Relapsed Myeloma: Updates and Next Questions

10:55–11:40 AM

Relapsed Disease Myeloma

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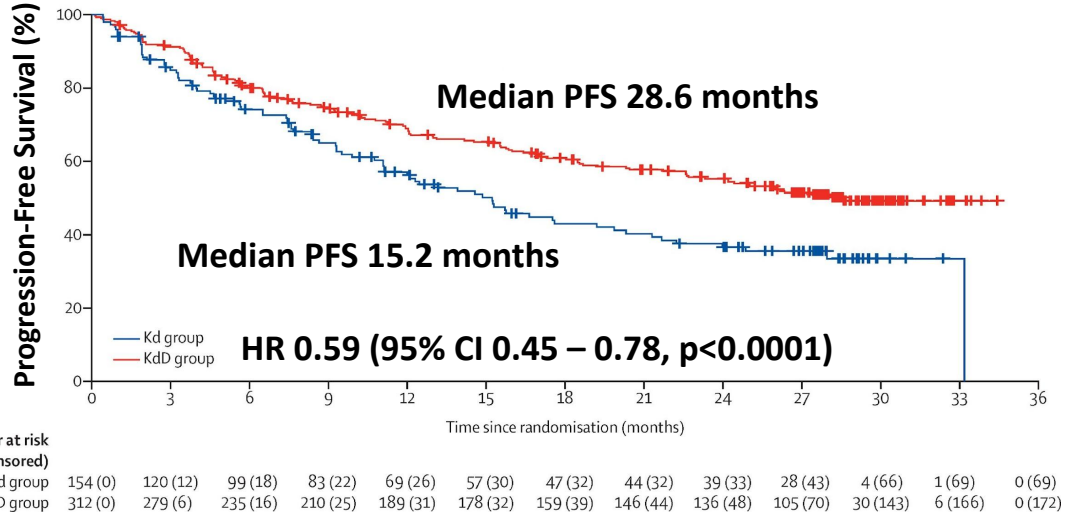
CD38 Monoclonal Antibodies for Multiple Myeloma in 1 – 3 Prior Lines of Therapy

- CANDOR: Phase III study of carfilzomib and dexamethasone ± daratumumab
- IKEMA: Phase III study of carfilzomib and dexamethasone ± isatuximab
- 1 – 3 prior lines of therapy, treatment until disease progression
- Median prior lines of therapy (experimental / control): CANDOR 2 / 2; IKEMA: 2 / 2
- Lenalidomide refractory (experimental / control): CANDOR 32% / 36%; IKEMA: 32% / 34%

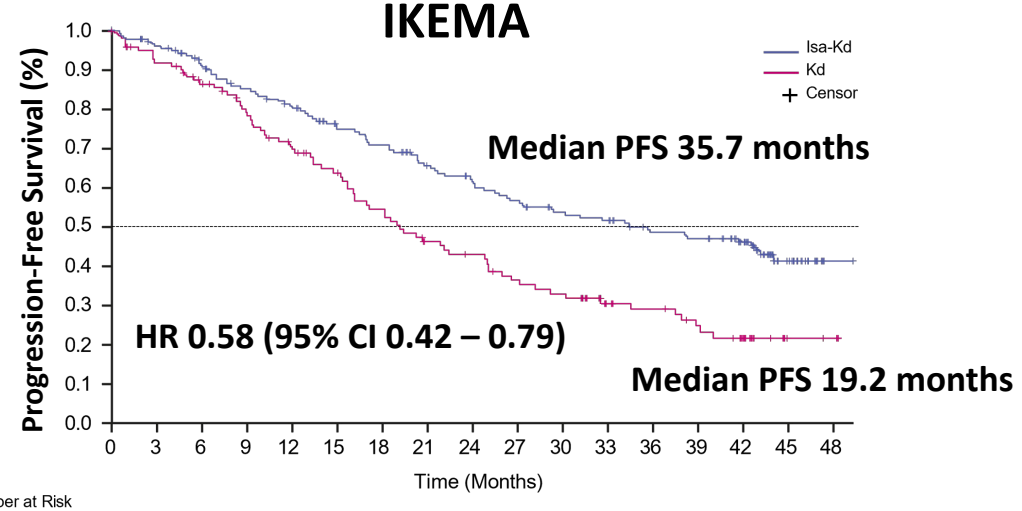
CANDOR



Number at risk (number censored)

Kd group	154 (0)	120 (12)	99 (18)	83 (22)	69 (26)	57 (30)	47 (32)	44 (32)	39 (33)	28 (43)	4 (66)	1 (69)	0 (69)
KdD group	312 (0)	279 (6)	235 (16)	210 (25)	189 (31)	178 (32)	159 (39)	146 (44)	136 (48)	105 (70)	30 (143)	6 (166)	0 (172)

IKEMA



Number at Risk

Isa-Kd	179	164	151	136	127	114	108	95	88	81	75	72	64	62	50	18	1
Kd	123	108	99	85	73	63	53	43	39	32	29	23	21	16	10	3	2

Dimoupolos M et al. *Lancet*. 2020;396:186-197. Moreau P et al. *Lancet*. 2021;397:2361-2371. Moreau P et al. ESMO 2022.
Usmani SZ et al. *Lancet Oncol*. 2022;23:65-716. Martin, T et al. *Blood Adv*. 2022;6:4506-15.

Maintenance/Continuation Therapy in Frontline CD38 Antibody Trials

Transplant-Ineligible	MAIA	CEPHEUS	IMROZ
Regimen	DRd vs Rd	D-RVd vs RVd	Isa-RVd vs RVd
CD38 mAb Treatment	Until PD	Until PD	Until PD

Transplant-Eligible	CASSIOPEIA	GRIFFIN	PERSEUS	S1801	GMMG HD7
Regimen	D-VTd vs VTd	D-RVd vs RVd	D-RVd vs RVd	R vs D-R maintenance	R vs Isa-R maintenance
CD38 mAb Treatment	2 years	2 years	Until PD but stop for sustained MRD-	2 years continuation vs stop for MRD-patients	3 years

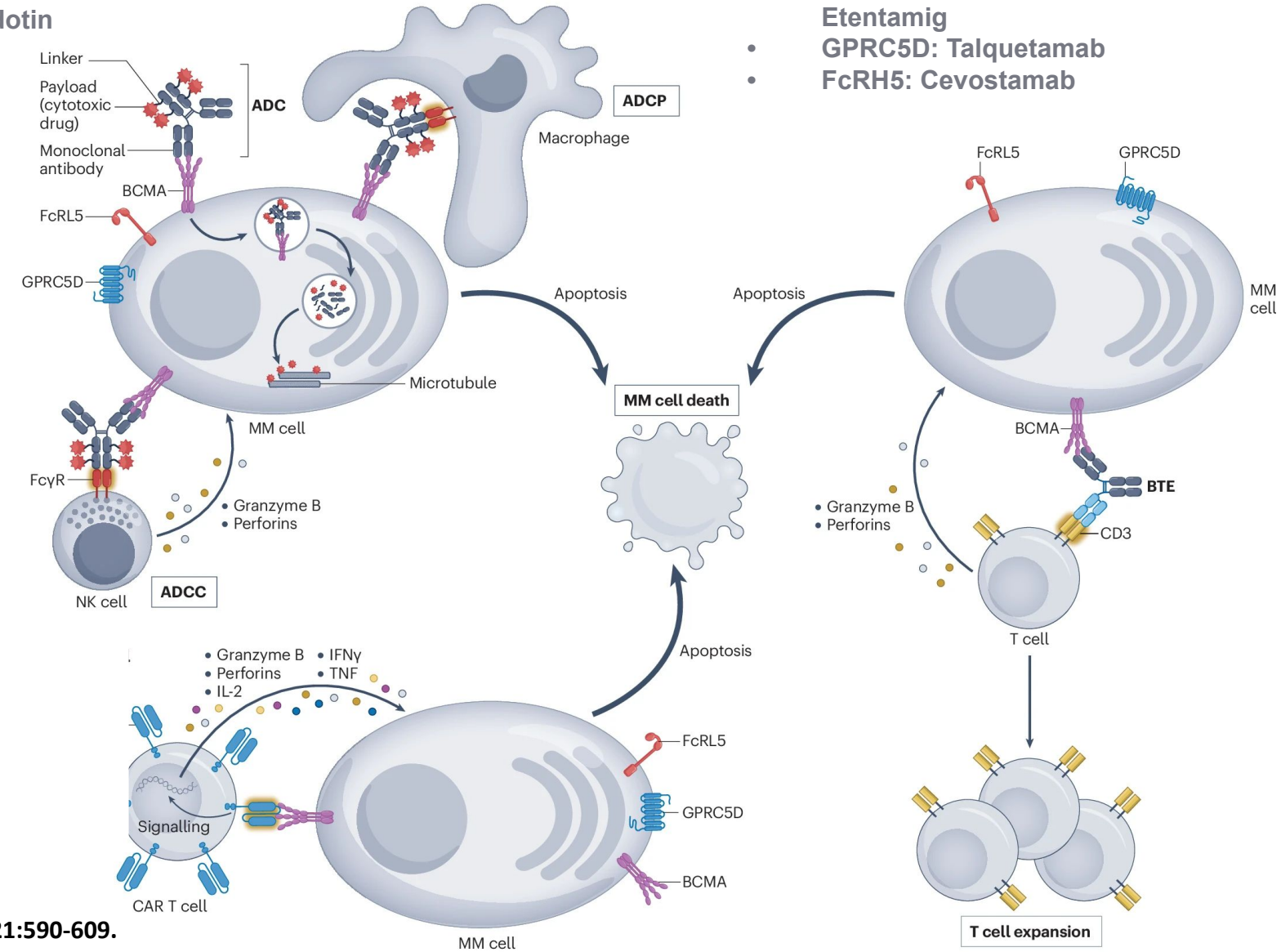
What to do with patients progressing on frontline CD38 mAbs and Len?

Immunotherapy in Relapsed/Refractory Myeloma

Antibody Drug Conjugates
- Belantamab mafodotin

Bispecific Monoclonal Antibodies
- BCMA: Teclistamab, Elranatamab, Linvoseltamab, Etentamig
- GPRC5D: Talquetamab
- FcRH5: Cevostamab

CAR T Cells
- Cilta-cel
- Ide-cel
- Anito-cel
- Arlo-cel



Neri P et al. *Nature Rev Oncol*. 2024;21:590-609.

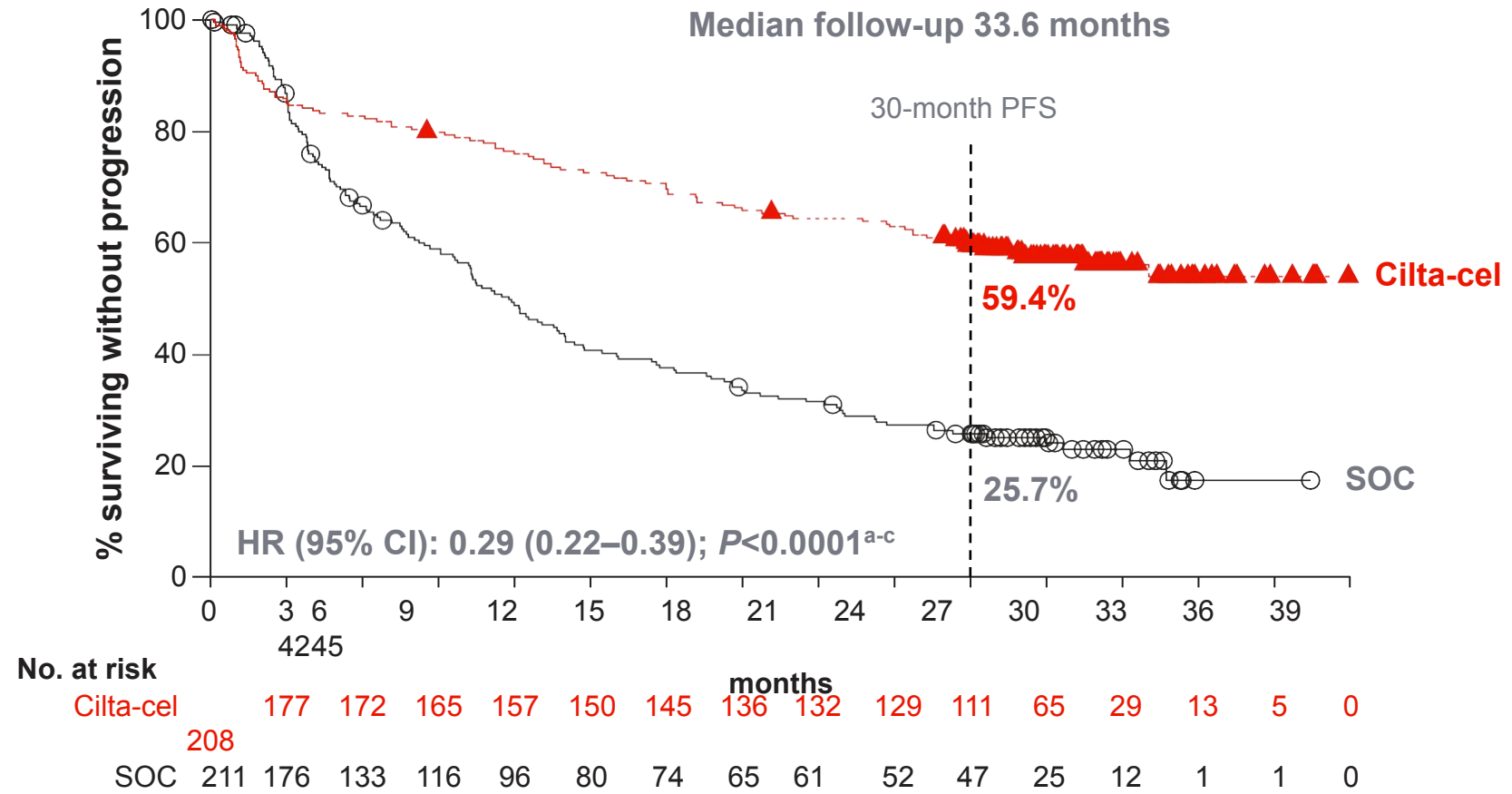
CARTITUDE-4: Ciltacabtagene Autoleucel for Myeloma in Early Relapse

Design

- 1 – 3 prior lines of therapy, lenalidomide refractory, PI exposed
- SoC regimens: Dara-Pom-Dex, Pom-Bortezomib-Dex
- 84.6% of pts assigned to Cilta-cel received it per protocol
- SoC Group: 86.7% DPd, 12.3% PVd
- Cilta-cel Group: No pts received therapy prior to apheresis, All received bridging therapy after apheresis (87.5% DPd, 12.5% PVd)

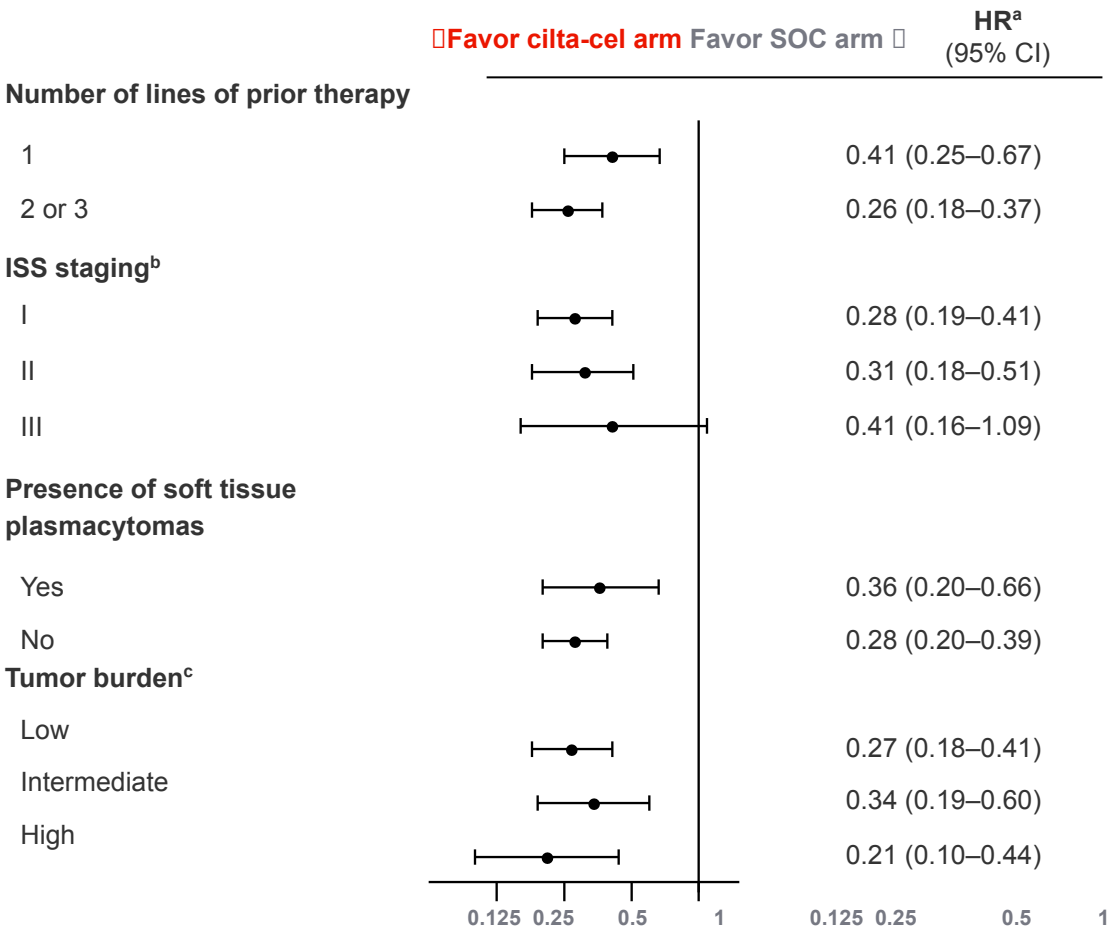
Baseline Characteristics

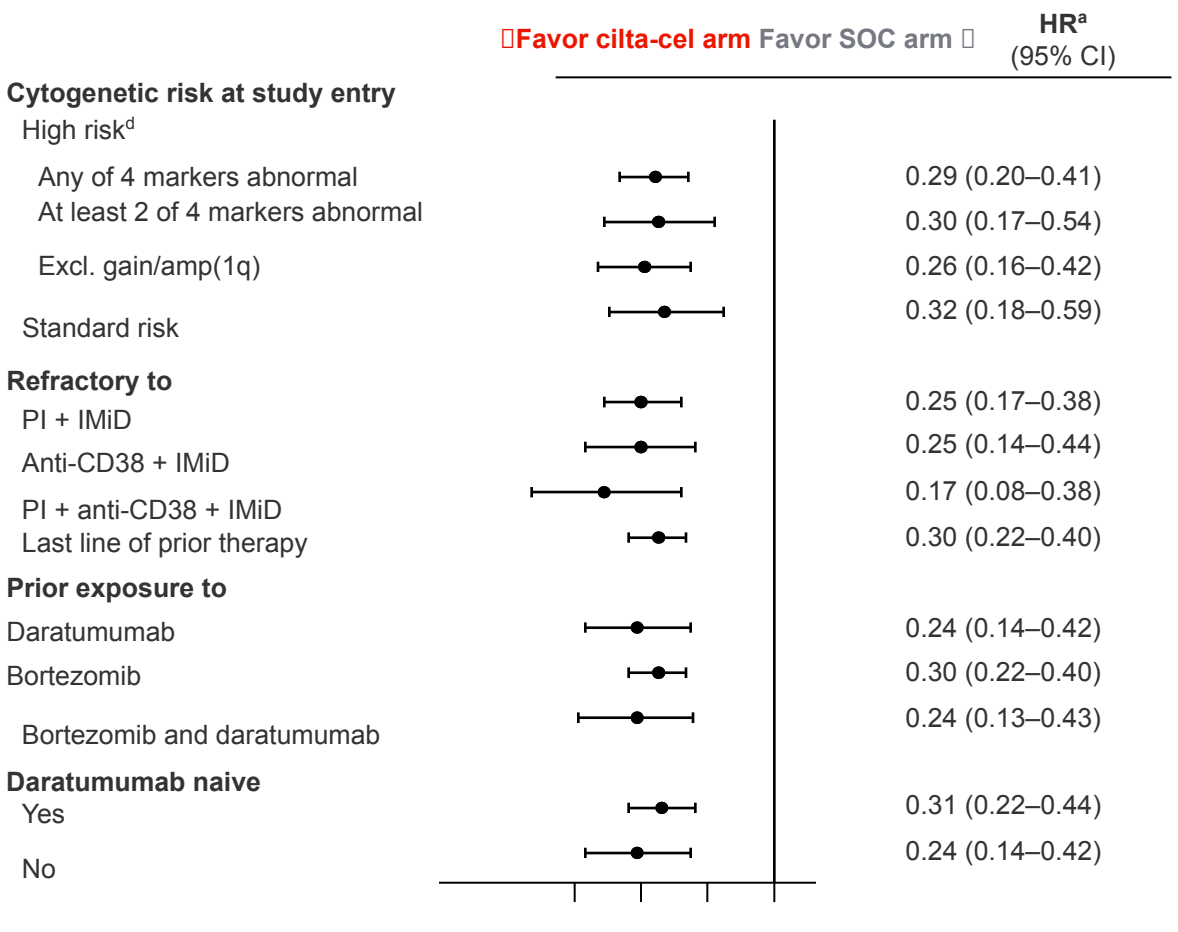
- Median prior lines of therapy: 2 (range 1 – 3)
- 100% Len refractory, 21.3 – 23.1% dara refractory, 14.4% - 15.6% triple class refractory disease
- 59.4% - 62.9% HRCGs



Mateos M-V et al. IMS 2024.

CARTITUDE-4: Progression-Free Survival





[a]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred >8 weeks post randomization. [b]Based on serum β_2-microglobulin and albumin. [c]Low tumor burden defined as meeting all following parameters (as applicable): bone marrow % plasma cell <50%, serum M-protein <3 g/dL, serum free light chain <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 free light chain ≥5000 mg/L; intermediate tumor burden did not fit either criteria of high or low tumor burden. [d]Positive for del(17p), t(14;16), t(4;14), and/or gain/amp(1q) by fluorescence in situ hybridization testing. Protocol-defined high-risk cytogenetics refers to "Any of 4 markers abnormal."
Cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; IMiD, immunomodulatory drug; ISS, International Staging System; PFS, progression-free survival; PI, proteasome inhibitor; SOC, standard of care.

Mateos M-V et al. IMS 2024.

CARTITUDE-4: Safety

Infections	Cilta-cel (n=208)	SOC (n=208)
Treatment-emergent infections, %		
All grade	63.5	76.4
Grade 3/4	28.4	29.8
Deaths due to TE- and non-TE infections, n	16	19
In first year, n	13	8
In second year, n	2	8

Cause of death	Cilta-cel (n=208)	SOC (n=208)
Deaths, n	**50**	**82**
Due to progressive disease	21	51
Due to TEAE	12	8

SPM	Cilta-cel (n=208)	SOC (n=208)
SPMs, n (%)	**27 (13.0)**	**24 (11.5)**
Hematologic[a]	7 (3.4)	1 (0.5)
MDS, n	4	0
Progressed to AML, n	2	–
AML, n	1	0
Peripheral T-cell lymphoma, n	2	0
EBV-associated lymphoma, n	0	1
Cutaneous/non-invasive[a]	15 (7.2)	15 (7.2)
Non-cutaneous/invasive[a]	6 (2.9)	8 (3.8)

- Cranial nerve palsies seen in 16 patients (9.1%), 2 grade 3
  - Recovered in 14 at time of original data cut-off
- Neuropathy seen in 5 patients (2.8%)
  - Recovered in 3 at time of original data cut-off
- 1 patient with grade 1 movement - neurotoxicity AE
- Rates of secondary hematologic malignancies in CARTITUDE-1: 9.3%

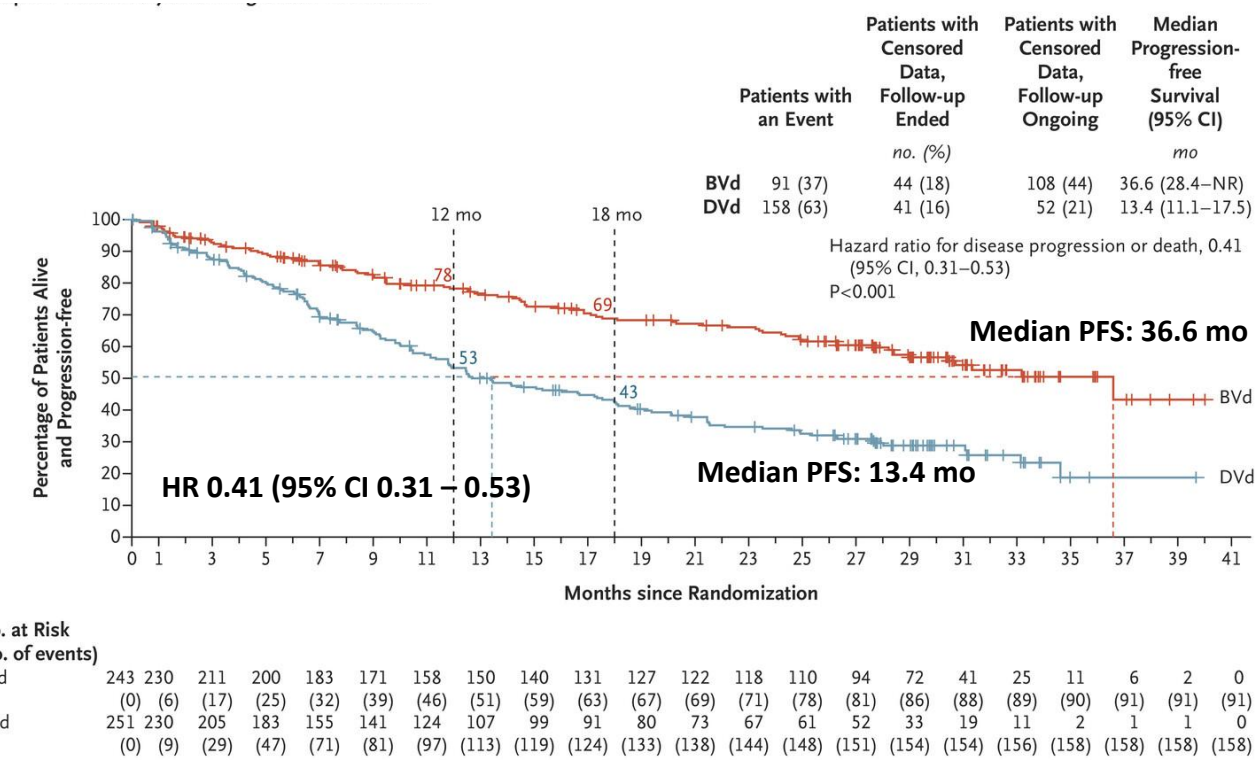
[a]Multiple SPMs could occur in the same patient.
AML, acute myeloid lymphoma; cilta-cel, ciltacabtagene autoleucel; EBV, Epstein-Barr virus; MDS, myelodysplastic syndrome; MNT, movement and neurocognitive treatment-emergent adverse event; TE, treatment-emergent; TEAE, treatment-emergent adverse event; SOC, standard of care; SPM, second primary malignancy.

Mateos M-V et al. IMS 2024.

Belantamab Mafodotin for Myeloma in Early Relapse: Progression-Free Survival

DREAMM-7

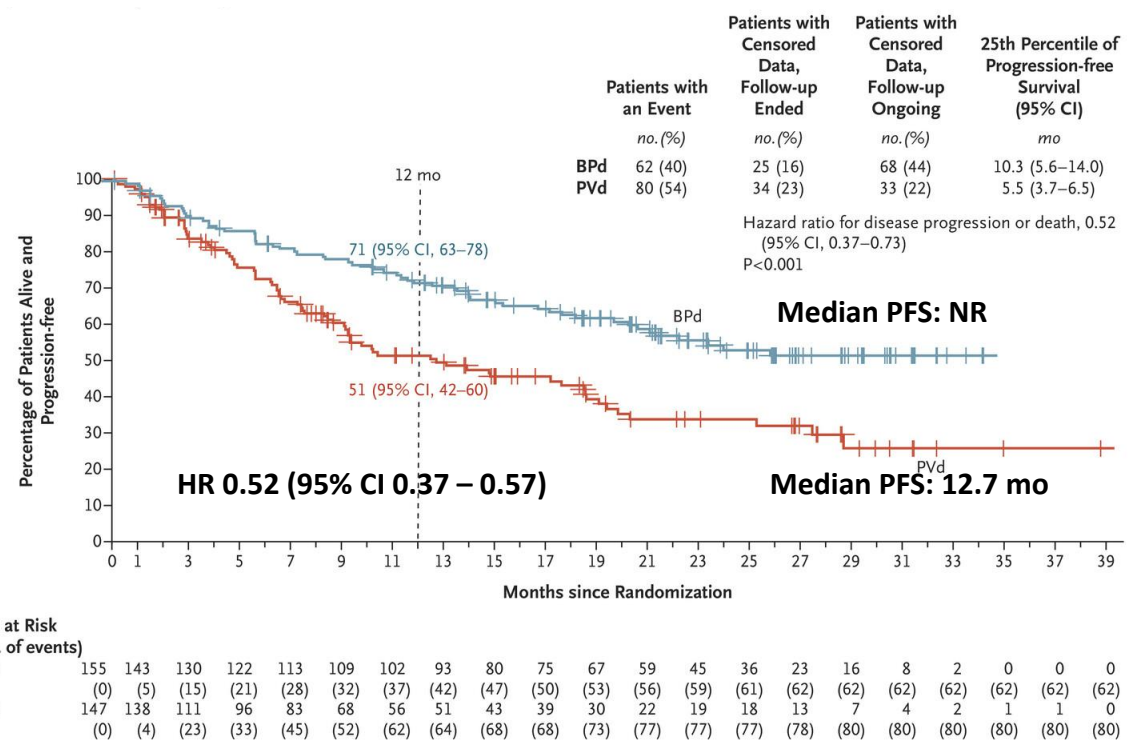
- DVd vs Bela-Vd
- ≥1 prior line of therapy, treatment until disease progression
- Lenalidomide refractory (experimental / control): 33% / 35%



Hungria V et al. *N Engl J Med*. 2024;391:393-407.

DREAMM-8

- PVd vs Bela-Pd
- ≥1 prior line of therapy, lenalidomide exposed
- Lenalidomide refractory (experimental / control): 81% / 76%, CD38 mAb refractory: 23% / 24%

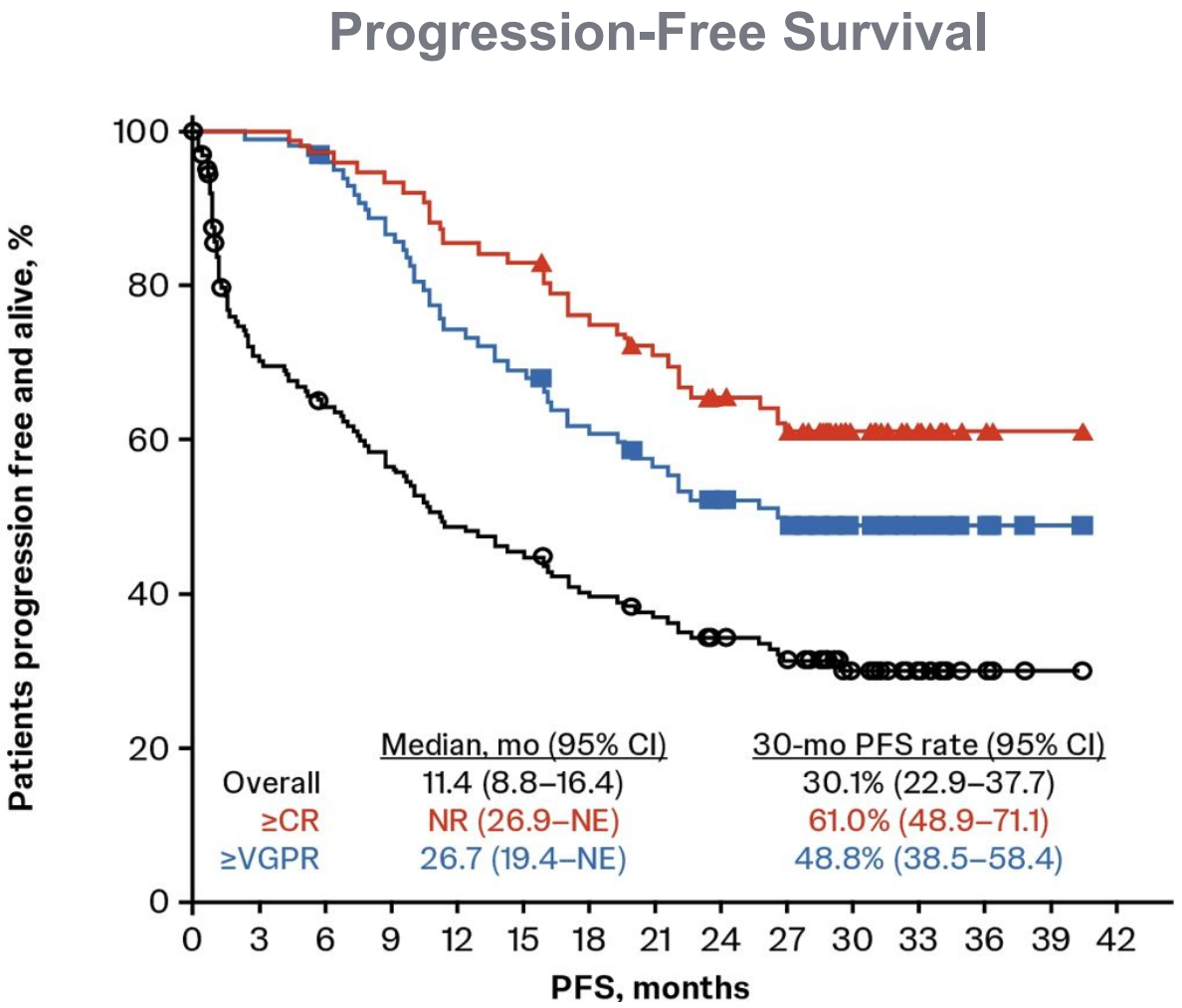


Dimopoulos M et al. *N Engl J Med*. 2024;391:408-421.

MajesTEC-1: Teclistamab Monotherapy in Relapsed/Refractory Myeloma

- 17% with EMM, 25.7% with HRCGs
- Median Prior Lines of Therapy: 5 (2 – 14)
- 77.6% triple class refractory, 89.7% refractory to last line of therapy

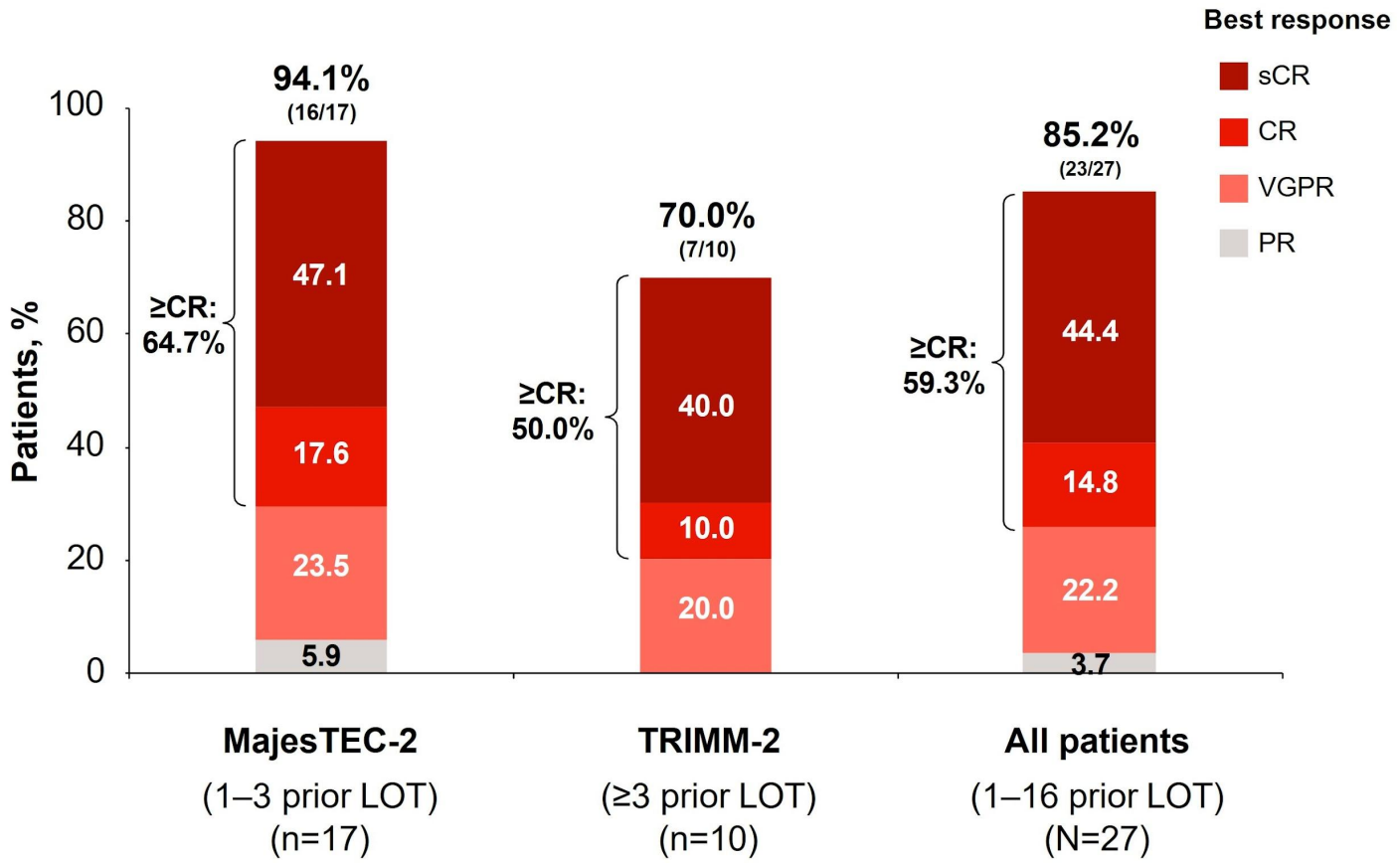
Outcome	Teclistamab (RP2D dose) N=165
ORR	63.0%
≥CR	46.1%
≥VGPR	59.4%
mDOR	24.0 mo
mOS	22.2 mo



Moreau P et al. *N Engl J Med*. 2022;387:495-505.
Garfall A et al. ASCO 2024.

Teclistamab + Daratumumab and Pomalidomide in Relapsed/Refractory Myeloma

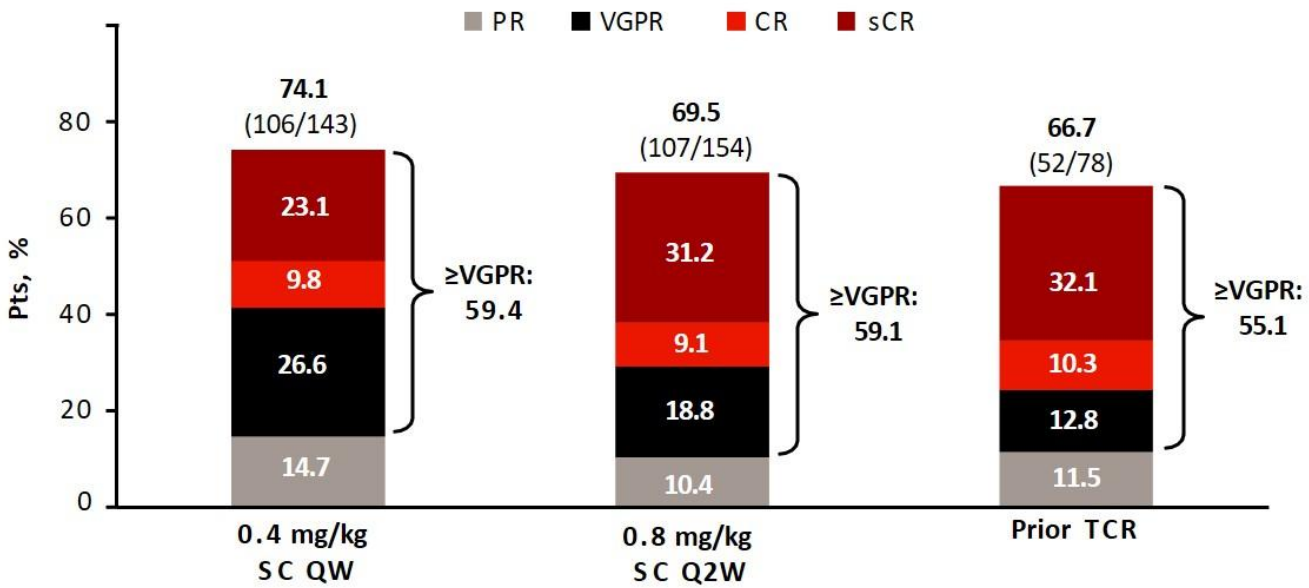
- MajesTEC-2 (N=17)
  - 1 – 3 prior lines of therapy
  - Len and PI exposed
  - EMD 0%, median prior LOT 1, CD38 exposed 17.6%, BCMA exposed 0%, triple class refractory 0%
- TRIMM-2 (N=10)
  - ≥3 prior lines of therapy
  - EMD 30%, median prior LOT 4, CD38 exposed 80%, BCMA exposed 30%, triple class refractory 70%
- Safety (N=27)
  - ≥grade 3 infection 63%
  - 6 patients with grade 5 infections
    - 4 due to COVID
    - None after implementation of more robust antimicrobial prophylaxis



D'Souza A et al. ASH 2024.

MonumenTAL-1

- GPRC5D-targeted bispecific monoclonal antibody
- Key Baseline Characteristics (0.4 mg/kg QW / 0.8 mg/kg Q2W): HR CGs 31.1% / 28.9%, Extramedullary disease 23.1% / 26.9%, ISS stage 3 disease 19.6% / 24.3%, 5 median prior lines of therapy, Triple class refractory 74.1% / 69.0%



Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)	Prior TCR (n=78)
mFU, mo	29.8	23.4	20.5
mDOR (95% CI),[a] mo	9.5 (6.7–13.4)	17.5 (12.5–NE)	N/A[b]
mDOR in pts with ≥CR (95% CI), mo	28.6 (19.4–NE)	NR (21.2–NE)	N/A[b]
mPFS (95% CI), mo	7.5 (5.7–9.4)	11.2 (8.4–14.6)	7.7 (4.1–14.5)
24-mo OS rate (95% CI), %	60.6 (51.7–68.4)	67.1 (58.3–74.4)	57.3 (43.5–68.9)

Chari A et al. *N Engl J Med*. 2022;387:2232-2244.
Rasche L et al. EHA 2024.

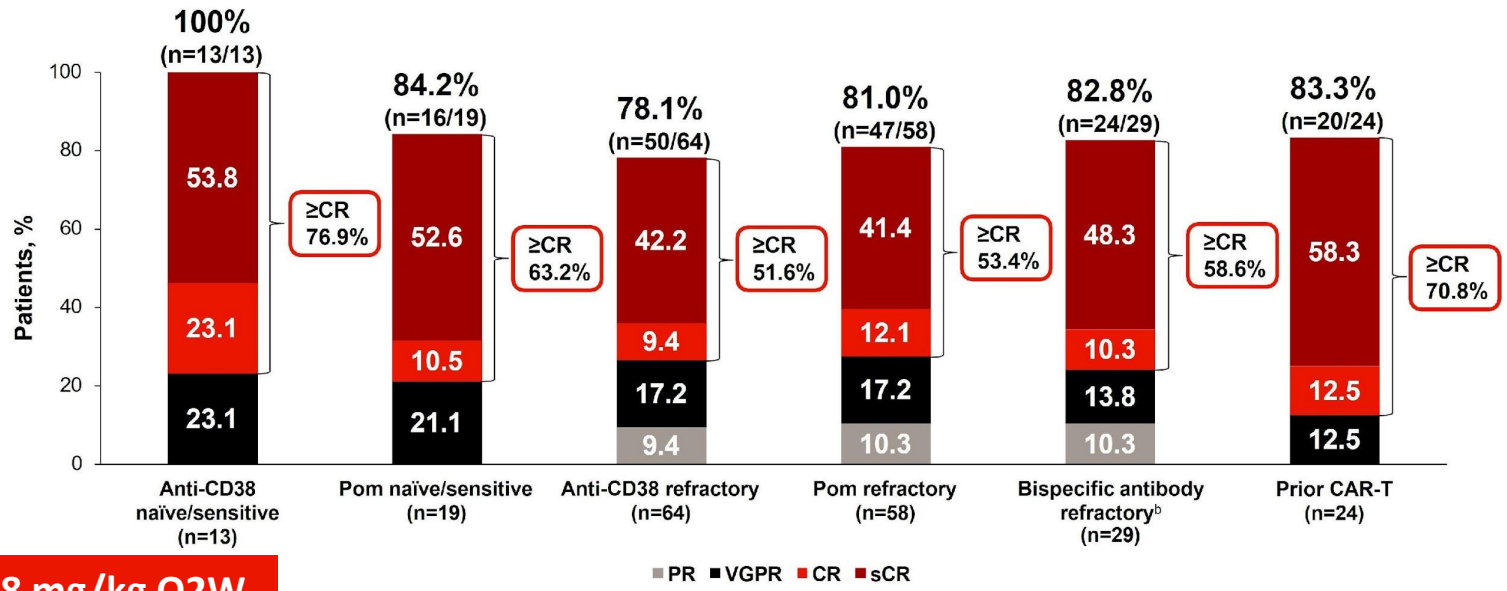
Talquetamab + Daratumumab and Pomalidomide in Relapsed/Refractory Myeloma

Treatment

- Dara standard dose and schedule; Pom 2 mg days 1 – 21 beginning with C2; Tal SUD □ 0.4 mg/kg SC weekly or 0.8 mg/kg SC every 2 weeks

Baseline Characteristics

- Median age: 62 - 64 (42 – 81)
- EMM: 22.2 – 23.7%
- HRCGs: 22.2 – 27.7%
- Median prior lines of therapy: 6 (1 – 17)
- 67.8 – 72.2% prior BCMA-targeted therapy
- 76.3 – 83.3% triple refractory
- 83.1 – 83.3%% CD38 mAb refractory
- 72.2 – 76.3% pomalidomide refractory



Parameter	Tal 0.4 mg/kg QW + dara + pom (n=18)	Tal 0.8 mg/kg Q2W + dara + pom (n=45)
Median (range) follow-up, months	15.8 (3.2–37.9)	17.5 (0.2–37.7)
Median DOR, months (95% CI)	13.8 (8.8–26.6)	26.4 (16.7–NE)
12-month DOR, % (95% CI)	62.7 (35.1–81.3)	73.1 (57.5–83.7)

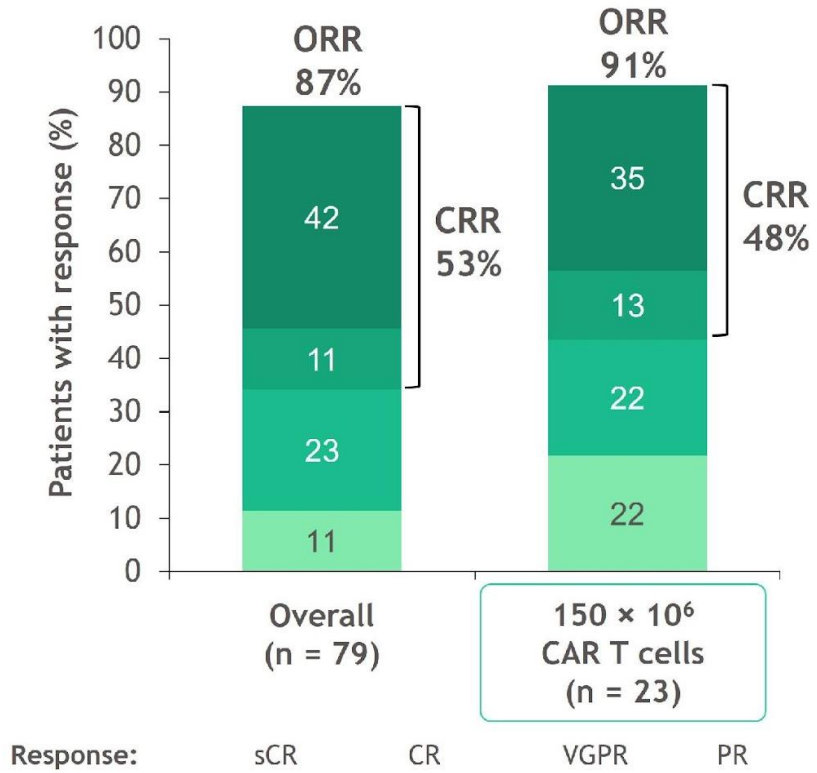
12-month DOR (QW + Q2W tal)

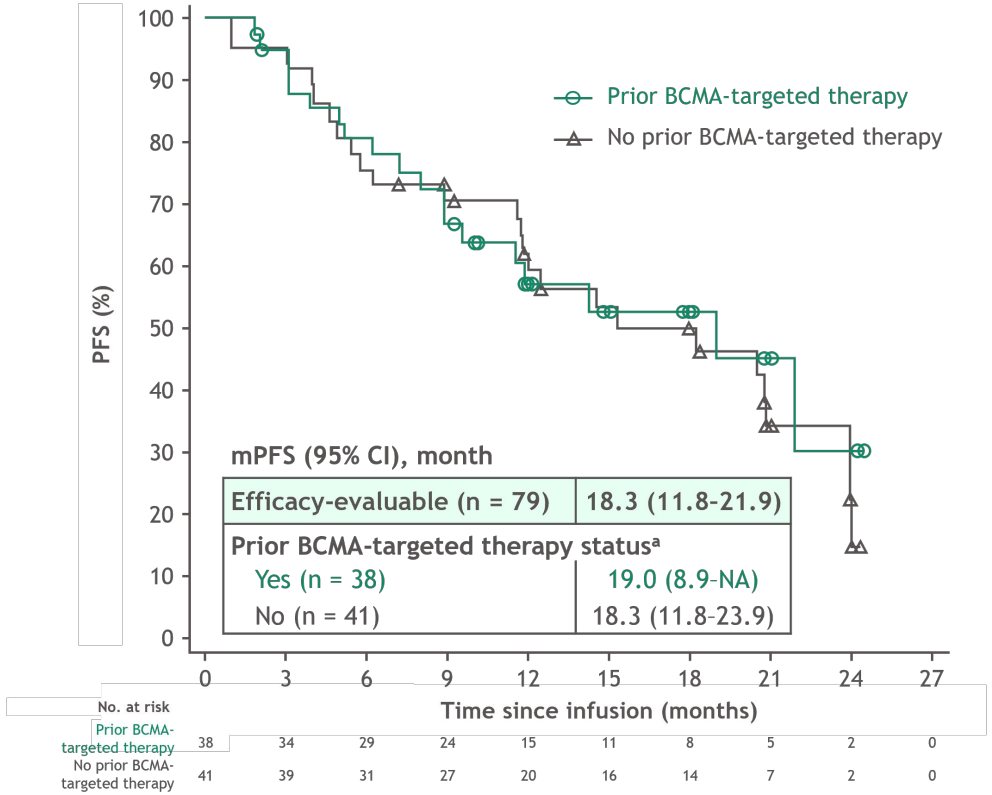
- Anti-CD38 naïve/sensitive (n=13): 83.9%
- Pom naïve/sensitive (n=16): 80.8%
- Anti-CD38 refractory (n=50): 67.0%
- Pom refractory (n=47): 67.0%
- Bispecific antibody refractory (n=24): 70.2%
- Prior CAR-T (n=20): 84.4%

Bahlis N et al. IMS 2024.

GPRC5D-Targeted CAR T Cell Therapy: Arlo-cel

- Phase I study, cohort A. ≥3 prior therapies (IMiD, PI, CD38 mAb, ASCT [if eligible[), prior BCMA-targeted therapy allowed
- Key Baseline Characteristics: HR CGs 42%, Extramedullary disease 46%, 5 median prior lines of therapy, Triple class refractory 76%, prior BCMA-targeted therapy 49% (20% refractory)



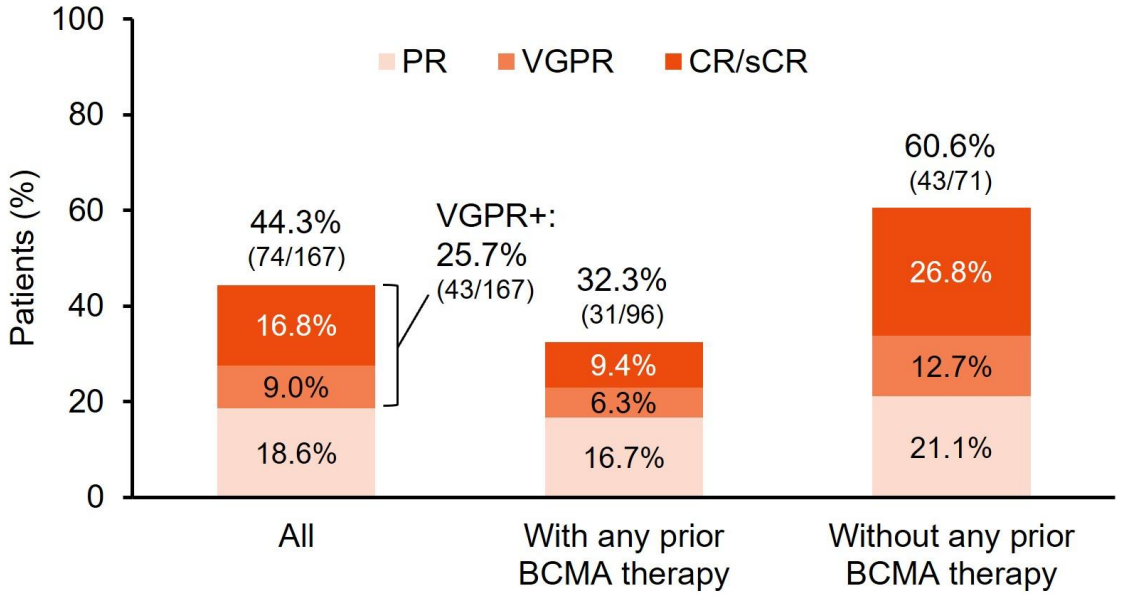


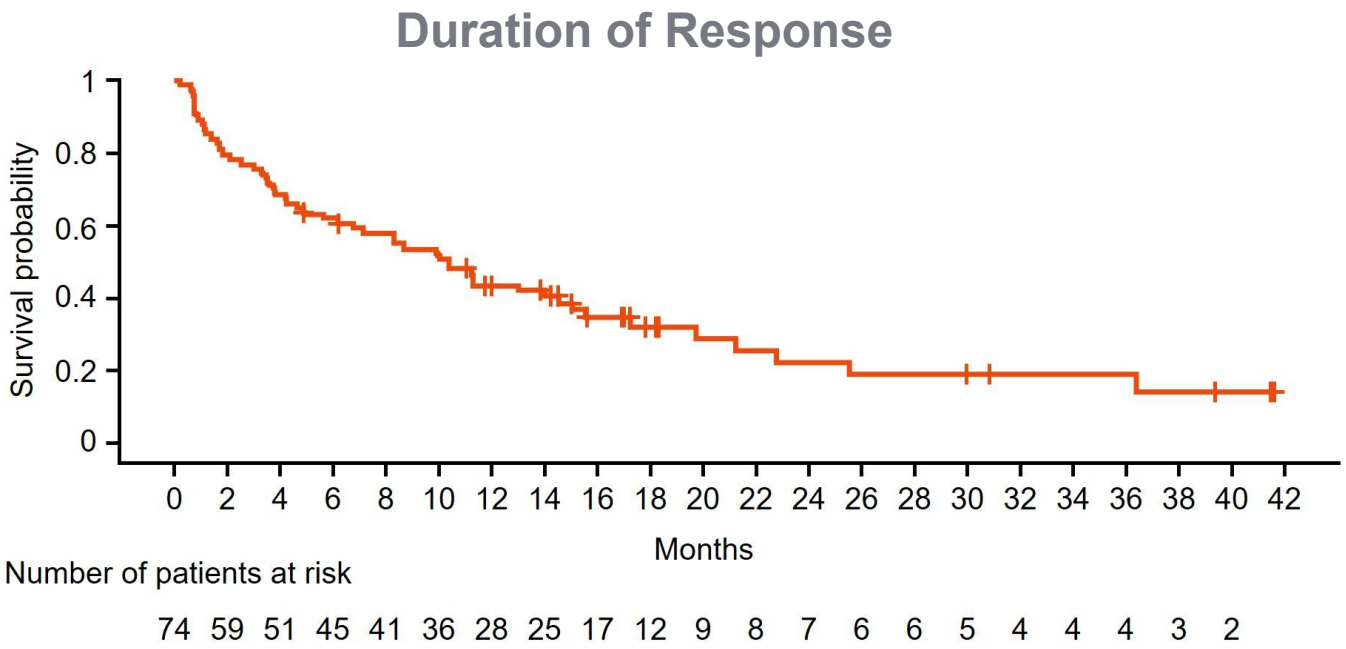
- High response rate irrespective of baseline characteristics (present vs absent): Triple class refractory status (87% vs 89%), EMD (86% vs 88%), HRCGs (84% vs 90%) or prior BCMA-targeted therapy (79% vs 95%)
- AEs: CRS 82% (4% Gr 3 / 4), ICANS 10% (2% Gr 3 / 4), other neurologic 12% (7% Gr 3 / 4), skin 30%, nail 19%, oral 32%, infections 55% (Gr 3 / 4 19%).

Bal S, et al. ASH 2024.

Cevostamab in Relapsed/Refractory Myeloma

- FcRH5-targeted bispecific monoclonal antibody
- Fixed duration therapy
- N = 167 pts
- Key Baseline Characteristics: HR CGs 38.4%, EMD 28.1%, ISS stage 3 disease 19.6% / 24.3%, 6 median prior lines of therapy (2 - 18), Triple class refractory 95.8%, BCMA exposed 57.5%



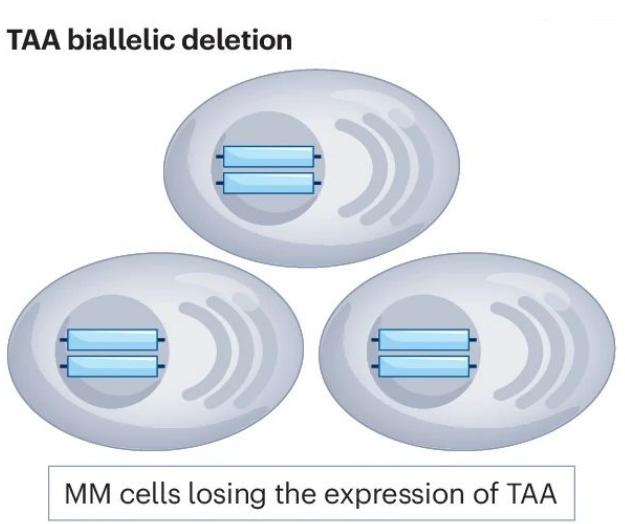


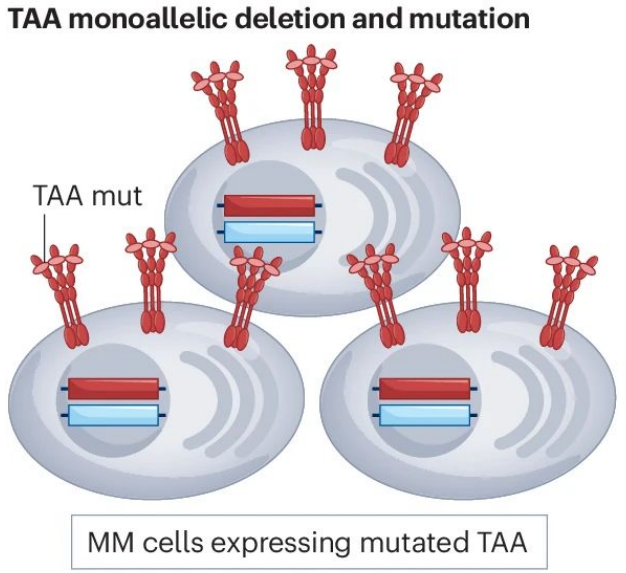
- mDoR in PR+ (n=74): 10.4 months (95% CI: 6.2, 15.0)
- mDoR in VGPR+ (n=43): 21.2 months (95% CI: 15.0, 36.4)*

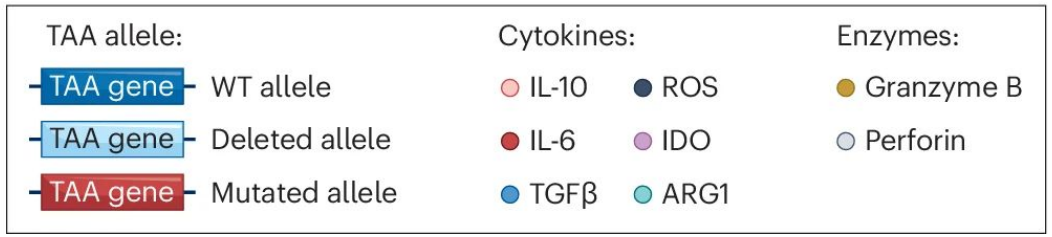
Richter J et al. ASH 2024.

Resistance to T-Cell–Redirecting Therapy: Antigen Escape

- CAR T
  - Biallelic loss of BCMA seen in ~4% of patients relapsing after BCMA-targeted CAR T-cell therapy
  - Loss of GPRC5D via IHC seen in 60% of patients relapsing after GPRC5D-targeted CAR T-cell therapy
- Bispecific Antibodies
  - Antigen loss/mutation seen in up to 42.8% of patients relapsing on BCMA-targeted bispecific antibodies
  - Antigen loss/mutation seen in 6 of 7 patients progressing on GPRC5D-targeted bispecific antibodies





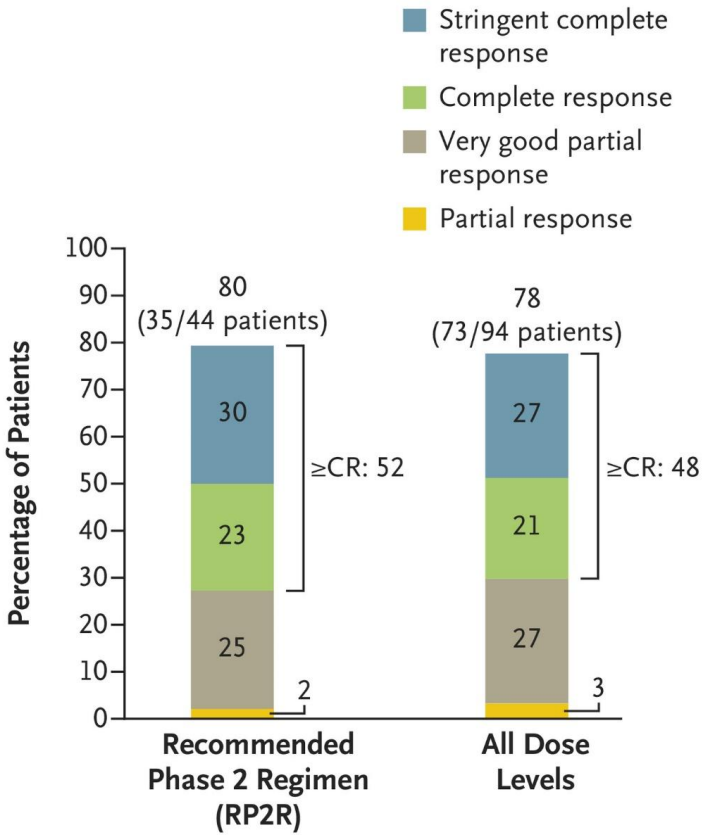


Lee H et al. *Nat Med*. 2023;29:2295-2306.
Neri P et al. *Nat Rev Clin Oncol*. 2024;21:590-609
Jurgens EM et al. *J Clin Oncol*. 2025;43:498-504

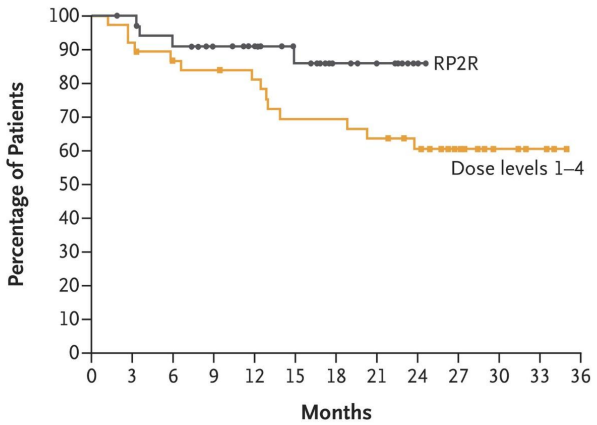
Lee H et al. IMS 0224.
Samur MK et al. *Nat Commun*. 2021;12:868

RedirecTT-1: Teclistamab + Talquetamab in Relapsed/Refractory Myeloma

- Phase I / II study of teclistamab + talquetamab in relapsed/refractory myeloma
- Key eligibility criteria: Triple class exposed, relapsed or refractory (or intolerant of) established therapies
- Key baseline characteristics: HRCGs 41%; EMD 36%; 86% triple class refractory; median prior lines of therapy 4 (range 1 – 11)

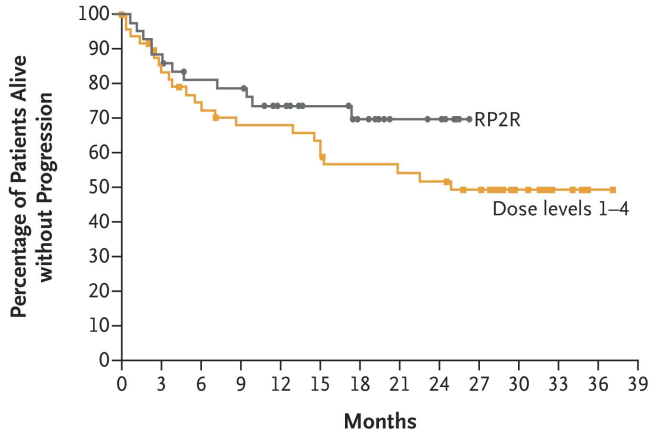


Duration of Response



No. at Risk													
RP2R	35	34	30	26	23	17	10	7	2	0	0	0	0
Dose levels 1–4	38	35	31	30	28	24	24	22	18	12	5	3	0
No. of Events													
RP2R	0	0	3	3	3	4	4	4	4	4	4	4	4
Dose levels 1–4	0	3	5	6	7	11	11	13	14	14	14	14	14
No. with Censored Data													
RP2R	0	1	2	6	9	14	21	24	29	31	31	31	31
Dose levels 1–4	0	0	2	2	3	3	3	3	6	12	19	21	24

Progression-Free Survival



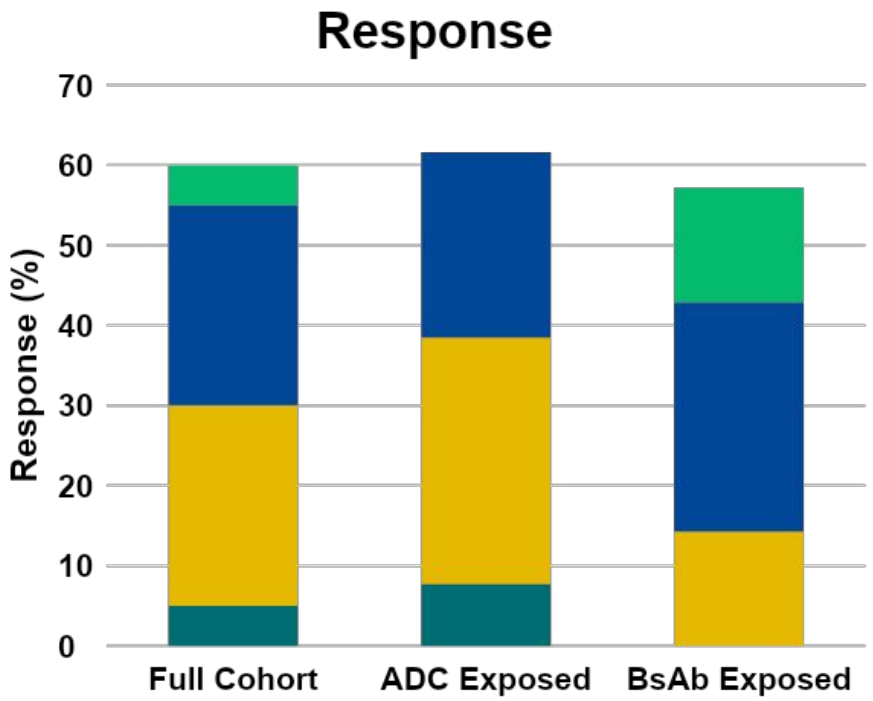
No. at Risk														
RP2R	44	38	33	32	26	20	16	8	7	0	0	0	0	0
Dose levels 1–4	50	39	34	30	30	28	24	23	22	19	10	4	1	0
No. of Events														
RP2R	0	5	8	9	11	11	12	12	12	12	12	12	12	12
Dose levels 1–4	0	8	12	15	15	17	20	21	22	23	23	23	23	23
No. with Censored Data														
RP2R	0	1	3	3	7	13	16	24	25	32	32	32	32	32
Dose levels 1–4	0	3	4	5	5	5	6	6	6	8	17	23	26	27

18-month DOR and PFS at the RP2D: 86% and 70%

Cohen Y et al. *N Engl J Med*. 2025;392:138-149.

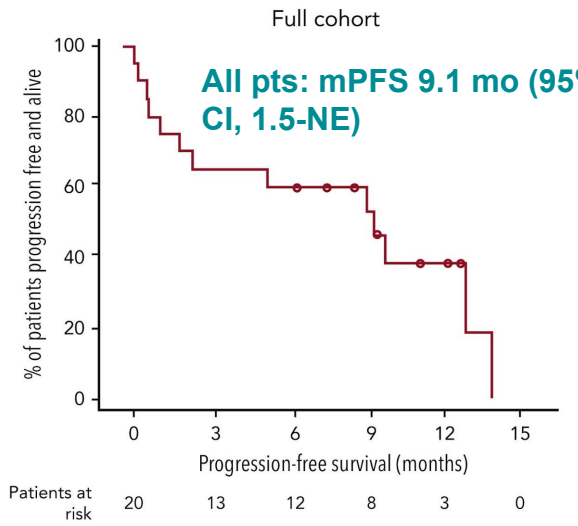
BCMA-Targeted CAR T-Cell Therapy After Prior BCMA-Targeted Therapy

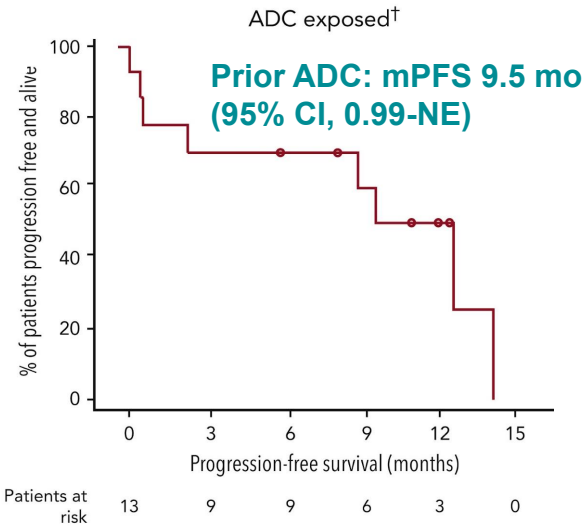
- CARTITUDE-2, cohort C
- N = 20
- Key eligibility criteria: RRMM; Triple class exposed; exposure to non-cellular BCMA-targeted therapy
- Key baseline characteristics: Median 8 prior lines of therapy (range 4 – 13); 90% triple class refractory; 80% BCMA-targeted therapy refractory; 30% received BCMA-targeted therapy in their last line

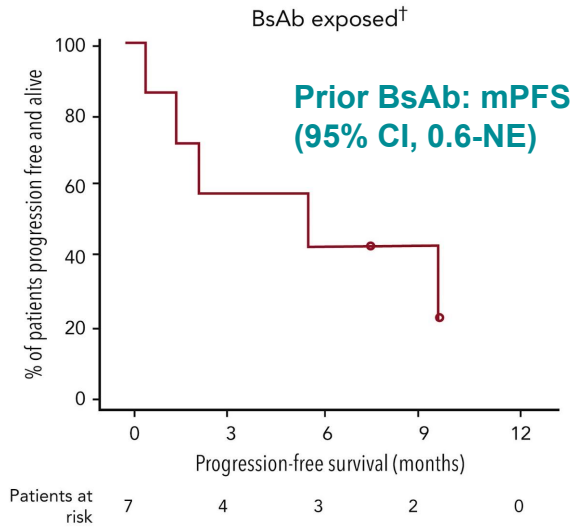


Median Duration of Response: 11.5 mo (95% CI 7.9-NE), 11.5 mo (95% CI 7.9-NE), and 8.2 mo (95% CI 4.4-NE), respectively

Progression-Free Survival





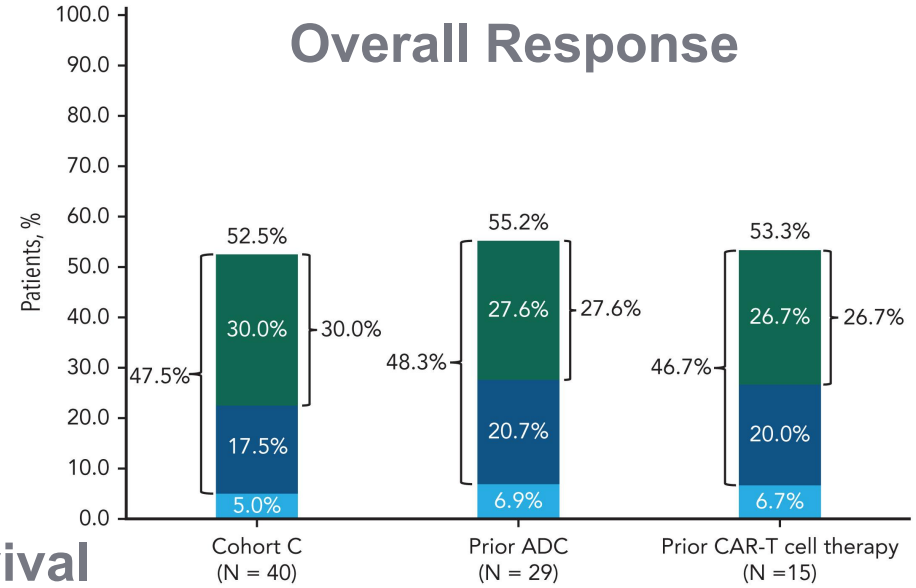


Cohen A et al. *Blood*. 2023;141:219-230.

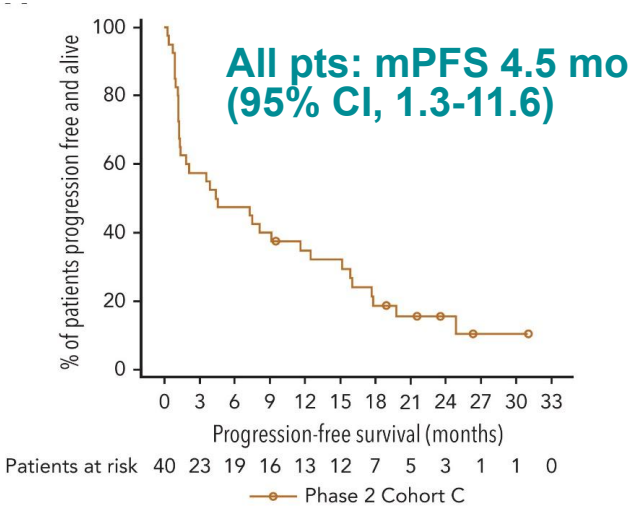
BCMA-Targeted Bispecific Antibodies After Prior BCMA-Targeted Therapy

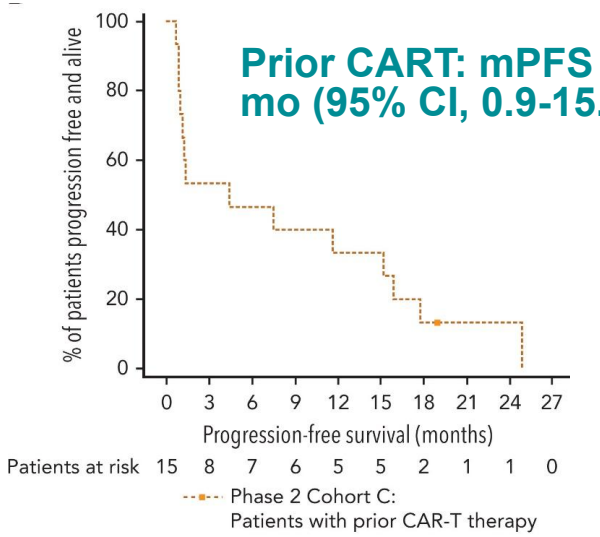
- MajesTEC-1, cohort C
- N = 40
- Key eligibility criteria: Triple class exposed, BCMA-targeted CAR T or ADC exposed, relapsing disease
- Key baseline characteristics: EMD 30%, HRCGs 33.3%, ADC exposed 72.5%, CAR T exposed 37.5%, 67.5% BCMA refractory
- 10 patients received Tec immediately after ADC (median interval between treatments 1.4 mo [range 0.7 – 4.8 mo]), 8 immediately after CAR T (median interval between treatments 4.6 mo [range 3.0 – 10.6]).
- 22 did not receive a BCMA-targeted ADC or CART as their most recent line of therapy.

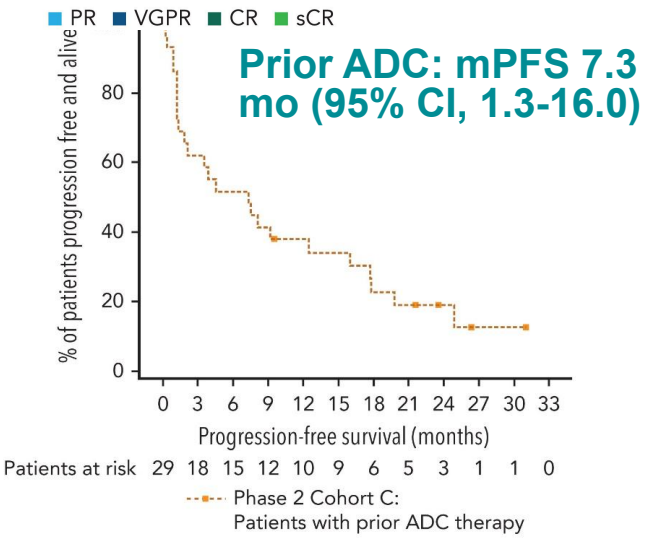
Overall Response



Progression-Free Survival







Median OS: 15.5 mo (95% CI, 8.3-27.9 mo)

Touzeau C et al. *Blood*. 2024;144:2375-2388.

Studies Poised to Change Standard of Care for Relapsed/Refractory Myeloma

- **Bispecific mAbs**
  - **MagesTEC-3**: Tec-Dara vs SoC (PVd or DPd), 1 – 3 prior lines of therapy, len and PI exposed
  - **MagesTEC-9**: Tec vs SoC (PVd or Kd), 1 – 3 prior lines of therapy, len and CD38 mAb exposed
  - **MagnetisMM-5**: Elran vs Dara-Elran vs DPd, ≥1 prior line of therapy, len and PI exposed
  - **MagnetIsMM-32**: Elran vs SoC (EPd, Kd, PVd), 1 – 3 prior lines of therapy, CD38 mAb exposed
  - **LINKER-MM3**: Linvo vs EPd, 1 – 4 prior lines of therapy, len and PI exposed
  - **CERVINO**: ABBV-383 vs SoC (EPd, Kd, Seli-Vd), ≥2 prior lines of therapy, IMiD, PI and CD38 mAb exposed
  - **MonumenTAL-3**: DPd vs Dara-Tal vs Dara-Pom-Tal, ≥1 prior line of therapy, len and PI exposed
  - **MonumenTAL-6**: Tal-Pom vs Tal-Tec vs SoC (EPd or PVd), 1 – 4 prior lines of therapy, len and CD38 mAb exposed
- **CAR T**
  - **iMMagine-3**: Anito-cel vs SoC, 1 – 3 prior lines of therapy
  - **QUINTESSENTIAL-2**: Arlo-cel vs SoC, 1 – 3 prior lines of therapy
- **CELMoDs**
  - **EXCALIBER**: Iber-Dara-d vs DVd, 1 – 2 prior lines of therapy
  - **SUCCESSOR-1**: MeziVd vs PVd, 1 – 3 prior lines of therapy, len exposed
  - **SUCCESSOR-2**: Mezi-Kd vs Kd, at least 1 prior line of therapy, len and CD38 mAb exposed

Questions Going Forward

- What is the right patient for Cilta-cel in first relapse?
- How do we weigh the efficacy of these highly active therapies with their toxicity?
  - Belantamab mafodotin: Keratopathy
  - BCMA-targeted bispecific antibodies: Infection
  - GPRC5D-targeted bispecific antibodies: Skin/nail, oral, cerebellar
  - Cilta-cel: Late neurotoxicity, IEC-associated HS, IEC-associated enterocolitis, SPMs
- What are the optimal sequencing/combination strategies?
- What is the role of IMID / PI / CD38 mAb regimens in the evolving era of immunotherapy? How will CELMoDs fit?
- How will the potential adoption of these therapies in front line transform the treatment of relapsed disease?

THANK YOU

PANEL DISCUSSION

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