Bispecific Antibodies for Multiple Myeloma

2024 CELL COAST CONFERENCE
Transformational Breakthroughs in Cell Therapies

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Pentecost Family Myeloma Research Center

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Relevant Disclosure and Mitigation Report

Under Accreditation Council for Continuing Medical Education (ACCME) guidelines disclosure must be made regarding all financial relationships with ineligible companies within the last 24 months.

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Commercial Interest/Ineligible Company	**Nature of Financial Relationship**	
	What was received?	For what role?
Bristol Myers Squibb	Speaker/Consultant Fee	Consultant/Speaker
Legend Biotech USA Inc.	Consulting Fee	Consultant

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Outline

- Overview treatment landscape/Immunotherapy in MM
- Overview of FDA approved BsAbs
- Sequencing
- Conclusions

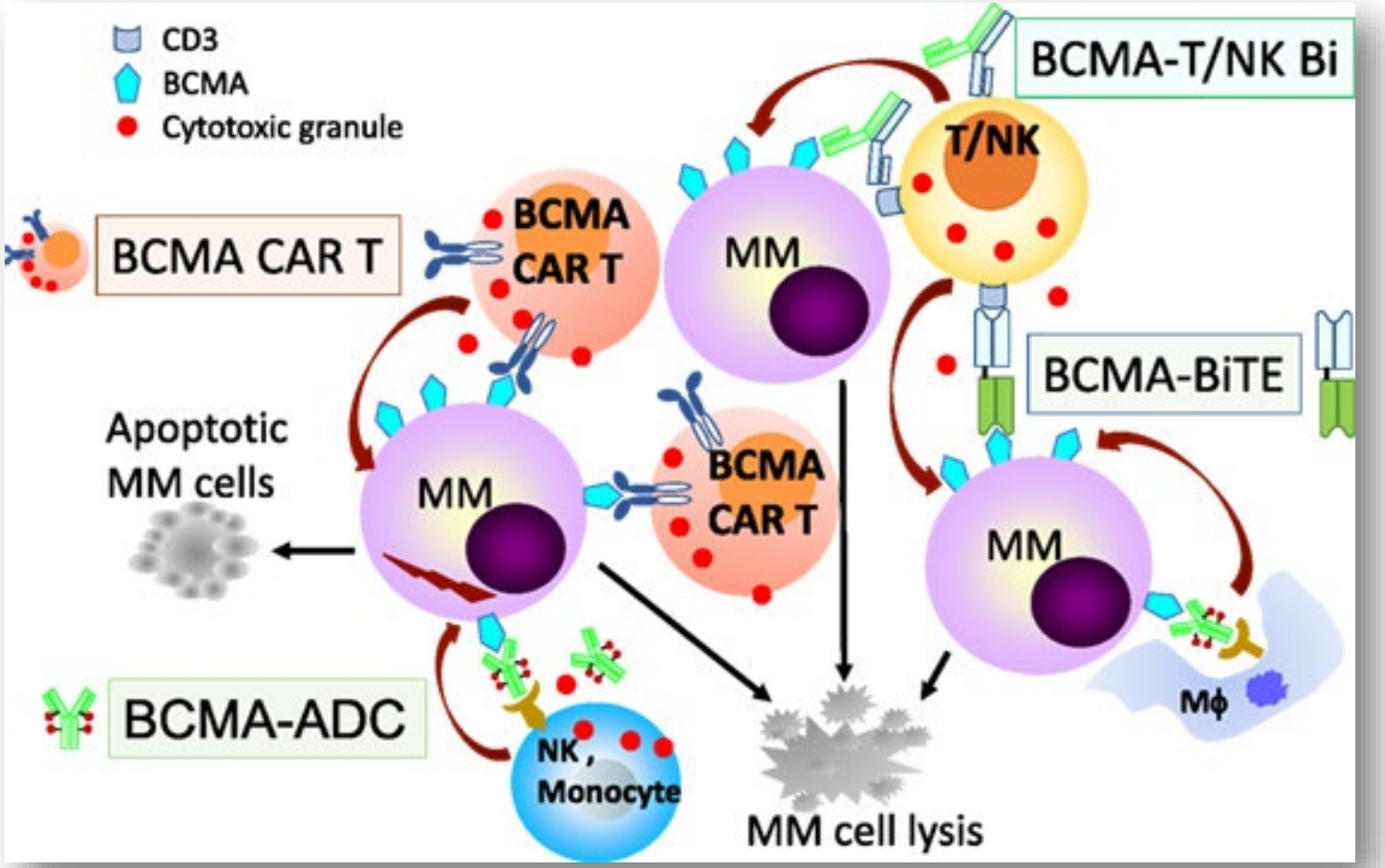
Immunotherapy Era in Multiple Myeloma

Multiple Options of Therapy

- CAR T-cells
- Bispecific antibodies (BsAb)
- Antibody drug conjugates
- Dual-affinity re-targeting Ab (DART)

Multiple Targets

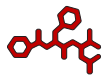
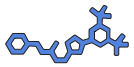
- BCMA
- FcHR5
- CS1/SLAMF7
- GPRC5D
- TACI
- CD138



Cho SF, et al. Front Immunol. 2018 Aug 10;9:1821

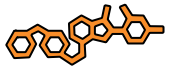
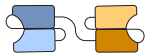
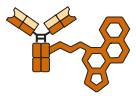
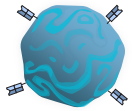
Current Treatment Options and Future Directions

Current Treatments

Agents		Frontline	→ RRMM
	IMiD agents	Lenalidomide	Pomalidomide Lenalidomide
	Proteasome inhibitors	Bortezomib	Bortezomib Ixazomib Carfilzomib
	Corticosteroids	Dexamethasone Prednisone	Dexamethasone
	Antibodies	Daratumumab	Daratumumab Elotuzumab Isatuximab
	Alkylating agents	Cyclophosphamide Melphalan	Cyclophosphamide
	Other agents		Selinexor Venetoclax

MM Cell inhibition

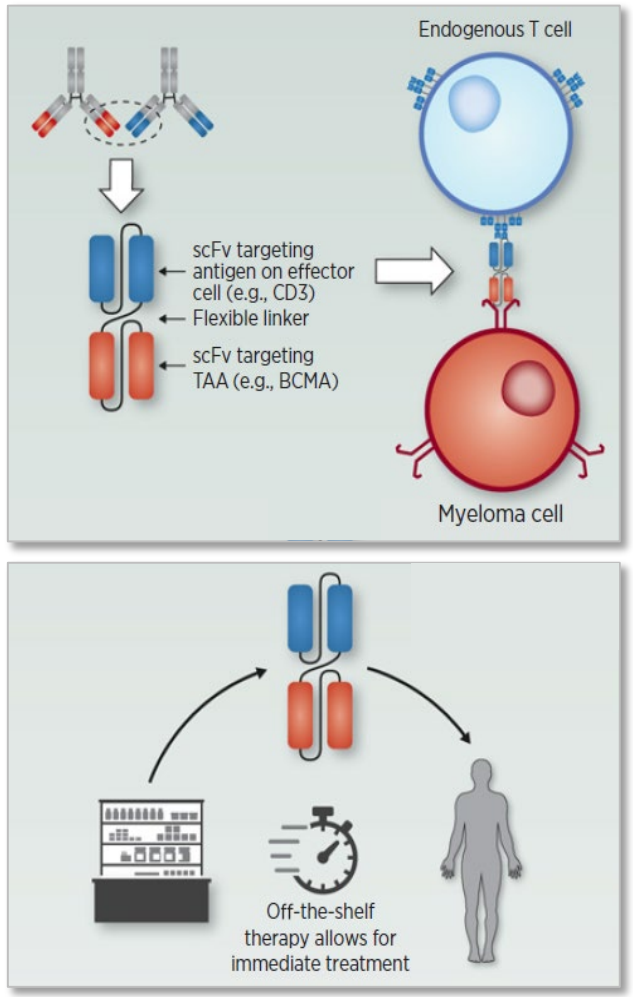
Future Directions

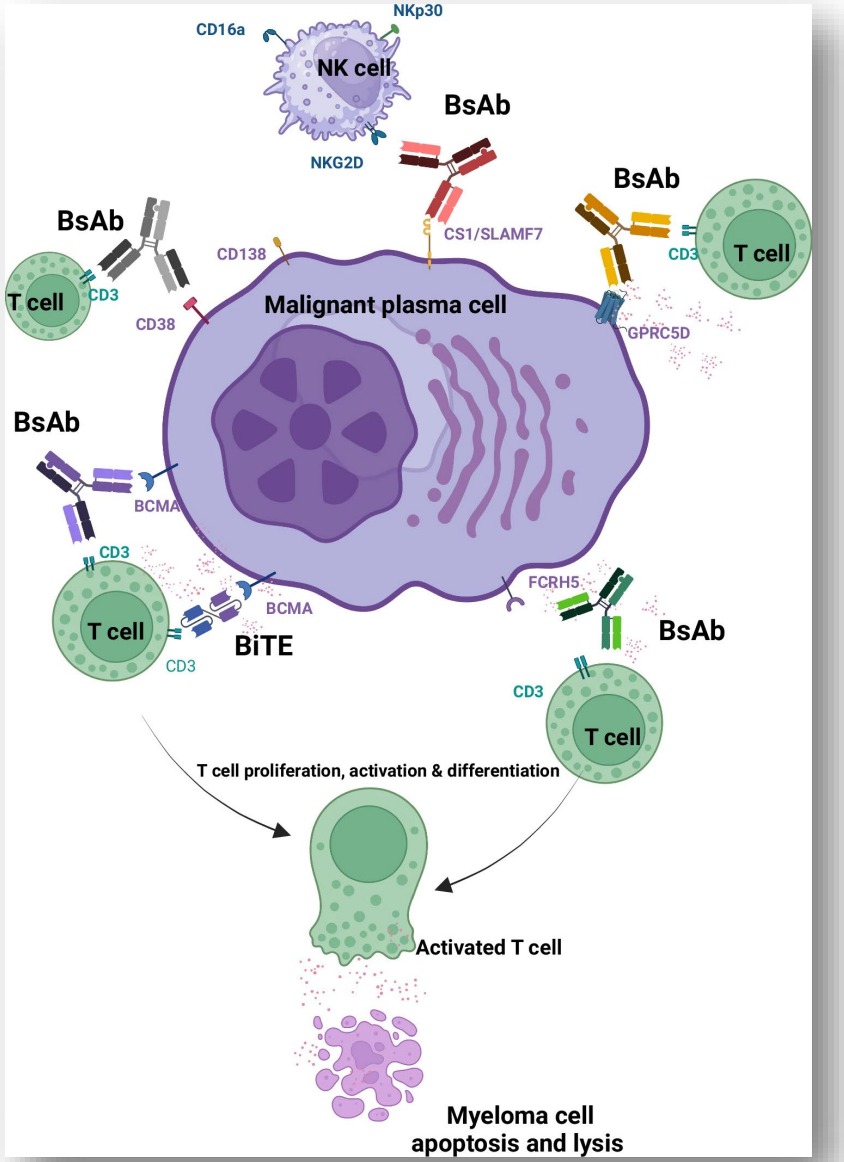
	CELMoD agents
	Bispecific T-cell engagers targeting: • BCMA • GPRC5D • FcRH5
	ADCs targeting: • BCMA
	Car T-cells targeting: • BCMA • GPRC5D • SLAMF7

Raje, N., Mateos, MV., Iida, S. et al. Blood Cancer J. 13, 41 (2023)

Bispecific Antibodies

- Bispecific antibodies are also referred to as dual specific abs, bifunctional abs, or T-cell engaging ab.
- Bispecific antibodies target 2 cell surface molecules at the same time (one on the MM cell and one on a T cell)
- Many different bispecific antibodies are in clinical development; and thus far 3 are approved for use in MM.
- Availability is off-the-shelf allowing for immediate treatment





Cohen A et al. *Clin Cancer Res.* 2020;26:1541

Devasia AJ et al. Blood Cancer J. 2024 Sep 12;14(1):158

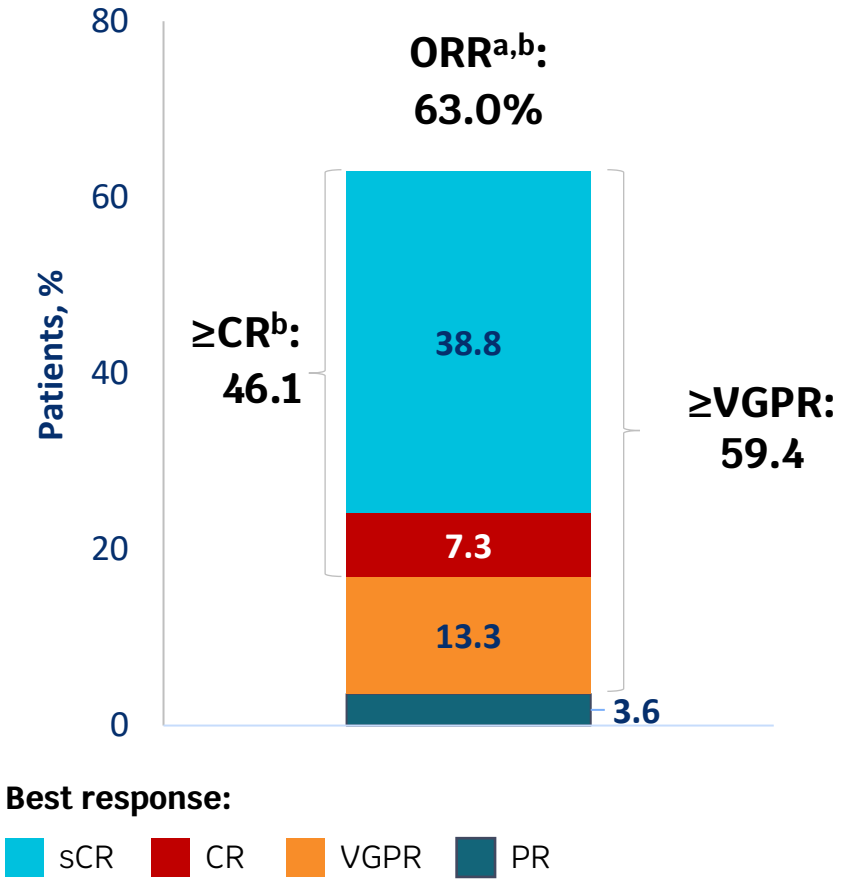
MajesTEC-1: Phase I/II Study of Teclistamab

Patients with RRMM ≥3 lines of therapy, including IMiD, PI, and anti-CD38 mAb

- 26% high-risk cytogenetics
- Median 5 prior lines of therapy
- 77.6% triple-class refractory; 30.3% penta-drug refractory

Teclistamab: 1.5 mg/kg SC weekly, after step-up

Event, Mo (95% CI)	All Patients (N = 165)
Median DoR	24 (17.0 – NE)
Median PFS	11.4 (8.8 – 16.4)
Median OS	22.2
Median time to 1st response	1.2
Median time to best response	3.8



[a]Response assessed by independent review committee. [b]At 30-month mFU of the phase 2 efficacy population (patients enrolled in Cohort A on or before March 18, 2021; n=110 patients supporting the USPI[1]): ORR, 61.8; ≥CR, 46.4% (n=51)

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

MajesTEC-1: Phase I/II Study of Teclistamab – Subgroups

	mDOR, mo (95% CI)	mPFS, mo (95% CI)	mOS, mo (95% CI)
All RP2D (N=165)	24.0 (17.0–NE)	11.4 (8.8–16.4)	22.2 (15.1–29.9)
≥CR (n=76)	NR (26.7–NE)	NR (26.9–NE)	NR (35.5–NE)
≥VGPR (n=98)	25.6 (18.1–NE)	26.7 (19.4–NE)	NR (31.0–NE)
MRD-neg (n=48)	NR (19.2–NE)	NR (21.0–NE)	NR (29.9–NE)
≤3 pLOT (n=43)	24.0 (14.0–NE)	21.7 (13.8–NE)	NR (18.3–NE)
>3 pLOT (n=122)	22.4 (14.9–NE)	9.7 (6.4–13.1)	17.7 (12.2–29.7)
Phase 2 efficacy (USPI) (n=110)	22.4 (14.9–NE)	10.8 (7.4–16.4)	21.7 (12.7–29.9)
≥CR (n=51)	NR (21.6–NE)	NR (22.8–NE)	NR (NE–NE)

Garfall. ASCO 2024. Abstract 7540.

MajesTEC-1: Phase I/II Study of Teclistamab for RRMM ≥3 LOT

Cytokine-Release Syndrome

- Rate of CRS: 72% (recurrent: 33%)
  - Step-up dose 1: 42%
  - Step-up dose 2: 35%
  - Initial treatment dose: 24%
  - Mostly grade 1 (50%) or grade 2 (21%)
  - <3% with subsequent doses
  - Median onset: 2 days (range: 1-6)
  - Median duration: 2 days (range: 1-9)

Neurotoxicity

- Most frequent: headache (25%), motor dysfunction (16%), encephalopathy (13%)
- 1 patient with grade 4 seizure and 1 fatal case of Guillain-Barré syndrome
- ICANS: 6% (recurrent: in 1.8%)
  - Step-up dose 1: 1.2%
  - Step-up dose 2: 0.6%
  - Initial treatment dose: 1.8%
  - <3% subsequent dosing
  - Median onset: 4 days (range: 2-8)
  - Median duration: 3 days (range: 1-20)

❖ Other meaningful toxicities included: Hepatotoxicity (Any grade: 28%-34%, Grade 3/4: 1%-2%), Neutropenia (Any grade: 84%, Grade 3/4: 56%), Infection (Serious infection 30%, Fatal infection 4%), Injection-site reaction 35% (grade 1/2)

Moreau. NEJM. 2022;387:495. Teclistamab-cqyv PI

MagnetisMM-3: Ph-II Trial Design & Primary Endpoint

Inclusion:

- age ≥18 with RRMM
- previously treated with PI, IMiD, and CD38mAb
- ECOG ≤2

Screened (*n = 237*)

Not enrolled (*n = 50*)
- Screen failure (*n = 45*)
- Not screening failure but not enrolled (*n = 5*)

Enrolled (*n = 187*)

Prior BCMA-directed therapy (*n = 64*)

No prior BCMA-directed therapy (*n = 123*)

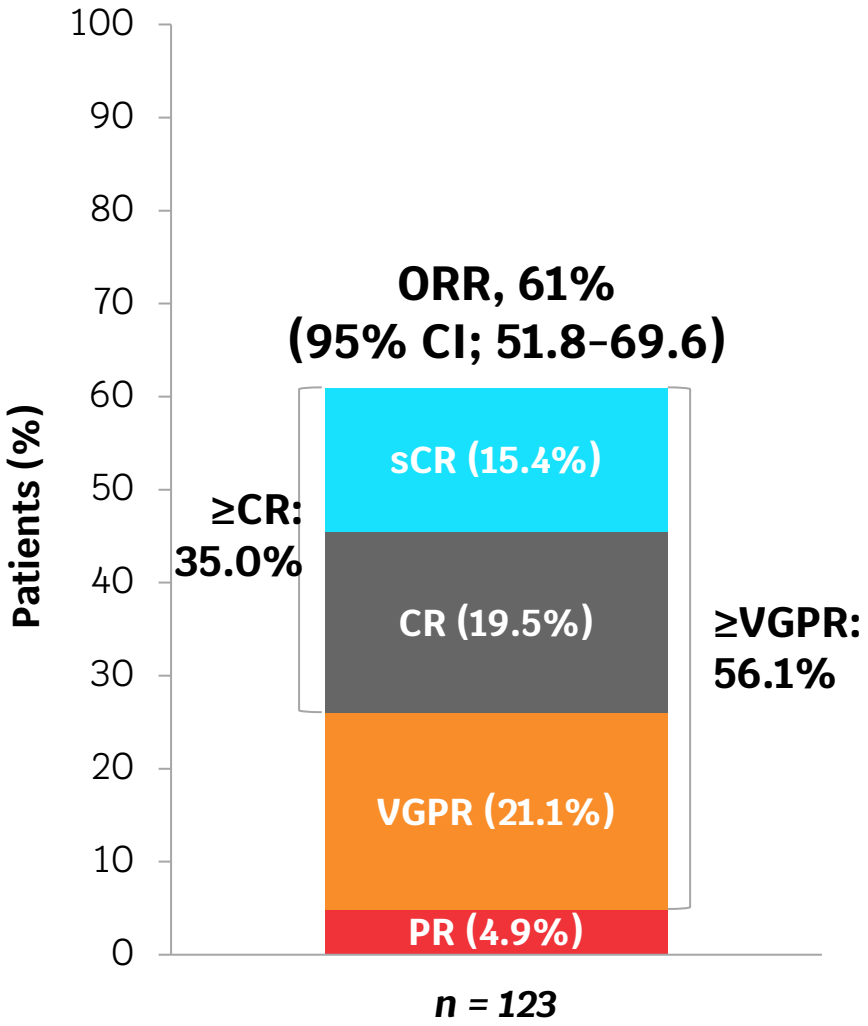
Received elranatamab (*n = 123*)

Ongoing elranatamab treatment (*n = 41*)
Discontinued treatment (*n = 82*)
- Disease progression (*n = 48*)
- AE (*n = 17*)
- Death (*n = 9*)
- Patient request (*n = 4*)
- Lack of efficacy (*n = 3*)
- Global deterioration of health status (*n=1*)

Ongoing follow-up (*n = 63*)
Discontinued follow-up (*n = 60*)
- Death (*n = 52*)
- Patient request (*n = 7*)
- Lost to follow-up (*n = 1*)

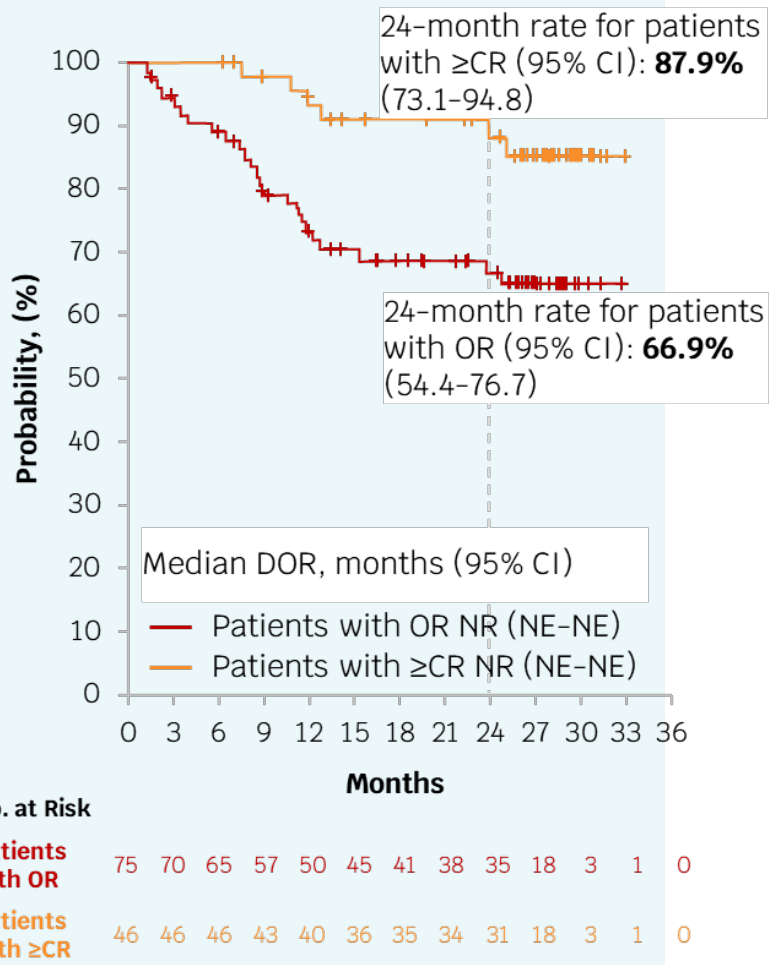
Primary Endpoint: ORR by BICR

Secondary Endpoints:
ORR by baseline extramedullary disease status, ORR by investigator, CR rate, TTR< DOR, DOCR, MRD, PFS< OS safety



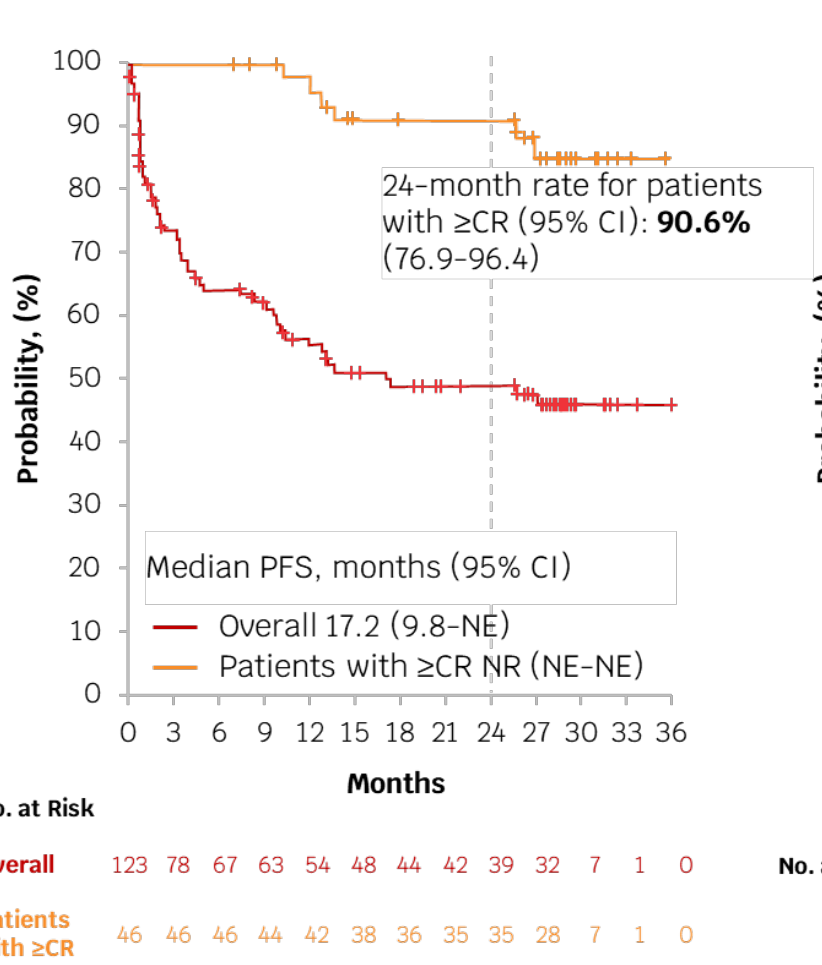
MagnetisMM-3: Secondary Endpoints

Duration of Response



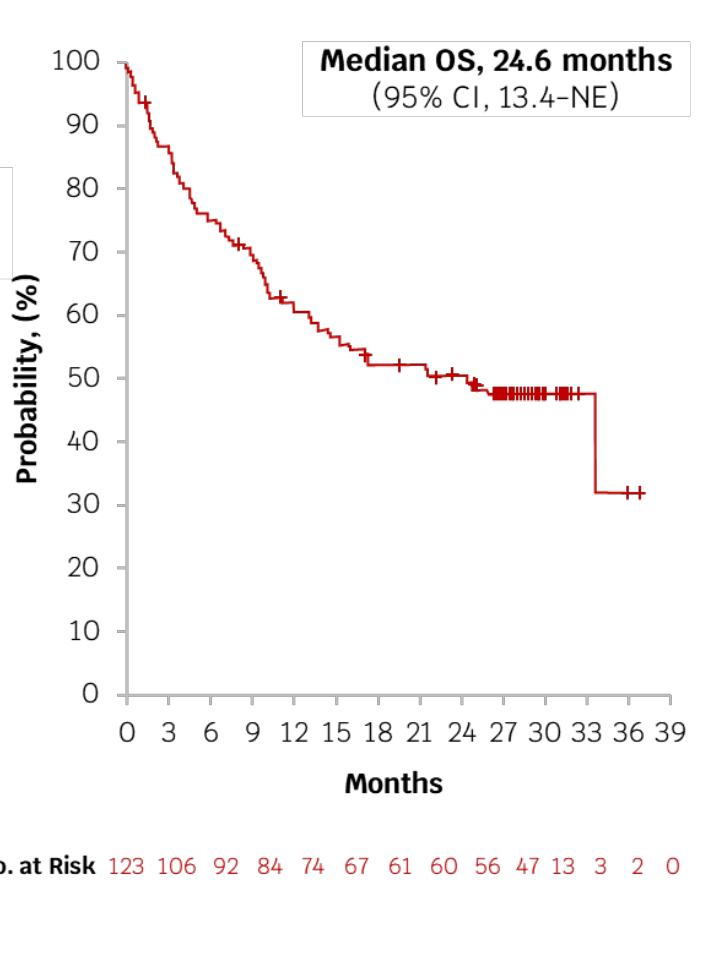
No. at Risk													
Patients with OR	75	70	65	57	50	45	41	38	35	18	3	1	0
Patients with ≥CR	46	46	46	43	40	36	35	34	31	18	3	1	0

Progression-free Survival



No. at Risk													
Overall	123	78	67	63	54	48	44	42	39	32	7	1	0
Patients with ≥CR	46	46	46	44	42	38	36	35	35	28	7	1	0

Overall Survival



No. at Risk													
	123	106	92	84	74	67	61	60	56	47	13	3	2	0

Mohty et. al., EHA 2024. Abstract 932.

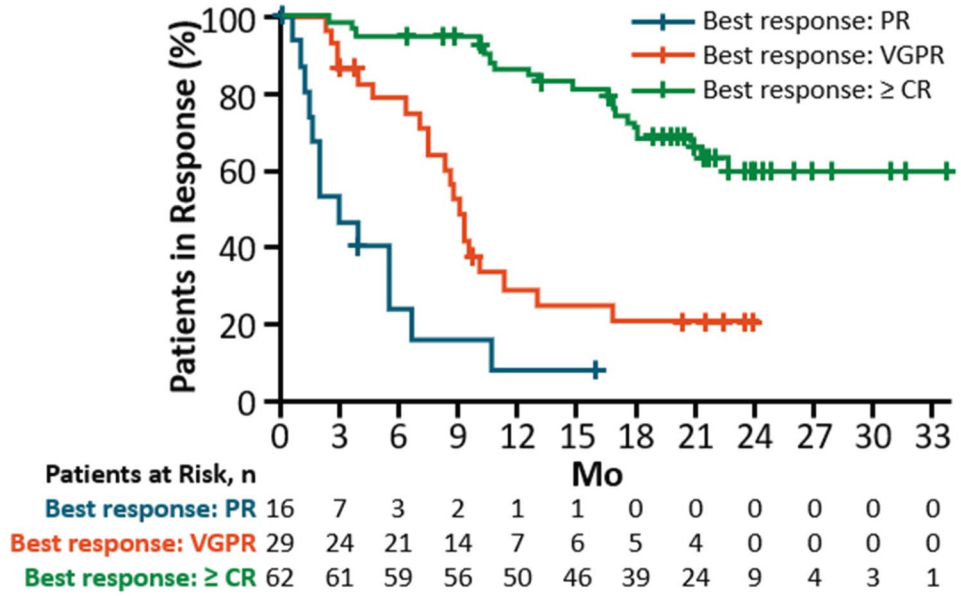
MagnetisMM-3: Safety

Treatment-emergent adverse events, n (%)	n = 123 Any grade	Grade 3 or 4
Any treatment-emergent adverse event	**123 (100)**	**87 (70.7)**
Hematologic		
Anemia	60 (48.8)	46 (37.4)
Neutropenia	60 (48.8)	60 (48.8)
Thrombocytopenia	38 (30.9)	29 (23.6)
Lymphopenia	33 (26.8)	31 (25.2)
Nonhematologic		
Cytokine release syndrome	71 (57.7)	0
ICANS	3.4%	0
Diarrhea	52 (42.3)	2 (1.6)
Fatigue	45 (36.6)	4 (3.3)
Decreased appetite	41 (33.3)	1 (0.8)
Pyrexia	37 (30.1)	5 (4.1)
COVID-19 related[b]	36 (29.3)[c]	19 (15.4)
Injection site reaction	33 (26.8)	0
Nausea	33 (26.8)	0
Hypokalemia	32 (26.0)	13 (10.6)
Cough	31 (25.2)	0
Headache	29 (23.6)	0

Lesokhin, A.M., *et al.* Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. *Nat Med* **29**, 2259–2267 (2023).

MonumenTAL-1: Talquetamab

- **Talquetamab is a novel first-in-class, off-the-shelf, T-cell redirecting bispecific antibody** directed against an antigen target called GPRC5D.
- **GPRC5D is a novel antigen target in myeloma** that is highly expressed on malignant plasma cells with limited expression in normal human tissues, including hematopoietic stem cells.
- **Pivotal phase 2 data showed > 70% ORR in heavily pretreated pts with RRMM.**
- **High response rates were also seen in pts with prior T-cell redirection therapy.**
- **The safety profile was clinically manageable** with low rates of high-grade infections and discontinuations.



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	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

Schinke et.al. ASH 2023. Abstract 8036.
Rasche. EHA 2024. Abstr P915

MonumenTAL-1: Key Efficacy Outcomes

Outcomes	Tal 0.4 mg/kg QW (n=143)	Tal 0.8 mg/kg Q2W (n=154)	Prior TCR (n=78)
Median follow-up, months	29.8	23.4	20.5
ORR, n (%)	106 (74.1)	107 (69.5)	52 (66.7)
≥VGPR, n(%)	85 (59.4)	91 (59.1)	43 (55.1)
≥CR, n(%)	47 (32.9)	62 (40.3)	33 (42.3)
Median DOR, months	9.5	17.5	N/A
(95% CI)	(6.7-13.4)	(12.5-NR)	
12-month DOR rate, %	43.8	60.6	55.8
(95% CI)	(34.1-53.1)	(50.4-69.4)	(40.8-68.4)
Median PFS, months	7.5	11.2	7.7
(95% CI)	(5.7-9.4)	(8.4-14.6)	(4.1-14.5)
12-month PFS rate, %	34.9	46.8	44.7
(95% CI)	(27.0-42.9)	(38.5-54.8)	(33.1-55.7)

EHA Library. Rasche L. 06/13/2024; 420979; P915

MonumenTAL-1: Adverse Effects

Most high-grade AEs were cytopenias

Infections

0.4 mg/kg QW
- Any grade: 57.3%
- Grade 3/4: 16.8%
- Opportunistic infection: 3.5%
- COVID-19: 9.1%
  - Grade 3/4: 0.7%

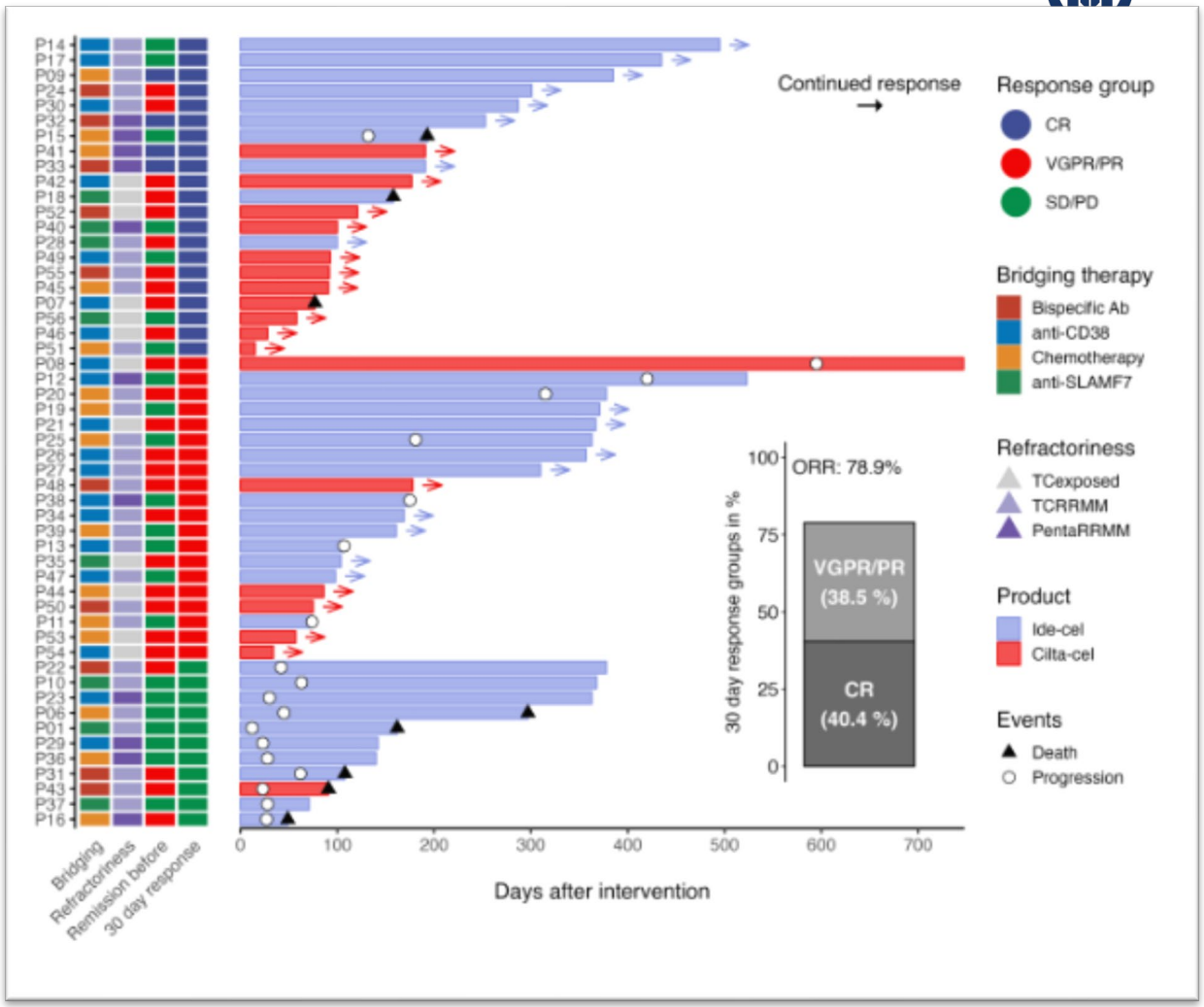
0.8 mg/kg Q2W
- Any grade: 50.3%
- Grade 3/4: 11.7%
- Opportunistic infection: 2.8%
- COVID-19: 11.0%
  - Grade 3/4: 2.1%

AEs (≥20% of any RP2D cohort)	0.4 mg/kg SC QW (n=143) Median Follow-up, 11.0 months		0.8 mg/kg SC Q2W (n=145) Median Follow-up, 5.1 months	
	Any Grade n (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
CRS	113 (79.0)	3 (2.1)	105 (72.4)	1 (0.7)
Anemia	64 (44.8)	45 (31.5)	57 (39.3)	36 (24.8)
Neutropenia	49 (34.3)	44 (30.8)	41 (28.3)	32 (22.1)
Lymphopenia	40 (28.0)	37 (25.9)	38 (26.2)	37 (25.5)
Thrombocytopenia	39 (27.3)	29 (20.3)	39 (26.9)	24 (16.6)
Skin-related AEs	80 (55.9)	0	98 (67.6)	1 (0.7)
Nail-related AEs	74 (51.7)	0	63 (43.4)	0
Dysgeusia	69 (48.3)	NA	67 (46.2)	NA
Rash-related AEs	56 (39.2)	2 (1.4)	39 (26.9)	8 (5.5)
Weight decreased	57 (39.9)	3 (2.1)	47 (32.4)	2 (1.4)
Pyrexia	53 (37.1)	4 (2.8)	35 (24.1)	1 (0.7)
Asthenia	37 (25.9)	3 (2.1)	13 (9.0)	2 (1.4)
Dry mouth	36 (25.2)	0	53 (36.6)	0
Diarrhea	34 (23.8)	3 (2.1)	32 (22.1)	0
Dysphagia	34 (23.8)	0	33 (22.8)	3 (2.1)
Fatigue	32 (22.4)	5 (3.5)	29 (20.0)	1 (0.7)
Decreased appetite	25 (17.5)	2 (1.4)	29 (20.0)	2 (1.4)

Chari et al., ASH 2022

Sequencing Immunotherapies

- How do you sequence anti-BCMA therapies?
  - Extremely carefully!
  - Prior BCMA-directed therapy is an independent predictor of inferior outcomes for response, PFS and OS as reported by the MM Immunotherapy Consortium (ORR 74% vs 88%; PFS 3.2 vs. 9.0mos). As well, in CARTITUDE-2 cohort-C, ORR was 60% instead of 98%.
  - Timing of CAR T-cell infusion to prior BCMA-directed therapy appears to be predictive of the likelihood of response.



- Patients who received BITEs as BT for subsequent anti-BCMA CAR-T therapy showed favorable expansion dynamics with higher capacity for CAR-T long-term persistence.
- Selection of CD8+ EM clones by BITE therapy prior to apheresis maintains T-cell fitness during CAR-T therapy.

Ferreri C, et al. Blood (2022) 140 (Supplement 1): 1856–1858
Cohen A, et al. Blood 2022; blood.2022015526
Fandrei D, et al. HemaSphere, 2024;8☹S1):S194

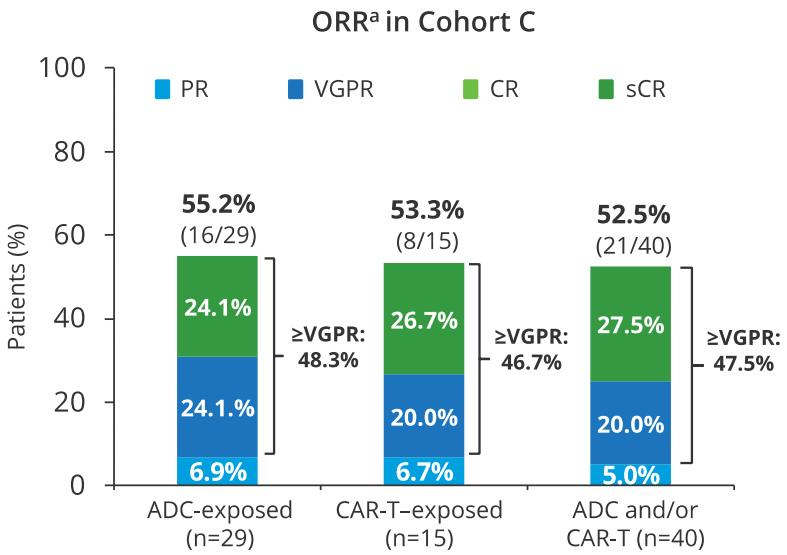
Sequencing immunotherapies

MajesTEC-1, cohort C

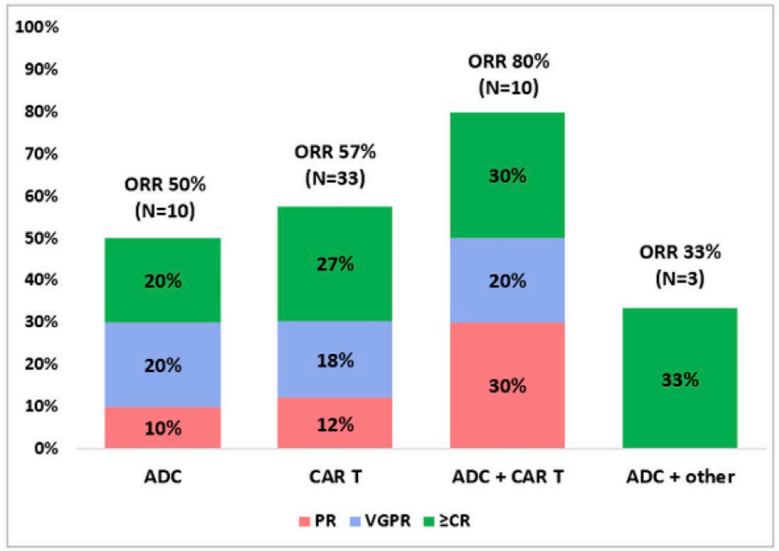
Cohort C

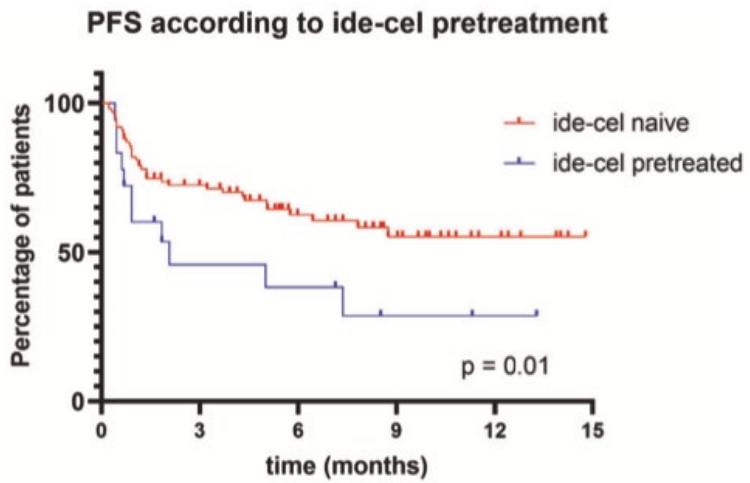
Key eligibility criteria

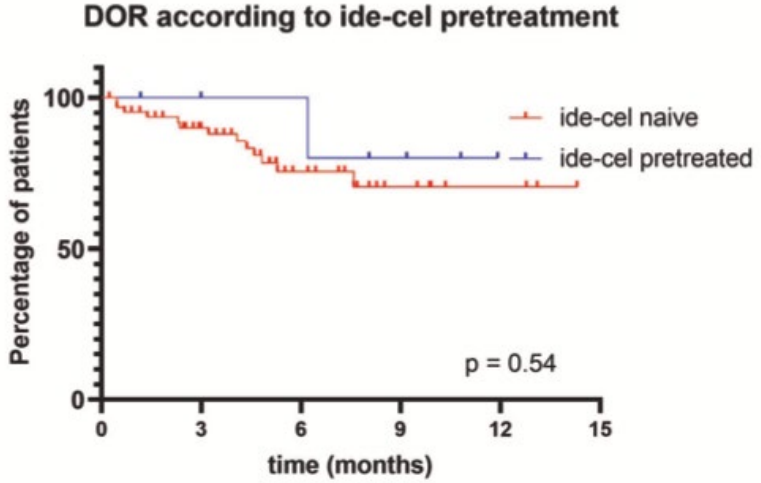
- Documented, measurable RRMM
- RRMM, ≥3 prior lines
- Prior PI, IMiD, and anti-CD38 mAb
- **Prior BCMA-targeted treatment (CAR-T and/or ADC)**



Real world experience







Riedhammer et al. *Leukemia* 2024. Dima D, et al. Transplant Cell Ther. 2024 Mar;30(3):308.e1-308.e13.

Conclusions

- BCMA/GPRC5D-directed BsAbs therapies have demonstrated impressive clinical results in the context of advanced triple-class exposed RRMM, leading to the approval of 3 BsAbs.
- BsAbs are safe and has shown deep responses. Only initial dosing as inpatient but increasingly done outpatient.
- Optimizing the sequencing of CAR T-cell and BsAb therapies is paramount for enhancing efficacy.

Thank You!!