Clinical Update: Multiple Myeloma

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Disclosures

- Advisory Boards: Abbvie, BMS, Janssen, Lava Therapeutics, Sanofi
- Consulting: BMS, Janssen, Karyopharm, Regeneron
- Research Funding (To Institution): Abbvie, GSK, Janssen, Nerviano Medical Sciences, Regeneron.

Outline

- Triple Class Refractory Multiple Myeloma
  - Prognosis
  - The target: B Cell Maturation Antigen (BCMA)
- BCMA-Targeted T Cell Redirecting Therapy in Late Relapse
  - BCMA-Targeted Bispecific Monoclonal Antibodies
  - BCMA-Targeted Chimeric Antigen Receptor (CAR) T Cell Therapy
- BCMA-Targeted T Cell Redirecting Therapy in Early Relapse
- Beyond BCMA-Targeted Therapy
  - BCMA-Targeted Therapy After BCMA-Targeted Therapy
  - New Targets: GPRC5D
    - GPRC5D-Targeted Bispecific Monoclonal Antibody Therapy
    - GPRC5D-Targeted CAR T Cell Therapy
- Conclusions

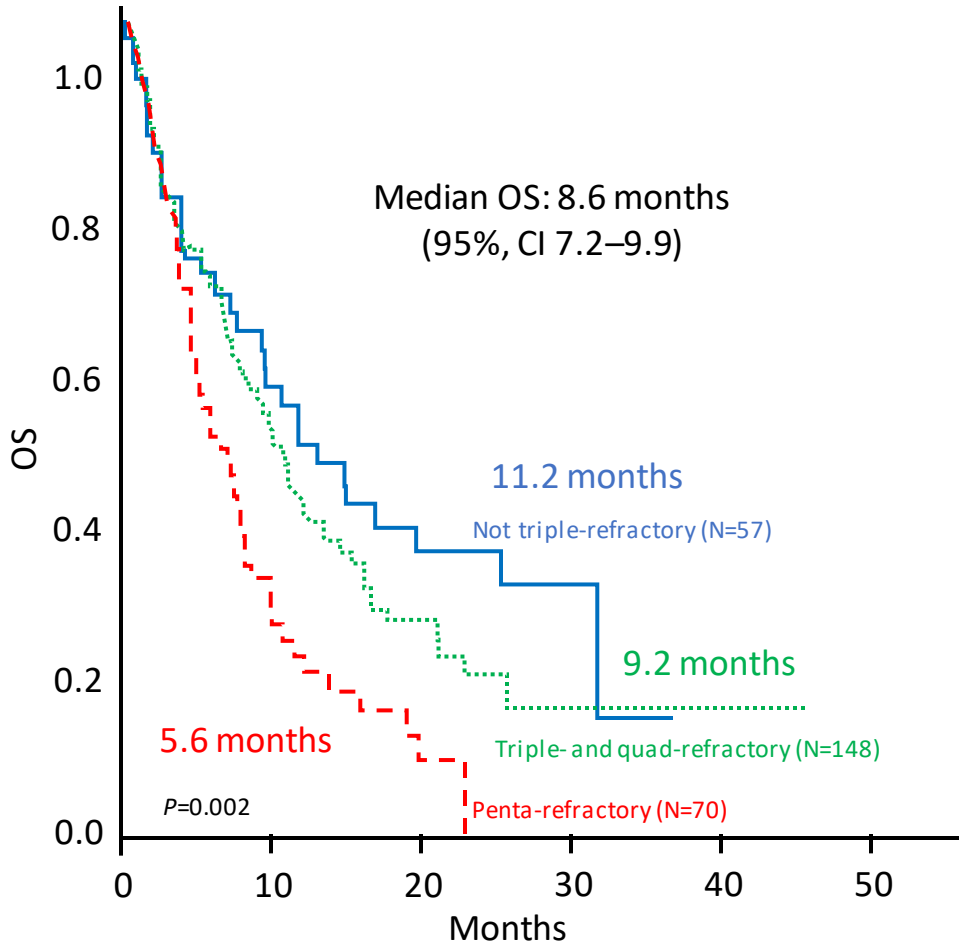
Triple Class Refractory Multiple Myeloma

PI/IMiD/CD38 mAb (Triple-Refractory) Disease

The MAMMOTH Trial

- Retrospective study of 275 patients with MM refractory to CD38 mAb therapy from 14 academic institutions
  - Triple-refractory: CD38 mAb + 1 PI + 1 IMiD
  - Quad-refractory: CD38 mAb + 1 PI + 2 IMiDs *OR* 2 PIs and 1 IMiD
  - Penta-refractory: CD38 mAb + 2 PIs + 2 IMiDs
- 54% triple- / quad-refractory, 25% penta-refractory
- Median 4 prior lines of therapy (range 1–16)

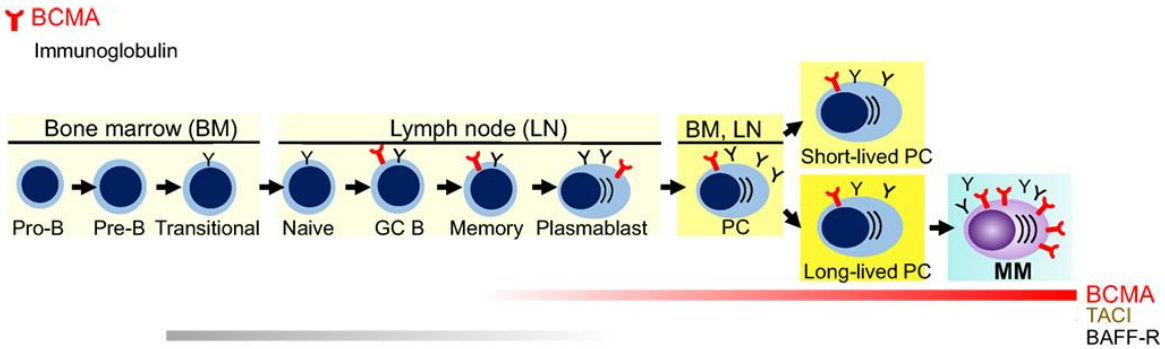
	Refractory (%)
Bortezomib	**68.4%**
Carfilzomib	**47.3%**
Lenalidomide	**76.7%**
Pomalidomide	**65.1%**



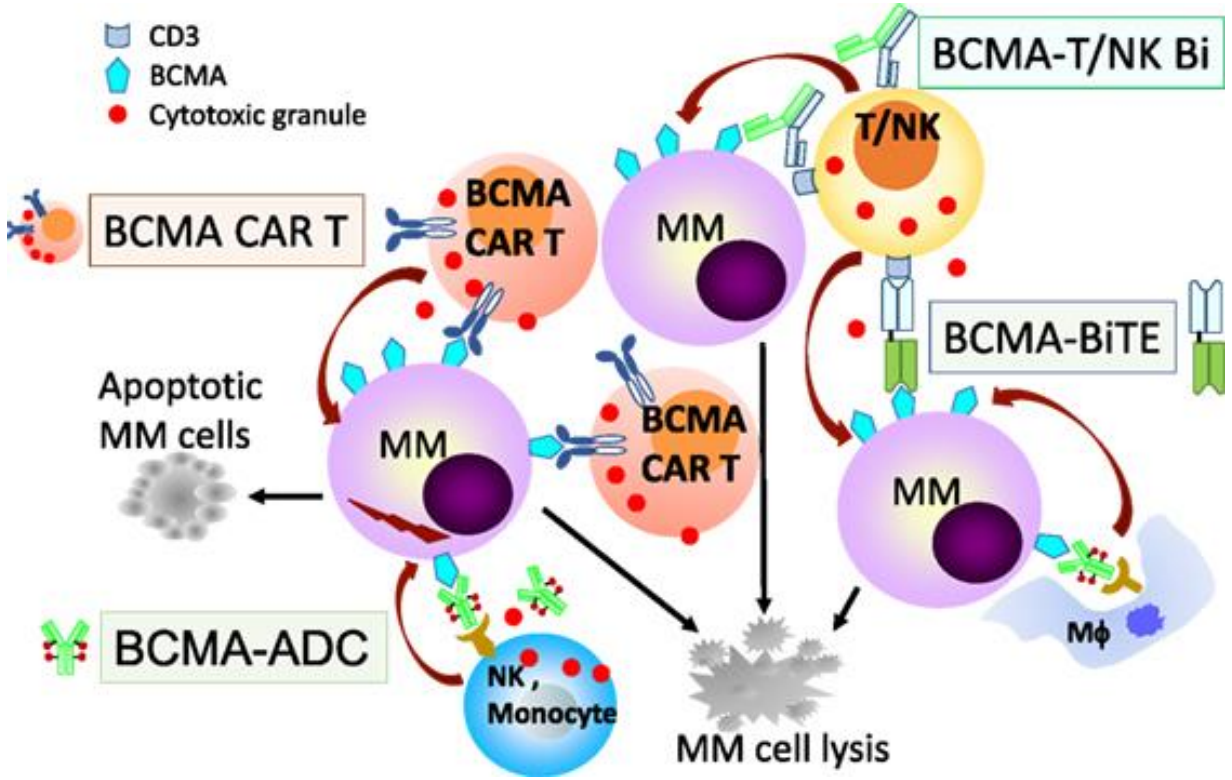
CI, confidence interval; IMiD immunomodulatory drug; mAb, monoclonal antibody; MM, multiple myeloma; OS, overall survival; PI, proteasome inhibitor.

Gandhi UH, et al. *Leukemia.* 2019;33:2266-75.

BCMA in Multiple Myeloma



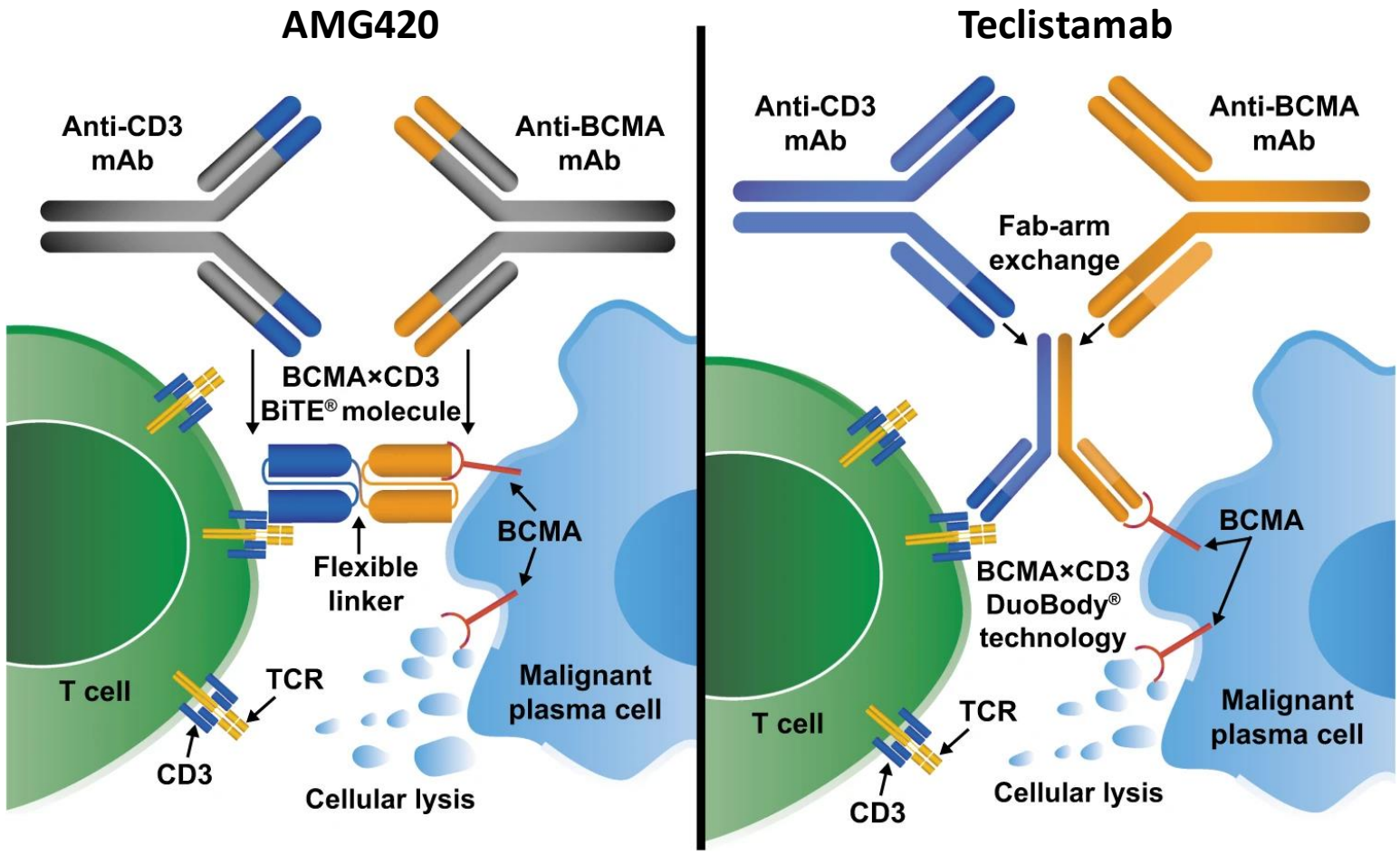
- **Expressed on late memory B cells committed to PC differentiation and PCs**
- **BCMA plays a role in survival of long-lived PCs**
- **γ-secretase cleaves BCMA from the cell surface, yielding soluble BCMA**



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

BCMA-Targeted Bispecific Monoclonal Antibody Therapy in Relapsed/Refractory Multiple Myeloma

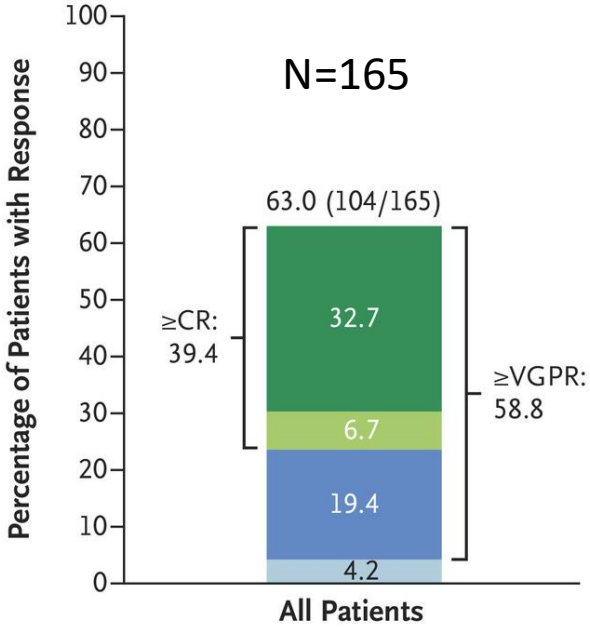
BCMA-Targeted Bispecific Monoclonal Antibody Therapy



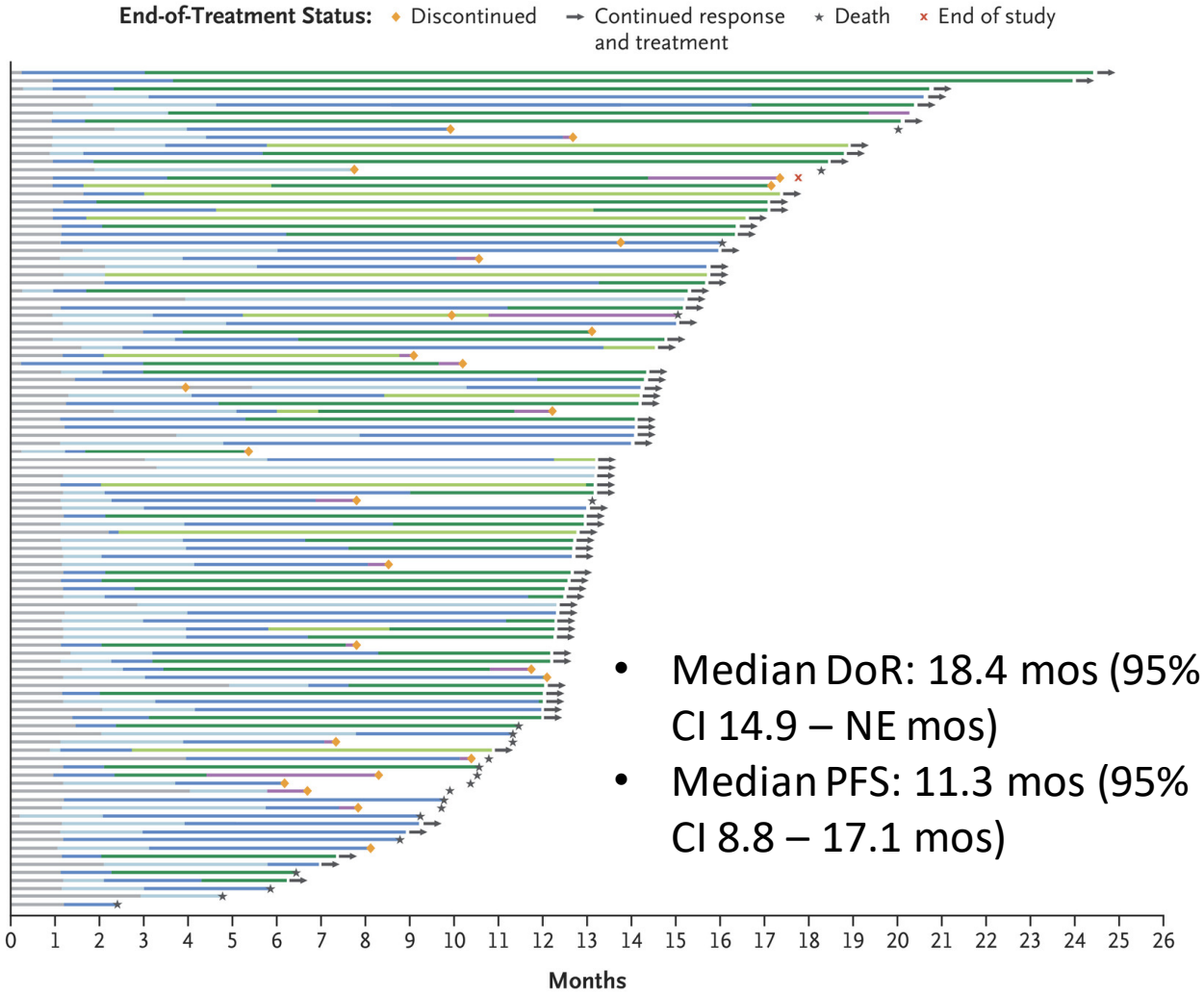
Shah N, et al. Leukemia 2020;34(4):985-1005.

MajesTEC-1: Phase I/II Study of Teclistamab in RRMM

- Enrollment 3/2020 – 8/2021
- 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



- Neutropenia 70.9% (64.2% ≥grade 3), hypogammaglobulinemia 74.5%
- Infections 76.4% (44.8% ≥grade 3)
- 12 COVID-19 deaths



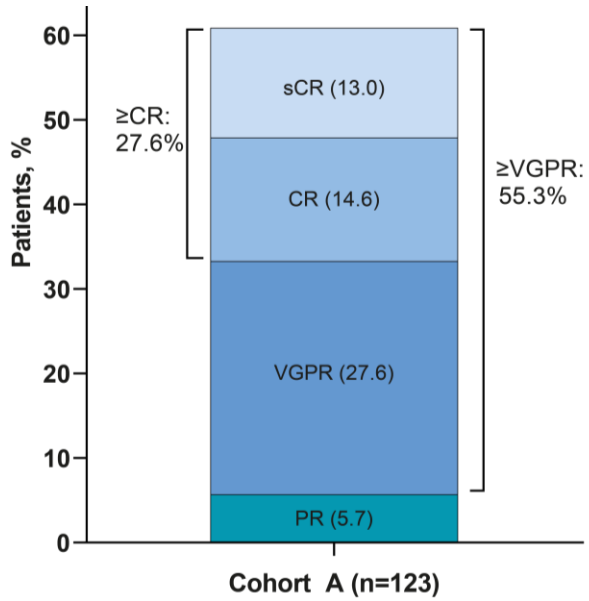
- Median DoR: 18.4 mos (95% CI 14.9 – NE mos)
- Median PFS: 11.3 mos (95% CI 8.8 – 17.1 mos)

Moreau P, et al. N Engl J Med 2022;387:495-505.

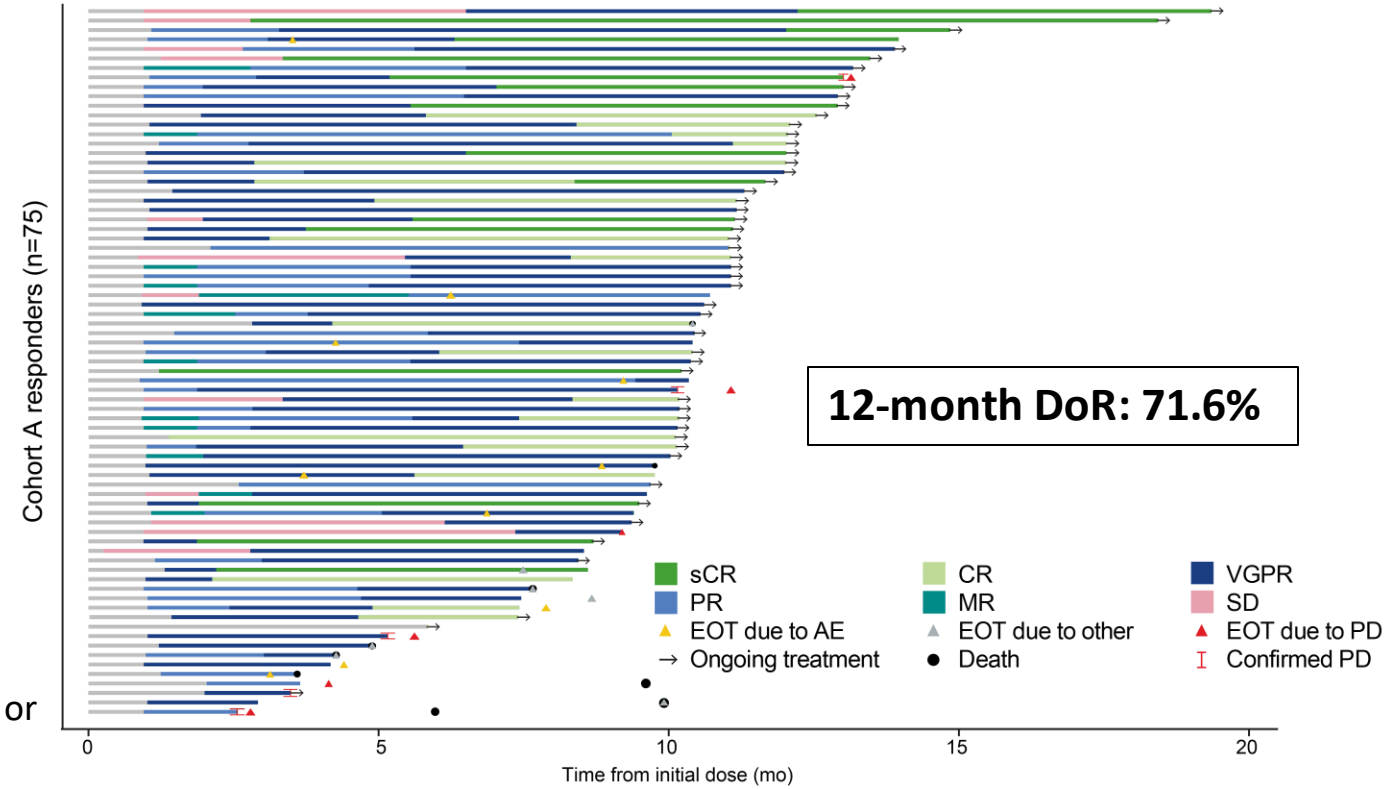
The BCMA-Targeted Bispecific Monoclonal Antibody Elranatamab in Relapsed/Refractory Multiple Myeloma: MagnetisMM-3

- **Phase II Study. 2 step-up doses followed by weekly dosing. Every other week dosing if ≥PR after 6 cycles lasting ≥2 months**
- **R-ISS 2 / 3 disease: 55.3% / 15.4%, HRCGs 25.2%, extramedullary disease 31.7%**
- **Median prior lines of therapy 5 (range 2 – 22), Triple class refractory 96.7%, penta-refractory 42.3%, refractory to last line of therapy 95.9%**

ORR, 61.0% (95% CI, 51.8–69.6)



- **Median time to response 1.2 mos (0.9 – 7.4 mos)**
- Responses lower for those with extramedullary, penta-refractory or R-ISS stage 3 disease, marrow burden of disease of ≥50%



12-month DoR: 71.6%

12-month PFS: 58.8%; 12-month OS: 63.6%

Bahlis N et al. ASH 2022, Abstract 159.

MagnetisMM-3: AEs of Interest

	All grades	Grade 3 and 4
CRS	57.5%	0.0%
Neurotoxicity	3.4%	0.0%
Infections	66.7%	35.0%
Neutropenia	48.0%	48.0%
Thrombocytopenia	30.1%	22.0%

- IVIg used in 40.7% of patients
- PJP pneumonia seen in 4.9%
- CMV reactivation seen in 4.9% CMV infection in 3.3%

Bahlis N et al. ASH 2022, Abstract 159.

The BCMA-Targeted Bispecific Monoclonal Antibody Landscape: Characteristics and Dosing

Agent	mAb Characteristics	Mode of Administration	Schedule
Teclistamab	1 BCMA binding domain, Duobody platform®	SC	2 step-up doses → 1.5 mg/kg qwk
Elranatamab	1 BCMA binding domain, humanized	SC	2 step-up doses → 72 mg qwk (q2wks after C6 for ≥PR)
Linvolseltamab	1 BCMA binding domain, Veloci-Bi platform®	IV	2 step-up doses → 200 mg qwk C1 – C3, q2 wks C4+ (q4wks for C6+ if ≥VGPR)
Alnuctamab	2 BCMA binding domains, humanized	SC	2 step-up doses → 10 - 60 mg qwk C1 and C2, q2wks C3 – 6, every 4 weeks C7+
ABBV-383	2 BCMA binding domains, low affinity CD3 binding domain	IV	60 mg every 3 weeks** (No step-up doses)

Moreau, P et al. New Engl J Med 2022;387:495-505.

Bahlis N et al. ASH 2022, Abstract 159.

Bumma N et al. ASH 2022, Abstract 4555.

Wong S et al. ASH 2022, Abstract 162.

Voorhees P et al. ASH 2022, Abstract 1919.

The BCMA-Targeted Bispecific Monoclonal Antibody Landscape: Efficacy

Agent	Median Follow-Up	ORR	≥VGPR	DoR	PFS
Teclistamab (1.5 mg/kg)	14.1 mos	63.0%	58.8%	12-mos: 68.5%	Median: 11.3 mos
Elranatamab (76 mg)	10.4 mos	61.0%	55.3%	12-mos: 71.6%	12-mos: 58.8%
Linvolseltamab	5.6 mos	71.0% (200 mg cohort)	59.0% (200 mg cohort)	12-mos: 79.2%	6-mo: 72.7%
Alnuctamab	4.1 mos	65.0% (30 mg cohort)	46.0% (30 mg cohort)	Not reported	Not reported
ABBV-383 (60 mg)	15.2 mos	61.0%	53.0%	12-mos: 68.6%	Median: 11.2 mos

Moreau, P et al. New Engl J Med 2022;387:495-505.

Bahlis N et al. ASH 2022, Abstract 159.

Bumma N et al. ASH 2022, Abstract 4555.

Lee H et al. ASCO 2023.

Voorhees P et al. ASH 2022, Abstract 1919.

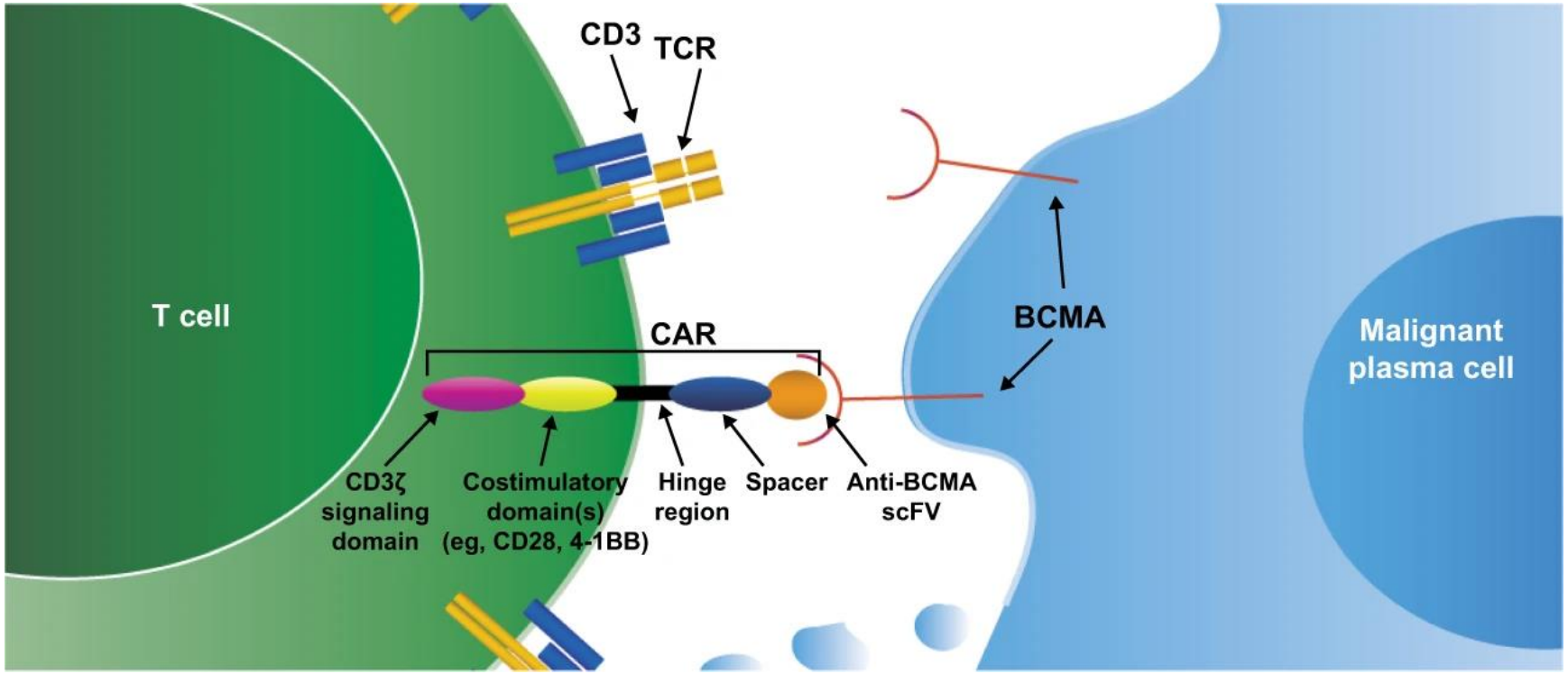
The BCMA-Targeted Bispecific Monoclonal Antibody Landscape: Safety

Agent	Median Follow-Up	CRS, All Grades	≥Grade 3 CRS	Neurotoxicity, All Grades	≥Grade 3 Neurotox	≥Grade 3 Neutropenia	≥Grade 3 Low Plts	≥Grade 3 Infection
Teclistamab (1.5 mg/kg)	14.1 mos	72.1%	0.6%	14.5%	0.6%	64.2%	21.2%	44.8%
Elranatamab (76 mg)	10.4 mos	57.5%	0.0%	3.4%	0.0%	48.0%	22.0%	35.0%
Linvolseltamab (200 mg)	5.6 mos	45.3%	0.9%	5.9% (All cohorts)	1.8% (All cohorts)	26.0%	13.7%	36.8%
Alnuctamab	4.1 mos	46.0% (≥30 mg cohorts)	0.0% (≥30 mg cohorts)	6.0% (All cohorts)	0.0% (All cohorts)	32.0% (All cohorts)	9.0% (All cohorts)	9.0% (All cohorts)
ABBV-383 (60 mg)	15.2 mos	70.0%	2.0%	5.0%	1.6%	34.0%	11.0%	22.0% (All cohorts)

Note: Apparent differences in AEs between agents could be impacted by confounders such as follow-up time, rigor of infection prophylaxis, timing of the study relative to the COVID-19 pandemic, etc.

Moreau, P et al. New Engl J Med 2022;387:495-505.
Bahlis N et al. ASH 2022, Abstract 159.
Lee H et al. ASCO 2023, Abstract 4555.
Wong S et al. ASH 2022, Abstract 162.
Voorhees P et al. ASH 2022, Abstract 1919.

BCMA-Targeted CAR T Cell Therapy



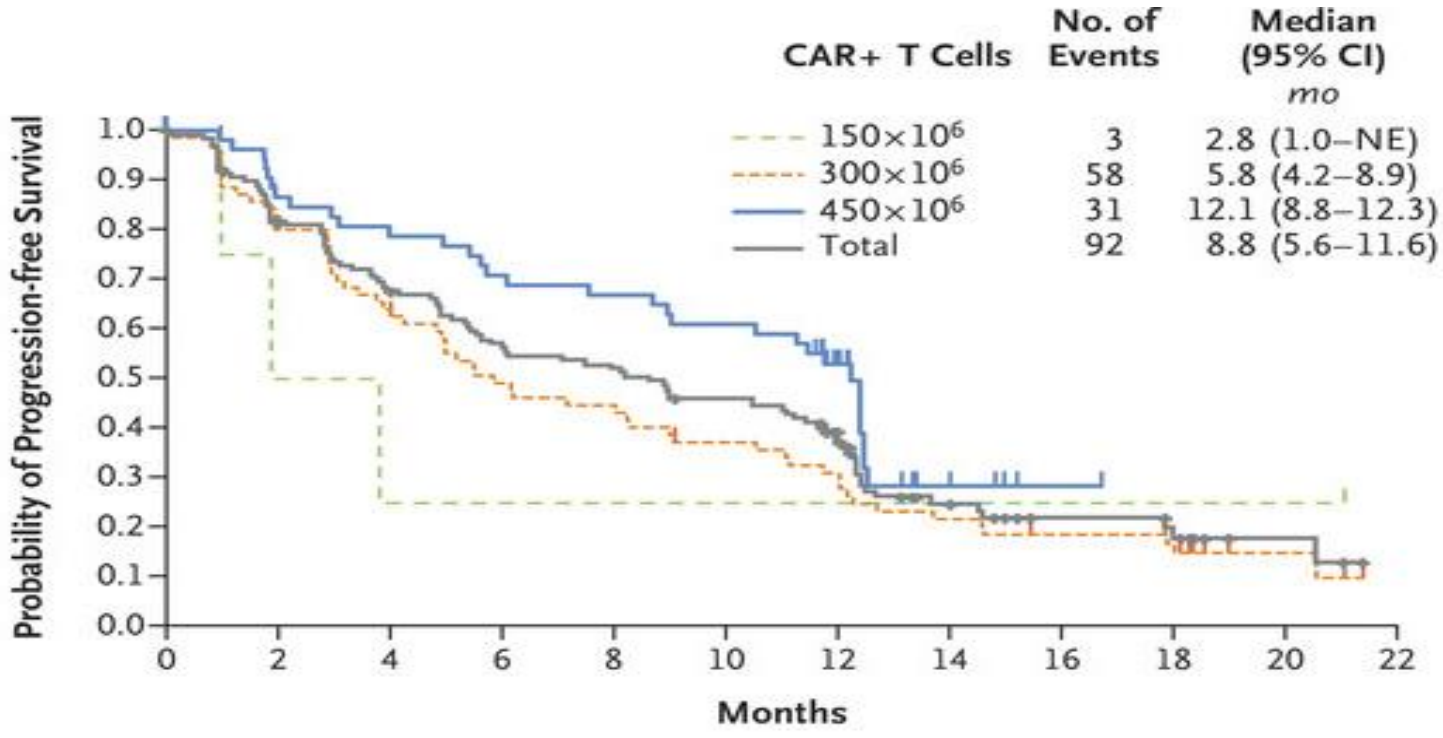
Shah N, et al. Leukemia 2020;34(4):985-1005.

Idecabtagene Vicleucel: The KarMMa-1 Trial

- High risk CGs 35%, Extramedullary plasmacytomas 39%, Median prior lines of therapy: 6 (3 – 16), Triple refractory 84%, Refractory to last line 100%

	Ide-Cel
ORR	**73%**
sCR + CR	**33%**
VGPR	**20%**
PR	**21%**
Median PFS, mos	**8.8**
Median DoR, mos	**10.7**

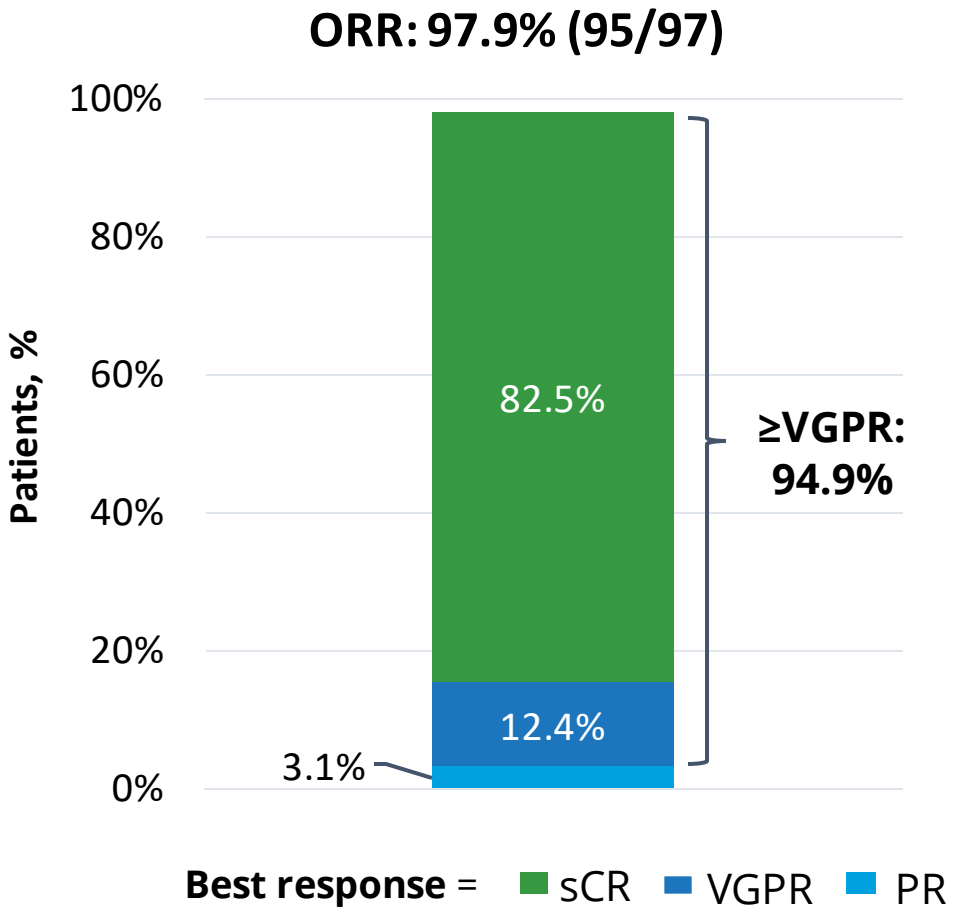
ORR to Bridging Therapy(N=112): 4%



Median OS (95% CI): 19.4 mo (18.2–NE)

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

Ciltacabtagene Autoleucel: A BCMA-Targeted CAR T Cell Therapy



ORR to Bridging Therapy(N=112): 21%

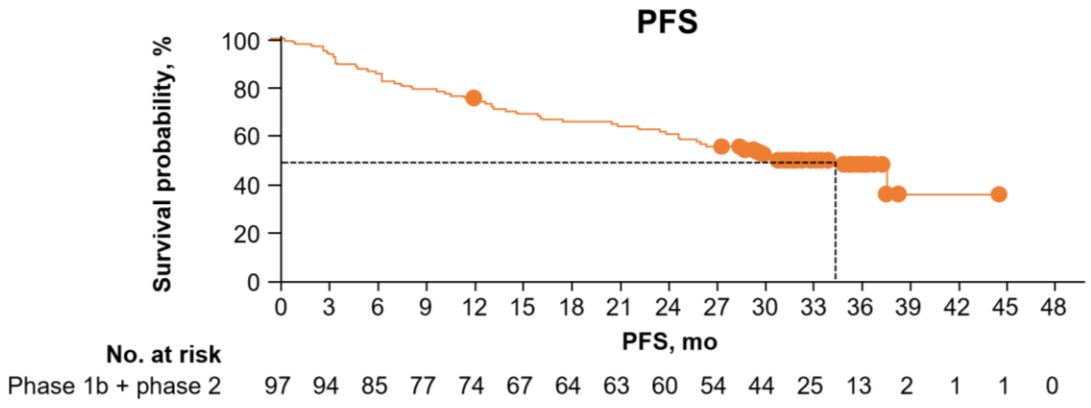
CARTITUDE-1

- Phase Ib/II study of the CAR T cell product ciltacabtagene autoleucel for RRMM
- High risk CGs 23.7%
- Extramedullary plasmacytomas 13.4%
- Median prior lines of therapy: 6 (3 – 18)
- Triple class refractory 87.6%
- Refractory to last line 99%

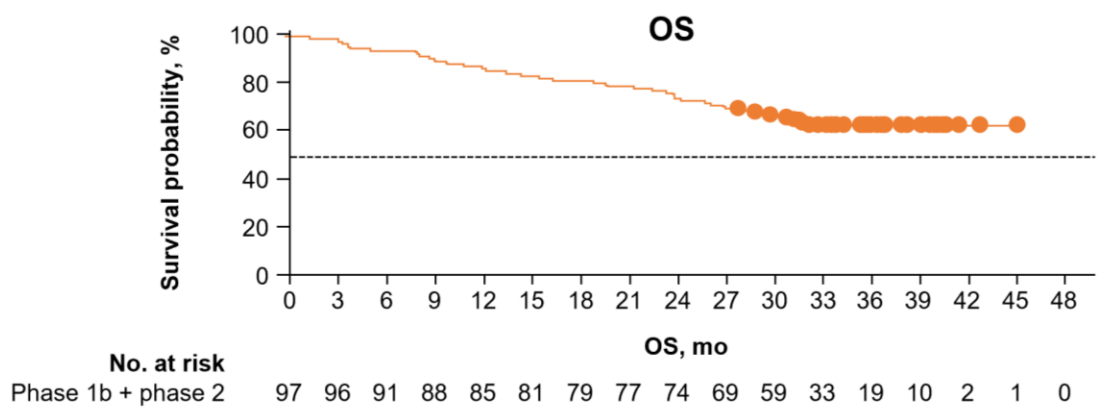
Of the 61 patients evaluable for MRD, 92% were MRD-negative (at 10^{-5})

Martin, T et al. ASH 2021.

CARTITUDE-1: Final PFS and OS



Median PFS: 34.9 Months (95% CI, 25.2–NE)



Median OS: Not reached

Median Follow-Up: 33.4 Months (Range 1.5 – 45.2)

Lin, Y et al. ASCO 2023.

CAR T Cell Toxicity

	KarMMa-1 (N = 128)		CARTITUDE-1 (N = 97)	
	All Grades	Grade 3+	All Grades	Grade 3+
CRS	84%	5%	94.8%	4.1%
ICANS / Neurotoxicity	18%	3%	21.6%	11.3%
Neutropenia	91%	89%	95.9%	94.8%
Thrombocytopenia	63%	52%	79.4%	59.8%
Infection	70%	27%	58%	20%

6 cases of Parkinsonism reported in CARTITUDE-1

9 cases of secondary hematologic malignancy reported in CARTITUDE-1 (1 low-grade NHL, 6 MDS, 3 AML)

Munshi N et al. N Engl J Med 2021;384:705-16
Martin, T et al. ASH 2021.

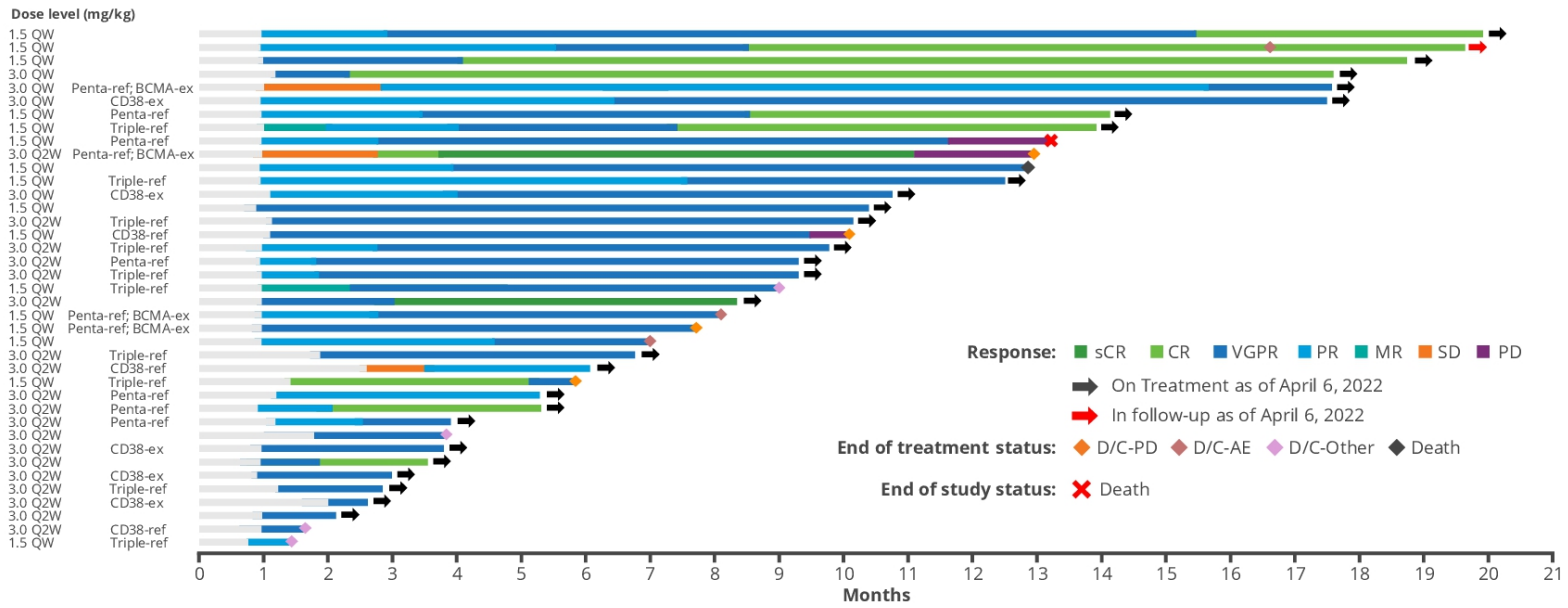
BCMA-Targeted T Cell Redirecting Therapy in Earlier Lines of Treatment

Phase I Study of Teclistamab + Daratumumab in RRMM (TRIMM-2)

- Median age: 67 (40 – 81)
- EMM: 23.1%
- HRCGs: 18.8%
- Median prior lines of therapy: 5 (1 – 15)
- 58.5% triple refractory
- 63.1% CD38 mAb refractory
- 80.0% refractory to last line of therapy

Best response	Response-evaluable patients[a] (n=51)		
	Dara SC 1800 mg		
	Tec 1.5 mg/kg QW (n=20)	Tec 3 mg/kg Q2W (n=27)	Tec 3 mg/kg QW (n=4)
ORR[b]	15 (75.0)	20 (74.1)	4 (100.0)
CR/sCR	6 (30.0)	3 (11.1)	2 (50.0)
VGPR	8 (40.0)	15 (55.6)	2 (50.0)
PR	1 (5.0)	2 (7.4)	0
SD	3 (15.0)	5 (18.5)	0
PD	2 (10.0)	2 (7.4)	0

Overall Response Rate: 76.5%
(73.7% in Dara exposed pts)

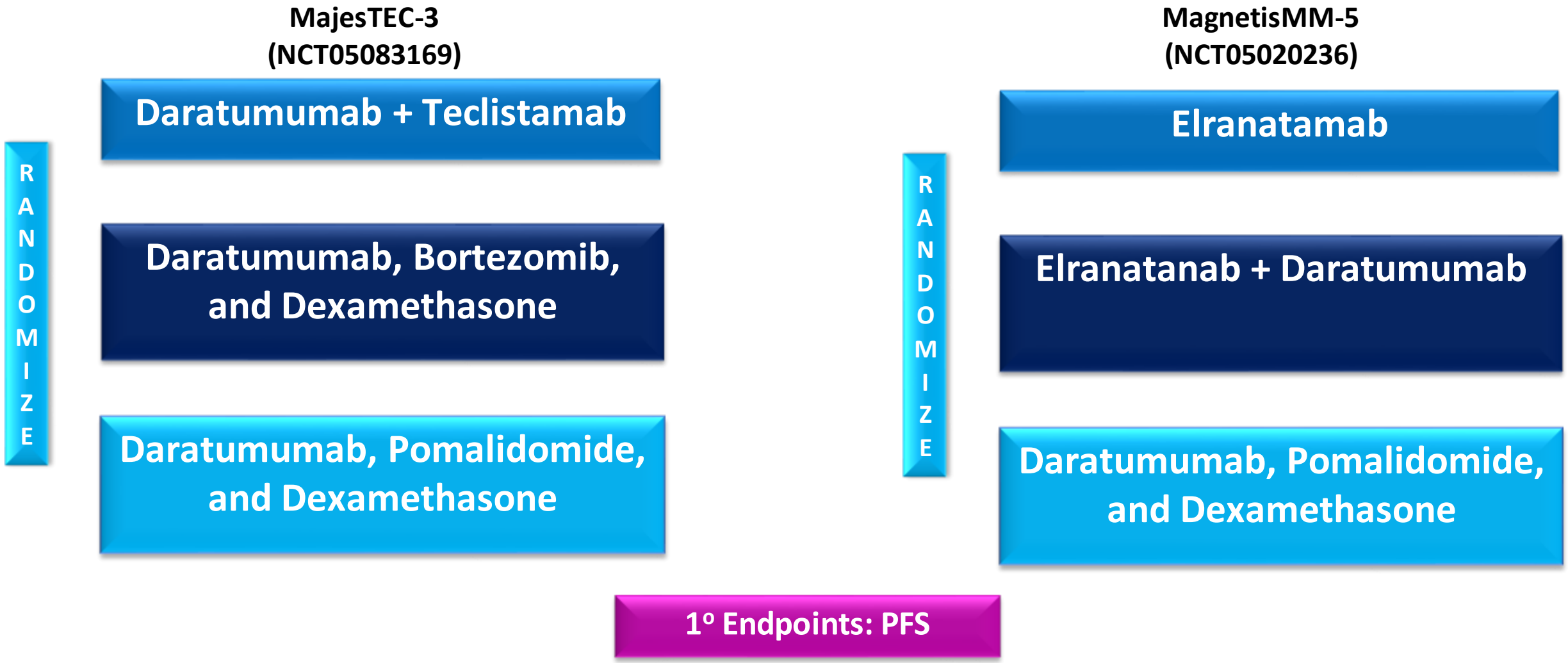


BCMA-ex, anti-BCMA exposed; CD38-ex, anti-CD38 exposed; CR, complete response; D/C, discontinued; MR, minimal response; PD, progressive disease; Penta-ref, penta-drug refractory; sCR, stringent CR; SD, stable disease; Trip-ref, triple-class refractory

- CRS: 67.7% (all grade 1 and 2)
- Infection: 67.7% (27.7% grade 3 or 4)

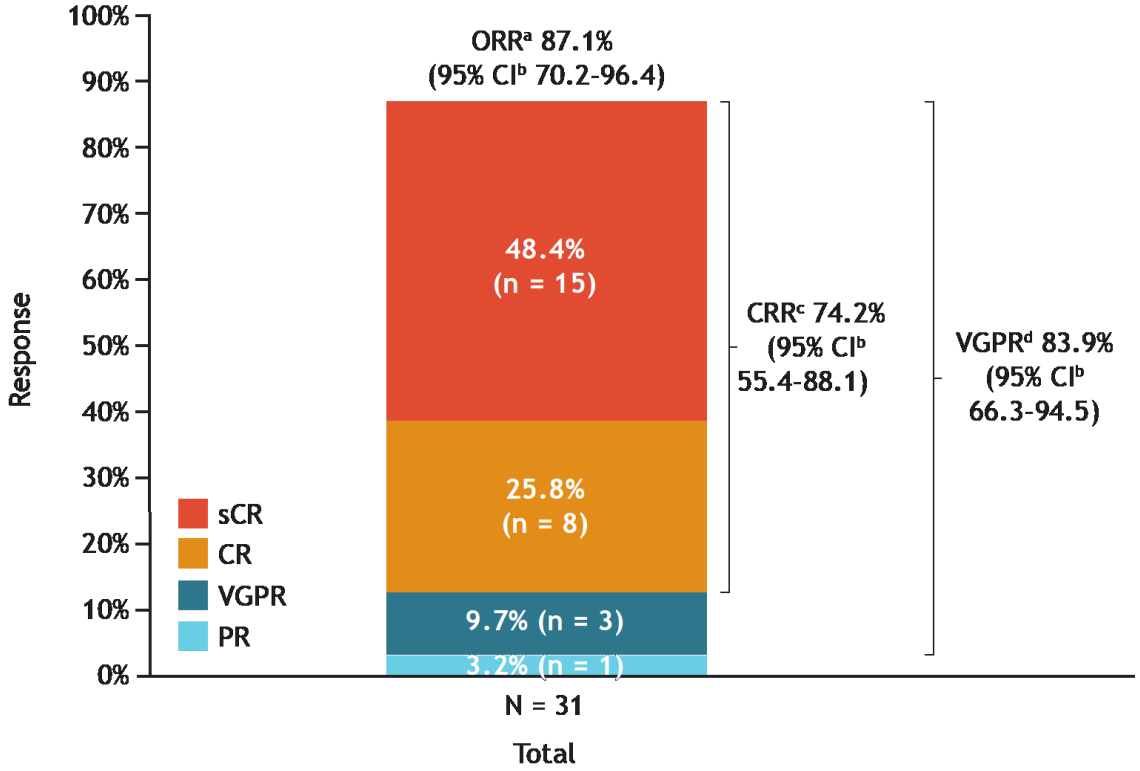
Otero PR, et al. ASCO 2022.

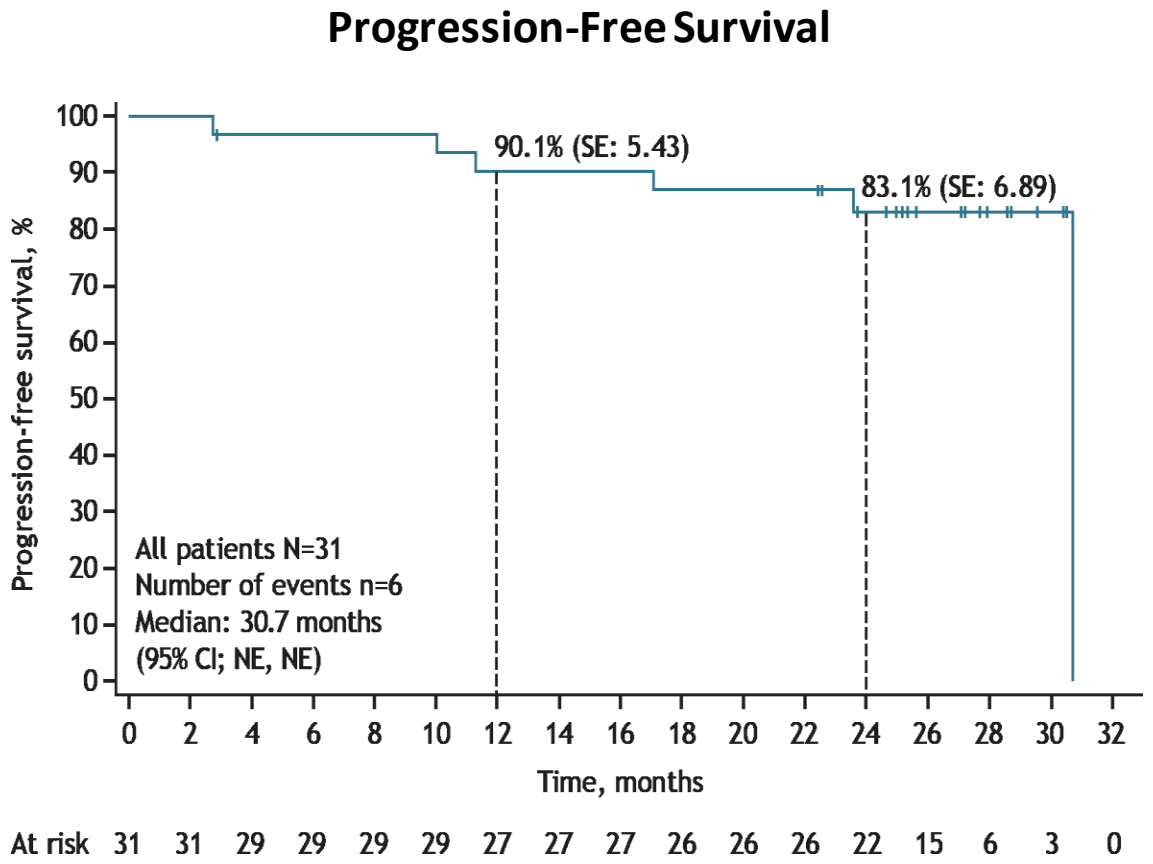
Bringing it Forward: MajesTEC-3 and MagnetisMM-5



Idecabtagene Vicleucel for Consolidation of Suboptimal Response after Induction / ASCT: KarMMA-2 Cohort 2c

- Key eligibility criteria: <VGPR after induction → ASCT
- 32 patients underwent leukapheresis, 31 received idecabtagene vicleucel
- Key characteristics: 9.7% with HR CGs (45.2% standard risk, 45.2% not evaluable), 6.5% with extramedullary disease, PR to frontline therapy 87.1%
- Median follow-up: 27.9 months (range 24 – 32)





Dhodapkar M et al. ASH 2022, Abstract 3314.

Idecabtagene Vicleucel for Consolidation of Suboptimal Response after Induction / ASCT: KarMMA-2 Cohort 2c

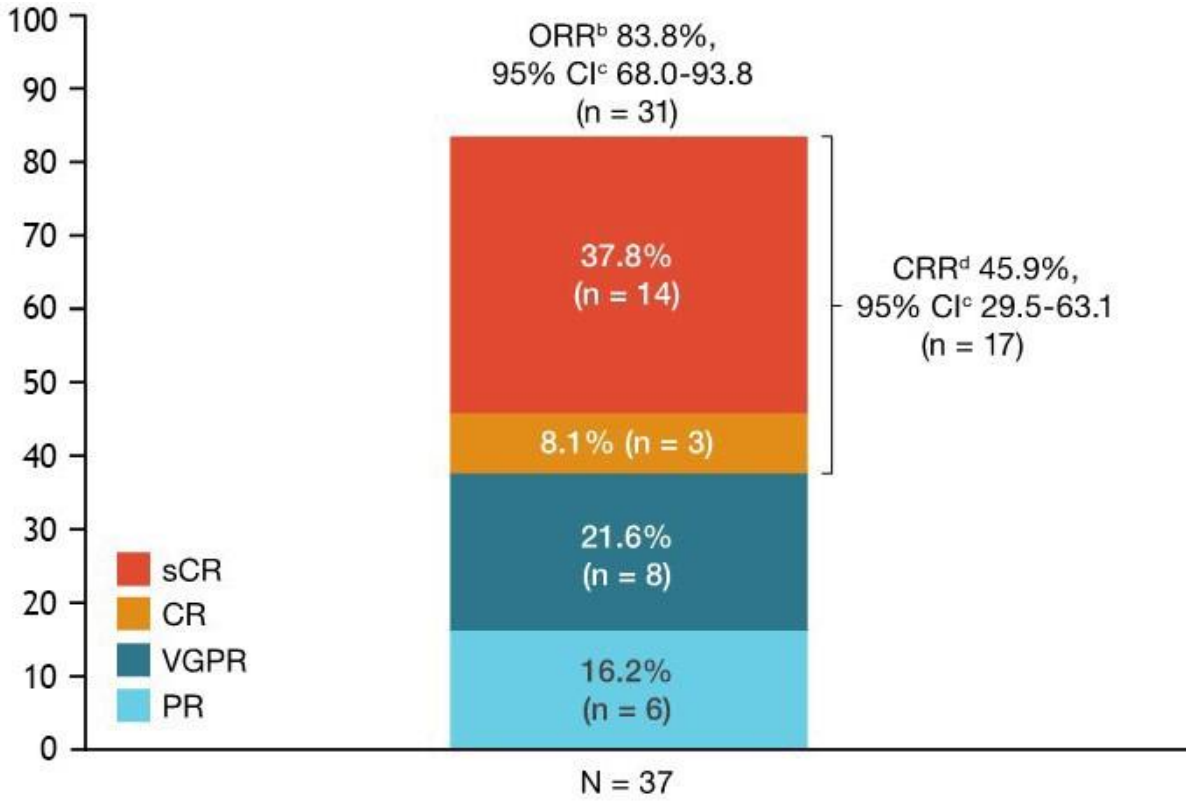
TEAEs of Interest

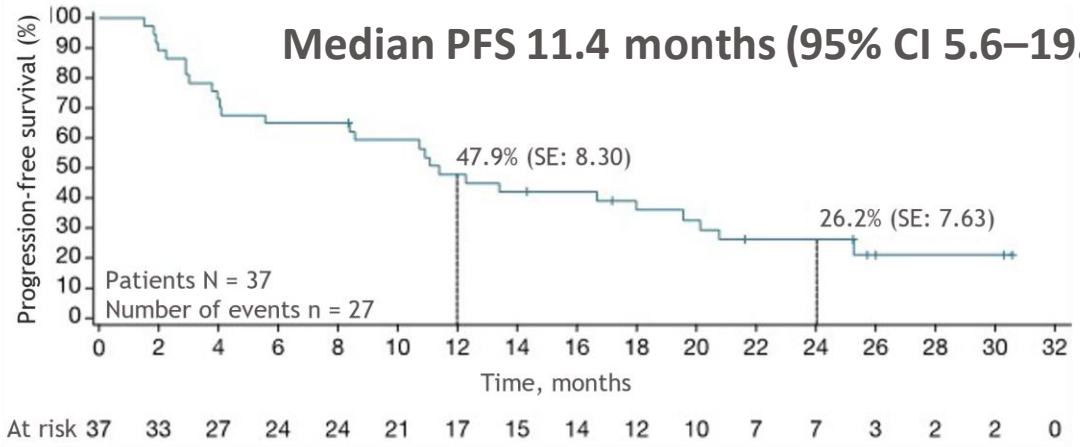
	All Grades	Grade 3 and 4
CRS	58.1%	0.0%
Neurotoxicity	6.5%	3.2%
Neutropenia	80.6%	80.6%
Thrombocytopenia	25.8%	12.9%
Infection	58.1%	12.9%

Dhodapkar M et al. ASH 2022, Abstract 3314.

Idecabtagene Vicleucel for Early Relapse after Induction / ASCT / Lenalidomide-Based Maintenance: KarMMA-2 Cohort 2a

- Key eligibility criteria: Progression of disease within 18 months of induction → ASCT → len-based maintenance
- 39 patients underwent leukapheresis, 37 received idecabtagene vicleucel
- Key characteristics: 12 of 22 evaluable pts with HR CGs (4 with>1 HR CG abnormality), 8.1% with extramedullary disease, ≥CR to frontline therapy 24.3%, **PD within 1 year of ASCT 89.2%**
- Median follow-up: 21.5 months (range 2–31)





24-Month OS: 84.7%

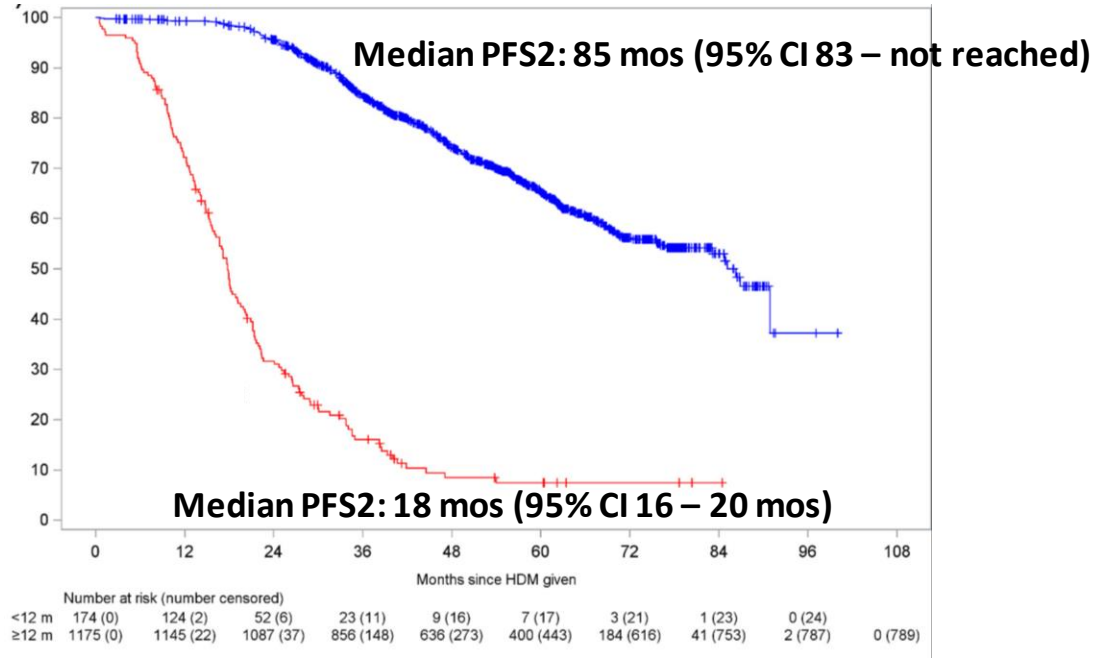
TEAEs of Interest

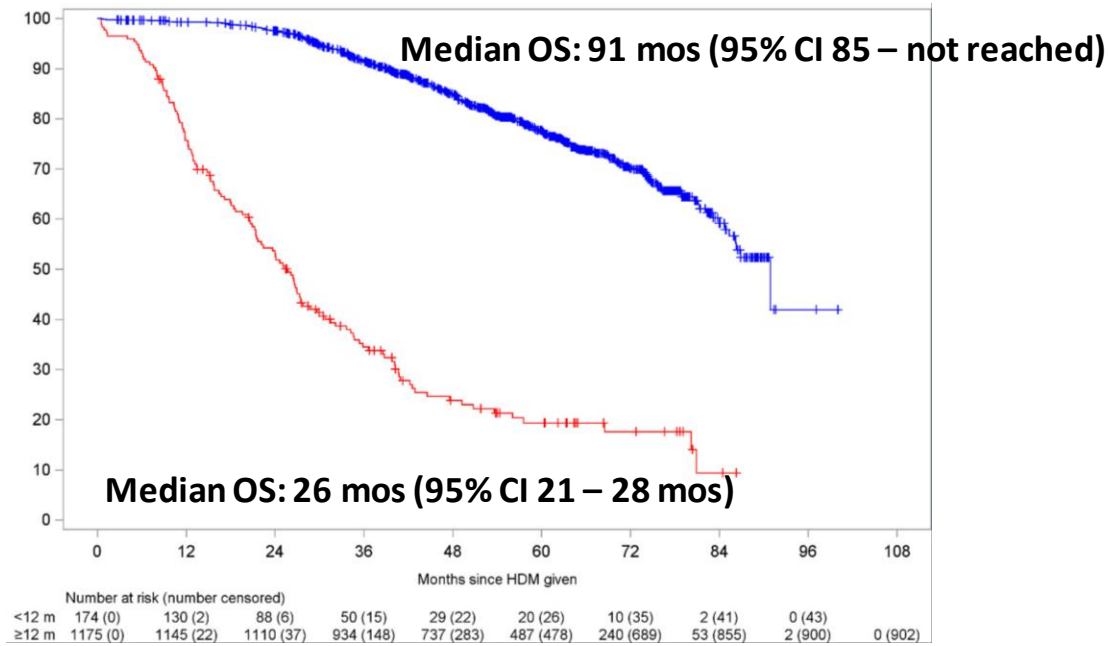
	All Grades	Grade 3 and 4
CRS	83.8%	2.7%
Neurotoxicity	21.6%	0.0%
Neutropenia	94.6%	94.6%
Thrombocytopenia	51.4%	37.8%
Infection	59.5%	21.6%

Usmani S et al. ASH 2022, Abstract 361.

Outcomes after Early Relapse post-ASCT: MRC XI

- MRC XI retrospective analysis of early vs late relapse post-ASCT
- Early relapse: Within 12 months of ASCT





PFS2 and OS measured from date of high dose melphalan

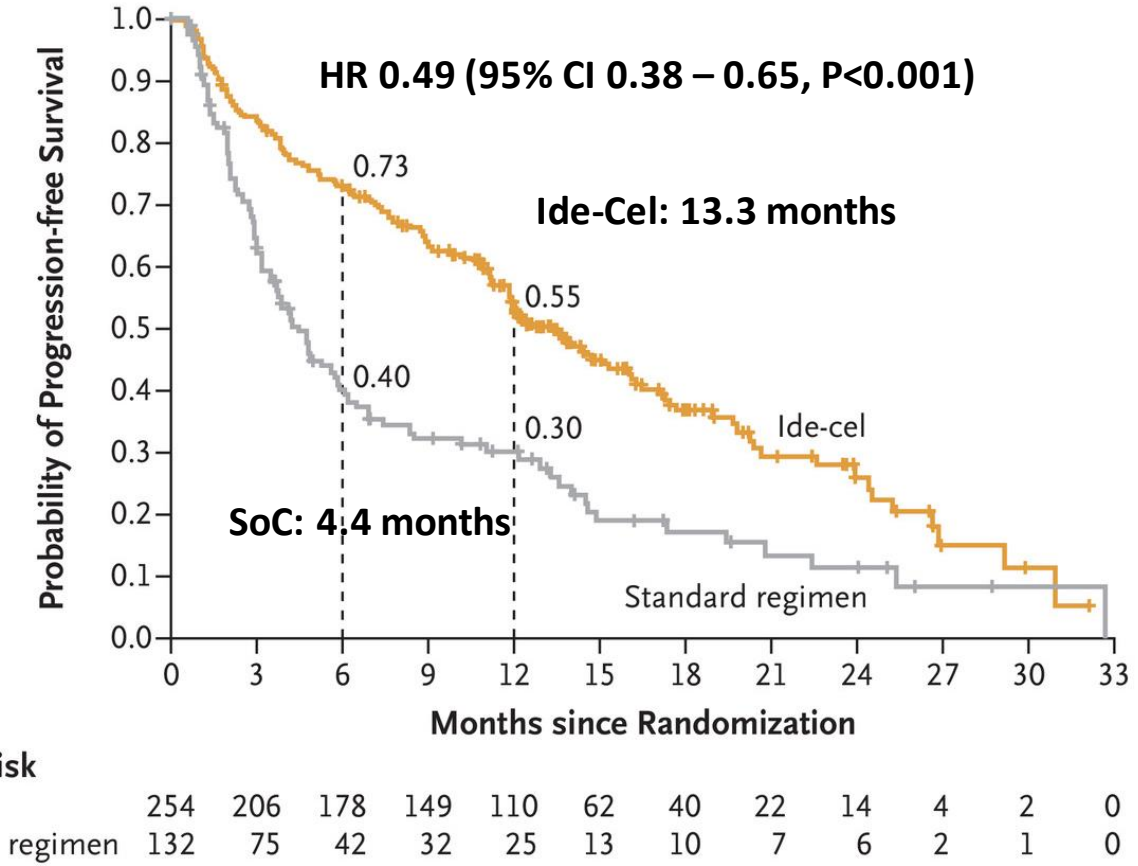
Bygrave, C et al. Br J Haematol 2021;193:551-5.

KarMMA-3: Phase III Study of Idecabtagene Vicleucel vs Investigators Choice for RRMM

- **2:1 randomization**
- **2 – 4 prior lines of therapy, dara/IMiD/PI exposed, PD within 60 days of last regimen**
- **SoC regimens: Dara-Pom-Dex (43), Elo-Pom-Dex (30), Dara-Bortezomib-Dex (7), Ixa-Len-Dex (22), Car-Dex (30)**

- Median prior lines of therapy: 3 (range 2 – 4)
- 90% IMiD refractory, 95% dara refractory, 74% PI refractory, 65% - 67% triple class refractory disease
- 42% - 46% HRCGs

	Ide-Cel	SoC
ORR	**71%**	**42%**
sCR	**35%**	**5%**
CR	**3%**	**1%**
VGPR	**22%**	**10%**
PR	**11%**	**27%**



Rodriguez-Otero P et al. N Engl J Med 2023;Online ahead of print

KarMMA-3: Safety

	Ide-Cel		SoC Regimens	
Adverse Event	**All Grades**	**Grade 3 and 4**	**All Grades**	**Grades 3 and 4**
Neutropenia	78%	76%	44%	40%
Anemia	66%	51%	36%	18%
Thrombocytopenia	54%	42%	29%	17%
Infections*	58%	24%	54%	18%
Fatigue	28%	2%	35%	2%
CRS†	88%	4%		
Neurotoxicity	15%	3%		
SAEs	52%		38%	
Treatment-Related Deaths	3%		1%	
SPMs	6%		4%	

*4% and 2% grade 5 infections, respectively
†1% grade 5

Rodriguez-Otero P et al. N Engl J Med 2023;Online ahead of print

CARTITUDE-4: Phase III Study of Ciltacabtagene Autoleucel vs Investigators Choice for RRMM

Design

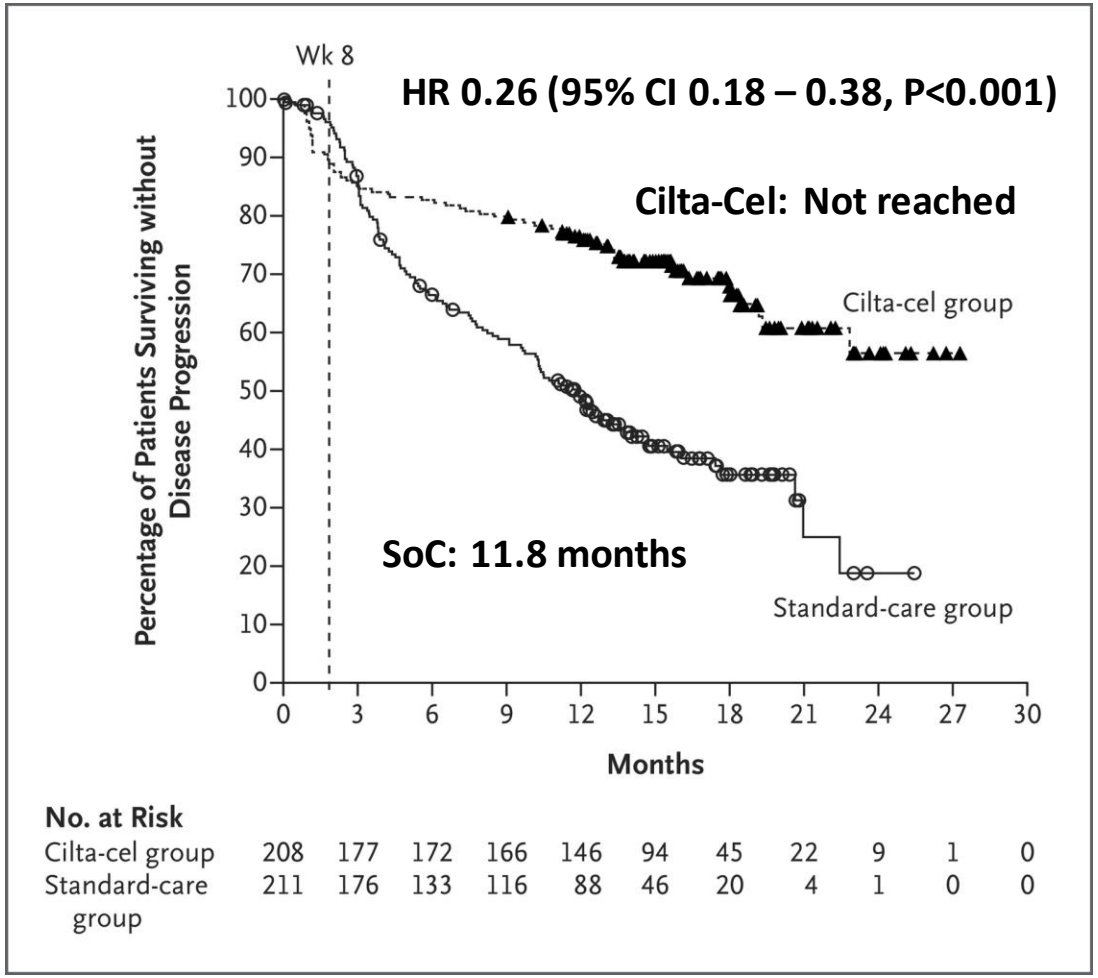
- 1 – 3 prior lines of therapy, lenalidomide refractory, PI exposed
- SoC regimens: Dara-Pom-Dex, Pom-Bortezomib-Dex
- 84.6% of pts assigned to Cilta-cel received it per protocol
- SoC Group: 86.7% DPd, 12.3% PVd
- Cilta-cel Group: No pts received therapy prior to apheresis, All received bridging therapy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

Baseline Characteristics

- Enrollment 7/2020 – 11/2021
- 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

	Cilta-Cel	SoC
ORR	71%	42%
sCR	58.2%	15.2%
CR	14.9%	6.6%
VGPR	8.2%	23.7%
PR	3.4%	21.8%
MRD (10^{-5})	60.6%*	15.6%*

*87.5% and 32.7% for those with MRD evaluable samples



Median Follow-Up: 15.9 Months

San-Miguel J et al. N Engl J Med 2023;389:335-47

CARTITUDE-4: Safety

	Cilta-Cel		SoC Regimens	
Adverse Event	All Grades	Grade 3 and 4	All Grades	Grades 3 and 4
Neutropenia	89.9%	89.9%	85.1%	82.2%
Anemia	54.3%	35.6%	26.0%	14.4%
Thrombocytopenia	54.3%	41.3%	31.2%	18.8%
Infections*	62.0%	26.9%	71.2%	24.5%
Fatigue	28.8%	1.9%	32.7%	1.0%
CRS	76.1%	1.1%		
Neurotoxicity ICANS Other†	20.5% 4.5% 17.0%	2.8% 0.1% 2.3%		
SAEs	44.2%		38.9%	
Treatment-Related Deaths	4.8%		2.7%	
SPMs	4.3%		6.7%	

*7 vs 1 patient died of COVID-19; 65.9% vs 12.5% of pts received IVIg prophylaxis, respectively

†1 pt with MNT, 16 with CN palsies, 5 with peripheral neuropathy

San-Miguel J et al. N Engl J Med 2023;389:335-47

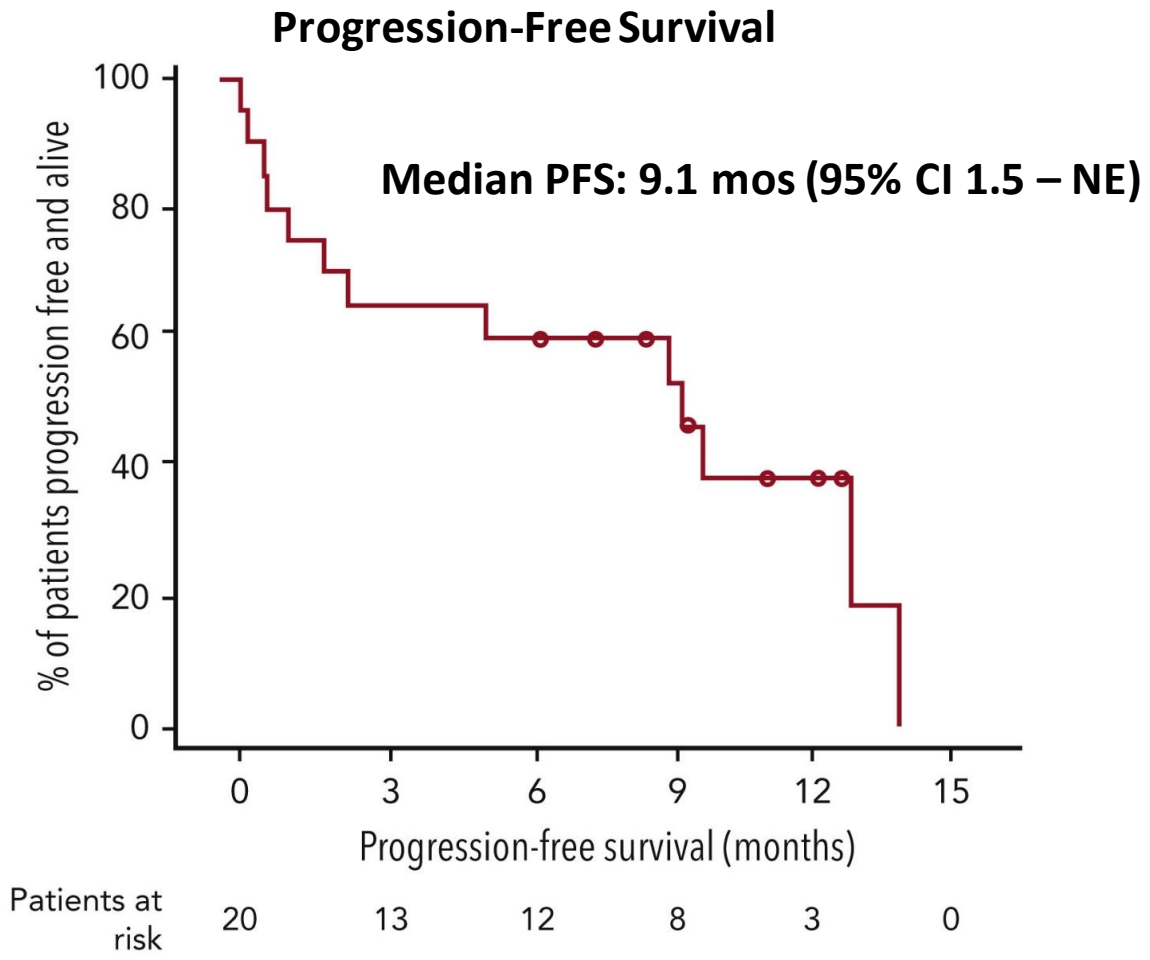
BCMA after BCMA

Ciltacabtagene Autoleucel after BCMA-Targeted Therapy

- ISS stage 3 disease 40%, Extramedullary plasmacytomas 25%, Median prior lines of therapy: 8 (4 – 13), Triple refractory 90%, Refractory to last line 95%
- 8 prior bispecific mAbs, 13 prior ADCs

	N = 20	Bispecific (N = 7)	ADC (N = 13)
ORR	**60%**	**57.1%**	**61.5%**
sCR + CR	**30%**	**14.3%**	**38.5%**
VGPR	**25%**	**28.6%**	**23.1%**
PR	**5%**	**14.3%**	**0%**
Median DoR, mos (95% CI)	**11.5 (7.9 – NE)**	**8.2 (4.4 – NE)**	**11.5 (7.9 – NE)**

Longer time from last BCMA-targeted therapy to Cilta-cel associated with better responses



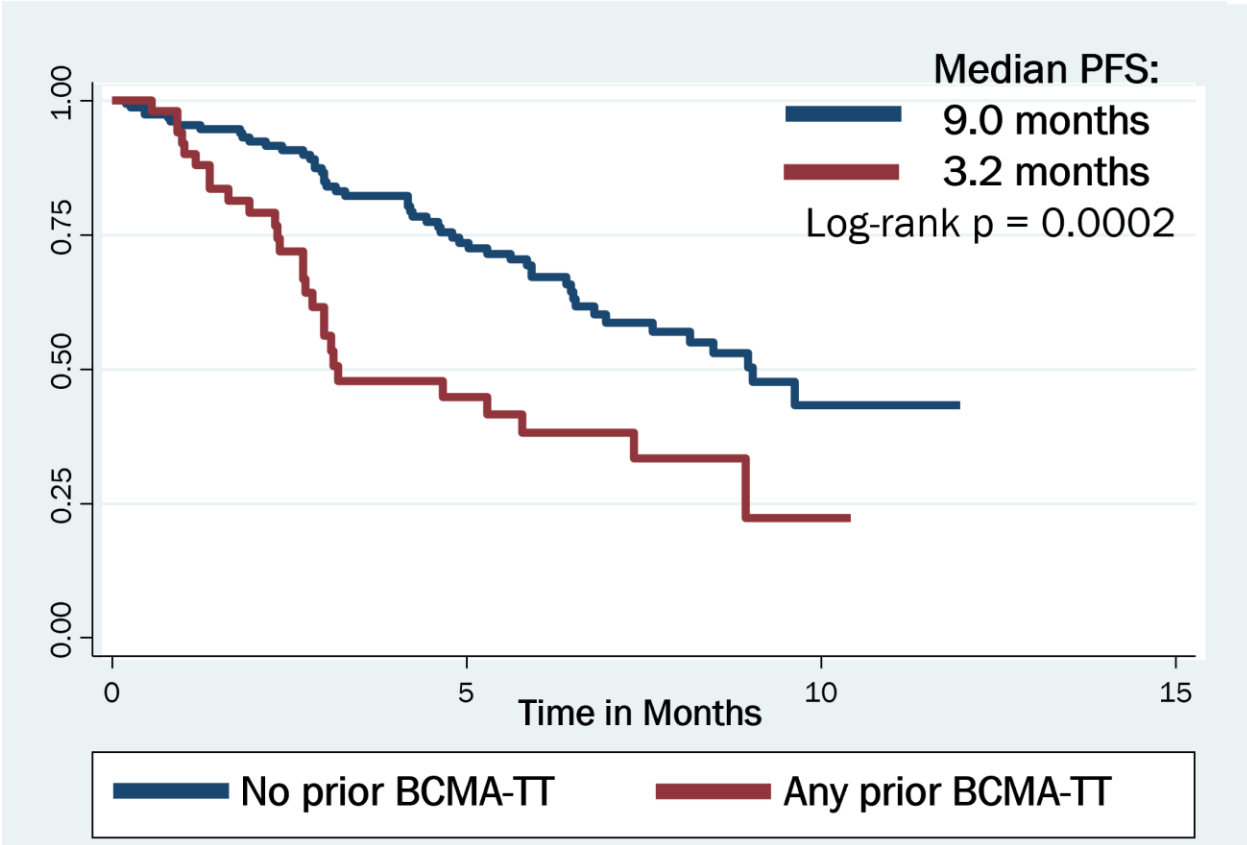
Median PFS for ADC exposed: 9.5 mos; Bispecific mAb exposed: 5.3 mos

Cohen A et al. Blood 2023;141:219-30

Real World Experience with Idecabtagene Vicleucel Post-BCMA- Targeted Therapy

- 11 Academic Centers from the United States
- Key characteristics in the BCMA cohort: 89% R-ISS stage 2 or 3, 36% HR CGs, 50% extramedullary disease, 9 median prior lines of therapy, 90% triple class refractory

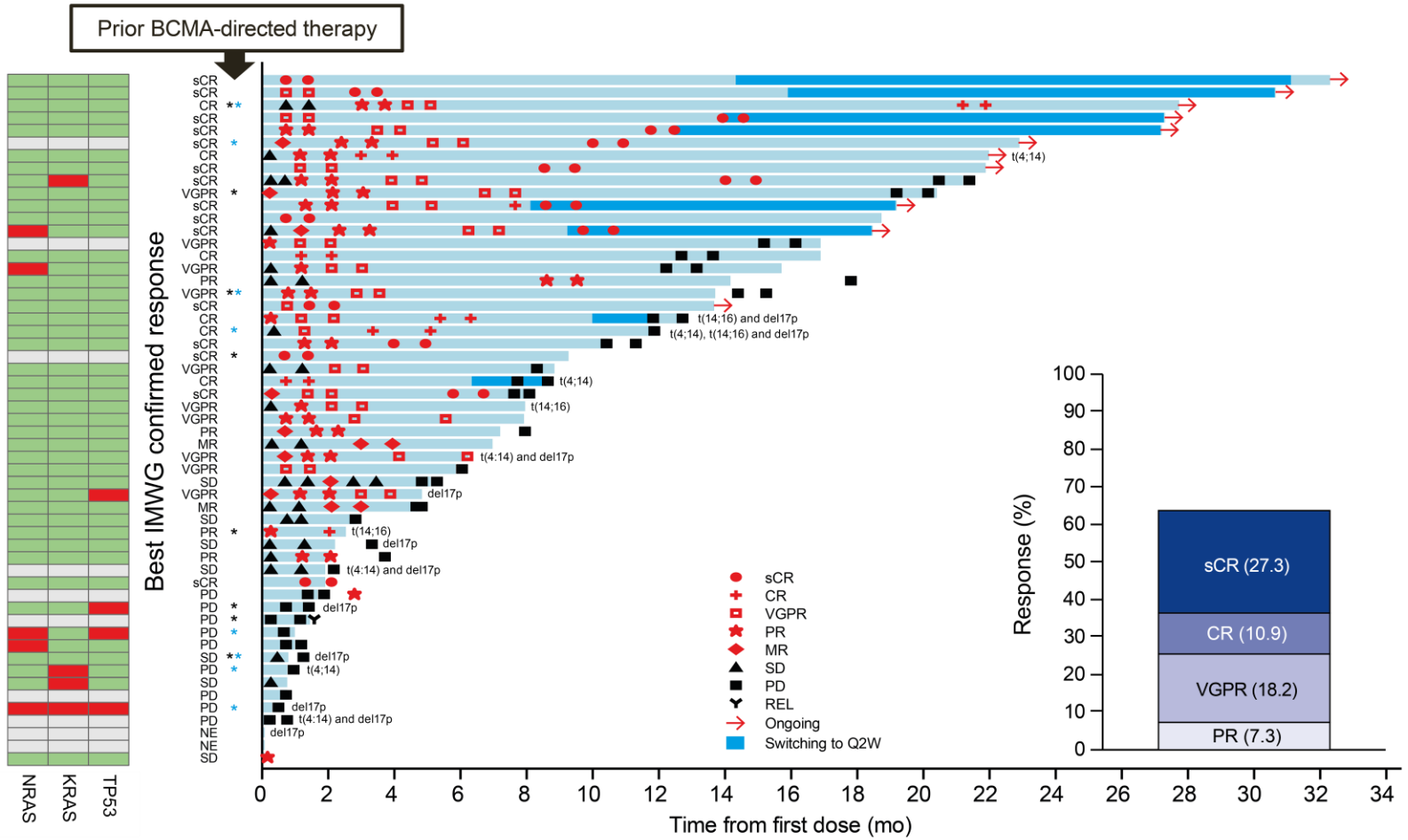
Response Category	Prior BCMA-Targeted Therapy (N = 49)	BCMA-Targeted Therapy Naïve (N = 144)
ORR	74%	88%
≥CR	29%	48%
VGPR	20%	22%
PR	25%	17%
ORR by Prior BCMA-Targeted Therapy		
ADC (N = 36)	68%	
Bispecific mAb (N = 7)	86%	
CAR T (N = 5)	100%	
ORR by Time Since Last BCMA-Targeted Therapy		
>6 months	83% (≥CR 35%)	
< 6 months	60% (≥CR 20%)	



- In multivariate analysis, ECOG PS ≥2, HR CGs and prior BCMA-targeted therapy were associated with inferior PFS and OS

Ferreri C et al. ASH 2022, Abstract 766.

MagnetisMM-1: Elranatamab in Relapsed / Refractory Multiple Myeloma



- Median duration of follow-up was 12.0 months (range 0.3–32.3)
- ORR was 64% (95% CI, 50–75) and CR/sCR rate was 38% (21/55)
- **54% (7/13) of patients with prior BCMA-directed therapy achieved response**
- For responders (N=35), median time to response was 36 days (range 7–262)

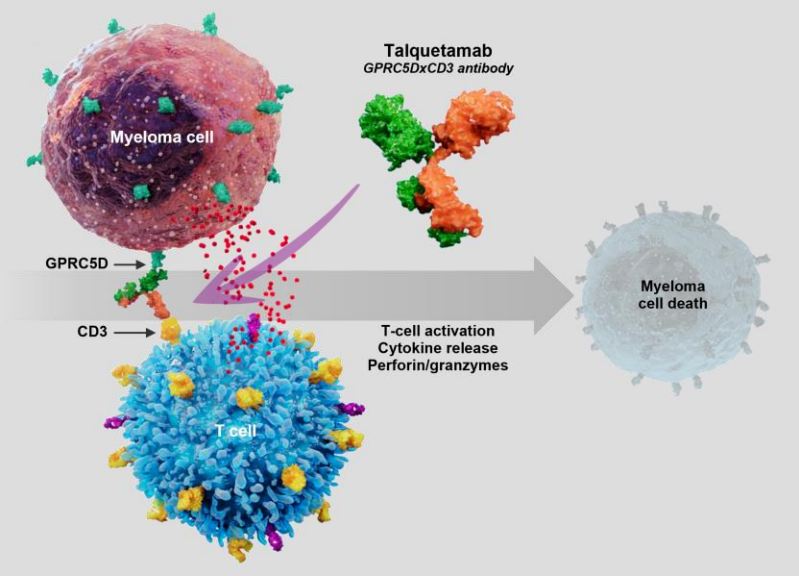
Data cutoff was September 30, 2022. Swimmer plot depicts disease assessments relevant to first response, confirmation of response, deepening of response, and best response. Mutational analysis was filtered on functional mutations annotated in OncoKB and normal allele frequency <5% in paired peripheral blood mononuclear cell samples. * Prior anti-BCMA ADC. * Prior BCMA-targeted CAR-T. ADC=antibody-drug conjugate; BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor T-cell therapy; CR=complete response; IMWG=International Myeloma Working Group; MR=minimal response; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; Q2W=every 2 weeks; REL=relapse; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response.

Raje N et al. ASH 2022, Abstract 158.

GPRC5D-Targeted Therapy

Talquetamab, a GPRC5D-Directed Bispecific Monoclonal Antibody, for Relapsed / Refractory Multiple Myeloma: MonumenTAL-1

- **Key objectives**
- **Describe the efficacy and safety at the RP2Ds**
- **Key eligibility criteria**
- **Adults with measurable MM**
- **Phase 1: Progression on or intolerance to all established therapies, ECOG PS 0–1**
- **Phase 2: ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 antibody, ECOG PS 0–2**



RP2D 0.4 mg/kg QW SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

(Phase 1 [n=21] + **Phase 2 [n=122]**: N=143)

RP2D 0.8 mg/kg Q2W SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

(Phase 1 [n=36] + **Phase 2 [n=109]**: N=145)

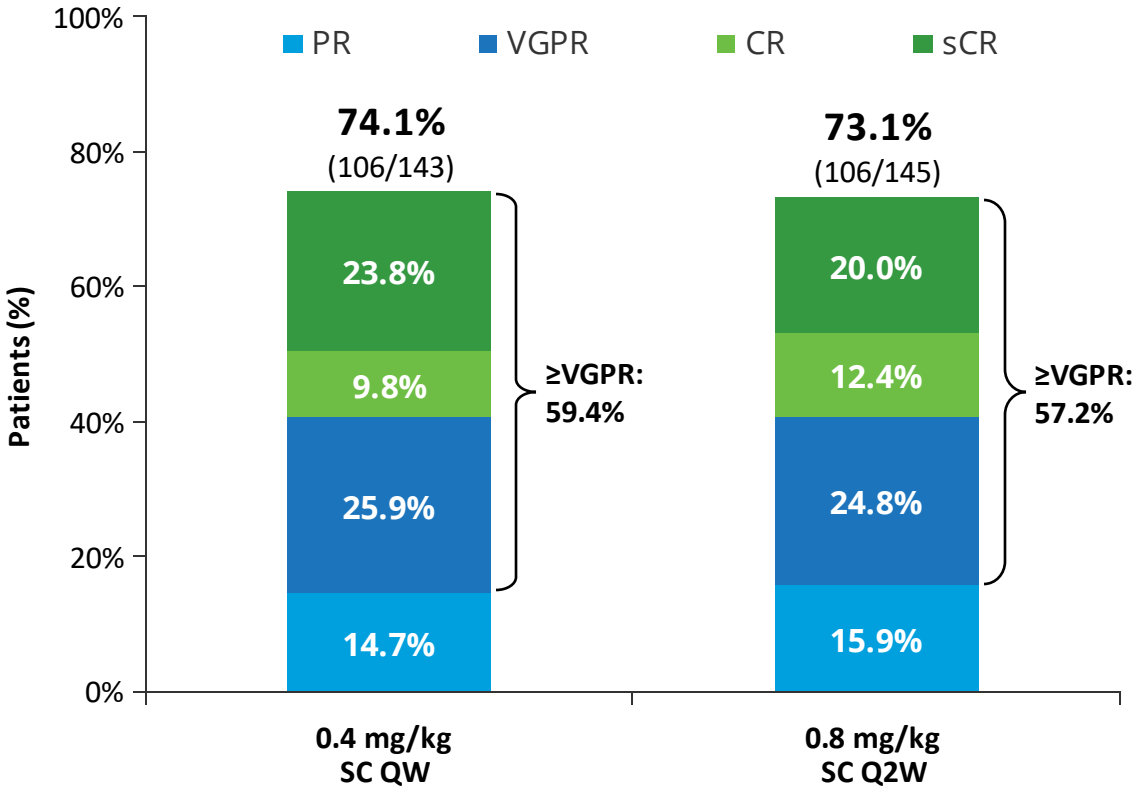
Prior T-cell redirection (QW and Q2W)
Previously exposed to T-cell redirection therapies
Dosed with either 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC

(Phase 1 [n=17] + **Phase 2 [n=34]**: N=51)

Chari A et al. ASH 2022, Abstract 157.

Talquetamab for Relapsed / Refractory Multiple Myeloma: MonumenTAL-1 Key Phase II Efficacy Results

Key eligibility criteria (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%



- **Median Time to Best Response**
  - **0.4 mg/kg QW: 2.2 months**
  - **0.8 mg/kg Q2W: 2.7 months**
- **Median Duration of Response**
  - **0.4 mg/kg QW: 9.3 months**
  - **0.8 mg/kg Q2W: 13.0 months**
- **Median Progression-Free Survival**
  - **0.4 mg/kg QW: 7.5 months**
  - **0.8 mg/kg Q2W: 11.9 months**

Chari A et al. ASH 2022, Abstract 157.

Talquetamab for Relapsed / Refractory Multiple Myeloma: MonumenTAL-1 Key Phase II Safety Results

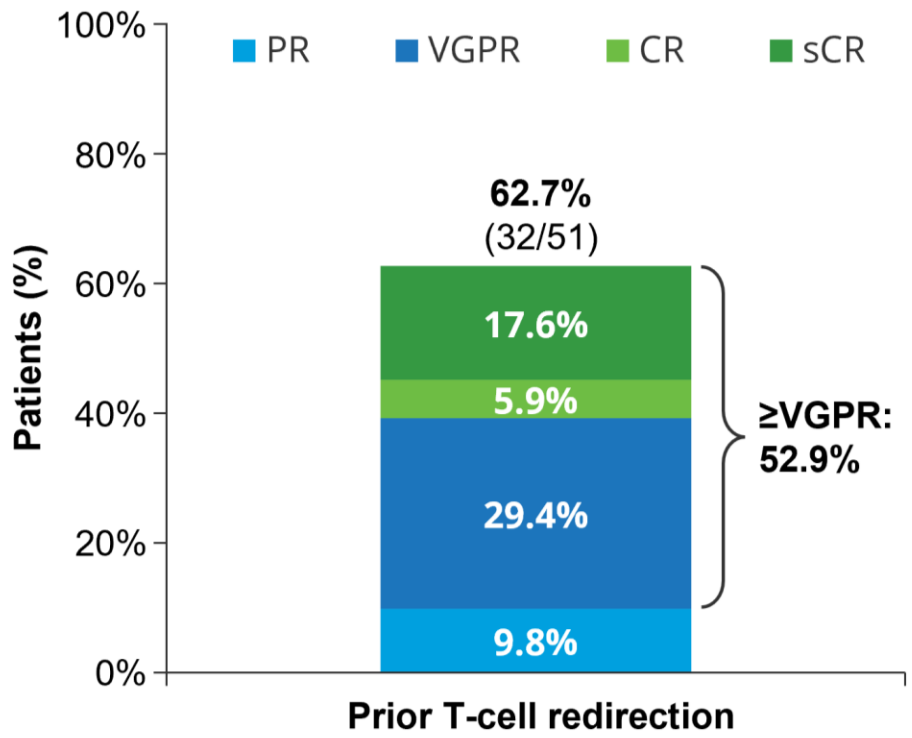
	0.4 mg/kg QW		0.8 mg/kg Q2W	
	All Grades	≥Grade 3	All Grades	≥Grade 3
Neutropenia	34.3%	30.8%	28.3%	22.1%
Thrombocytopenia	27.3%	20.3%	26.9%	16.6%
Infections*	57.3%	16.8%	50.3%	11.7%
CRS	79.0%	2.1%	72.4%	0.7%
Neurotoxicity	10.7%	1.6%	10.1%	1.8%
Skin-Related AEs	55.9%	0.0%	67.6%	0.7%
Nail-Related AEs	51.7%	0.0%	43.4%	0.0%
Dysgeusia	48.3%	NA	46.2%	NA
Dry Mouth	25.2%	0.0%	36.6%	0.0%
Dysphagia	23.8%	0.0%	22.8%	2.1%
Loss of appetite	17.5%	1.4%	20.0%	1.4%
Weight loss	39.9%	2.1%	32.4%	1.4%

*Opportunistic infections seen in 3.5% and 2.8%, respectively.

Chari A et al. ASH 2022, Abstract 157.

Talquetamab after Exposure to T cell Redirecting Therapy

- Median prior lines of therapy: 6 (3 – 15)
- 70.6% (N = 36) prior CAR T cell therapy, 35.3% (N = 18) prior bispecific antibody therapy (3 patients received both)



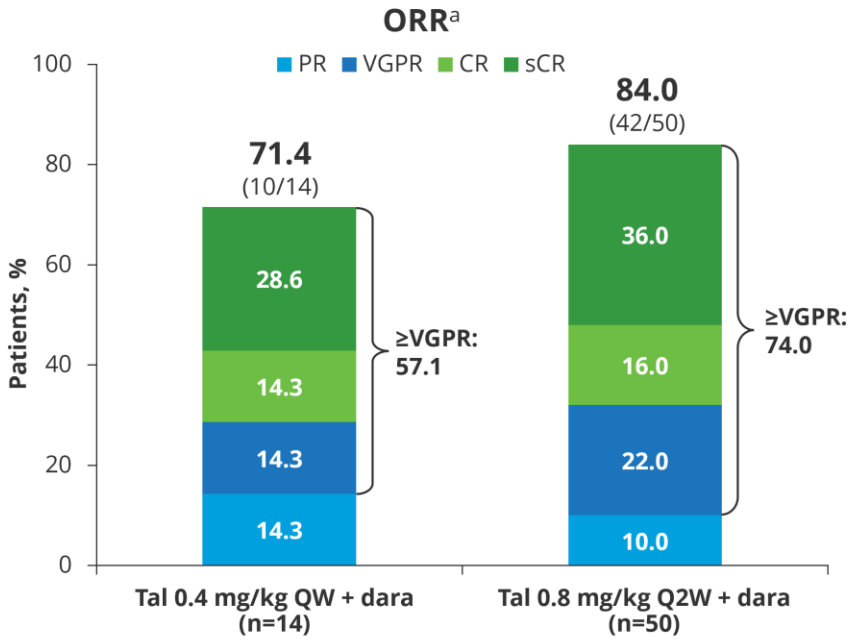
- **ORR with prior CAR T: 70.6%**
- **ORR with prior bispecific antibodies: 44.4%**
- **Median DoR: 12.7 months (range 3.7 months - not reached)**
  - **Median follow-up: 11.8 months (1.0 – 25.4 months)**
  - **56.3% of patients censored**

Chari A et al. ASH 2022, Abstract 157.

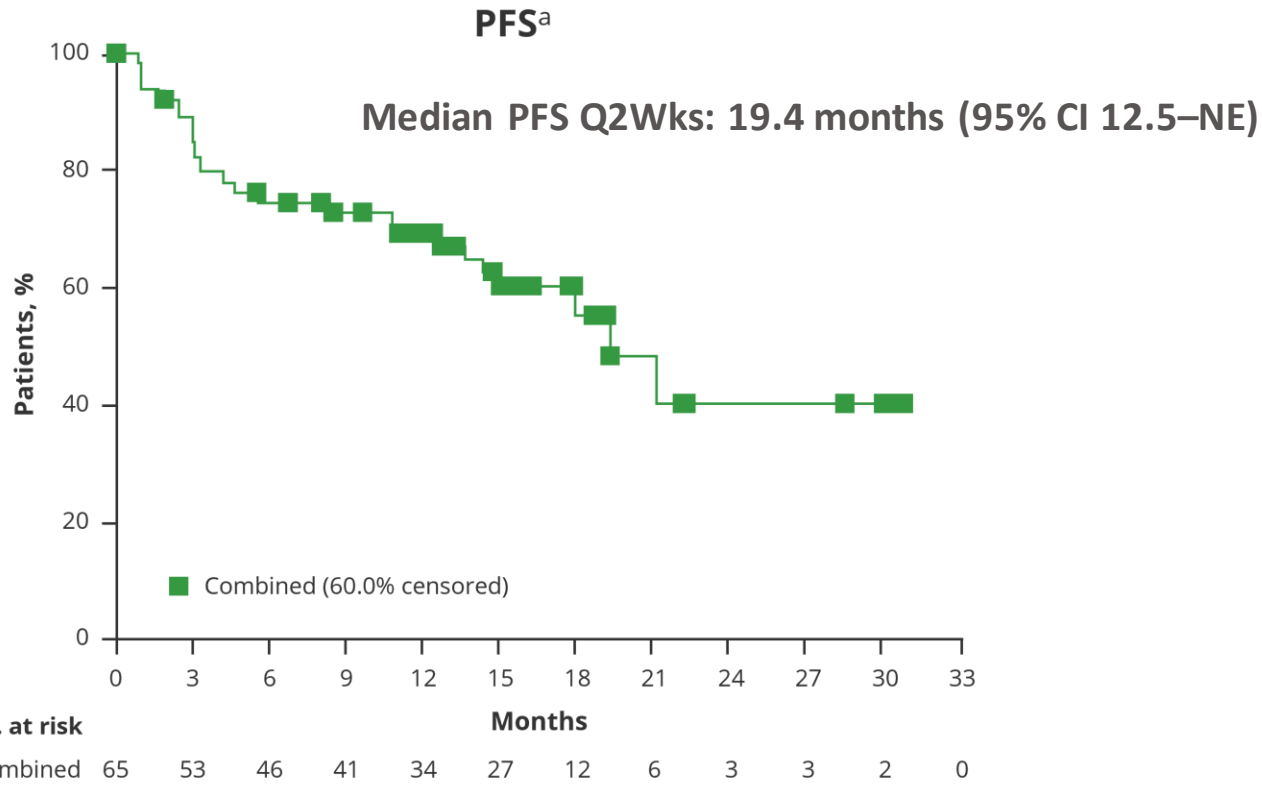
Phase I Study of Talquetamab + Daratumumab in RRMM (TRIMM-2)

Baseline Characteristics Q2Wk Cohort

- **Median age: 61 (37 – 81)**
- **EMM: 25.5%**
- **HRCGs: 21.2%**
- **Median prior lines of therapy: 5 (2 – 14)**
- **52.9% prior BCMA-targeted therapy**
- **60.8% triple refractory**
- **78.4% CD38 mAb refractory**
-



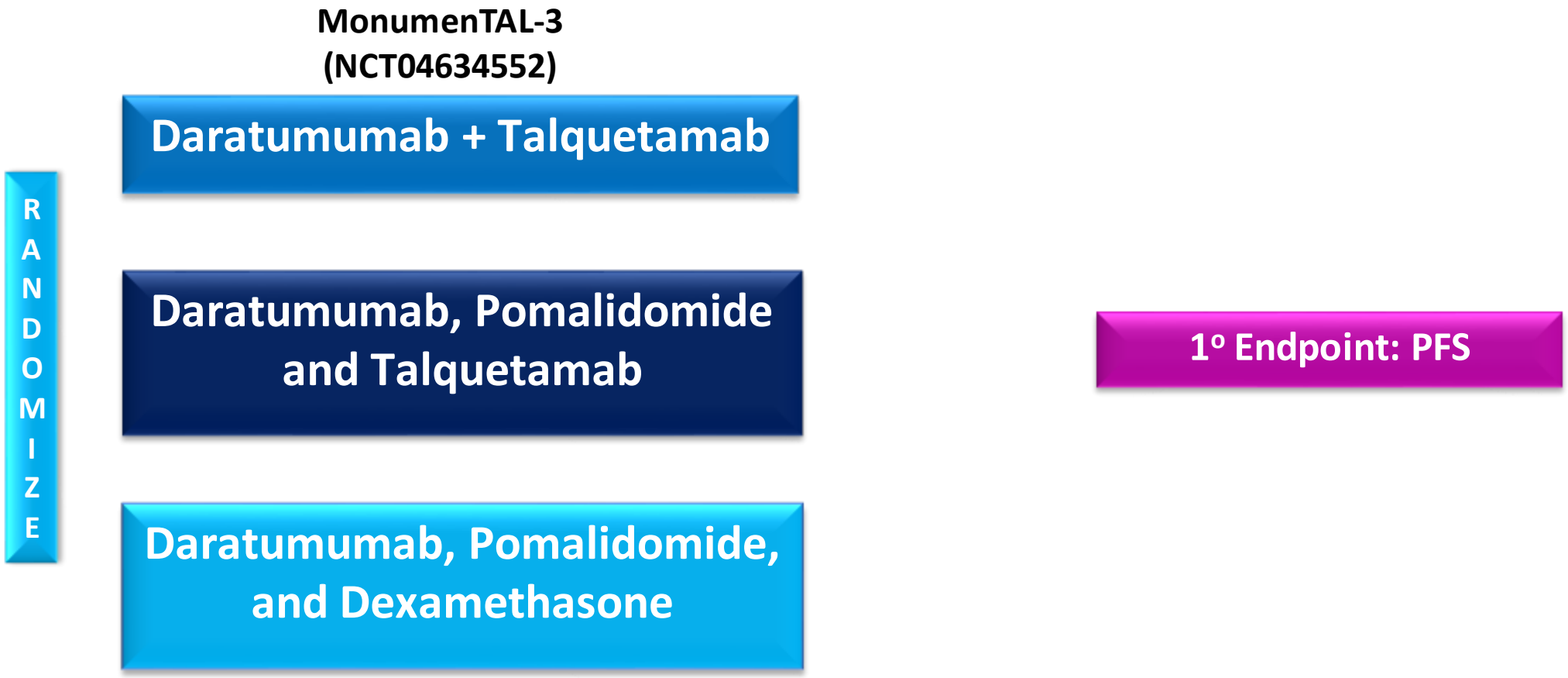
ORR in CD38 mAB Refractory Disease: 80%; ORR in T Cell Redirection Therapy Exposed: 78.9%



- All infections: 72.5% (25.5% grade 3/4)
  - 1 treatment-related death due to pneumonia
- 10.8% had opportunistic infections and 3.1% had cytomegalovirus reactivation
- IgG <500 mg/dL: 35.4% at baseline and 86.2% post-baseline; of these, 33.8% received IVIG

Dholaria B, et al. ASCO 2023.

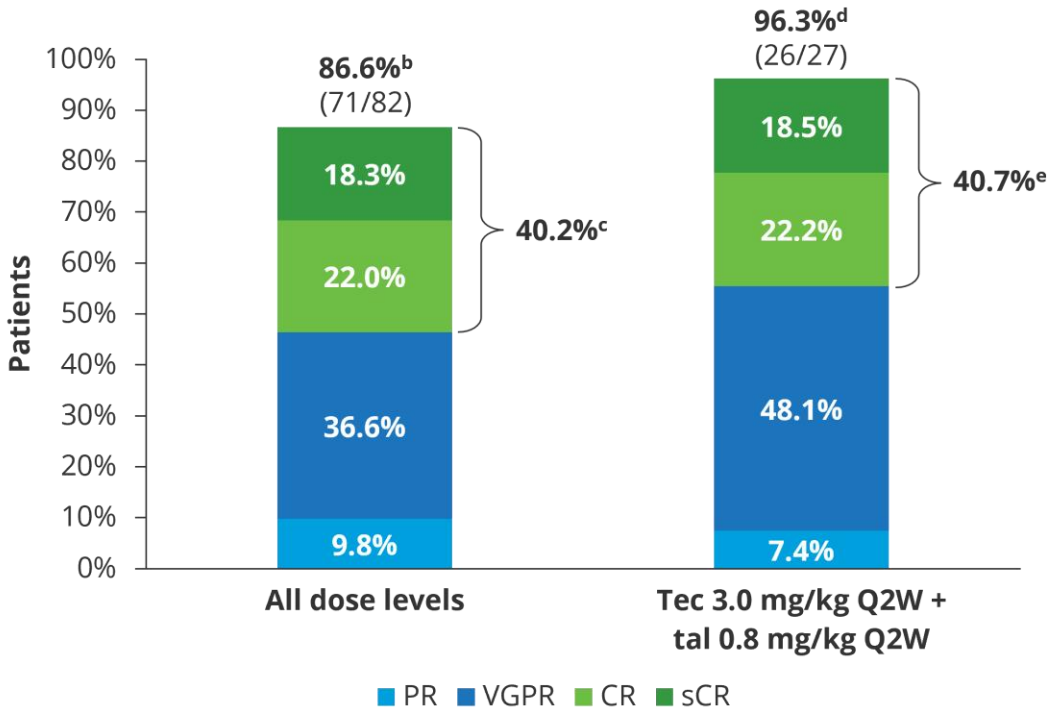
Bringing it Forward: MonumenTAL-3



Phase I Study of Talquetamab + Teclistamab in RRMM (RedirecTT-1)

Tec 3.0 mg/kg + Tal 0.8 mg/kg Q8Wks
Baseline Characteristics

- **Median age: 65 (41 – 80)**
- **EMM: 32.4%**
- **HRCGs: 33.3%**
- **Median prior lines of therapy: 4 (2 – 10)**
- **76.5% triple refractory**
- **88.2% refractory to last line of therapy**



	All dose levels (N=93)	Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34)
Median follow-up, months (range)	13.4 (0.3–25.6)	8.1 (0.7–15.0)
Median DOR, months (95% CI)	NE (NE–NE)	NE (NE–NE)
Median time to first response, months (range)	1.97 (0–7.7)	1.48 (0–4.0)
Median time to best response, months (range)	3.98 (1.1–15.7)	3.22 (1.4–10.7)
Median PFS, months (95% CI)	20.9 (13.0–NE)	NE (9.9–NE)
9-month PFS rate (95% CI)	70.1 (58.0–79.4)	77.1 (50.8–90.5)

- Infections (all cohorts): 83.9% (52.7% grade 3/4)
- Death due to drug-related TEAE: 6.5%
- 81.7% with ≥1 postbaseline IgG value <400 mg/dL or hypogammaglobulinemia TEAE (all grade 1 or 2)

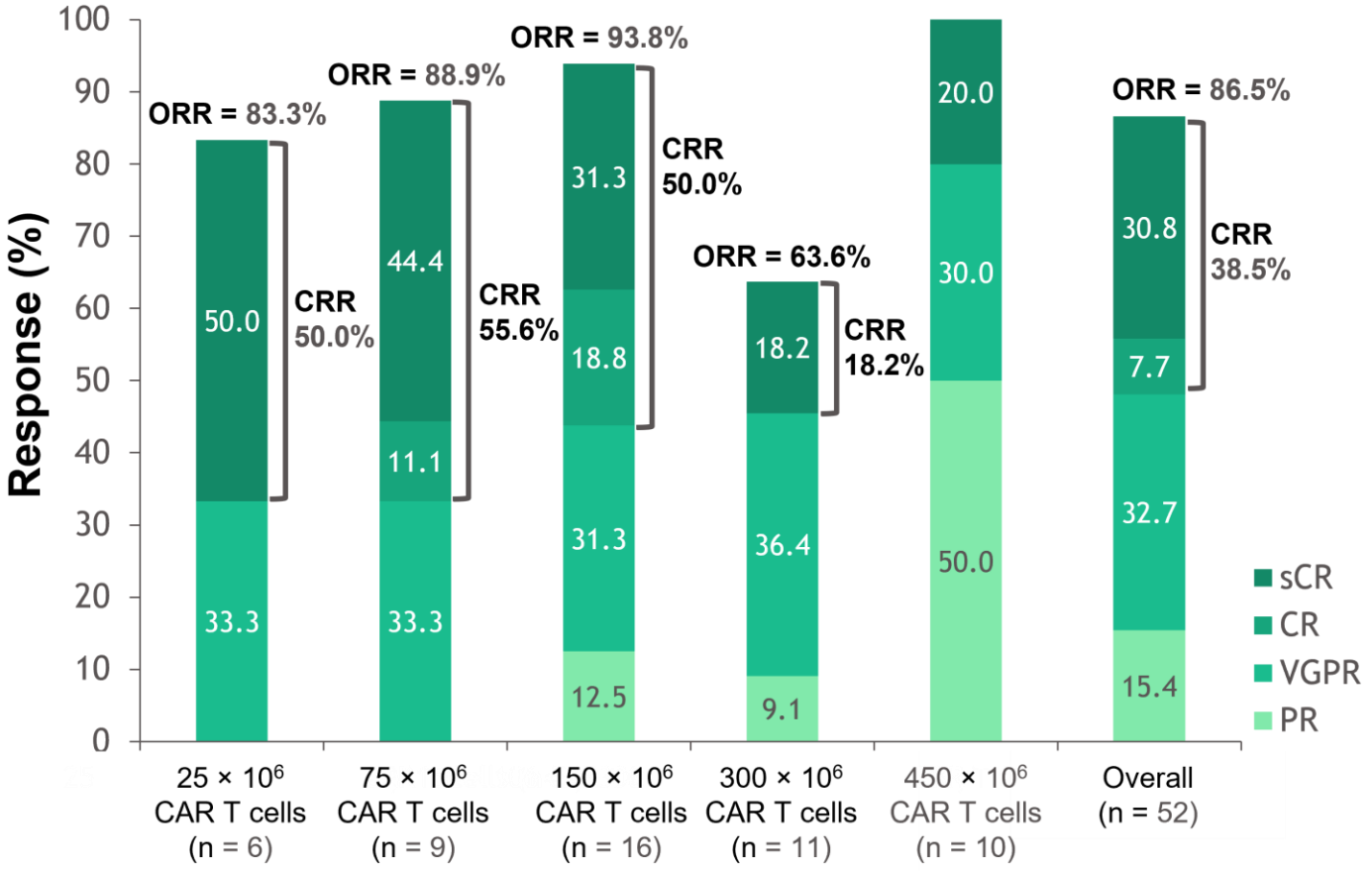
Cohen Y, et al. ASCO 2023.

Phase I Study of 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

Dose Escalation: 25 (N=6) → 75 (N=9) → 150 (N=12) → 300 (N=6)→ 450 x 10^6 (N=3) CAR T cells
Dose Escalation: 150 (N=12), 300 (N=11), 450 (N=8) x 10^6 CAR T cells

Baseline Characteristics

- **Median age: 63 (39 – 80)**
- **EMM: 41.8%**
- **HRCGs: 47.8%**
- **Median prior lines of therapy: 4 (3 – 13)**
- **44.8% prior BCMA-targeted therapy**
- **77.6% triple refractory**



ORR in BCMA-targeted therapy exposed pts: 76.0%

Bal S, et al. EHA 2023.

Phase I Study of BMS-986393 (CC-95266) for Relapsed/Refractory Multiple Myeloma: Safety

Adverse Event		
	All Grades	≥Grade 3
Neutropenia	64.2%	59.7%
Thrombocytopenia	46.3%	29.9%
Infections	35.8%	14.9%
CRS*	86.6%	4.5%
Skin-Related AEs	20.9%	0.0%
Nail-Related AEs	9.0%	0.0%
Dysgeusia	17.9%	NA
Dysphagia	1.5%	0.0%
Neurotoxicity†		
ICANS	10.4%	3.0%
Dizziness	10.4%	1.5%
Headache	10.4%	0.0%
Ataxia	3.0%	0.0%
Neurotoxicity	3.0%	0.0%
Gait Disturbance	1.5%	0.0%
Dysarthria	1.5%	0.0%
Paresthesias	0.0%	0.0%

*1 grade 5 CRS event, MAS / HLH in 3 pts treated at 300 – 450 x 106
† 1 cerebellar toxicity, 1 ICANS

Bal S, et al. EHA 2023.

Conclusions

- BCMA-targeted T cell redirecting therapies are SoC in triple class refractory multiple myeloma
  - Idecabtagene vicleucel, ciltacabtagene autoleucel, teclistamab
  - Access impacted by requirement for ≥4 prior lines of therapy, operational logistics, manufacturing / apheresis and cell processing lab bandwidth / inpt bed availability constraints
- BCMA-targeted CAR T cell therapy has outperformed SoC regimens in early relapse
  - Potential CAR T cell approval in earlier lines of therapy
  - Access issues will become more significant as the eligible patient pool grows
- Optimal sequencing of BCMA-targeted therapy remains to be seen
  - Early evidence supports CAR T → bispecific mAb
- As BCMA-targeted therapy moves to earlier lines of therapy, we will need to be mindful of the risks
  - CAR T: CRS, neurotoxicity
  - Bispecifics: infection
- Talquetamab is a new SoC for RRMM
  - Access impacted by requirement for ≥4 prior lines of therapy, operational logistics, inpt bed availability
  - Optimal sequencing with BCMA-targeted therapy remains to be seen
    - Post-BCMA-targeted therapy relapse an obvious place to position this agent
  - Randomized studies of Tal-based combinations in early relapse underway and planned
  - Other GPRC5D-targeted therapies in development with promising early results

Questions?

- Thanks to our patients, investigators and other members of the research team at Levine Cancer Institute