Where Science Becomes Hope

BCMA VS GPRC5D AS TARGETS FOR MULTIPLE MYELOMA

BCMA

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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

DISCLOSURES

Ajay K. Nooka has served on advisory boards and received honorarium from Adaptive Biotechnologies, Amgen, AstraZeneca, Bristol Myers Squibb, Cellectar biosciences, GlaxoSmithKline, Janssen, K36 therapeutics, ONK therapeutics, Pfizer, Sanofi, Sebia, and Takeda

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Received grant/research support for investigator-initiated studies from Amgen, GlaxoSmithKline, Janssen, Merck, and Takeda

TALKING POINTS (EVIDENCE BASED)

Data on the 5 available BCMA targeting agents

Data on efficacy that led to the approvals in myeloma

Data on safety

Data on BCMA expression and immune health post anti-BCMA targeted therapy

Data on retreatment with BCMA targeting agents

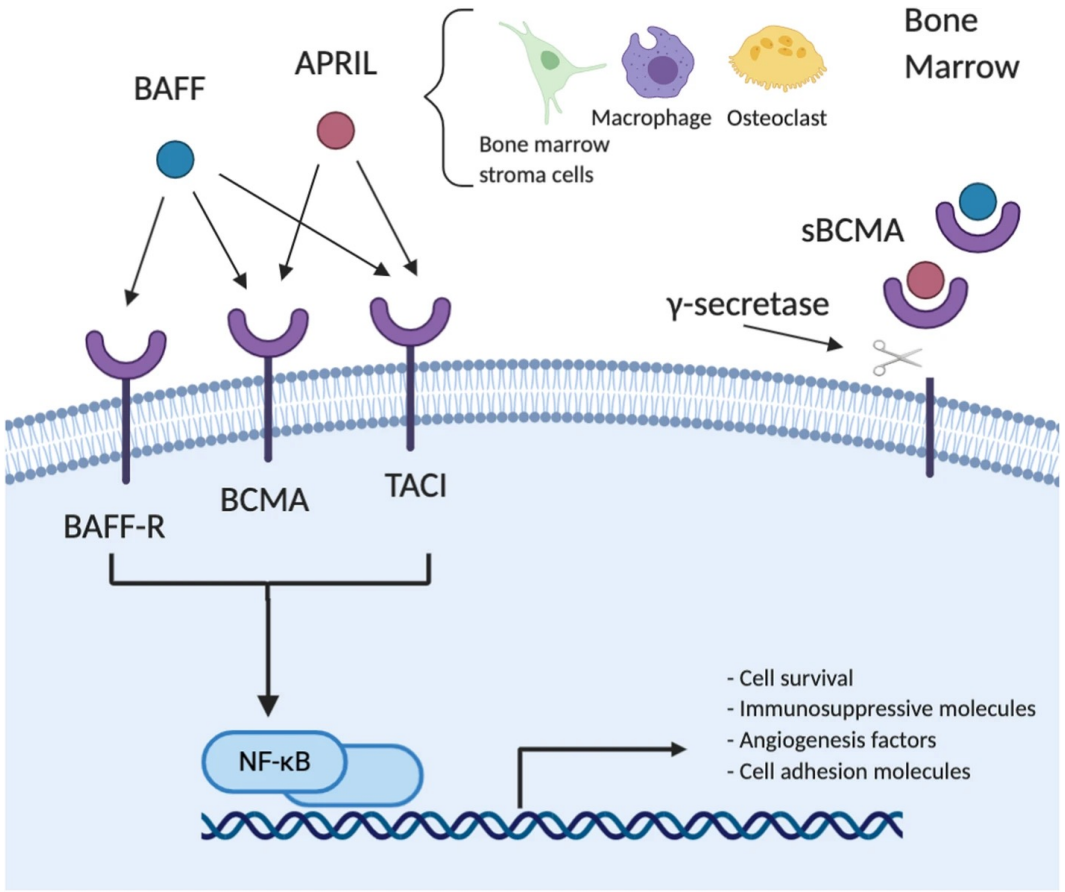
BCMA: EXPRESSION ON PLASMA CALLS

Expressed

- on surface of nearly all MM cell lines
- in malignant PCs > in normal PCs

↑ BCMA levels are associated with ↓ outcomes

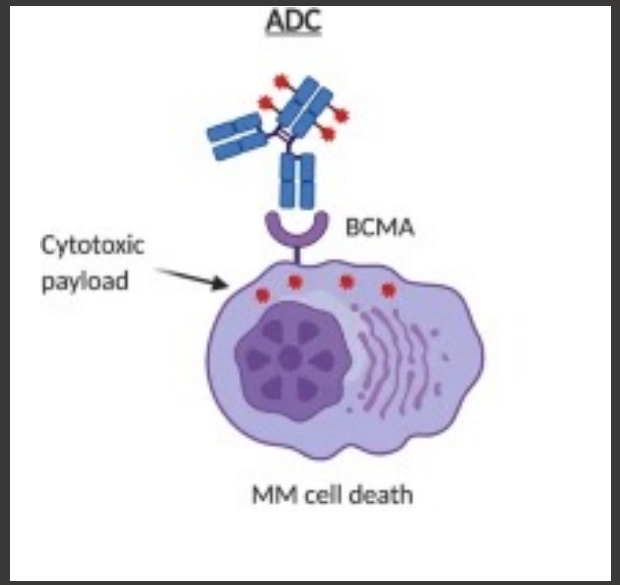
Upregulated expression during MM pathogenesis and evolution (normal → MGUS → SMM → active MM)



Yu B, et al. *J Hematol Oncol*. 2020;13:125.

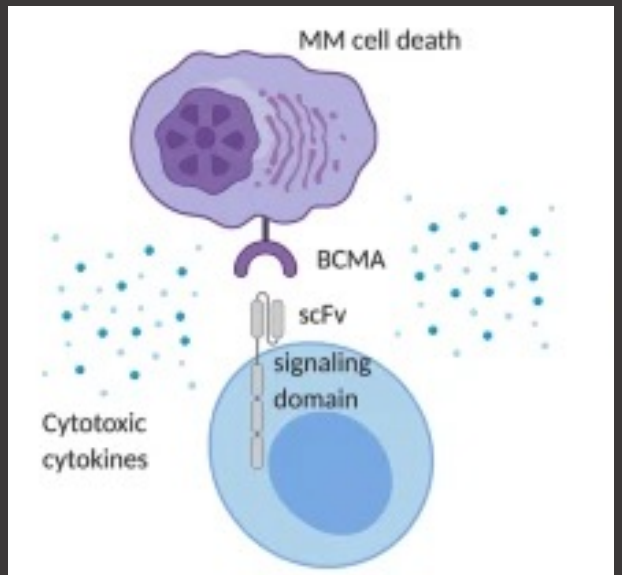
BCMA-TARGETED THERAPY FOR RRMM

ADC[1]



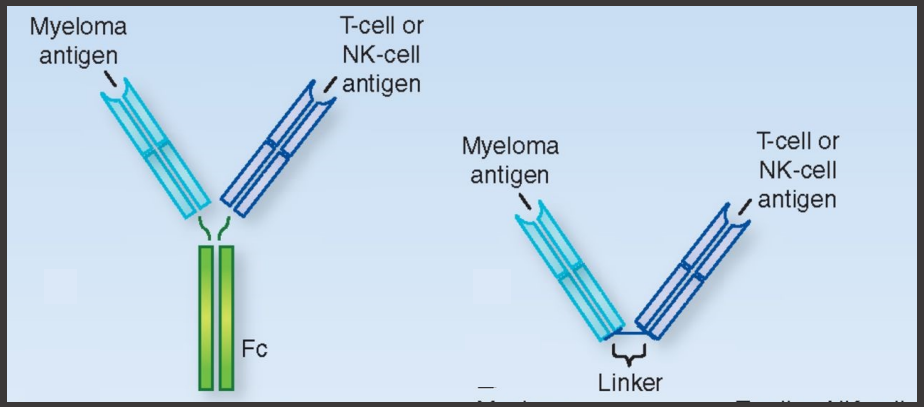
- ADC binds to BCMA on MM cell surface and is internalized
- Linker hydrolysis inside of lysosomes/endosomes
- **Cytotoxic payload released to induce cell death**.

CAR T[2]



- Ectodomain of BCMA scFv on CAR T cells binds to BCMA on MM cell surface; leads to:
  - **CAR T-cell activation, cytotoxic cytokine release, and MM cell death**

Bispecific Ab[2]

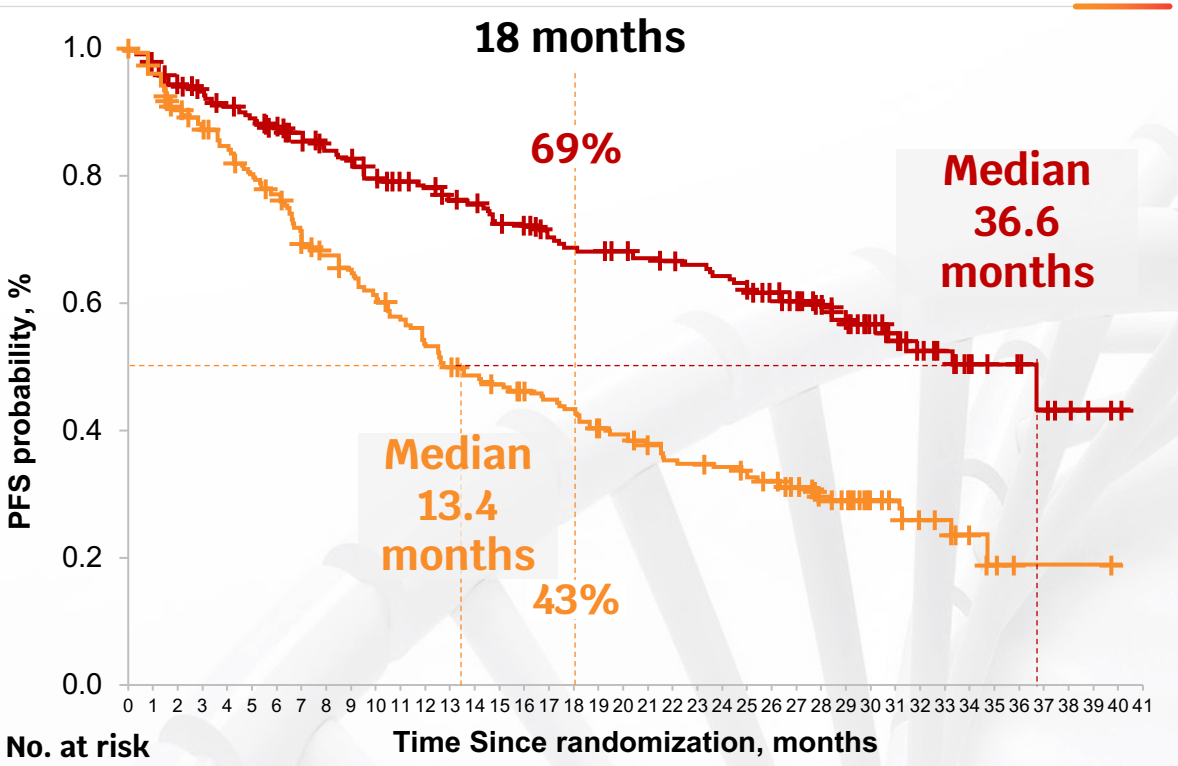


- Bispecific antibodies bind both a target on malignant plasma cells and on cytotoxic immune effector cells [T cells/NK cells] to create an immunologic synapse; leads to:
  - **T/NK-cell activation** and destruction of malignant plasma cells

1. Yu B, et al. *J Hematol Oncol*. 2020;13:125.
2. Lancman G, et al. *Blood Cancer Discov*. 2021;2:423-433.

DREAMM-7: PFS AND OS IN THE ITT

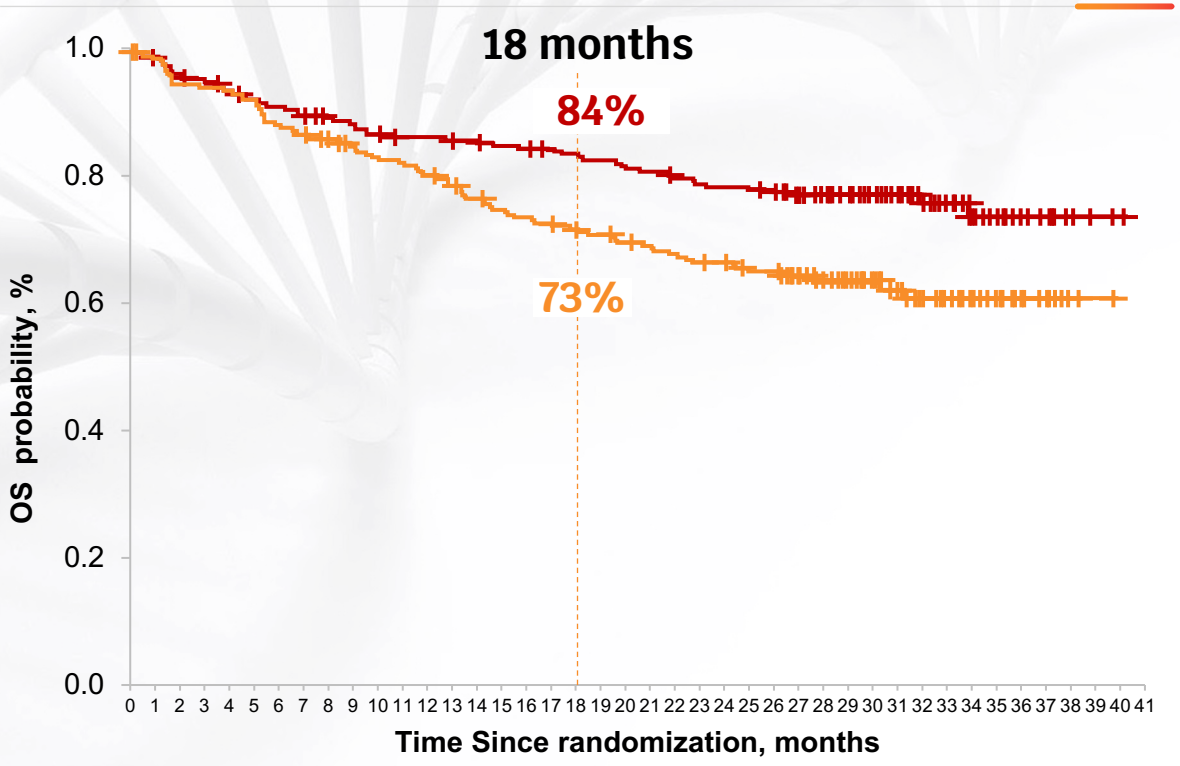
PFS



No. at risk

PFS[a]	BVd (N=243)	DVd (N=251)
Events, n(%)	91 (37)	158 (63)
PFS, median (95% CI), mo[b]	**36.6 (28.4-NR)**	**13.4 (11.1-17.5)**
HR (95% CI)[c]	0.41 (0.31-0.53)	
P value[d]	<.00001	

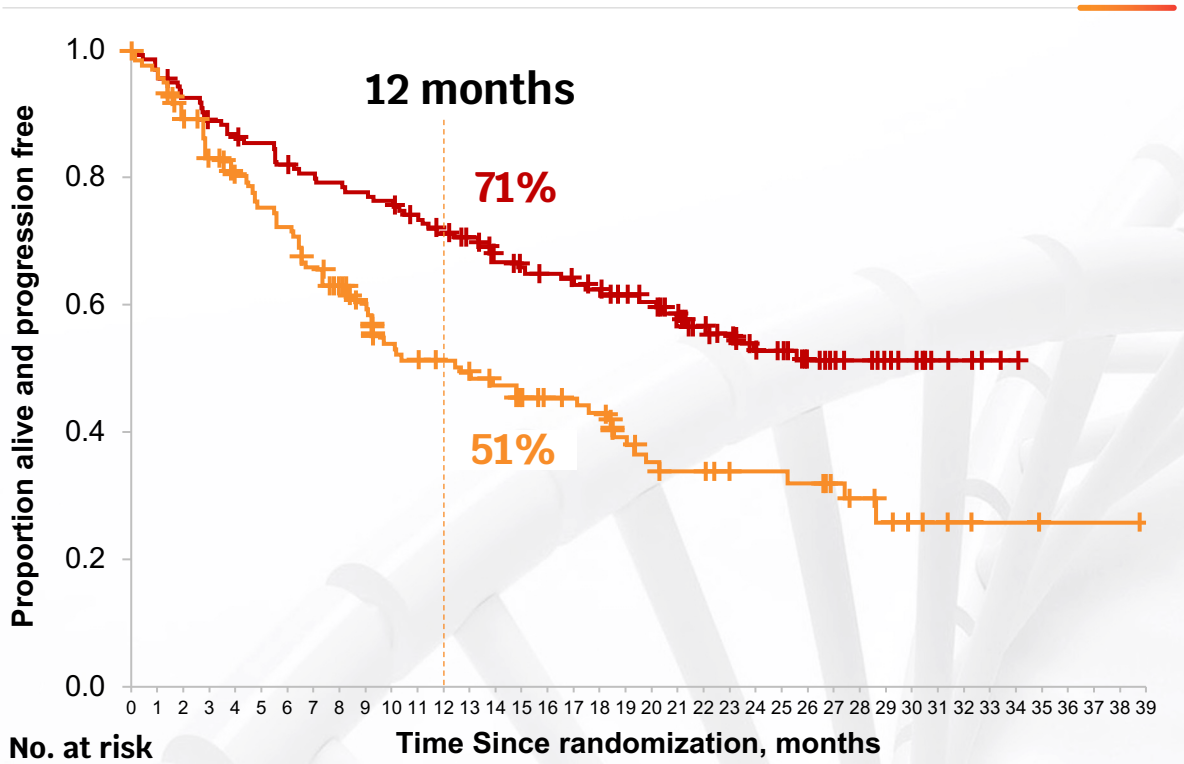
OS



OS[a]	BVd (N=243)	DVd (N=251)
Events, n(%)	54 (22)	87 (35)
OS, median (95% CI), mo[b]	NR	NR
HR (95% CI)[c]	0.57 (0.4-0.8)	
P value[d]	.00049[e]	

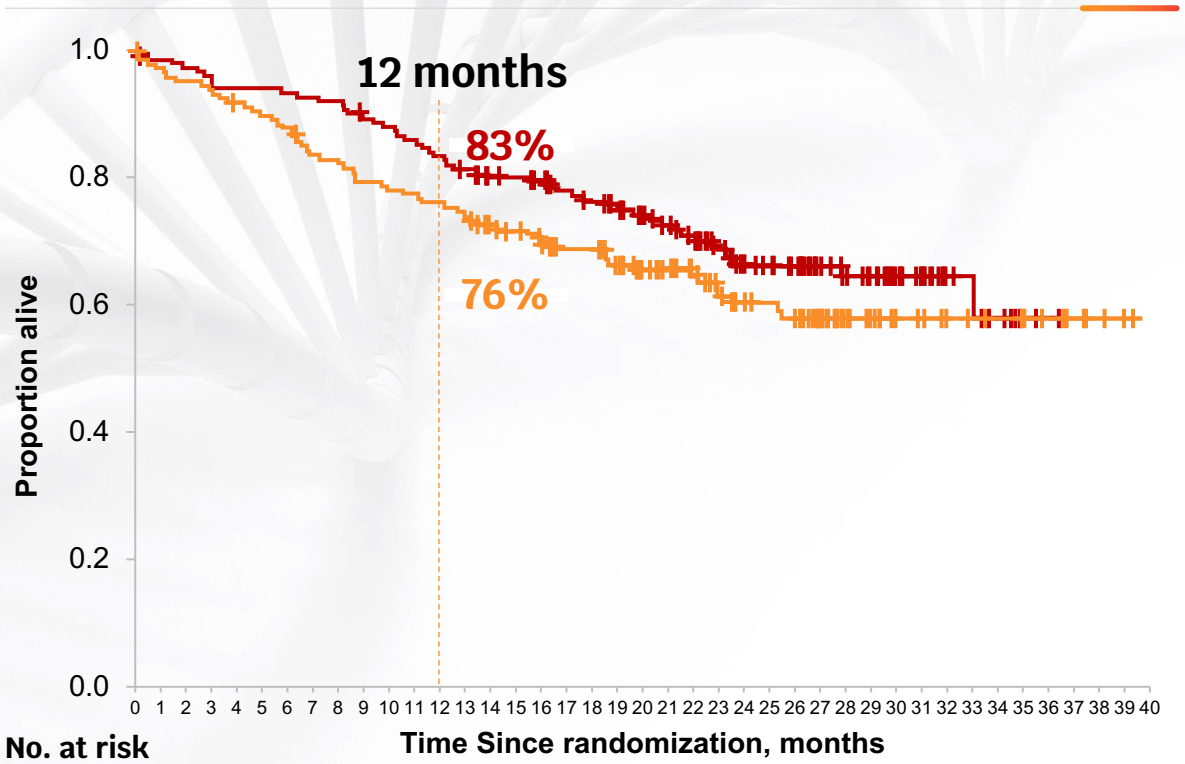
DREAMM-8: EFFICACY

PFS



PFS[a]	BPd (N=155)	PVd (N=147)
Events, n(%)	62 (40)	80 (54)
Median PFS (95% CI), months	NR (20.6-NR)	12.7 (9.1-18.5)
HR (95% CI); *P* value	**0.52** (0.37-0.73); **<.001**	

Positive OS Trend Favoring BPd vs PVd

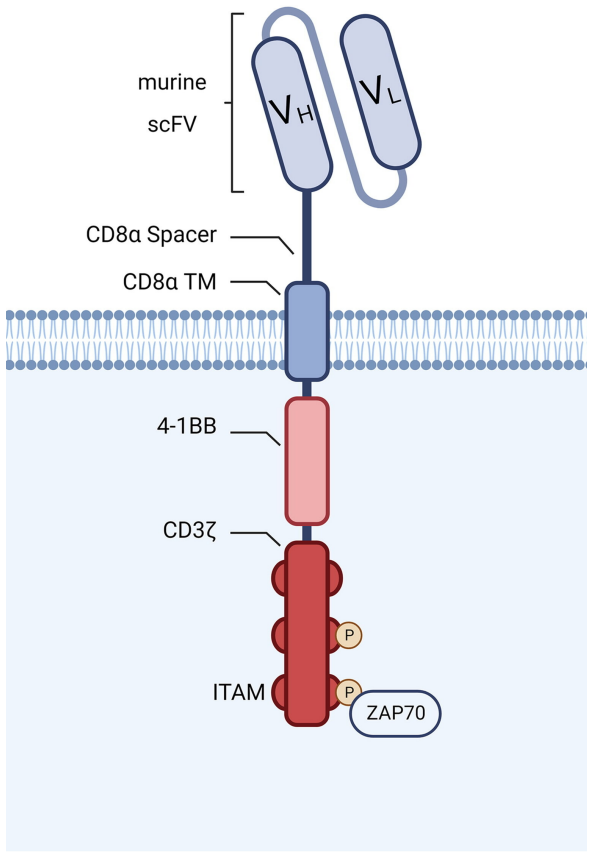


Interim OS	BPd (N=155)	PVd (N=147)
Events, n(%)[a]	49 (32)	56 (38)
Median OS (95% CI), months	**NR** (33.0-NR)	**NR** (25.2-NR)
HR (95% CI)[b]	**0.77** (0.53-1.14)	

Trudel et. al. ASCO 2024. J Clin Oncol 42, 2024 (suppl 17; abstr LBA105)

BCMA-DIRECTED CAR-T IN MULTIPLE MYELOMA

Ide-cel



FDA Approved: Mar 26, 2021

KarMMa Trial

Phase II (n=128)

ORR: 72%

95% CI, 63.2 – 80.8

ORR = sCR + VGPR + PR

mDOR: 11.3 months

95% CI, 10.3 – 15.3

mPFS: 22.6 months

95% CI, 14.39 – NE

mOS: 24.0 months

95% CI, 18.96 – NE

Cilta-cel

FDA Approved: Feb 28, 2022

CARTITUDE-1 Trial

Phase Ib/II (n=97)

ORR: 98%

- 95% CI 92.7–99.7
- ORR = sCR + VGPR + PR

mDOR: 33.9 months

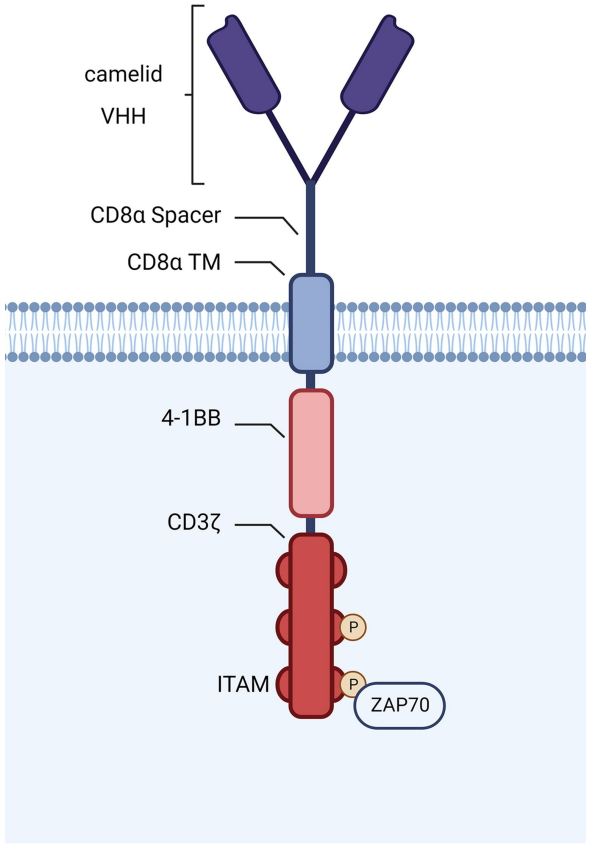
- 95% CI: 25.5 – NE

mPFS: 34.9 months

- 95% CI: 25.2 – NE

mOS: NR

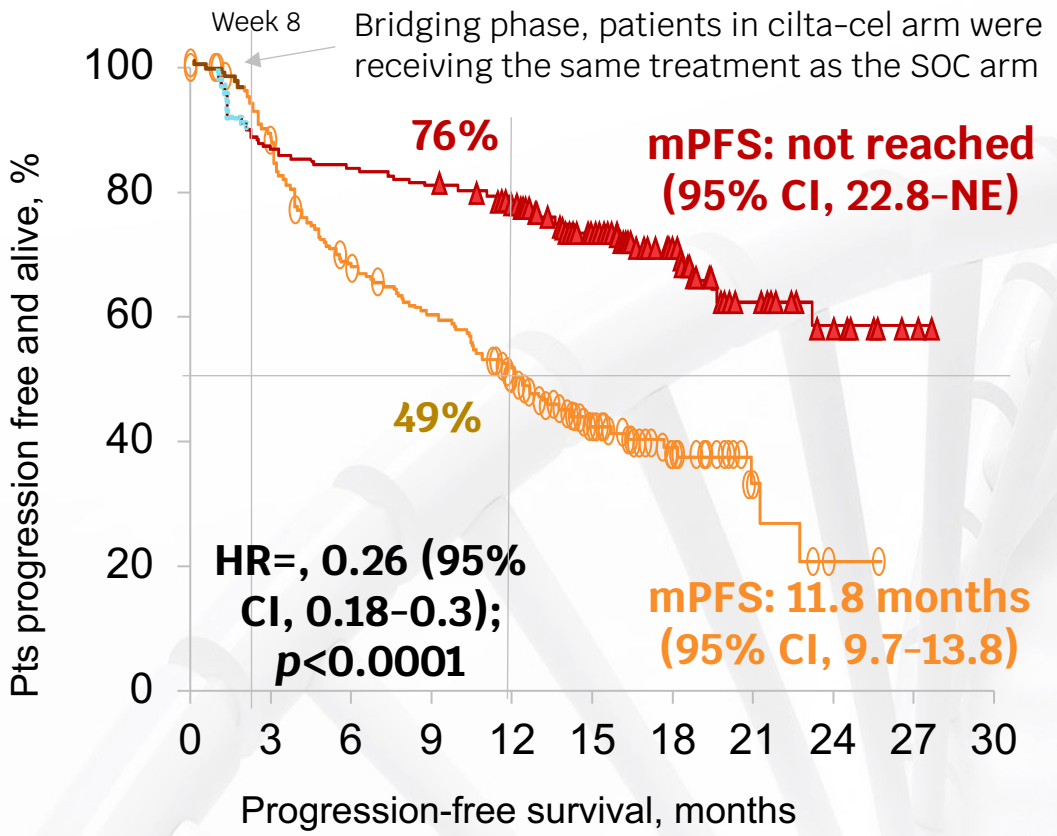
- 62.9% OS at 36 months



https://www.abecmahcp.com/ (Accessed Feb 15, 2024); Yi Lin et al. *JCO* 41, 8009-8009 (2023).

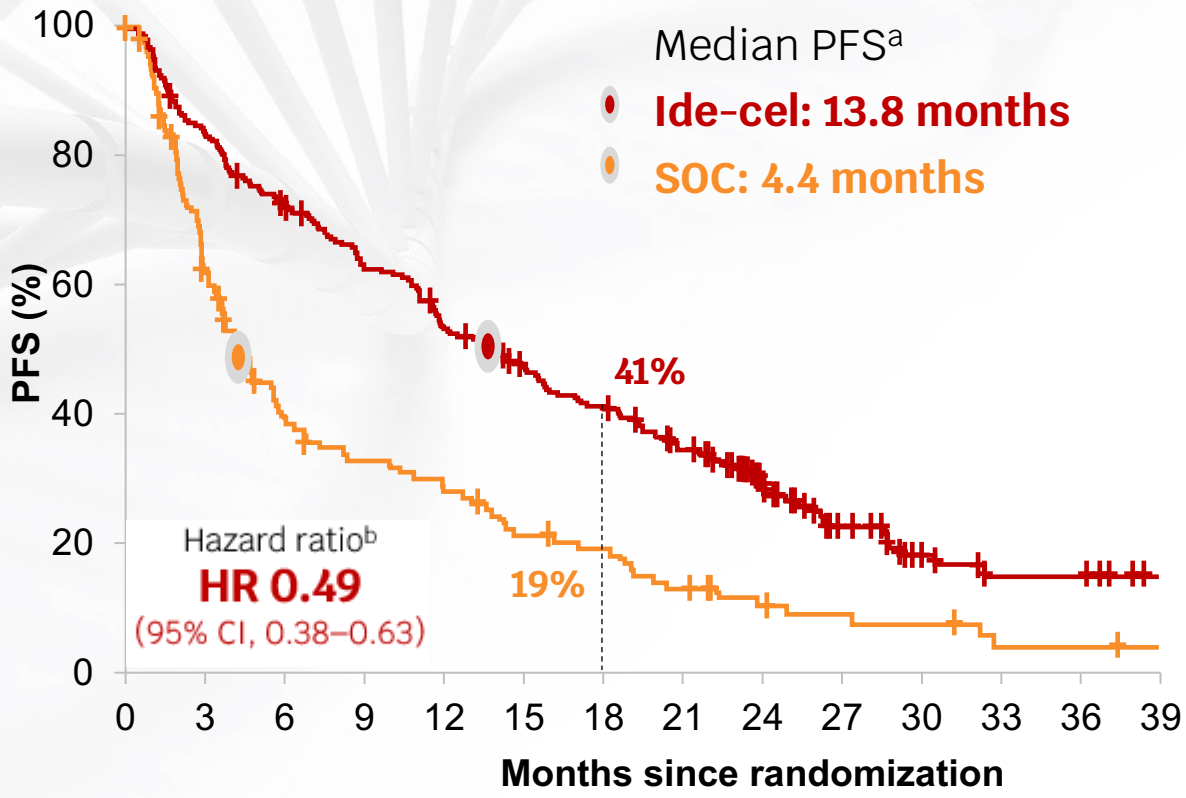
EFFICACY OF CAR-T AS AN EARLIER LOT

CARTITUDE-4: Primary Endpoint- PFS (ITT Population)



FDA APPROVED IN 2L AS OF 4/5/24

KarMMa-3 Primary Endpoint: PFS analysis (ITT)

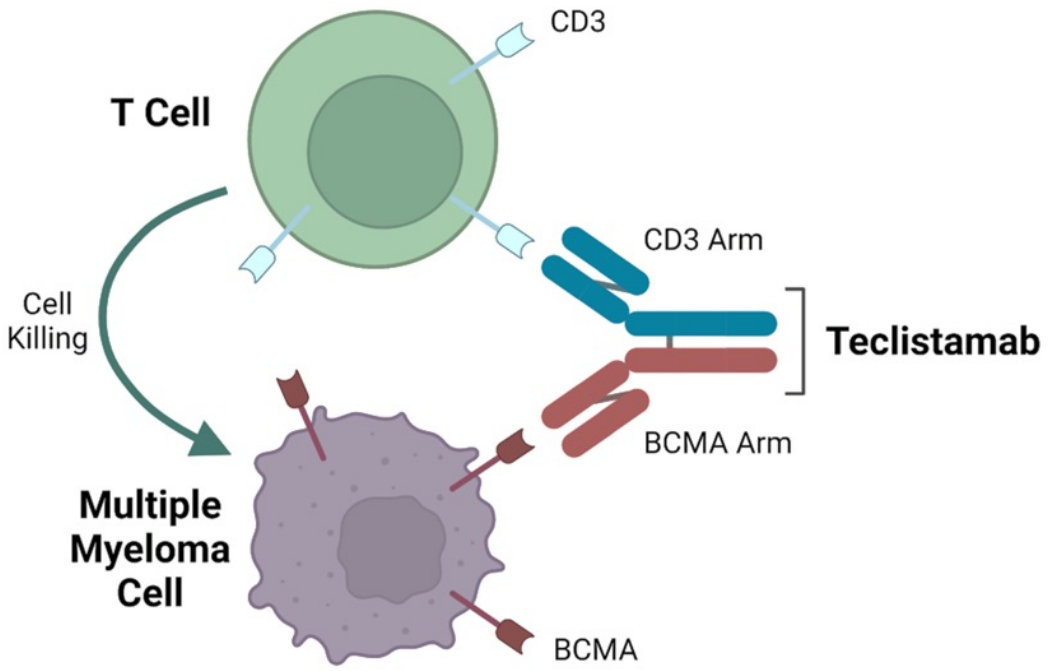


FDA APPROVED IN 3L AS OF 4/5/24

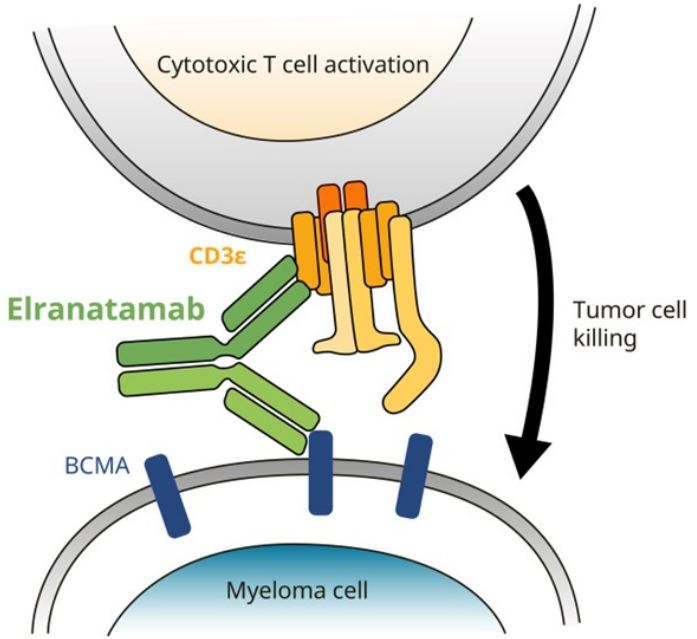
Dhakal et. al. ASCO 2023. J Clin Oncol 41, 2023 (suppl 17; abstr LBA106)

BCMA-DIRECTED BISPECIFICS IN MULTIPLE MYELOMA

teclistamab



elranatamab



MAJESTEC-1: TECLISTAMAB IN PATIENTS WITH TCE RRMM: LONG-TERM FOLLOW-UP

Teclistamab Dosing Schedule

SUD 1: 0.06 mg/kg → **SUD 2: 0.3 mg/kg** → **Tx dose 1 (RP2D): 1.5 mg/kg** → **Subsequent Tx doses: 1.5 mg/kg QW**

2–4 days allowed between step-up doses (SUD) 1, SUD 2 and treatment dose

Option to transition to Q2W if:
- ≥PR after ≥4 cycles (Phase 1)
- ≥CR for ≥6 months (Phase 2)

Less frequent dosing was permitted if patients continued to respond on Q2W

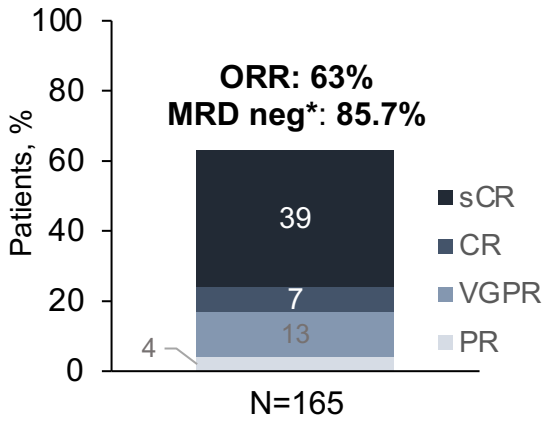
Study Population (Median Follow-up: 30.4 months)

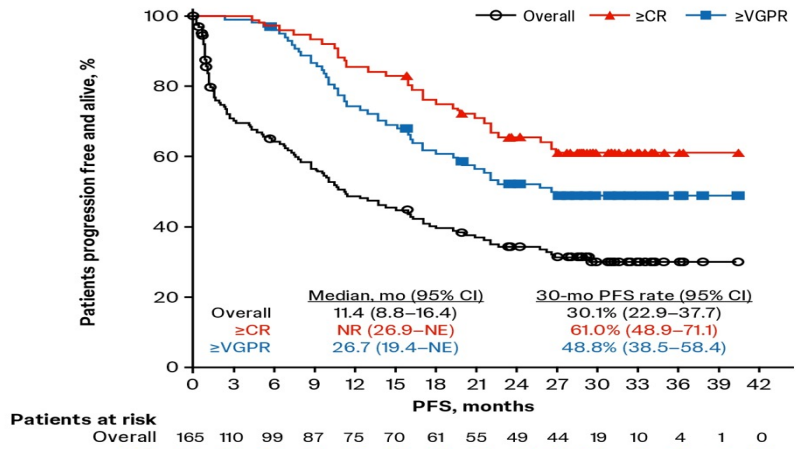
165 patients had received teclistamab at RP2D

65 Transitioned to less frequent dosing

38 Remain on treatment (**37** on less frequent dosing)

Efficacy ((Median Follow-up: 30.4-months)





Safety (N=165)

AE	Any grade, n (%)	Grade ≥3, n (%)
Neutropenia	118 (71.5)	108 (65.5)
Anaemia	91 (55.2)	62 (37.6)
Thrombocytopenia	69 (41.8)	38 (23.0)
Infections	130 (78.8)	91 (55.2)
CRS	119 (72.1)	1 (0.6)

Decreased onset of new **severe infections** aligned with switch to **Q2W dosing**

With the longest follow-up of any BsAb in MM, teclistamab continued to demonstrate deep and durable responses, including in patients who switched to less frequent dosing (e.g., Q2W)

*MRD negativity threshold: 10^{-5}

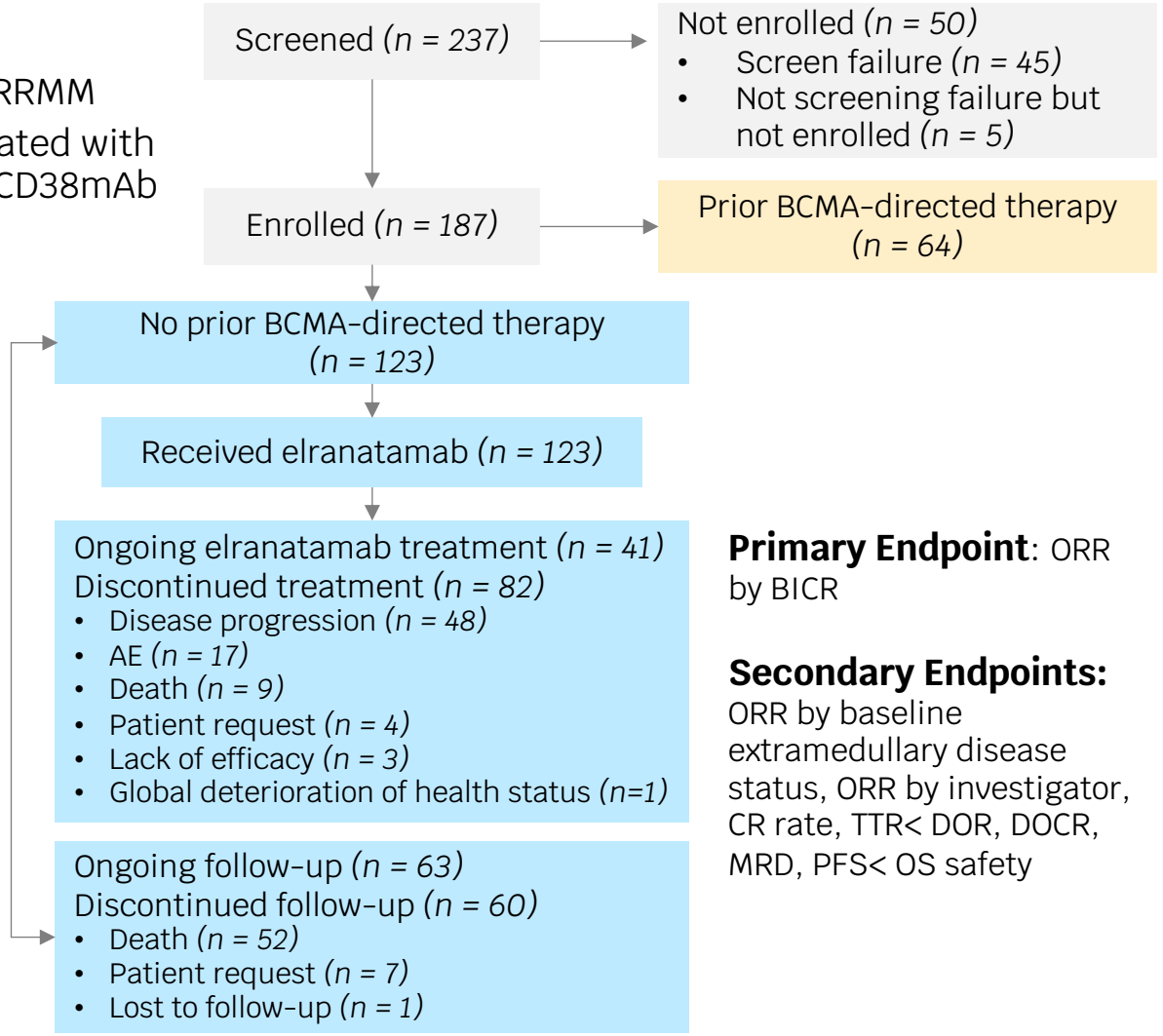
Garfall AL, et al. Presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4; Chicago, IL, USA & Virtual

(See slide notes for abbreviations)

MAGNETISMM-3: PHASE II TRIAL DESIGN AND PRIMARY ENDPOINT

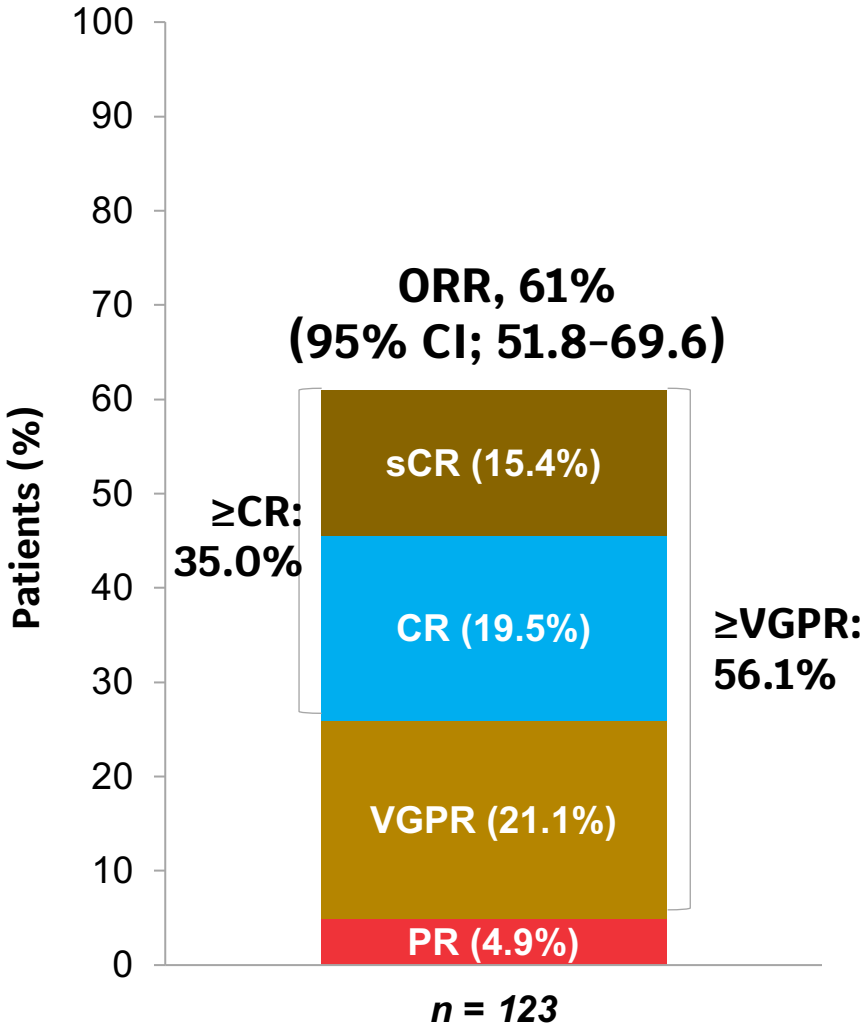
Inclusion:

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



Primary Endpoint: ORR by BICR

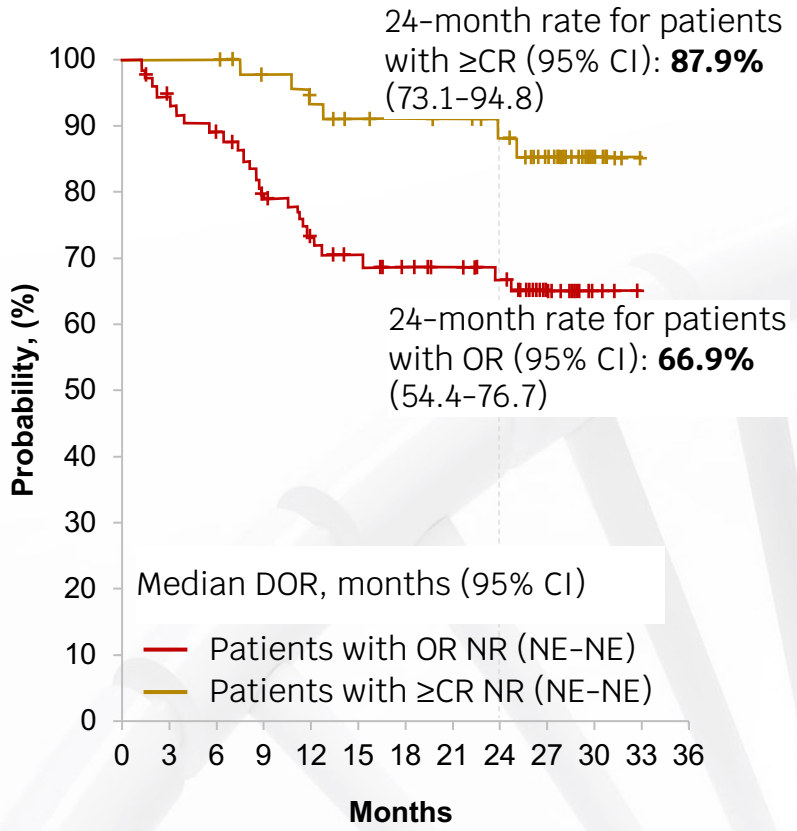
Secondary Endpoints: ORR by baseline extramedullary disease status, ORR by investigator, CR rate, TTR< DOR, DOCR, MRD, PFS< OS safety



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

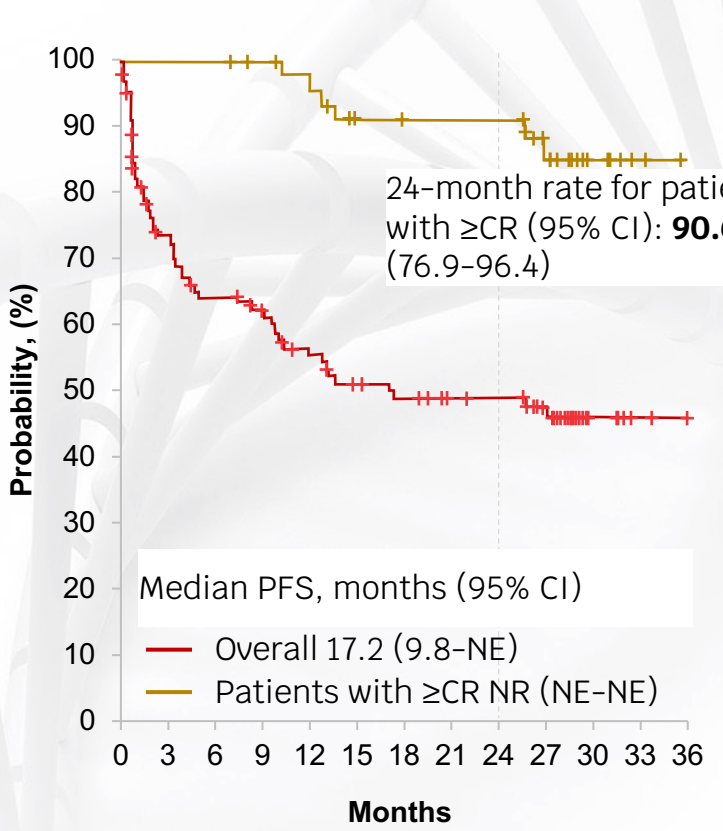
MAGNETISMM-3: SECONDARY ENDPOINTS

Duration of Response



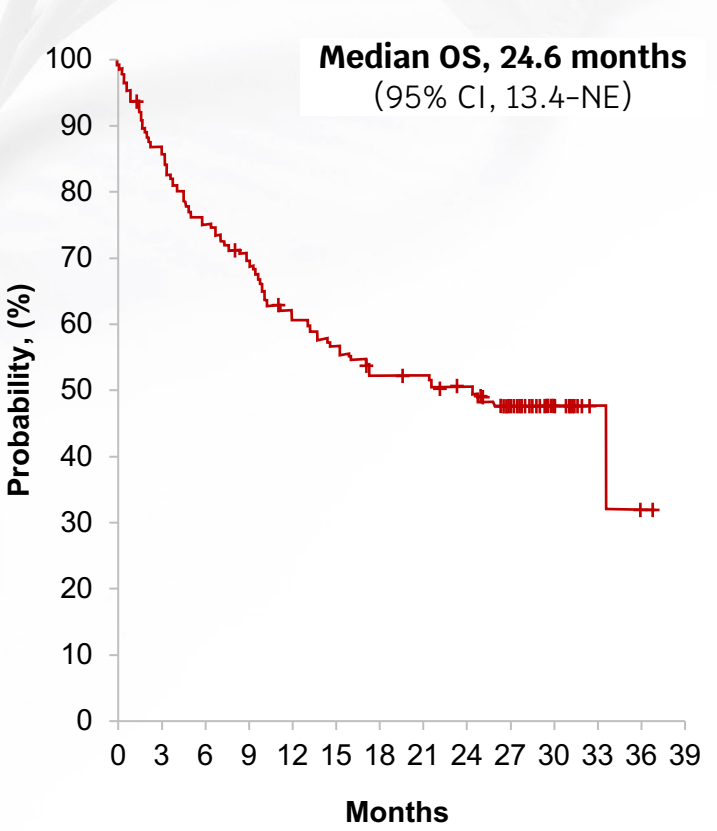
No. at Risk													
Patients with OR	75	70	65	57	50	45	41	38	35	18	3	1	0
Patients with ≥CR	46	46	46	43	40	36	35	34	31	18	3	1	0

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

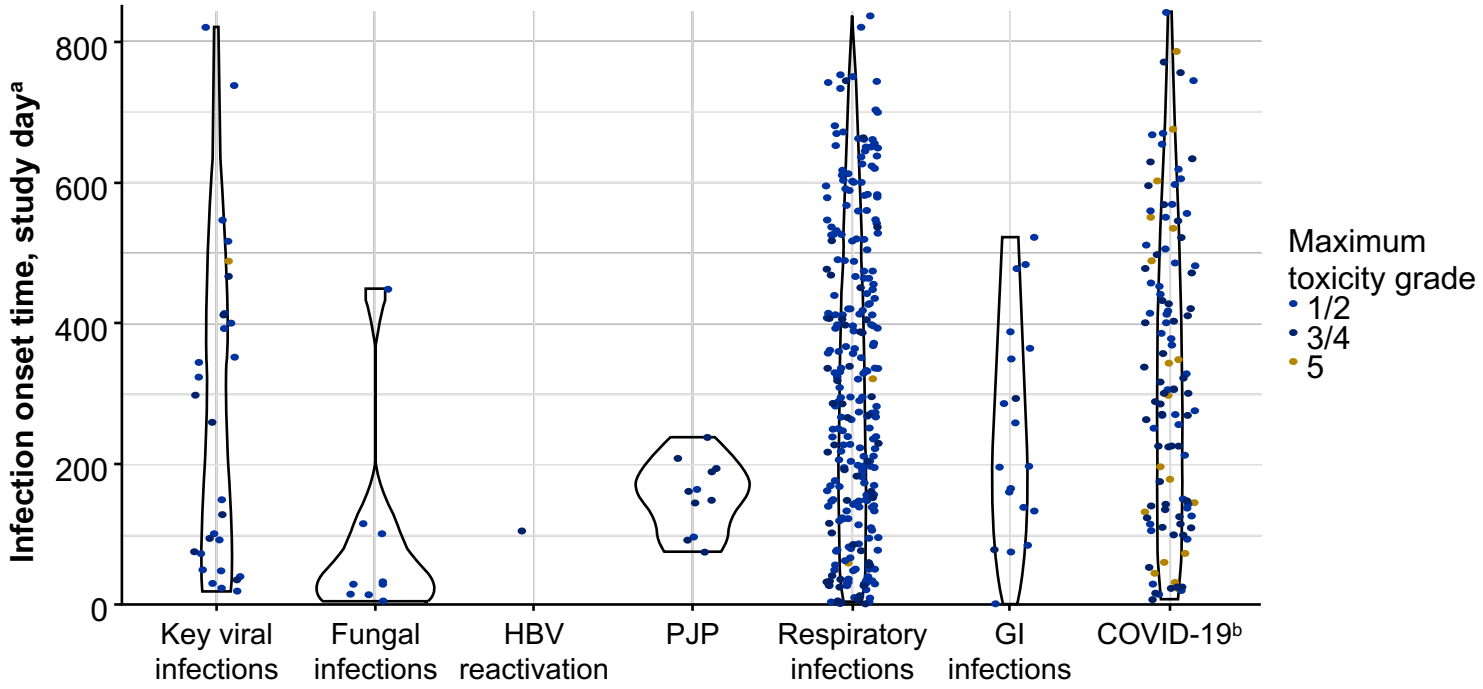


No. at Risk														
	123	106	92	84	74	67	61	60	56	47	13	3	2	0

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

TIMING AND MAXIMUM TOXICITY GRADE OF CLINICALLY RELEVANT INFECTIONS DURING TECLISTAMAB TREATMENT

- Respiratory infections occurred throughout the study (mostly grade 1/2)
- COVID-19 infections of all grades were observed throughout the study
- Most viral infections occurred during the first 12 months
- GI infections were seen throughout the study
- Most fungal and PJP infections were observed early

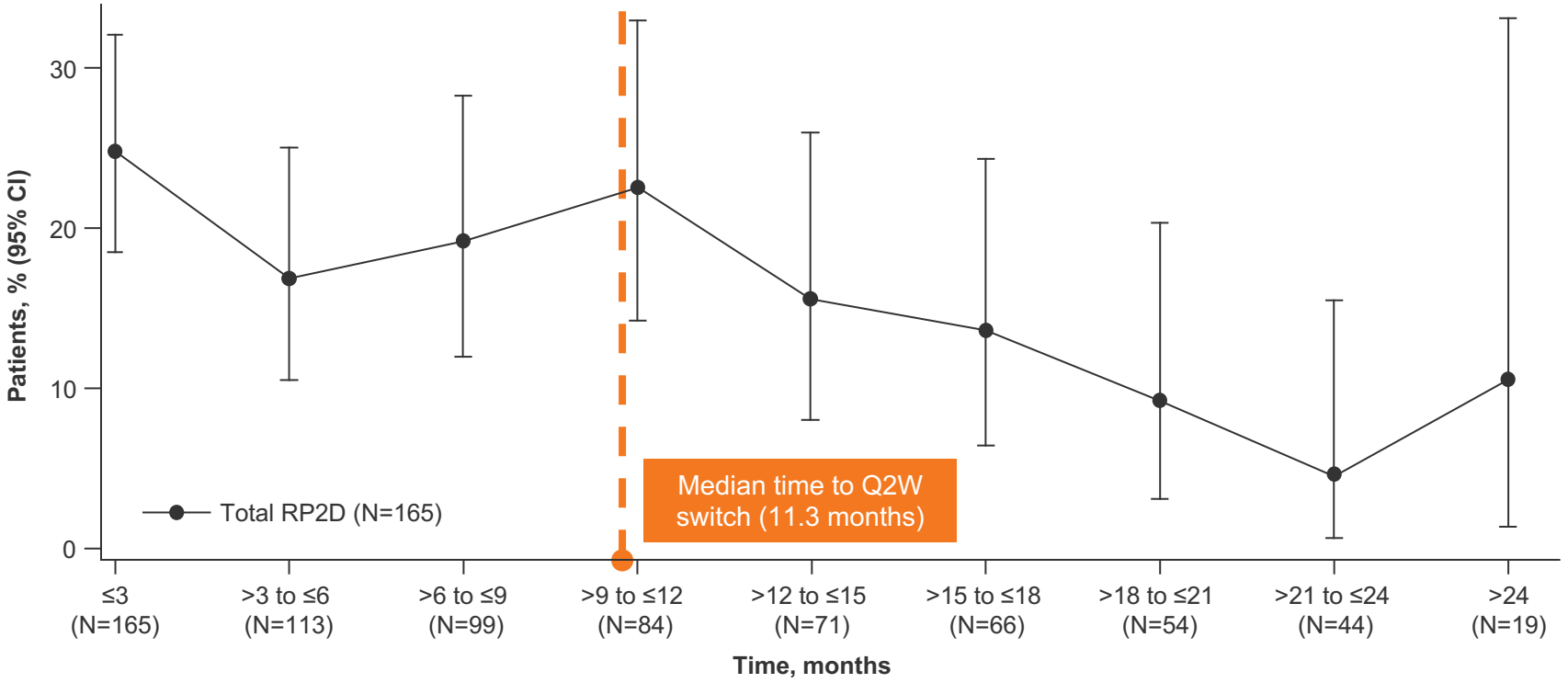


Continued monitoring throughout treatment is recommended, although improvements are expected with increased awareness and vigilance, new expert management guidelines, and additional strategies

Nooka Cancer 2024

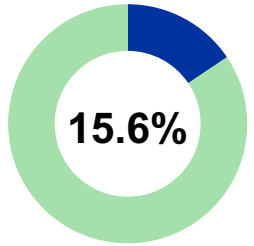
NEW-ONSET GRADE ≥3 INFECTIONS DECREASED OVER TIME IN MAJESTEC-1, WITH FEWER INFECTIONS IN PATIENTS SWITCHING TO Q2W

New-onset grade ≥3 infections in the overall MajesTEC-1 study population

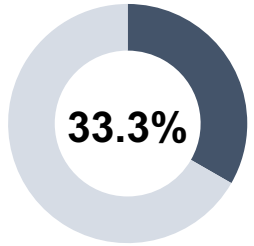


New-onset grade ≥3 infections at 1–1.5 years[1]

Patients switching to Q2W dosing by 1 year



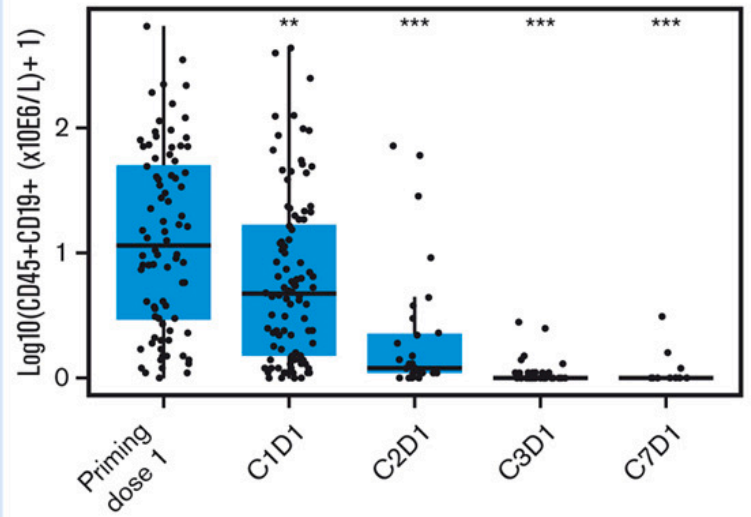
Patients remaining on QW dosing at 1 year



VandeDonk, Neils DGHO 2023

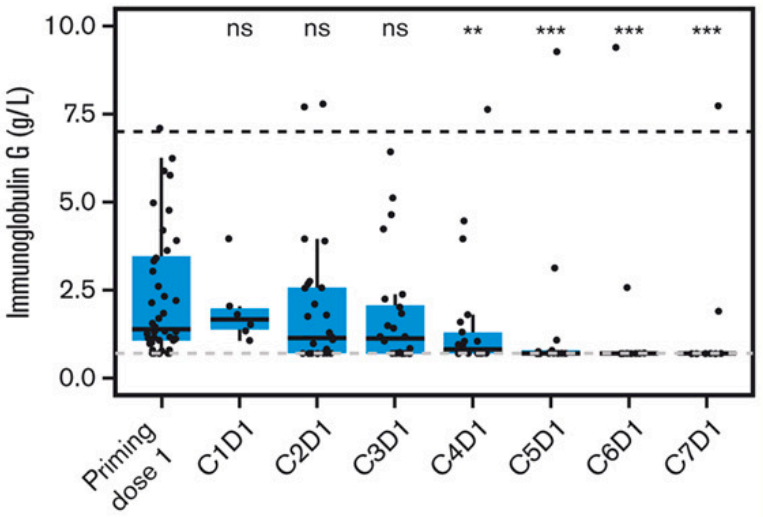
TECLISTAMAB IMPAIRS HUMORAL IMMUNITY IN PATIENTS WITH HEAVILY PRETREATED MYELOMA: IMPORTANCE OF IVIG SUPPLEMENTATION

Teclistamab depletes peripheral blood B cells and eliminates normal plasma cells



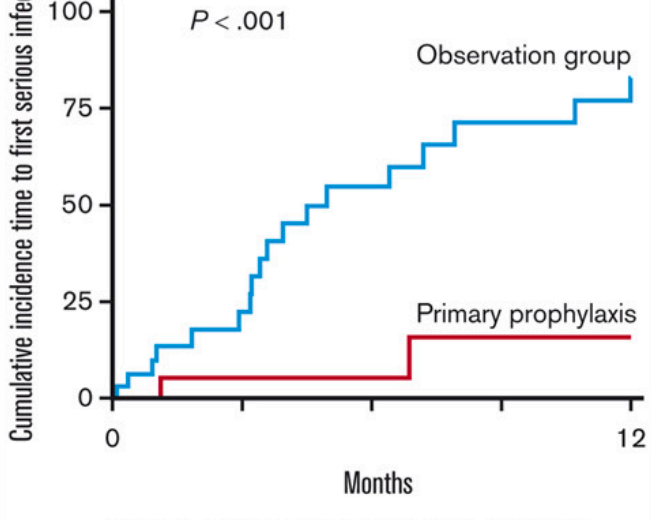
Impact of teclistamab on B-cells

Teclistamab treatment results in reduced levels of polyclonal immunoglobulins and impaired vaccination responses



Impact of teclistamab on polyclonal IgG levels

The negative impact of teclistamab on humoral immunity can be partly reversed by IVIG supplementation



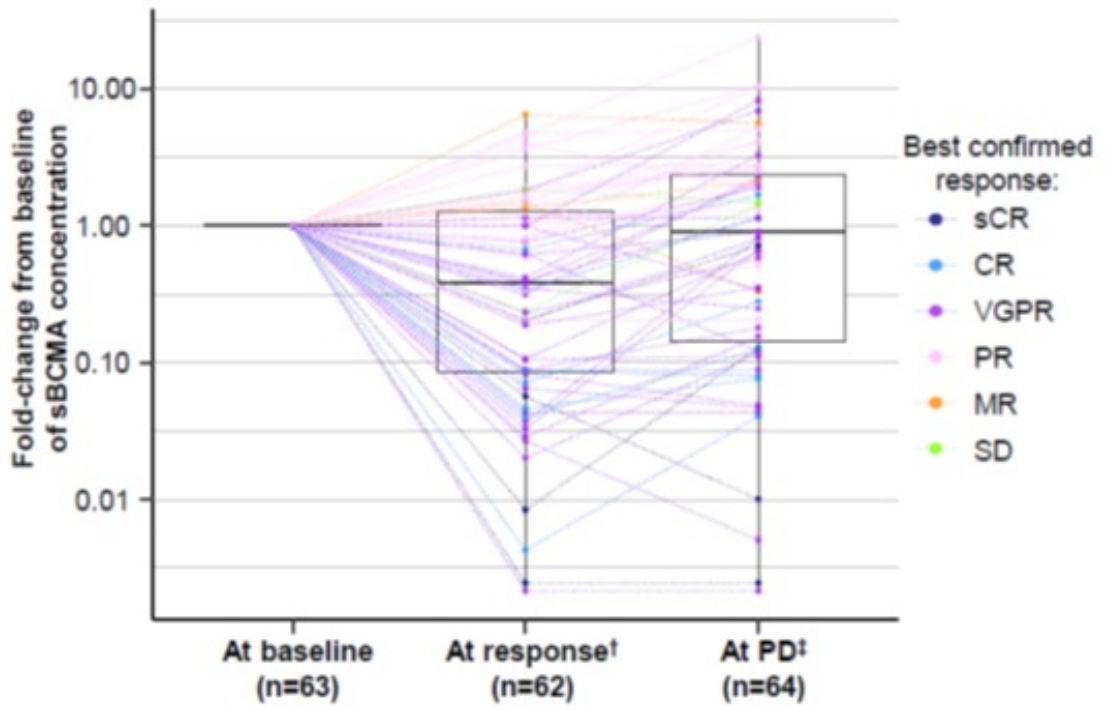
Impact of IVIG supplementation on risk of serious infections

Kristine A. Frerichs, et al, *Blood Adv* (2024) 8 (1): 194–206

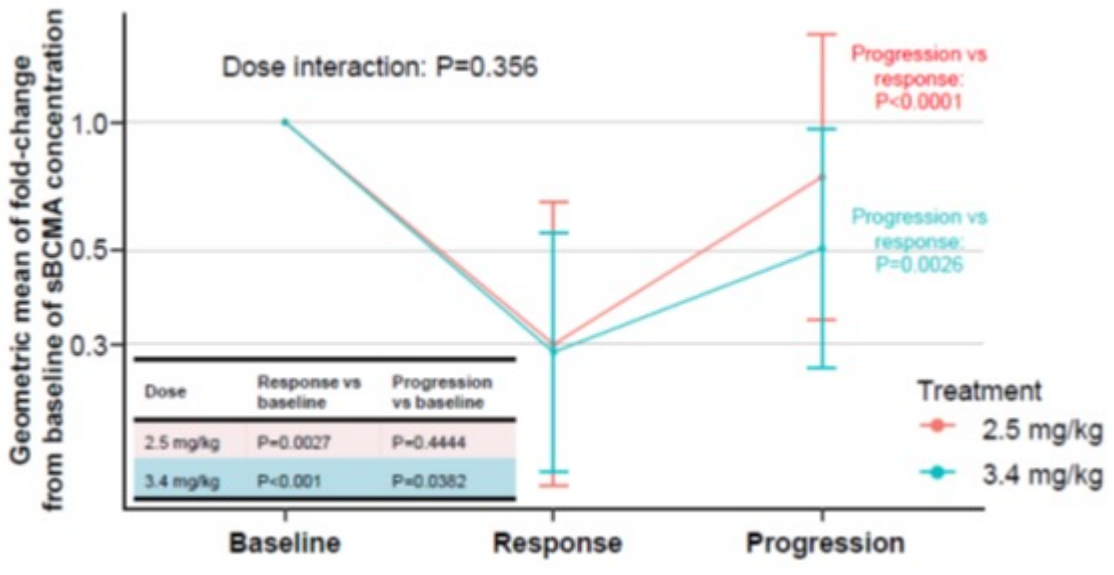
SBCMA LEVELS AFTER ANTI-BCMA ADC

Correlative Analysis: sBCMA Levels Return to Near Baseline Upon PD

sBCMA at baseline, response and PD



Aggregate sBCMA at baseline, response, and PD



sBCMA levels showed a pronounced drop during response, but returned to near baseline upon progression

Longitudinal monitoring of patients' systemic immune cell populations showed no change in immune cell ratios or major cell populations, regardless of response status

†At response, minimum within best achieved response; ‡At PD, latest recorded measure at PD or later. CR, complete response; MR, minimal response; PD, progressive disease; PR, partial response; sBCMA, soluble B cell maturation antigen; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

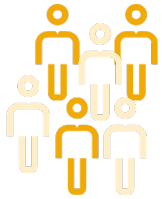
Lowther DE, et al. *Blood* (2022) 140 (Supplement 1): 611–613.

IMMUNE CELL HEALTH AFTER BCMA ADC

Treatment with Belamaf Did Not Result in Exhaustion of T cells or NK Cells

DREAMM-5 – Substudy 3: Post-hoc analyses to assess the impact of belamaf on immune cell populations

Patients with RRMM



Belamaf + nirogacestat
Belamaf: 1 mg/kg or 1.4 mg/kg
(C1: Q4W, C2+: Q8W)
OR
Belamaf monotherapy
(Belamaf: 2.5 mg/kg Q3W)

- Complete and differential blood counts were collected
- Total lymphocyte counts and neutrophil-to lymphocyte ratios were analysed
- Multicolour flow cytometric analysis was used to detect phenotype markers on patient immune cells
- Ki67 expression was analysed to assess cell cycling capacity

Immune cell health in patients treated with belamaf

Measured markers in CD4+/CD8+ T cells and NK cells	Finding*
PD-1 and TIGIT	No increase in cell exhaustion from baseline
Ki67	Maintained cell cycling capacity
Granzyme B and CD107a	Maintained immune cell activity

- Cellular markers on CD4+/CD8+ T cells and NK cells showed that immune cell health was maintained from baseline levels
- There was no evidence of immune cell exhaustion, reduced cell cycling capacity, or reduced activity
- Post-hoc data analysis showed that the neutrophil-to-lymphocyte ratio and lymphocyte counts remained consistent over time with belamaf (0.95 mg/kg Q3W) + nirogacestat or belamaf 2.5 mg/kg Q3W monotherapy†

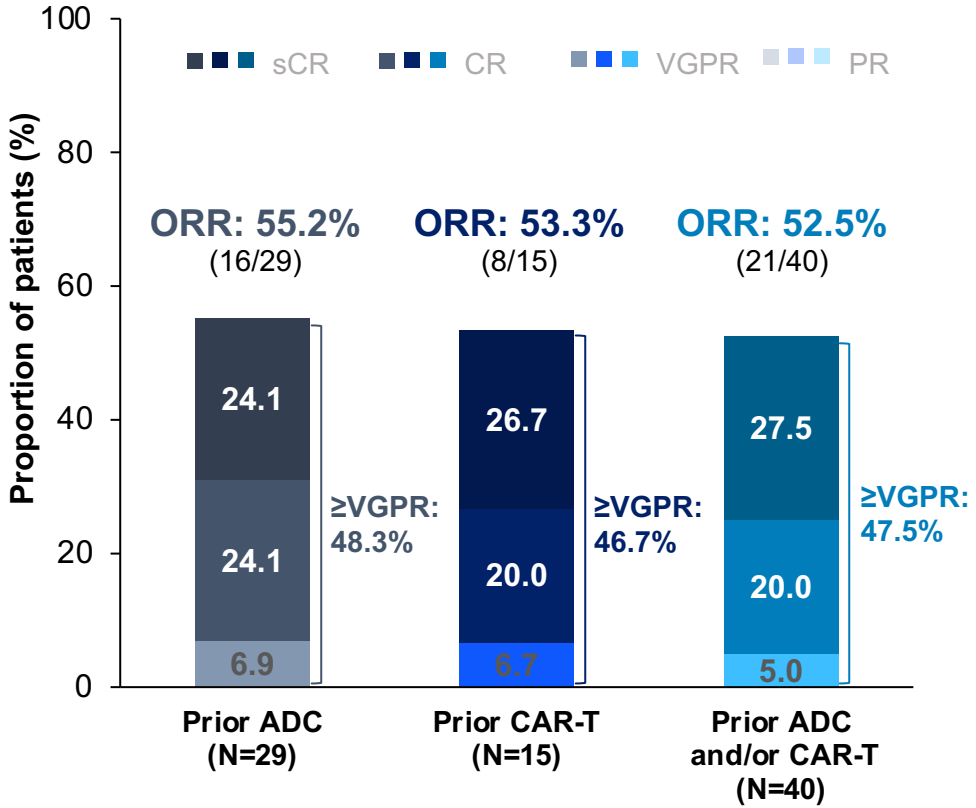
*In patients treated with belantamab mafodotin at 1 mg/kg or 1.4 mg/kg (Cycle 1 Q4W, Cycle ≥2 Q8W) plus nirogacestat; †Generalized least squares or mixed models were used to detect statistical differences in longitudinal data. Only absolute lymphocyte count on Cycle 1, Day 8 showed a significant difference in mean levels compared with Cycle 1, Day 1.

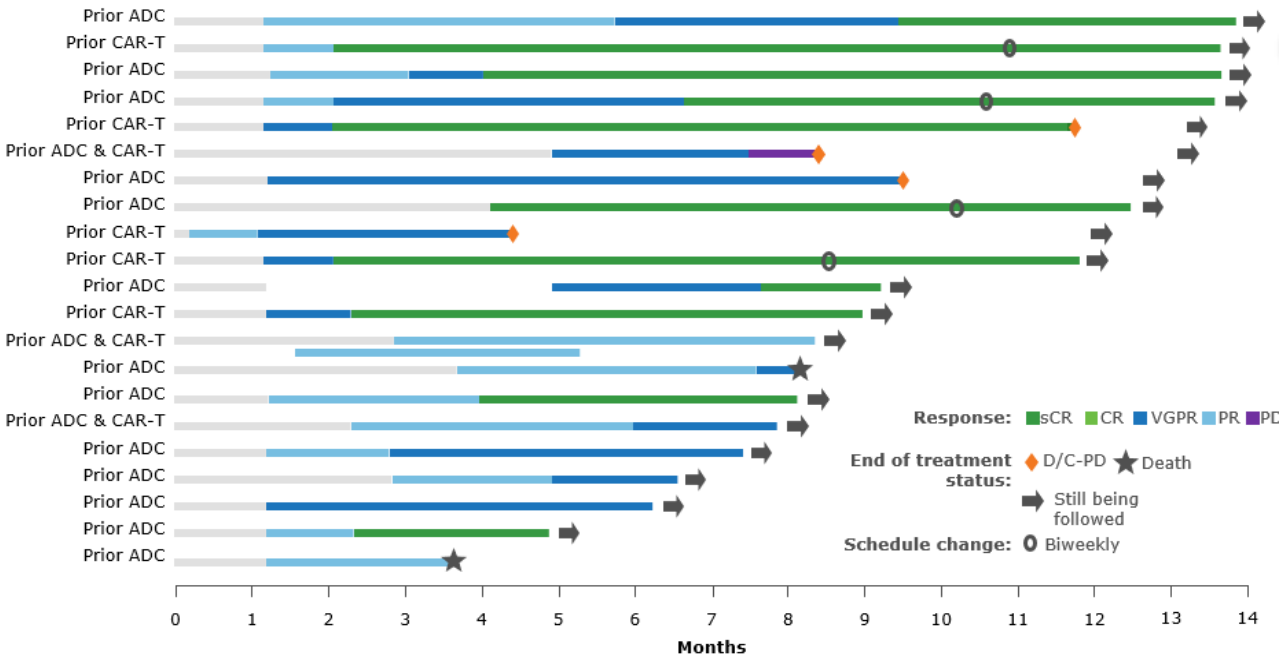
BID, twice a day; C, cycle; CD, cluster of differentiation; NK, natural killer; Q#W, every # weeks; PD-1, programmed cell death protein-1; RRMM, relapsed/refractory multiple myeloma; TIGIT, T cell immunoglobulin and ITIM domain.

Mielnik M, et al. Presented at the 2024 European Hematology Association Annual Meeting; June 13-16, 2024; Madrid, Spain. Abstract P890.

ANTI-BCMA BSAB (TECLISTAMAB) AFTER VARIOUS ANTI-BCMA THERAPIES

MajesTEC-1 Cohort C





71% of those who responded to treatment **maintained their response** at 11.8-month follow-up

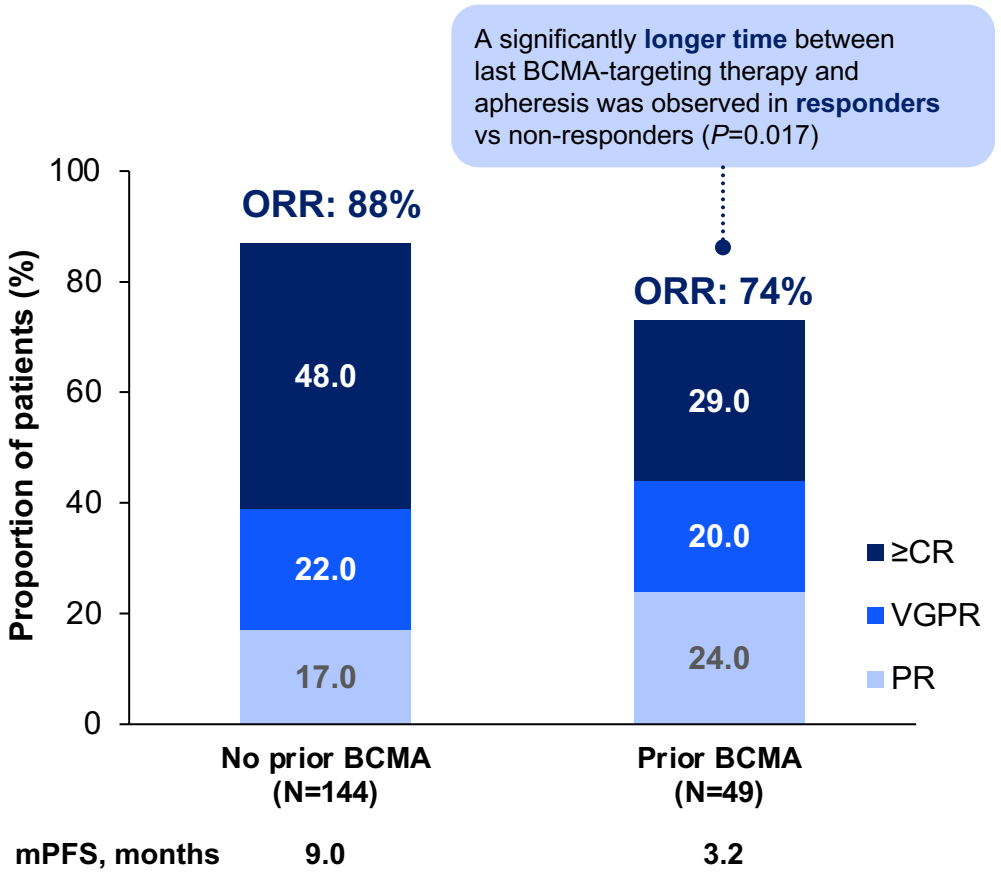
ADC, antibody drug conjugate; BCMA, B-cell maturing antigen; CAR-T, chimeric antigen receptor T cell; CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Touzeau C, et al. *J Clin Onc* 2022; 40,(16 suppl): 8013.

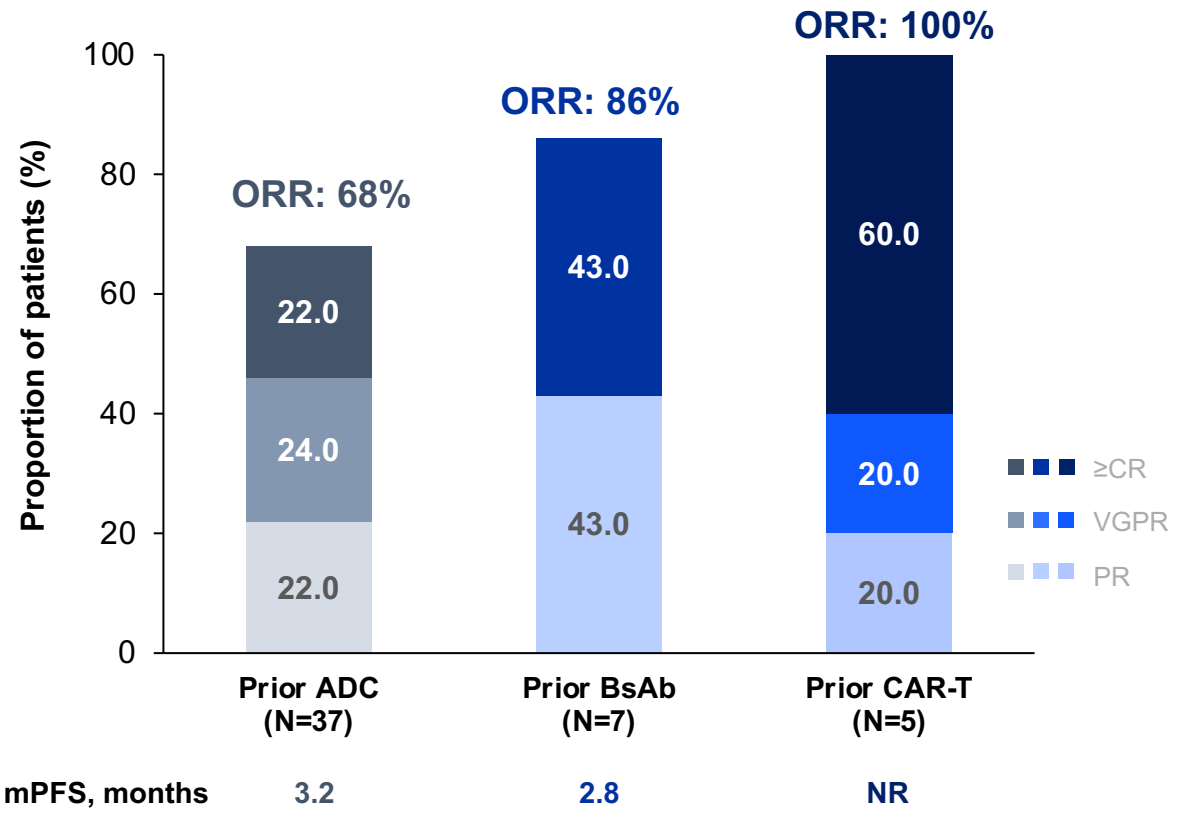
ANTI-BCMA CAR-T THERAPY (IDE-CEL) AFTER VARIOUS ANTI-BCMA THERAPIES

CAR-T/ BsAb/ADC (BCMA) → CAR-T (BCMA)

RWE: Ide-cel ORR (prior vs no prior anti-BCMA)



RWE: Ide-cel ORR post–anti-BCMA ADC/BsAb/CAR-T



ADC, antibody-drug conjugate; BCMA, B cell maturation antigen; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T cell; CR, complete response; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; VGPR, very good partial response.

Ferreri CJ et al. *Blood Cancer J* 2023;13:117.

CONCLUSIONS

Data on the 5 available BCMA targeting agents

Data on efficacy that led to the approvals in myeloma

Data on safety

Data on BCMA expression and immune health post anti-BCMA targeted therapy

Data on retreatment with BCMA targeting agents

All 5 available BCMA targeting agents' are active agents

The efficacy led to the approvals of these agents in myeloma, confirmatory studies ongoing

Infection signal is higher, can be mitigated with proactive IVIG, antimicrobial prophylaxis

BCMA expression and immune health not affected post anti-BCMA targeted therapy

Retreatment with other BCMA targeting modalities is a viable option

QUESTIONS

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