophylaxis on Infection-Free Survival in Recipients of BCMA-Directed Bispecific Ab for MM





No primary IVIG prophylaxis				
At risk	221	12	2	0
Events	0	89	92	94
Primary prophylaxis				
At risk	13	41	10	2
Events	0	25	36	37

No primary IVIG prophylaxis				
At risk	223	33	9	2
Events	0	60	67	71
Primary prophylaxis				
At risk	13	48	13	2
Events	0	12	23	24

Mohan. Blood Cancer J. 2025;15:74.

Preventing Infection With Bispecific Antibody Therapy

Antiviral (HSV, VZV)

Agent: Acyclovir or valacyclovir

Timing: Throughout treatment

Recommendations: Continue for 3 mo off treatment or until CD4 >200/µL

Pneumocystis

Agent: Trimethoprim/sulfamethoxazole or atovaquone

Timing: Throughout treatment

Recommendations: Continue until CD4 cell count >200/µL

Other Supportive Care

Agent: IVIG or G-CSF

Recommendations: IVIG replacement can be used for the duration of bispecific therapy, continue off therapy if IgG concentrations remain <400 mg/dL; use G-CSF as needed for grade ≥3 ANC, avoid when patient is at risk for CRS

Antibacterial

Agent: Local guidelines or quinolone

Timing: During neutropenia

Recommendations: Bacterial infection risk highest in 1st 5 cycles during neutropenia or if prolonged steroids are needed

Other Viral (CMV, HepB)

Agent: Entecavir for those at risk of reactivation

Timing: Throughout treatment

Recommendations: Perform cytomegalovirus PCR at start; if positive, consider monitoring; follow local guidelines for monitoring vs preemptive treatment

Antifungal

Agent: Local guidelines or azole

Timing: During neutropenia

Recommendations: Consider if fungal infection risk is low; higher risk during prolonged neutropenia or steroid use

Rodriguez-Otero. Lancet Oncol. 2024;25:e205. Raje. Blood Cancer J. 2023;13:116. NCCN. Clinical practice guidelines in oncology: multiple myeloma v2.2026. nccn.org. NCCN. Clinical practice guidelines in oncology: Prevention and treatment of cancer-related infections. v1.2025. nccn.org

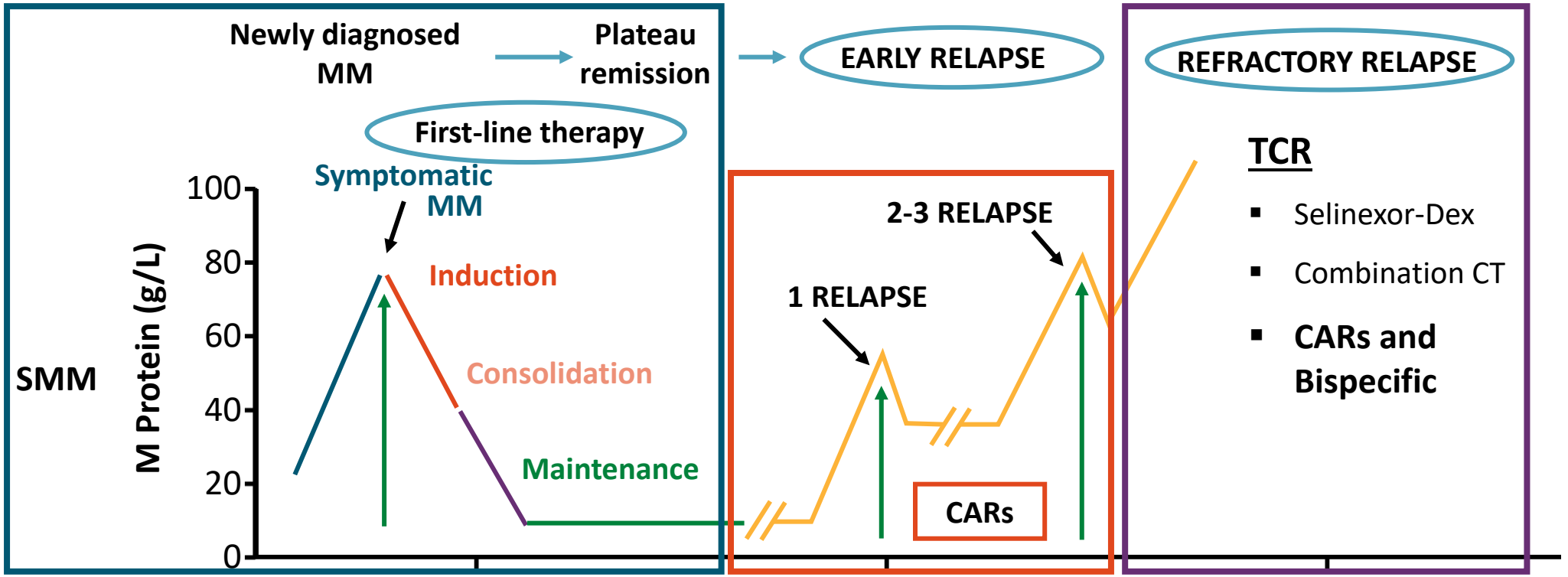
Pearls for Managing GPRC5D-Associated AEs

AE	Recommendation
Dysgeusia	▪ Delay or reduce dose intensity at time of response
Oral events ▪ Xerostomia ▪ Periodontal disease/caries ▪ Weight loss ▪ Treatment of oral comorbidities	 ▪ Hydrate (eg, saliva substitutes), sugar-free chewing gum to stimulate saliva flow, SLS-free toothpastes ▪ Regular dental review ▪ Nutritional supplements ▪ eg, thrush or nutritional deficiencies resulting to glossitis
Skin reactions ▪ Prevention ▪ Low-grade rash ▪ Rash grade ≥3 or refractory to topical medications ▪ Rash occurring C2+ or refractory to above	 ▪ Skin emollients (eg, urea 10% cream, ammonium lactate 12% cream), sunscreen ▪ Low-potency corticosteroids for topical application, escalate to medium potency ▪ Short durations of oral steroids (eg, prednisone) ▪ Consult dermatologist
Nail fragility	▪ Nail hardener, vitamin E oil/emollients

Rodriguez-Otero. Blood Cancer J. 2024;14:24. Chari. Clin Lymphoma Myeloma Leuk. 2024;24:665. Lery. J Am Acad Dermatol. 2024;90:376. Talquetamab PI.

Sequencing Immunotherapies in R/R MM

Deploying Available Agents



Frontline
Triplets/Quads

Early Relapse
(1-3 prior lines): triplets
Bela triplets

Late Relapse
Recycle agents,
Survival <12 mos

Trials:

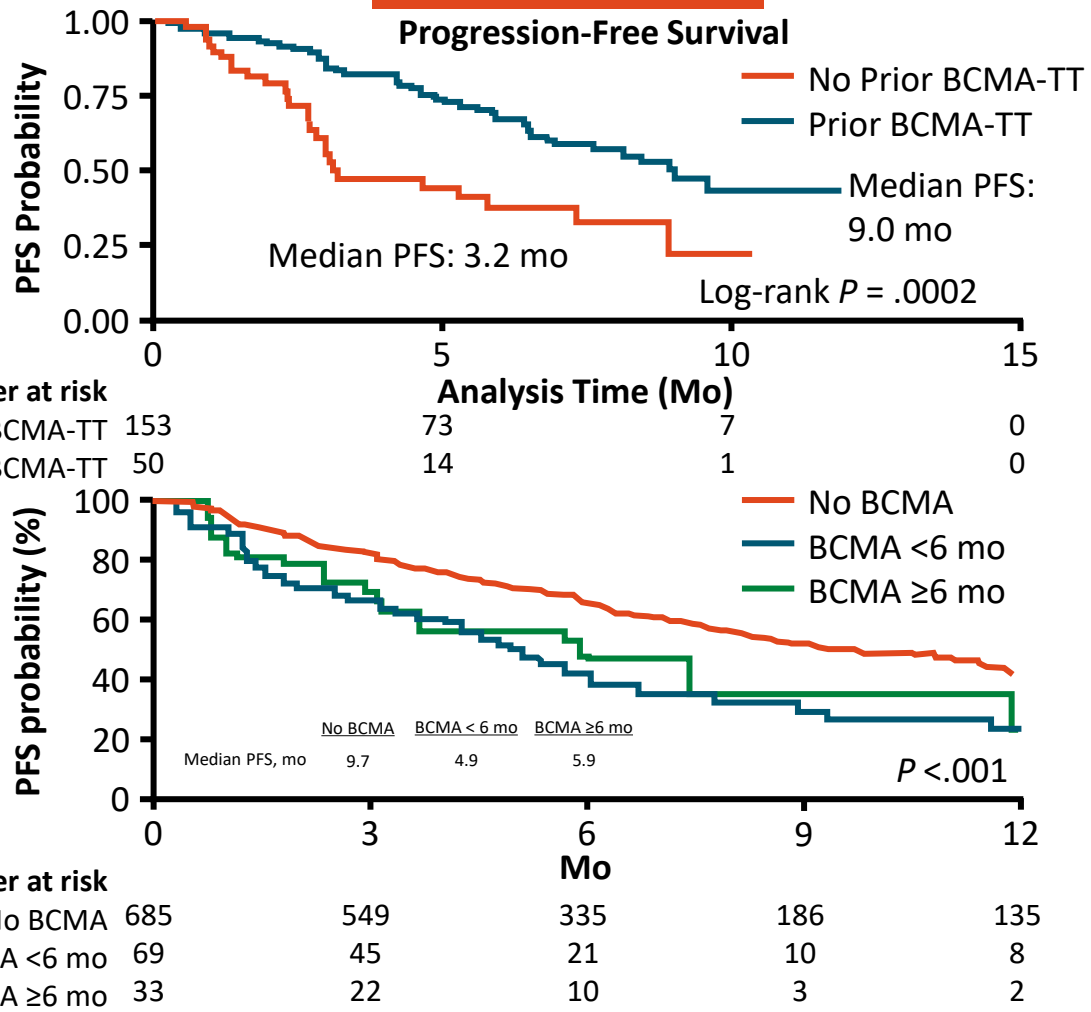
Bispecifics/CAR T-cell therapies

Bispecifics/ trispecifics

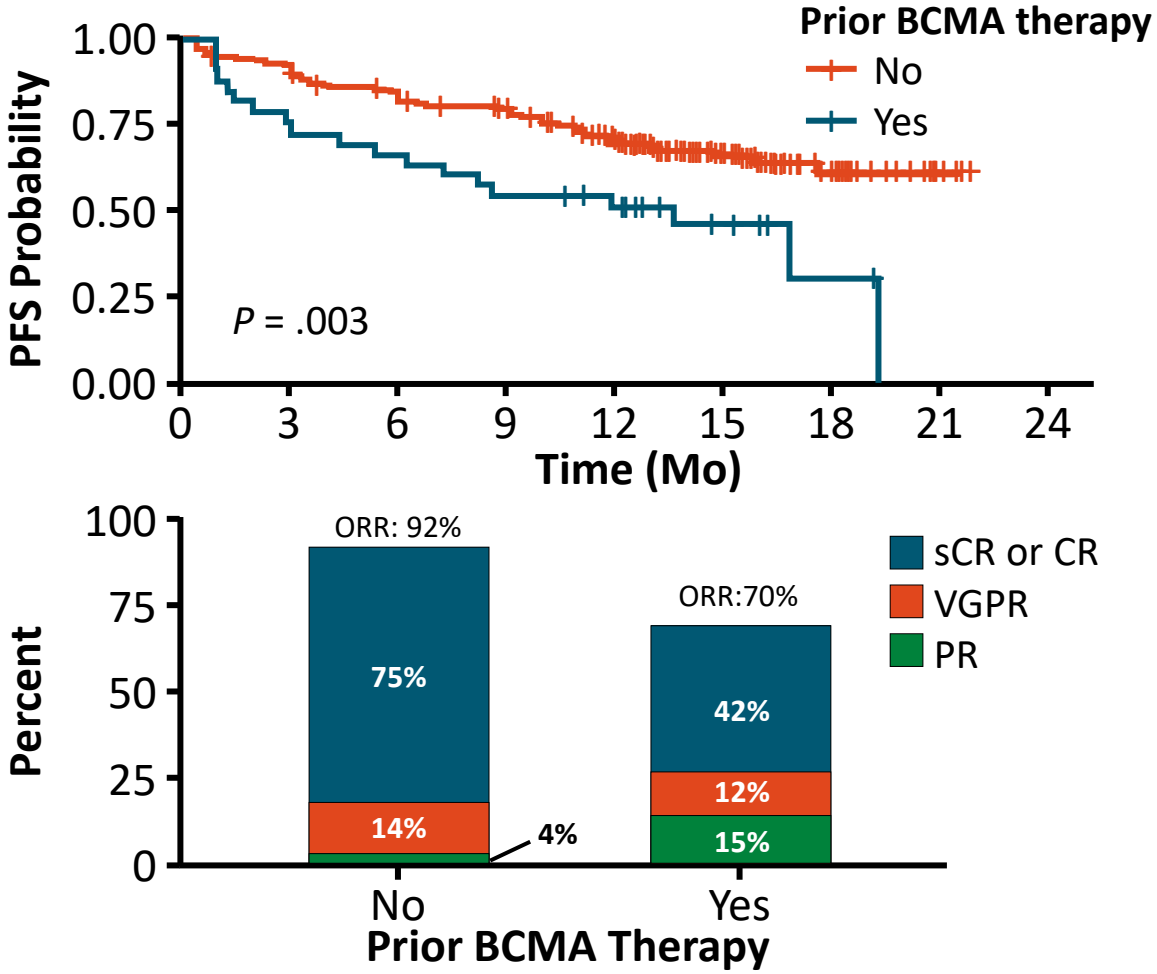
Courtesy of Thomas Martin, MD.

Lower Efficacy of Ide-cel and Cilta-cel After Prior BCMA-Directed Therapy

Ide-cel[1,2]

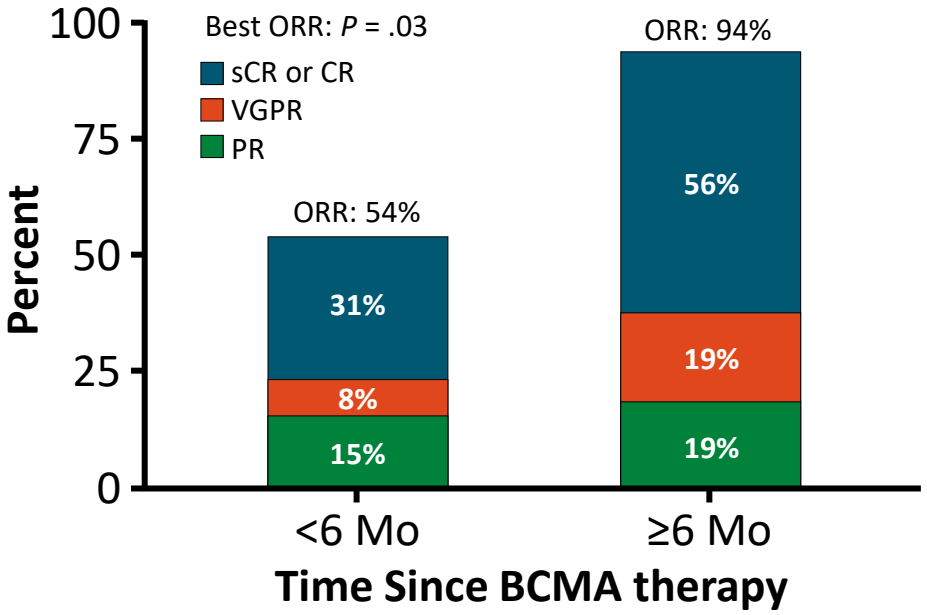


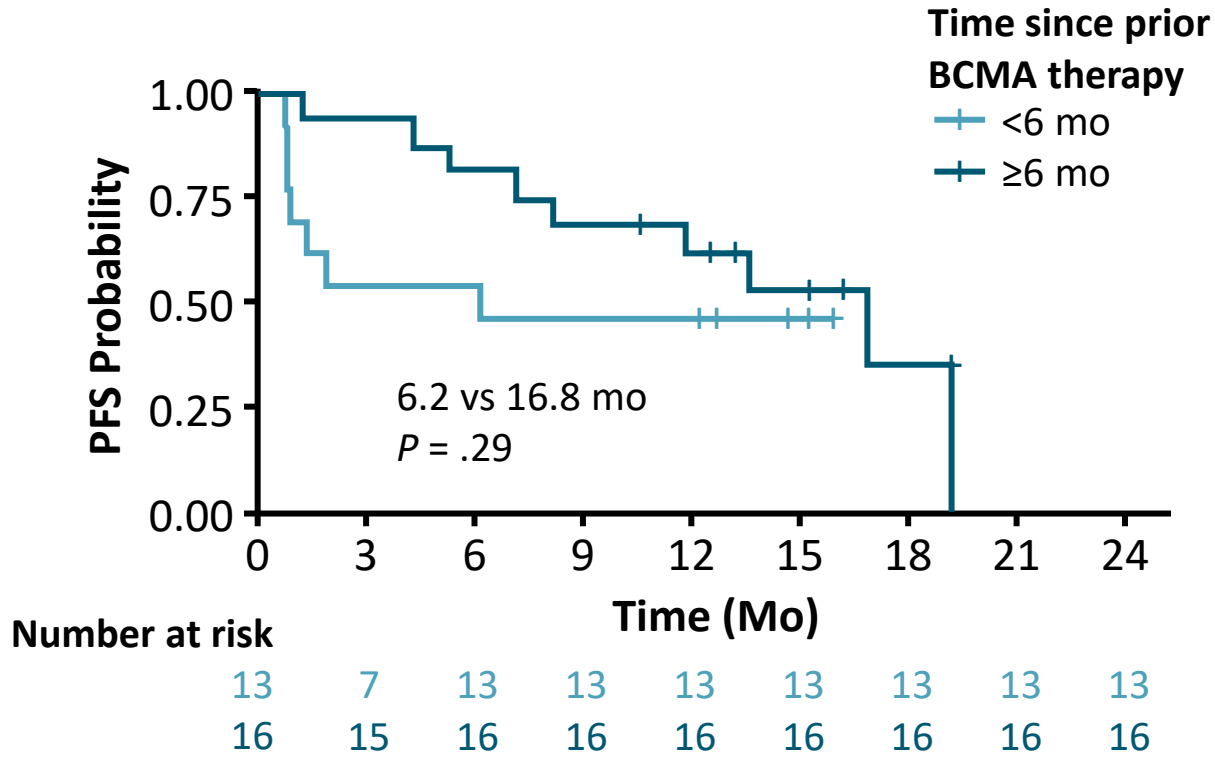
Cilta-cel[3]



1. Ferreri. Blood Cancer J. 2023;13:117. 2. Sidana. Blood. 2025;146:167. 3. Sidana. Blood. 2025;145:85.

Cilta-cel After Prior BCMA Therapy: Timing Matters!



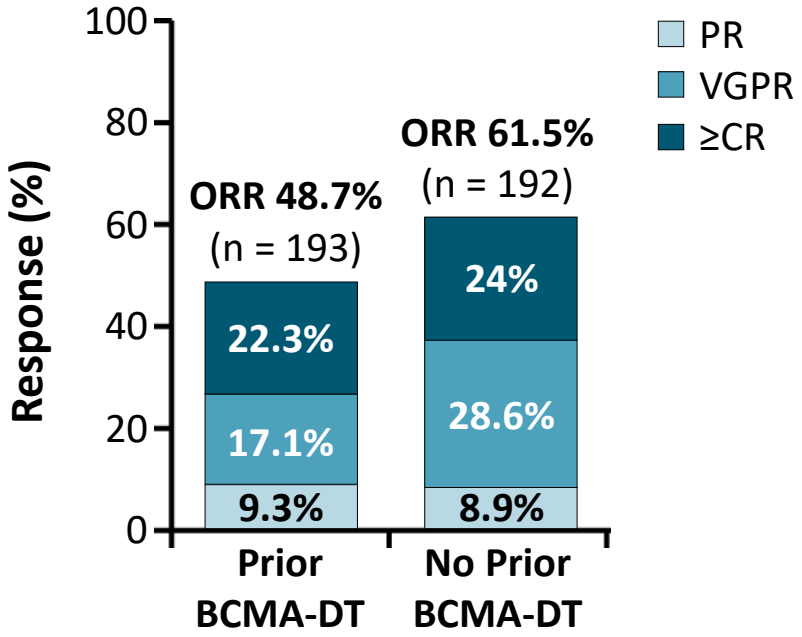


Patients with last BCMA-targeted therapy <6 mo prior to cilta-cel had lower response rates and numerically lower PFS

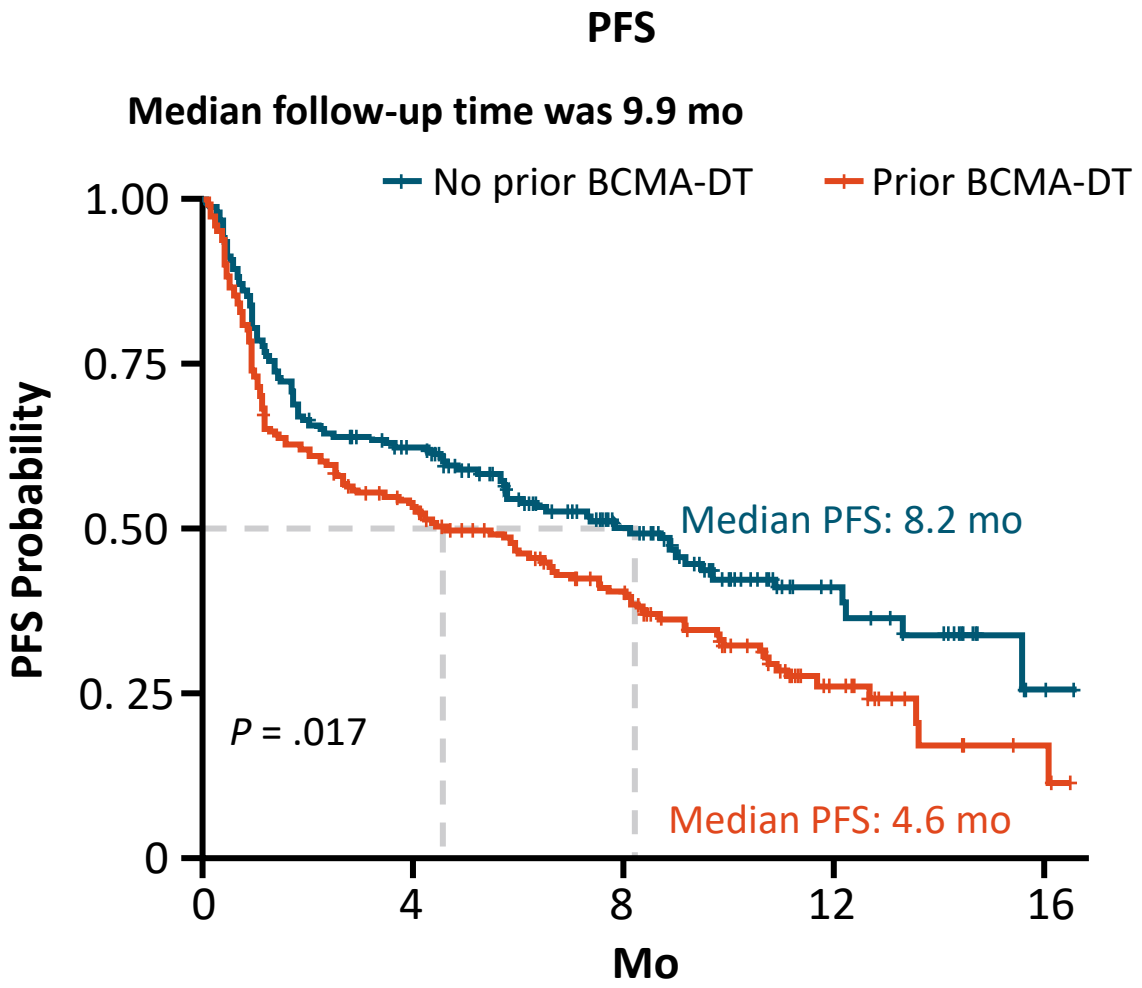
Time From Last BCMA Therapy Exposure	Evaluable Patients (n = 29)
≥6 mo, n (%)	16 (55)
<6 mo, n (%)	13 (45)

Sidana. Blood. 2025;145:85.

Real-World Evidence With Teclistamab in R/R MM: Response and PFS



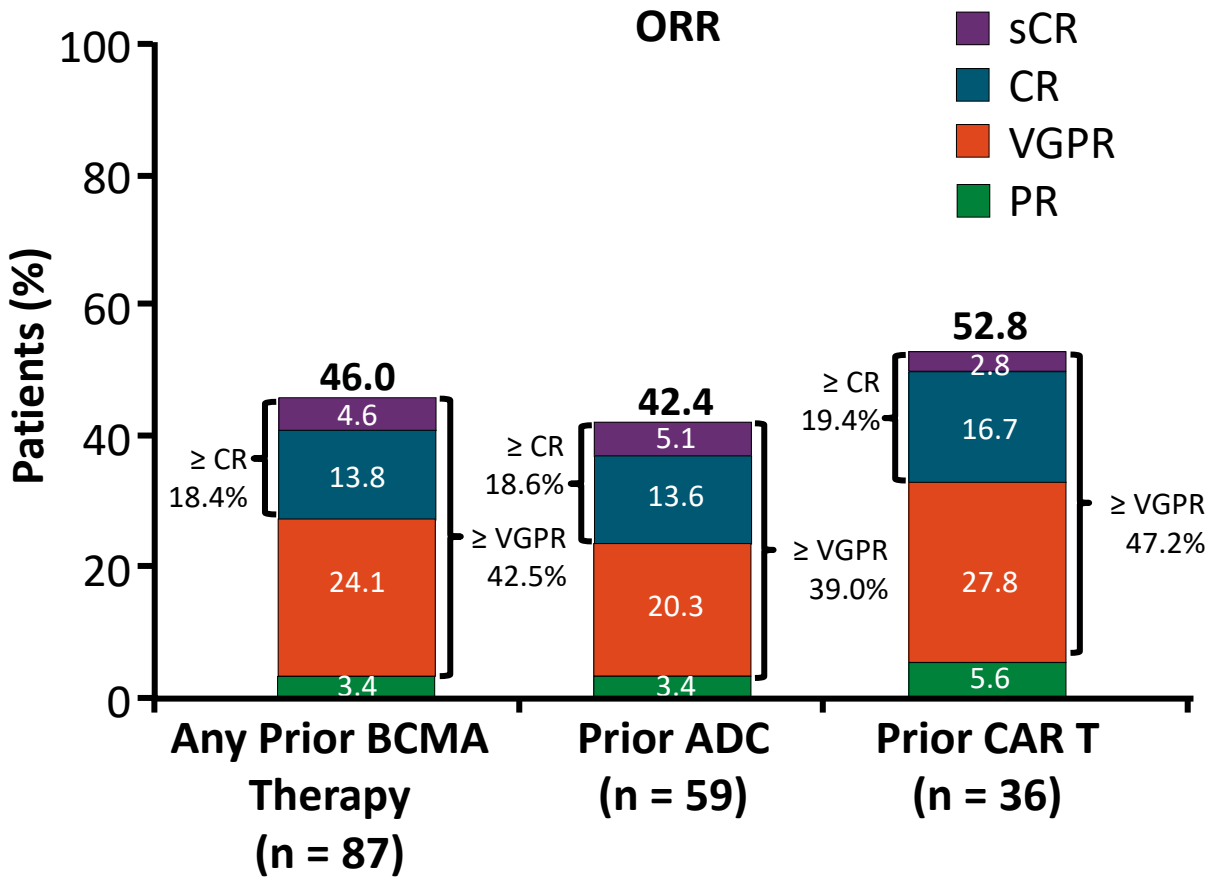
Prior BCMA-DT (Yes vs No)	*P*
ORR	.012
≥CR	.78
≥VGPR	.009



Dima. Blood Cancer J. 2025;15:111. Dima. ASH 2024. Abstr 897.

Sequencing Considerations in RRMM: Elranatamab After Prior BCMA-Targeted Therapy

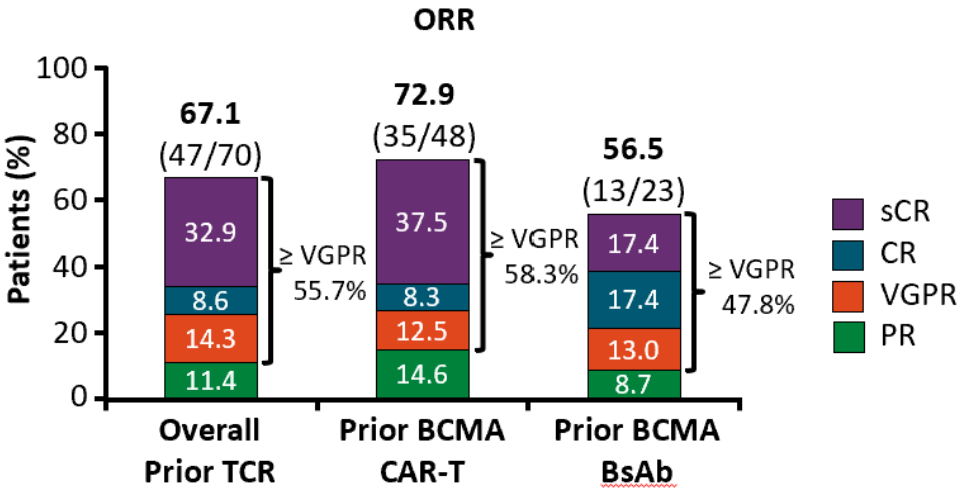
- Pooled analysis from MagnetisMM trials (n = 87)



Nooka. ASCO 2023. Abstr 8008.

Sequencing Considerations in R/R MM: Talquetamab After Prior TCR Therapy

MonumenTAL-1b



Outcome	Overall Prior TCR (N = 70)	Prior BCMA CAR-T (n = 48*)	Prior BCMA BsAb (n = 23*)
mFU,** mo	18.4	18.4	16.3
12-mo PFS rate, % (95% CI)	44.1 (32.1-55.4)	50.0 (34.9-63.4)	30.4 (13.5-49.3)
12-mo DoR rate, % (95% CI)	55.2 (39.3-68.5)	54.7 (36.0-70.0)	43.3 (16.3-67.9)

Jakuwobiak. ASH2023. Poster 3377. Chari. Lancet Haematol. 2025;12:e269

Bispecific Antibodies in R/R MM: Efficacy by Type of Prior Anti-BCMA Therapy

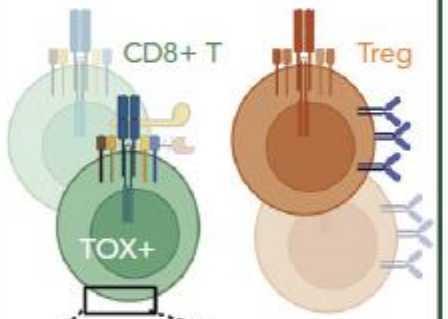
Parameter	Teclistamab[1]			Elranatamab[2,3]			Talquetamab[4]	Linvoseltamab[5]
Pivotal study (target)	MajesTEC-1 Cohort C (BCMA)			Pooled analysis: MagnetisMM trials (BCMA)[2,3]			MonumenTAL-1 (GPRC5D)	LINKER-MM1 (BCMA)
Prior BCMA tx	ADC	CAR T	BCMA-TT (ADC ± CAR T)	ADC	CAR T	BCMA-TT (Any prior BCMA tx)	Prior TCR†	ADC
Patients, n	29	15	**40**	59	36	**87**	**78**	**117**
Prior LoT, n		6 (3-14)			7 (3-19)		**6 (5-8)**	**5 (2-16)**
High-risk cytogenetics, %		33			24		**37**	**39.3**
Median f/u, mo		28			10.3		**21**	**14.3**
ORR/≥CR, %	55/28	53/27	**53/30**	42/19	53/19	**46/18**	**67/42**	**70.9/49.6**
mDoR, mo	15	14	**15**	NR	NR	NR	N/A	29.4
mPFS, mo	7.3	4.4	**4.5**	3.9	10	**5.5**	**8**	NR
mOS, mo	16	15	15	12.1	12.1	12.1 9 mo: 60%	NR 24 mo: 57%	31.4

1. Touzeau. Blood. 2024;144: 2375. 2. Nooka. ASCO 2023. Abst 8008. 3. Quach. Blood. 2024;144:2365.
4. Chari. Lancet Haematol. 2025;12:e269. 5. Bumma. JCO. 2024;42:2702.

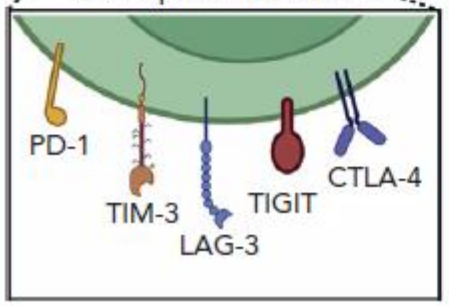
Mechanisms of Resistance to BisAbs & CART

T cell dysfunction

T cell exhaustion
↑ CD8+ Tex
↓ CD8+ Teff
Checkpoint receptor expression
Lack of clonotypic expansion
CD4+ regulatory T cells (Treg)

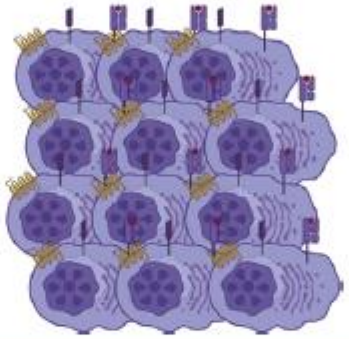


Checkpoint molecules



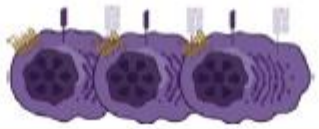
Tumor intrinsic

Tumor Biology
BMPC >50-60%
R-ISS stage III
Extramedullary disease



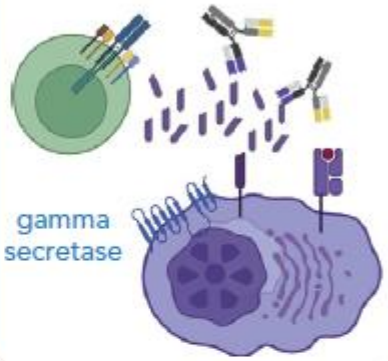
Target antigen loss

MHC downregulation

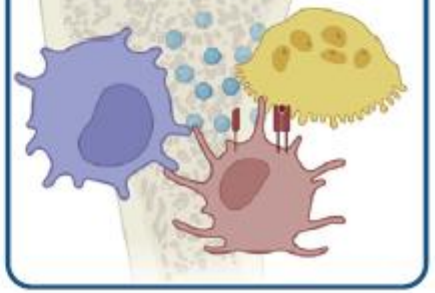


Tumor microenvironment

Soluble BCMA sink



Immunosuppressive cells & cytokines
Osteoclasts, tumor associated macrophages, plasmacytoid DC, myeloid-derived suppressor cells
IL-6, IL-10, TGF-β, IDO



Acquired resistance to T-cell based therapies:
→ Predominantly driven by target antigenic loss post BCMA or GPRC5D TCE (+++) and CAR-T (+).

→T cell phenotype CAR T (++) and TCE (+)
Presence of exhausted T_{EX} ($CD57^+$, TOX^+, $GZMB^+$, $CD28^-$, $PDCD1^+$, $TIGIT^+$, $LAG3^+$)

→Composition of myeloid/DC compartment
Immuno-suppressive environment

Primary resistance:
→ High serum soluble BCMA
→ High disease burden (E:T ratio)
→ Extramedullary disease
→ Pre-existing T cell "exhaustion" ($CD8^+$ TOX^+)

Lee H et al. Blood 143:1211, 2024

Conclusions

- **CAR T-cell therapies** show high efficacy with durable responses in MM
- Use in earlier lines even more beneficial due to immune fitness
- New products with different targets have shown promising data in patients with R/R MM
- **Bispecific antibodies** are currently approved after 4 LoTs; under investigation in earlier lines of therapy
- **Optimal sequencing** of T-cell redirecting therapies is yet to be determined

- **Resistance**: Antigen escape, TME exhaustion, BCMA sink