ADC, TCE e CAR-T: sequencing e re-treatment

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Disclosures, Mattia D'Agostino

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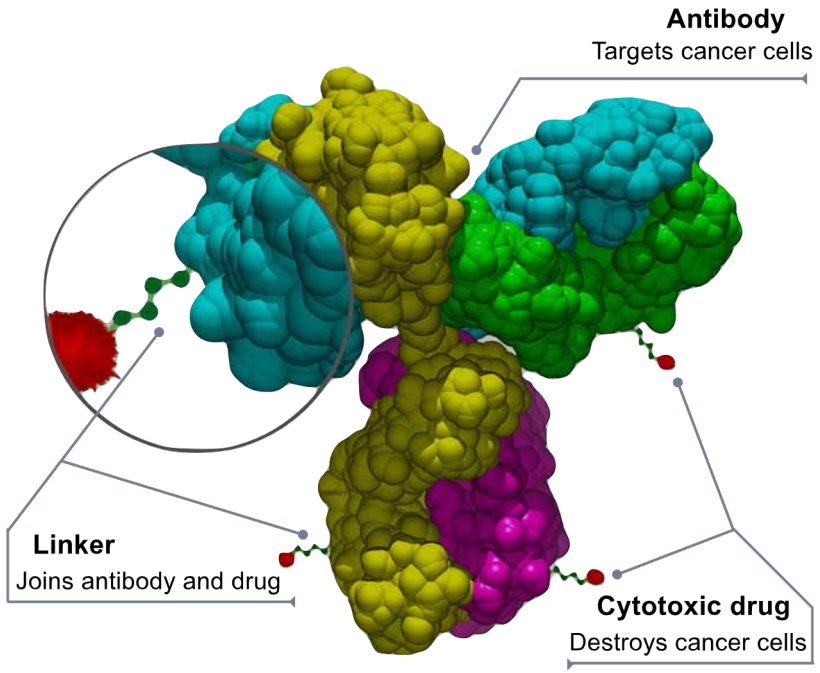
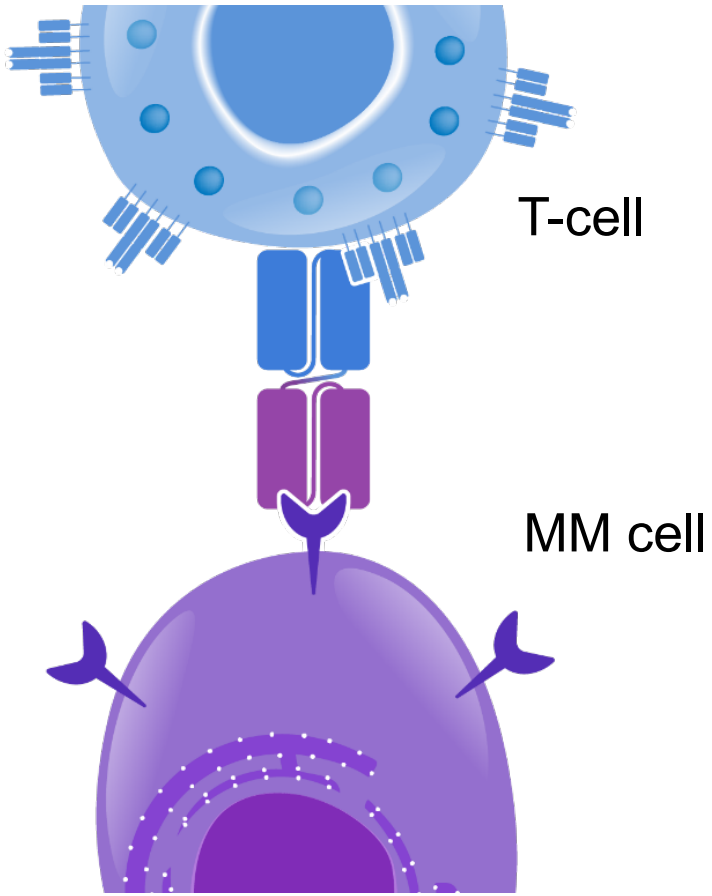
Scientific Advisory Board	Sanofi, GSK

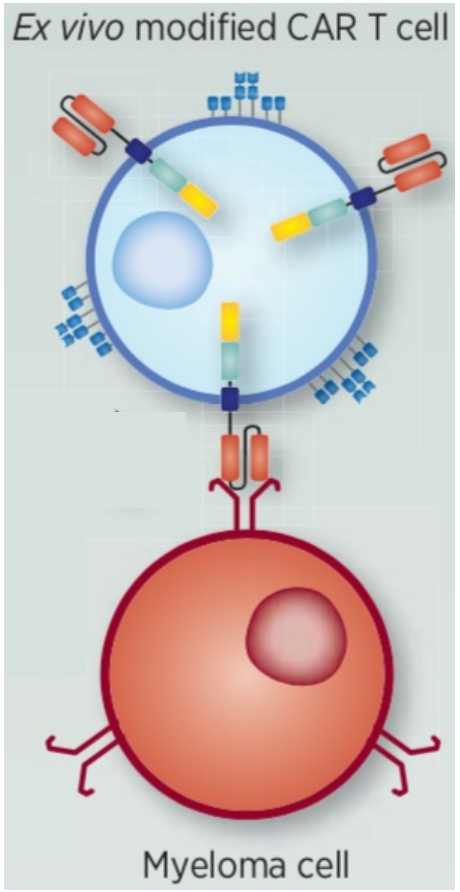
ADC[1]



TCE[2]



CAR-T[3]



Abbreviations. ADC: antibody drug conjugate; TCE: T-cell engager; CAR: chimeric antigen receptor

1. Anderson et al, AACR 2016. 2. Yuraszeck T et al, Clin Pharmacol Ther 2017 3. Cohen et al Clin Can Res 2019.

EMA approvals

ADC

- **Belantamab mafodotin (2020)**

≥ 4 prior therapies
triple-refractory (PI, IMiDs, anti-CD38 mAb)
progression on last line

TCE

- **Teclistamab (2022)**

≥ 3 prior therapies
triple-exposed (PI, IMiDs, anti-CD38 mAb)
progression on last line

CAR-T

- **Idecabtagene vicleucel (2021)**
- **Ciltacabtagene autoleucel (2022)**

≥ 3 prior therapies
triple-exposed (PI, IMiDs, anti-CD38 mAb)
progression on last line

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triple-exposed (PI, IMiDs, anti-CD38 mAb)
progression on last line

Trials leading to registration of these agents did not include patients with prior anti-BCMA treatment

Abbreviations. ADC: antibody drug conjugate; TCE: T-cell engager; CAR: chimeric antigen receptor; PI: proteasome inhibitors; IMiDs: immunomodulatory drugs; mAb: monoclonal antibody

EMA approvals

ADC

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Ongoing studies in combination and in earlier lines!

Abbreviations. PI: proteasome inhibitors; IMiDs: immunomodulatory drugs; mAb: monoclonal antibody

ADC, TCE, CAR T-cell: how and when to pick the right one?

	ADC[1]	TCE[3]	CAR T[5,6]
Response	ORR: 32% CR: 7%	ORR: 43-79% CR: 21-43%	ORR: 73-97% CR: 33-83%
Safety	Kerathopathy, change in BCVA, thrombocytopenia	CRS, ICANS, cytopenia, and infections	CRS, ICANS/late neurotox, cytopenia, and infections
Dosing	Q3W-Q4W until PD	Q1W/Q2W/Q4W until PD[4]	Single dose
Accessibility	Off the shelf[2]	Off the shelf	Turnaround time
Administration	Outpatient[2,7] Available in community setting[7]	Inpatient for first doses/outpatient[7] Available in community setting[7]	Inpatient[7] Available in community setting[7]

Courtesy of doctor Mina

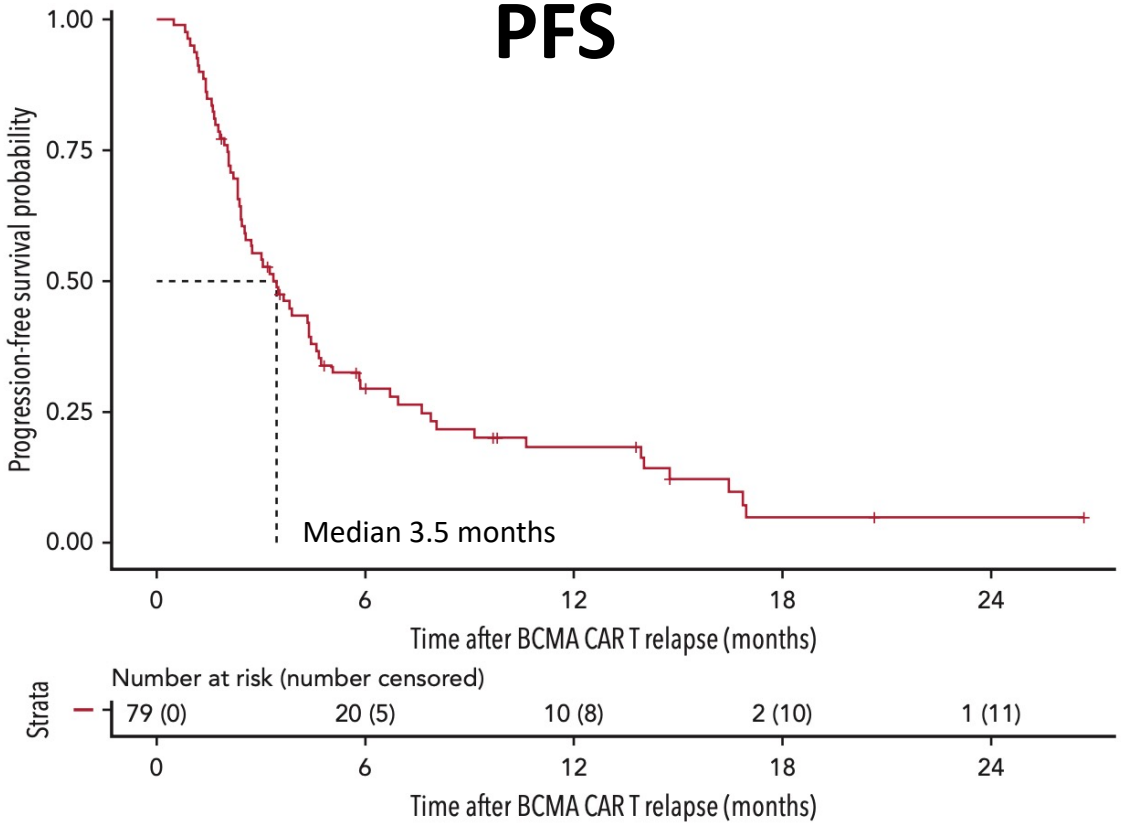
1. Lonial S, et al. Cancer. 2021;127:4198-212. 2. Becnel MR, et al. Ther Adv Hematol. 2020;11:2040620720979813. 3. Mailankody, S. N Engl J Med. 2022;387:558-61. 4. Minnema MC, et al. Oral presentation at EHA 2022; EHA Library;357046;abstract S182. 5. Munshi NC, et al. N Engl J Med. 2021;384:705-16. 6. Berdeja JG, et al. Lancet. 2021;398:314-24. 7. Mina R personal opinion on the future direction therapy.

Outcome of patients relapsed after anti-BCMA CAR-T cells

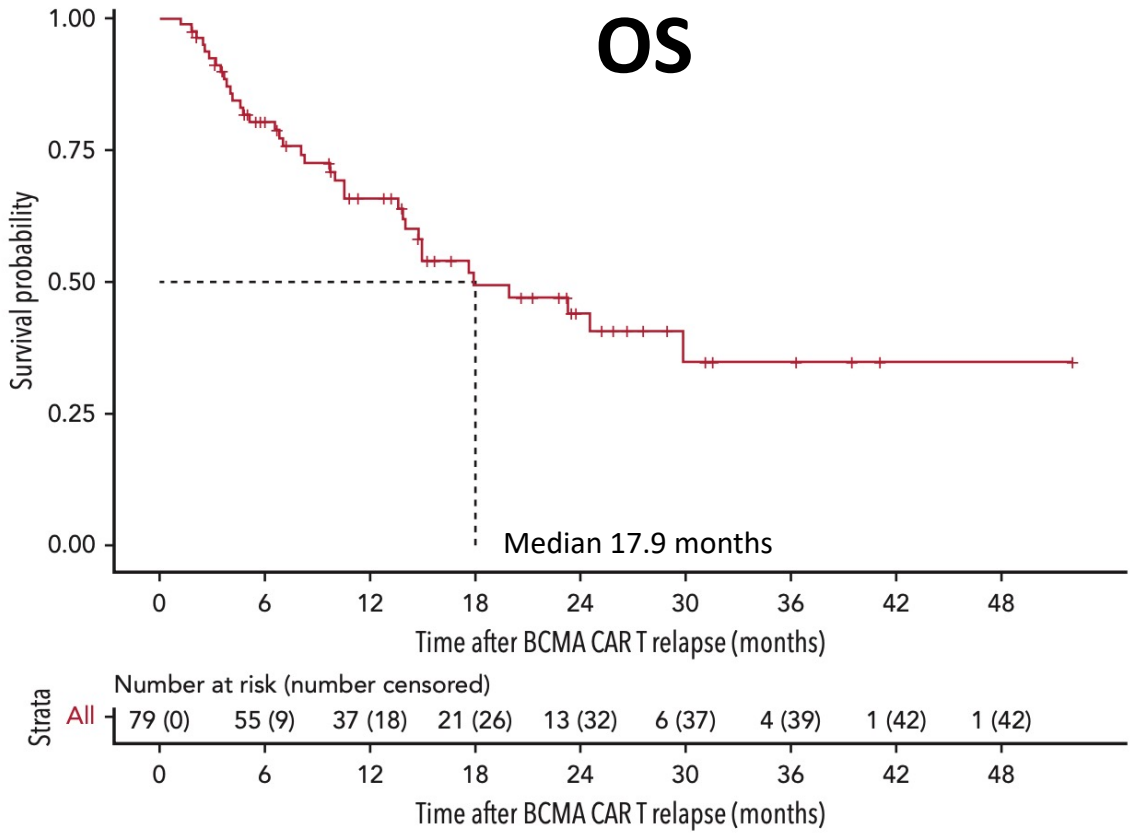
- 79 RRMM relapsed after an autologous BCMA-directed CAR T therapy in clinical trials (Mount Sinai Hospital and MSKCC)

- Triple-class refractory: 83.5%; Penta-class refractory: 38.0%

PFS



OS



Van Oekelen O et al Blood 2023

Treatment landscape in relapsed patients after anti-BCMA CAR-T cells

Treatment group	First line of salvage treatment				All lines of salvage treatment			
	N	% used	N ≥ PR *ORR*	N ≥ VGPR %	N	% used	N ≥ PR *ORR*	N ≥ VGPR %
Allo-SCT	0	0.0%	0/0 N/A	0/0 N/A	7	3.0%	4/4 100.0%	2/4 50.0%
Auto-SCT	3	3.8%	1/3 33.3%	1/3 33.3%	14	5.9%	10/14 71.4%	7/14< 50.0%
BCMA ADC	1	1.3%	0/1 0.0%	0/1 0.0%	9	3.8%	2/8 25.0%	2/8 25.0%
Bispecific trial	11	13.9%	7/10 70.0%	5/10 50.0%	32	13.5%	17/29 58.6%	12/29 41.4%
BCMA-directed bispecific trial	2	2.5%	1 out of 2 50.0%	0 out of 2 0.0%	9	3.8%	4 out of 9 44.4%	3 out of 9 33.3%
Non-BCMA–directed bispecific trial	9	11.4%	6 out of 8 75.0%	5 out of 8 62.5%	23	9.7%	13 out of 20 65.0%	9 out of 20 45.0%
CAR T trial	2	2.5%	2 out of 2 100.0%	1 out of 2 50.0%	6	2.5%	5 out of 6 83.3%	3 out of 6 50.0%
Chemotherapy with or without stem cell support	20	25.3%	11 out of 19 57.9%	4 out of 19 21.1%	53	22.4%	29 out of 51 56.9%	12 out of 51 23.5%
Doublet/triplet/ quadruplet combination of approved agents	23	29.1%	7 out of 22 31.8%	2 out of 22 9.1%	56	23.6%	15 out of 53 28.3%	4 out of 53 7.5%
Selinexor-based therapy	5	6.3%	2 out of 5 40.0%	2 out of 5 40.0%	15	6.3%	3 out of 14 21.4%	3 out of 14 21.4%
Venetoclax-based therapy	3	3.8%	2 out of 3 66.7%	1 out of 3 33.3%	14	5.9%	5 out of 14 35.7%	2 out of 14 14.3%
Other combinations (including MAPKi, checkpoint inhibitor or other trial)	11	13.9%	1 out of 11 9.1%	0 out of 11 0.0%	31	13.1%	12 out of 31 38.7%	1 out of 31 3.2%
All treatment groups	79	100.0%	33 out of 76 43.4%	16 out of 76 21.1%	237	100.0%	101 out of 224 45.1%	48 out of 224 21.4%
	Total N = 79		Total N = 76		Total N = 237		Total N = 224	

PR, partial response; VGPR, very good partial response.

Van Oekelen O et al Blood 2023

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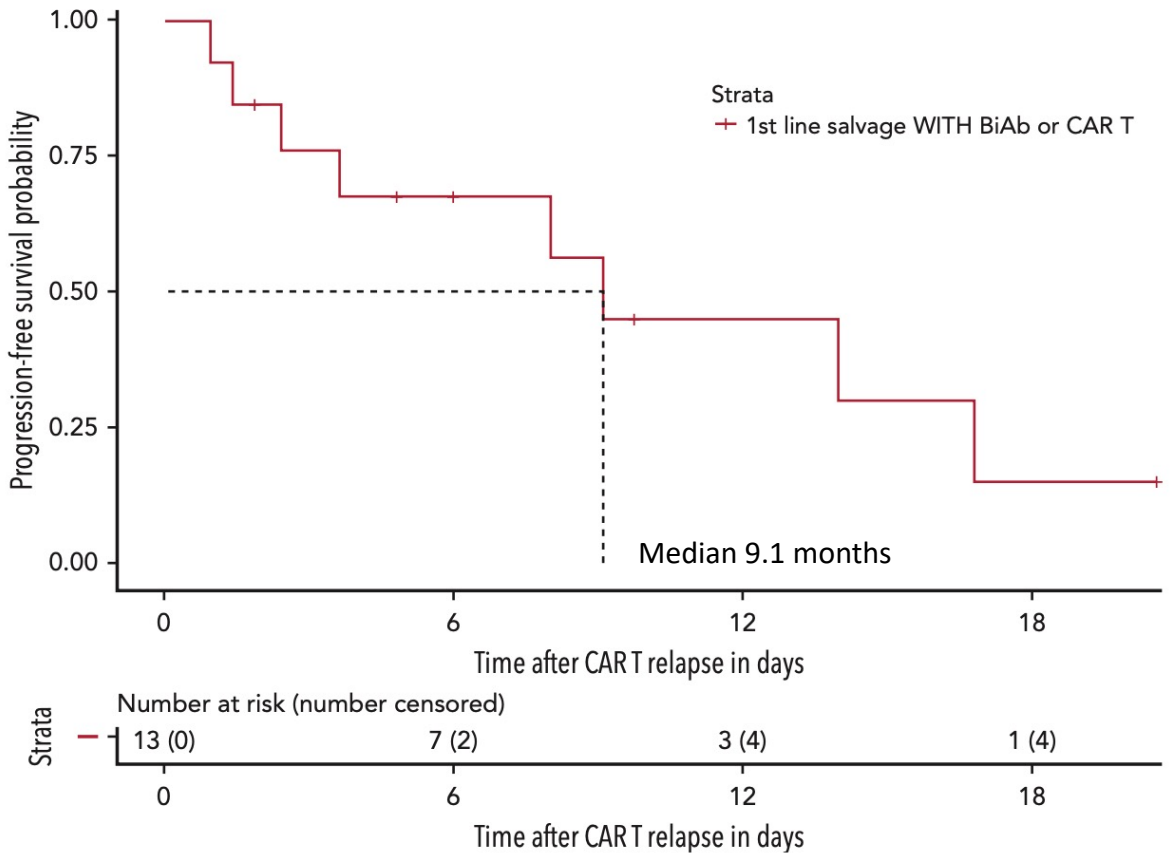
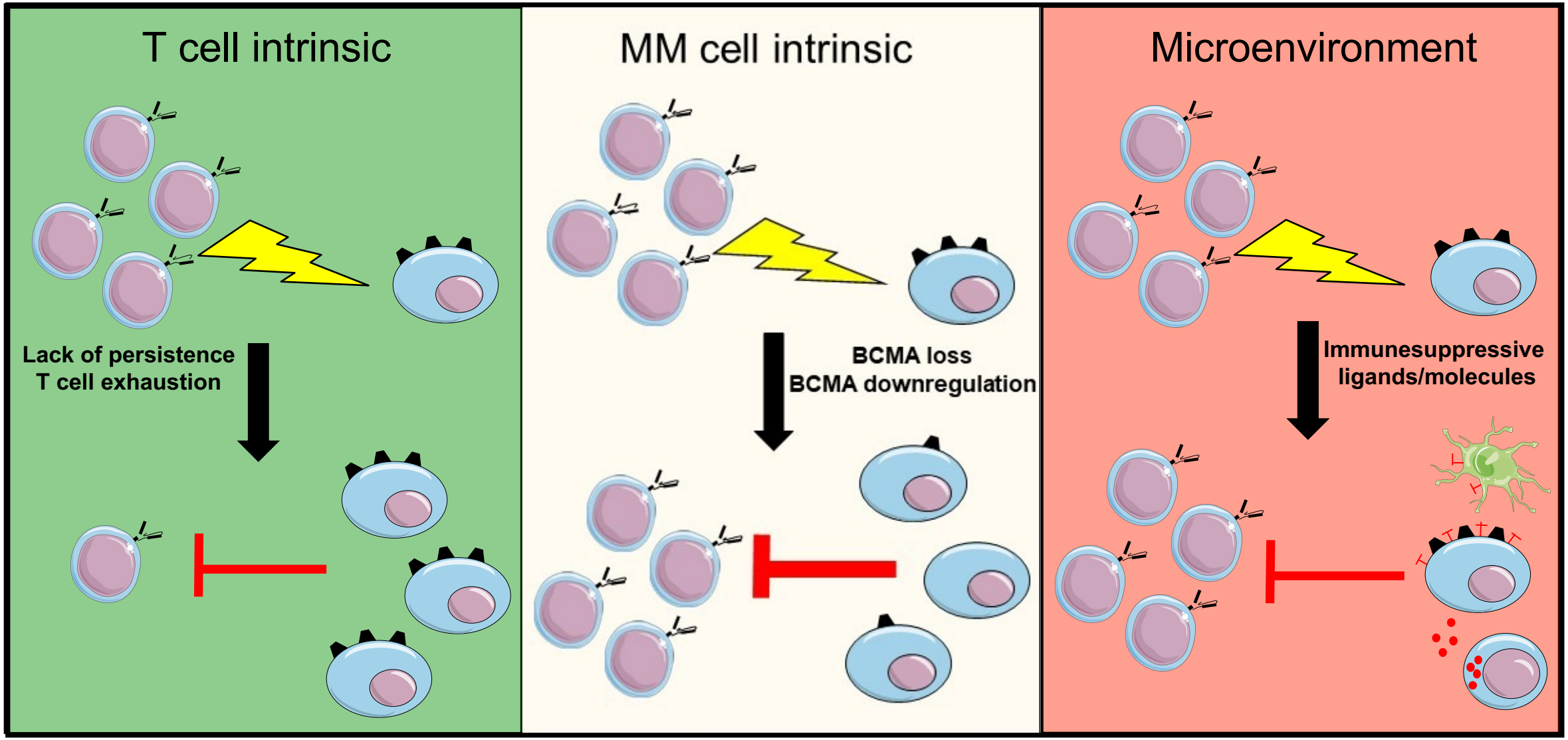


11/13 patients received Non-BCMA directed treatment

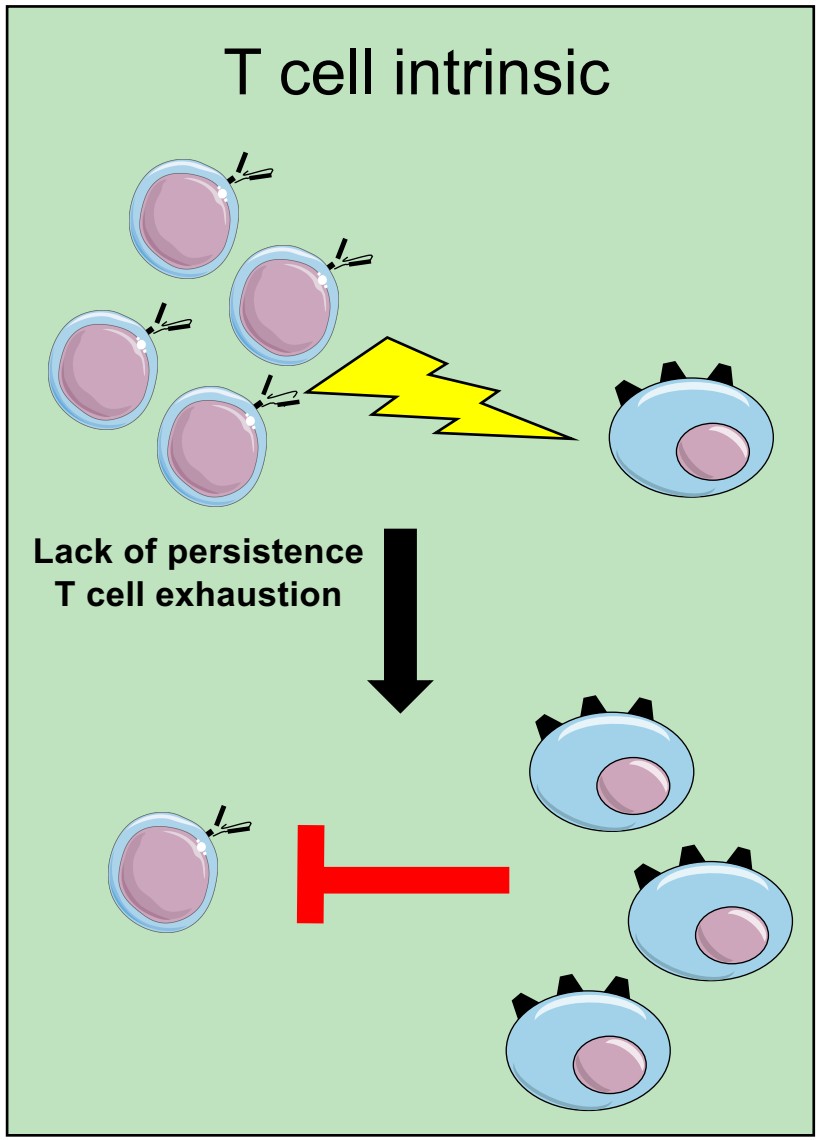
Van Oekelen O et al Blood 2023

Mechanisms of resistance to anti-BCMA immunotherapy



M D'Agostino, N Raje. Leukemia 34 (1), 21-34, 2020

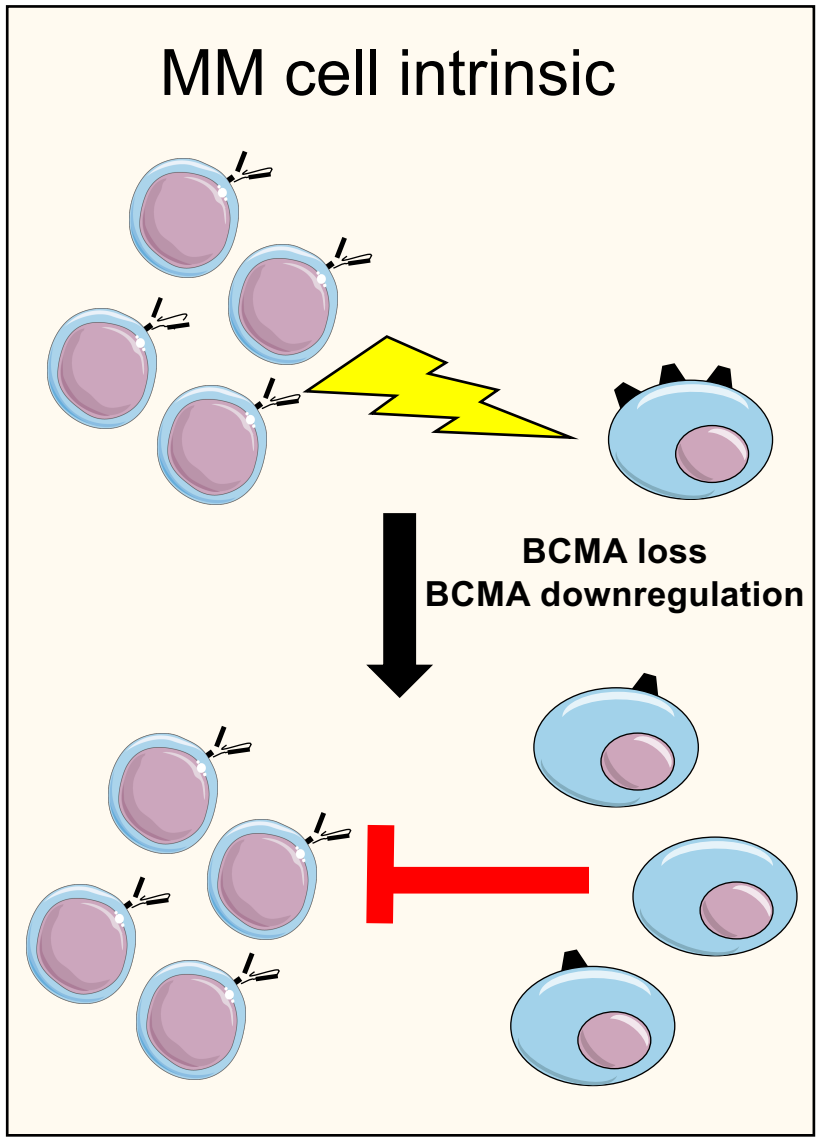
Mechanisms of resistance to anti-BCMA immunotherapy



- BCMA^{+} relapses are frequently reported after anti-BCMA T cell therapy suggesting a loss of effective therapeutic pressure towards MM cells
- In CAR T cell field *in vivo* expansion and persistence of infused CAR T are important factors for a strong and long-lasting anti-tumor effect
- Having fitter T cells can possibly limit BCMA+ relapses
- BCMA+ relapses represent an opportunity for retreatment with BCMA-directed agents

M D'Agostino, N Raje, Leukemia 34 (1), 21-34, 2020

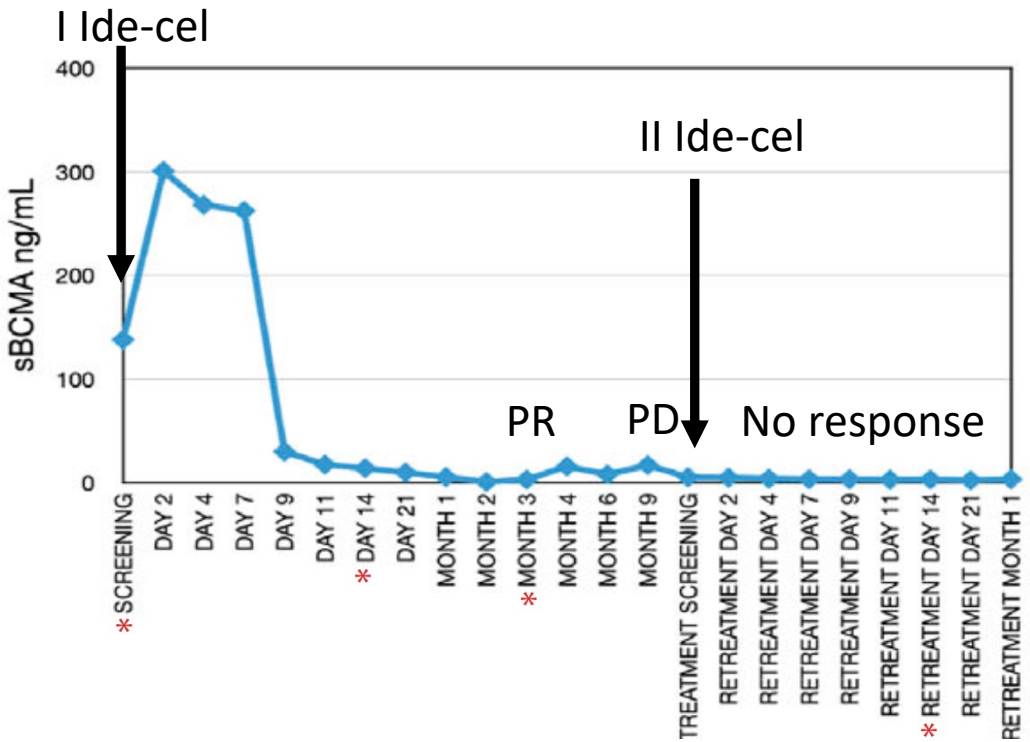
Mechanisms of resistance to anti-BCMA immunotherapy

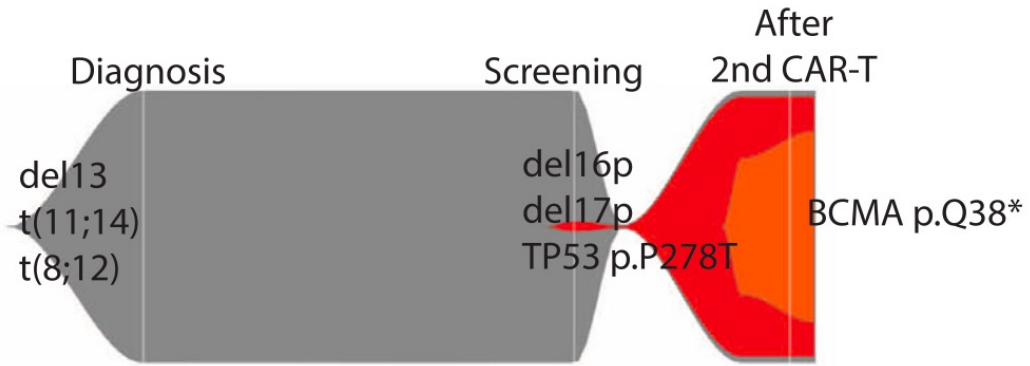


Zhou X et al Haematologica 2022

- BCMA^{-} or BCMA^{dim} relapses have been (rarely) described after anti-BCMA therapy
- BCMA loss was found in 3 out of 71 patients (4%) at progression in the KarMMa study with ide-cel. Described also with TCE but not with ADC.
- The simultaneous targeting of other antigens besides BCMA can possibly limit BCMA^{-}/BCMA^{dim} relapses
- BCMA negative relapses are theoretically crossresistant to any anti-BCMA-directed agents.
- BCMA mutations in the binding site of a specific drug may not confer crossresistance to other BCMA-targeting agents.
- High risk patients may have worse outcomes independently from BCMA loss/downregulation

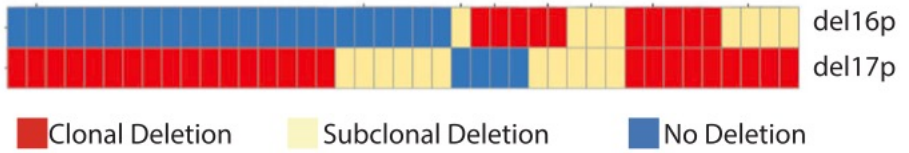
Mechanisms of resistance to anti-BCMA immunotherapy





4% subclonal del(17p)

300 NDMM patients



- del(16p) in 6% patients (44% were subclonal deletions)

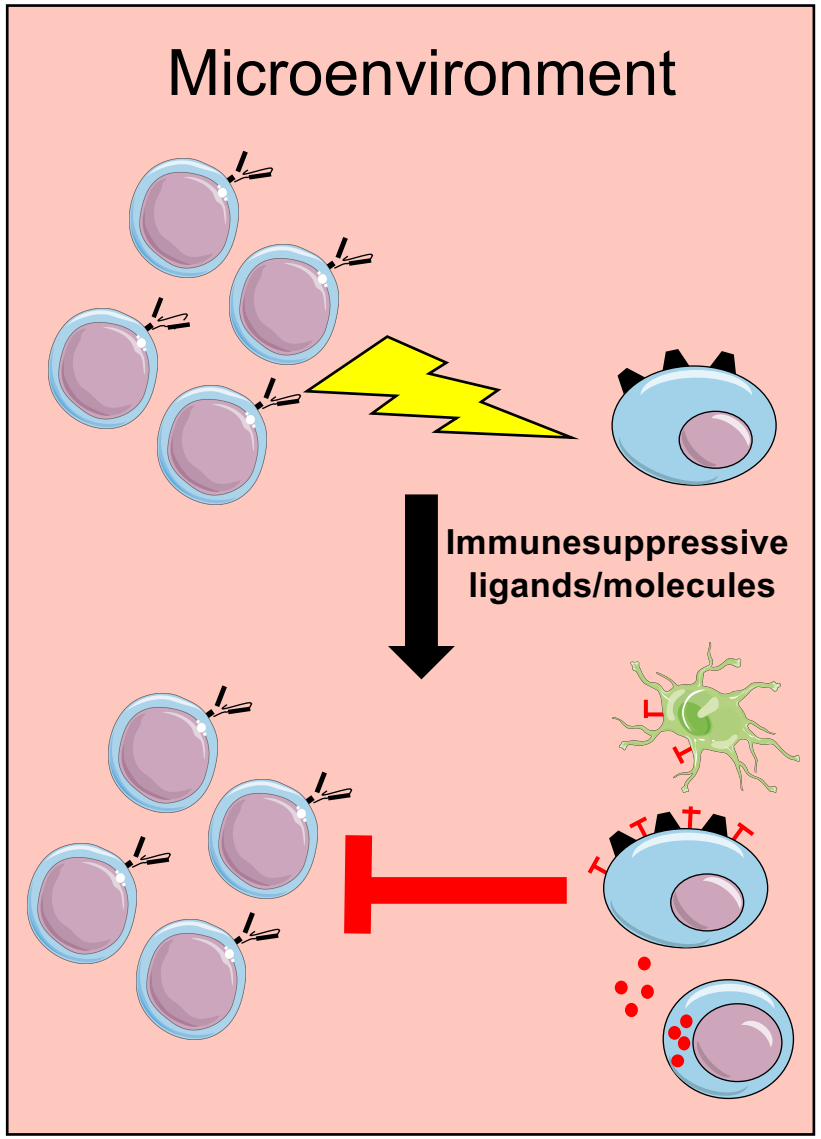
- del(16p) co-occurred with del17p in 77% of cases (sixfold encrichment)

- 36% of del(17p) also carried del(16p)

- The co-occurrence of 16p deletion in patients with del(17p) underscores the need to further evaluate the role of BCMA targeted therapies in high-risk del17p MM

Samur M et al, Nature communications 2021

Mechanisms of resistance to anti-BCMA immunotherapy

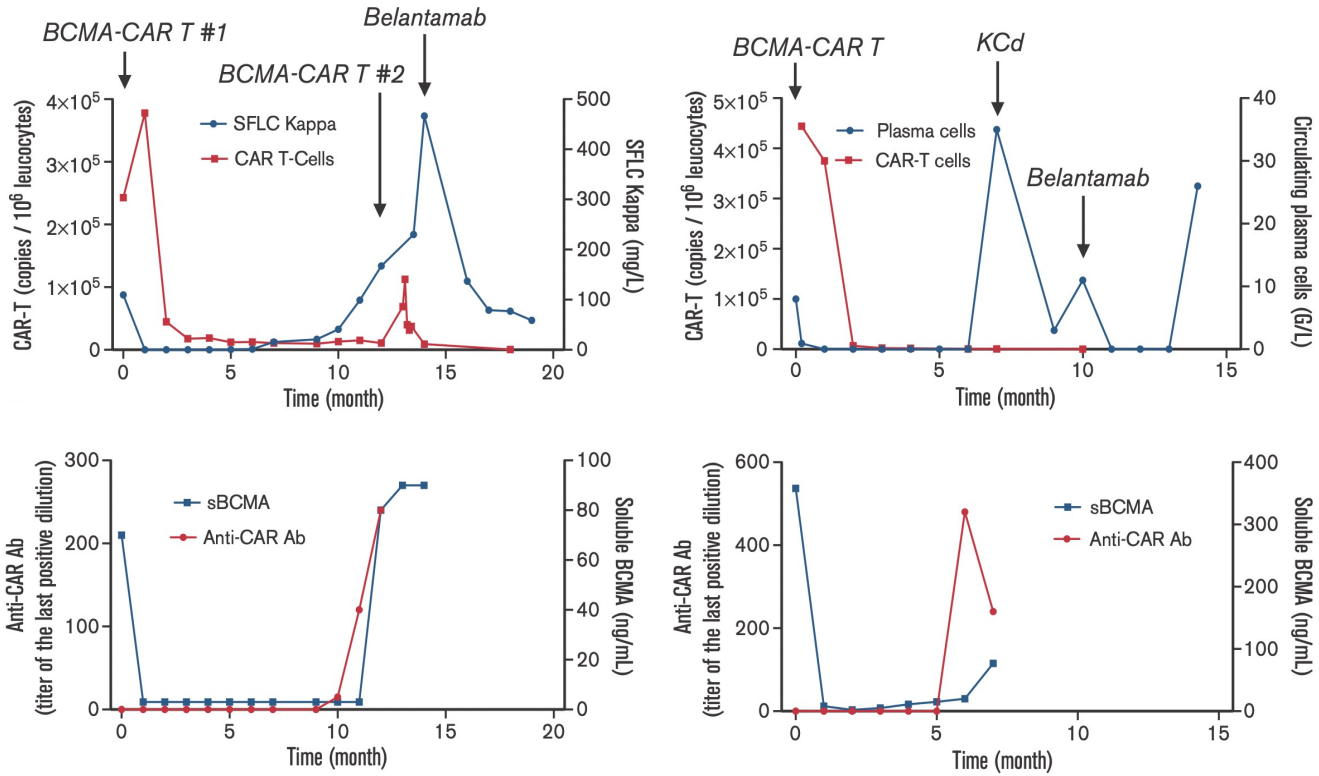


- BCMA positive relapses in the presence of detectable and functional circulating CAR T cells have been observed
- The role of immunosuppressive MM microenvironment is very likely in this context
- Combination treatment or “armored” CAR T cells capable of resisting immunosuppressive microenvironment can overcome this issue

M D'Agostino, N Raje, Leukemia 34 (1), 21-34, 2020

ADC in anti-BCMA exposed/refractory

Study author	First line of anti-BCMA therapy	First response to anti-BCMA therapy	Second line of anti-BCMA therapy	Second response to anti-BCMA therapy	Comments
Gazeau, et al	BCMA-directed CAR-T (bb2121, KarMMa)	sCR for 1 year before progression	Belantamab mafodotin (Blenrep)	VGPR	Anti-CAR antibodies present at response after CAR-T
Gazeau, et al.	BCMA-directed CAR-T (bb2121, KarMMa)	sCR for 10 months before progression	Belantamab mafodotin (Blenrep)	Not evaluable	After Blenrep, subject's plasma cells cleared but no response on M-spike
Cohen, et al.	BCMA-directed CAR-T (product not specified)	MR	Belantamab mafodotin (Blenrep)	MR	Progressed off Blenrep Jan 2017. Biopsy in Feb 2017 showed continued BCMA expression on MM cells



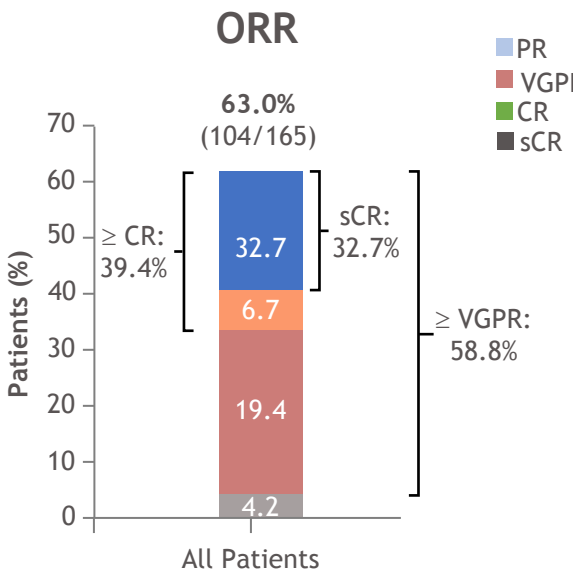
Golden E et al Touch medical media 2022; Gazeau et al Blood Adv 2021; Cohen AD et al Blood Adv 2019

Anti-BCMA TCE in anti-BCMA exposed/refractory

Teclistamab, MAJESTEC-1

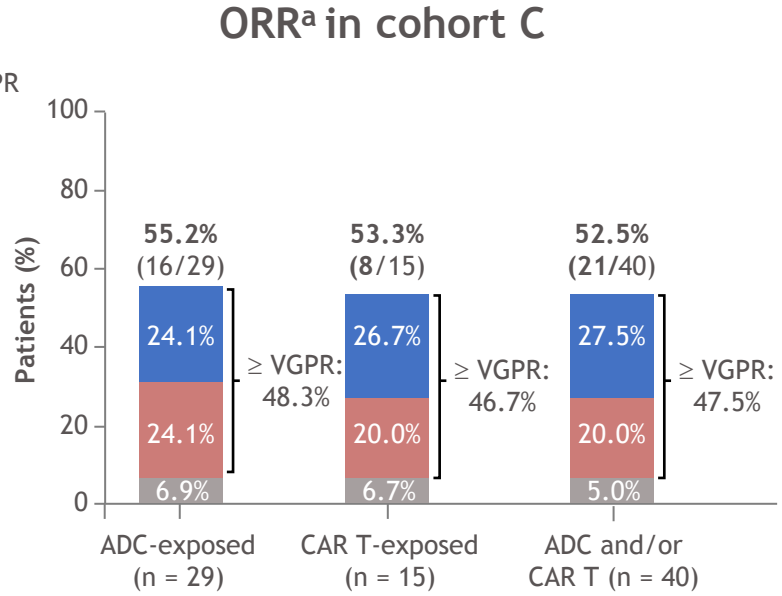
No prior BCMA

MAJESTEC-1, cohort A: no prior anti-BCMA agents[1]



Prior BCMA

MAJESTEC-1, cohort C: Teclistamab for RRMM patients previously exposed to anti-BCMA agents[2]

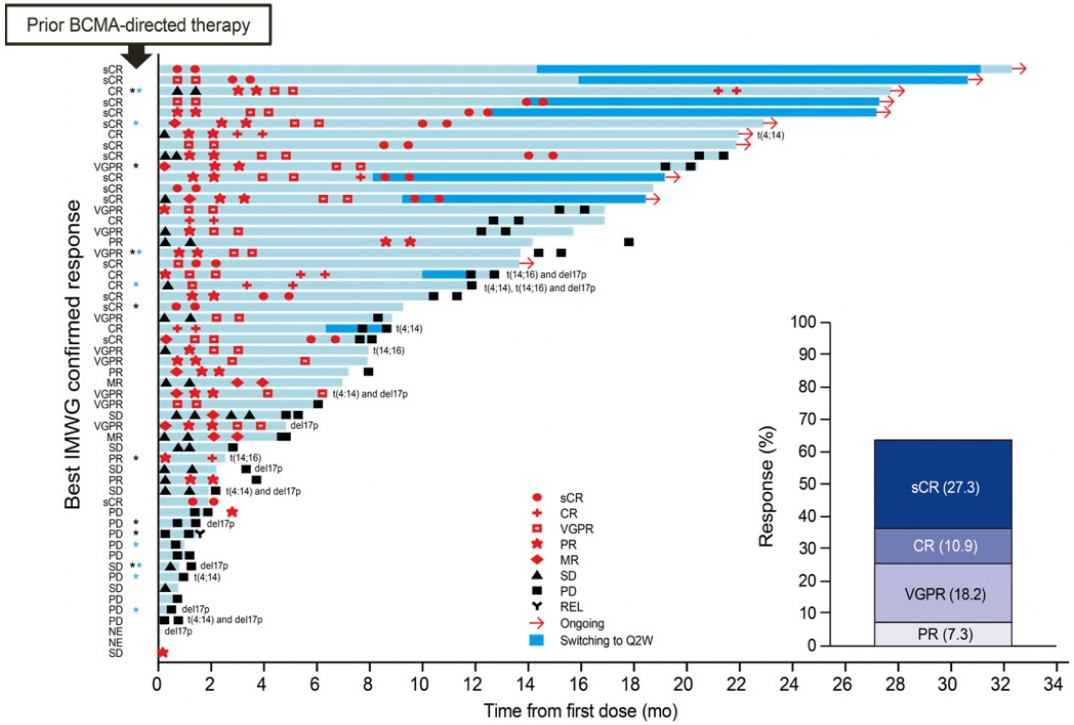


At data cutoff
(median follow-up 12.5 months)
71.4% of responders maintained response

Elranatamab, MAGNETISMM-1

23.6% received prior anti-BCMA agents; 14.5% ADC, 16.4% CAR-T

54% of previously BCMA-exposed patients achieved a response vs 64% in the overall population[3]

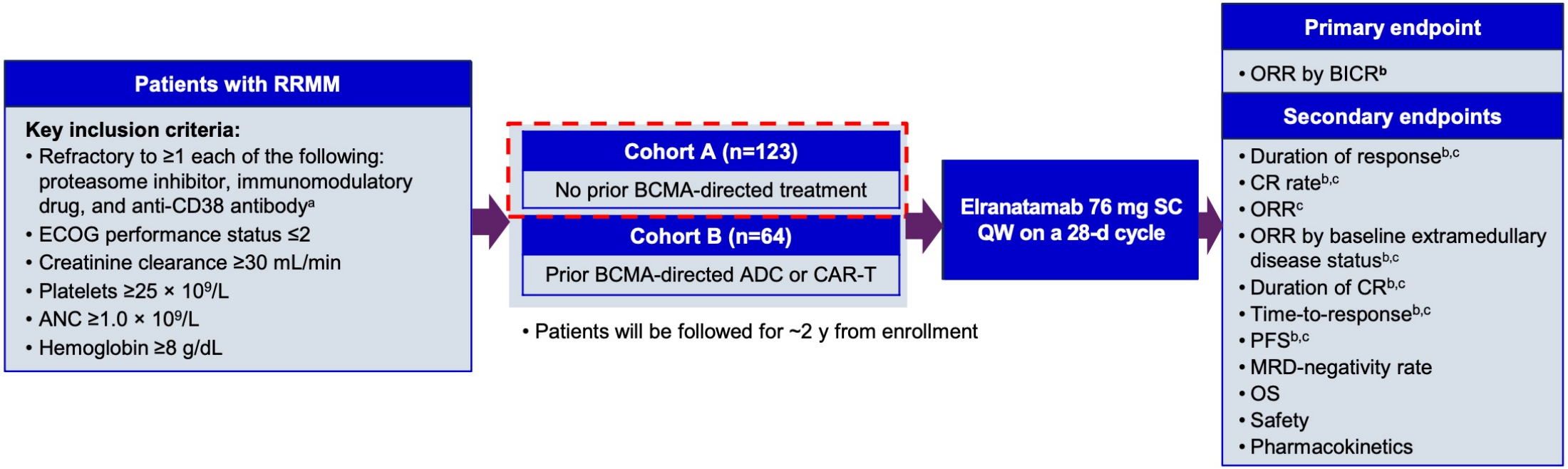


1.Moreau P, et al. N Engl J Med. 2022;387:495-505.; 2. Touzeau C, et al. Poster presented at ASCO 2022; J Clin Oncol. 2022;40;abstract 8013. 3. Raje N et al ASH 2022

Anti-BCMA TCE in anti-BCMA exposed/refractory

MagnetisMM-3

- MagnetisMM-3 is an open-label, multicenter, non-randomized, phase 2 study



[a] Refractory was defined as having disease progression while on therapy or within 60 d of last dose in any line, regardless of response. [b] By BICR assessment per IMWG response criteria. (Kumar S, et al. Lancet Oncol 2016;17:e328-46). [c] By investigator assessment per IMWG response criteria. ADC=antibody-drug conjugate; ANC=absolute neutrophil count; BCMA=B-cell maturation antigen; BICR=blinded independent central review; CAR-T=chimeric antigen receptor T-cell; CR=complete response; ECOG=Eastern Cooperative Oncology Group; IMWG=International Myeloma Working Group; MRD=minimal residual disease; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QW=weekly; SC=subcutaneous.

Abbreviations. PI: proteasome inhibitors; IMiDs: immunomodulatory drugs; mAb: monoclonal antibody

Anti-GPRC5D in anti-BCMA exposed/refractory

TALQUETAMAB: MonumenTAL 1[1]

Median follow-up 14.9

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

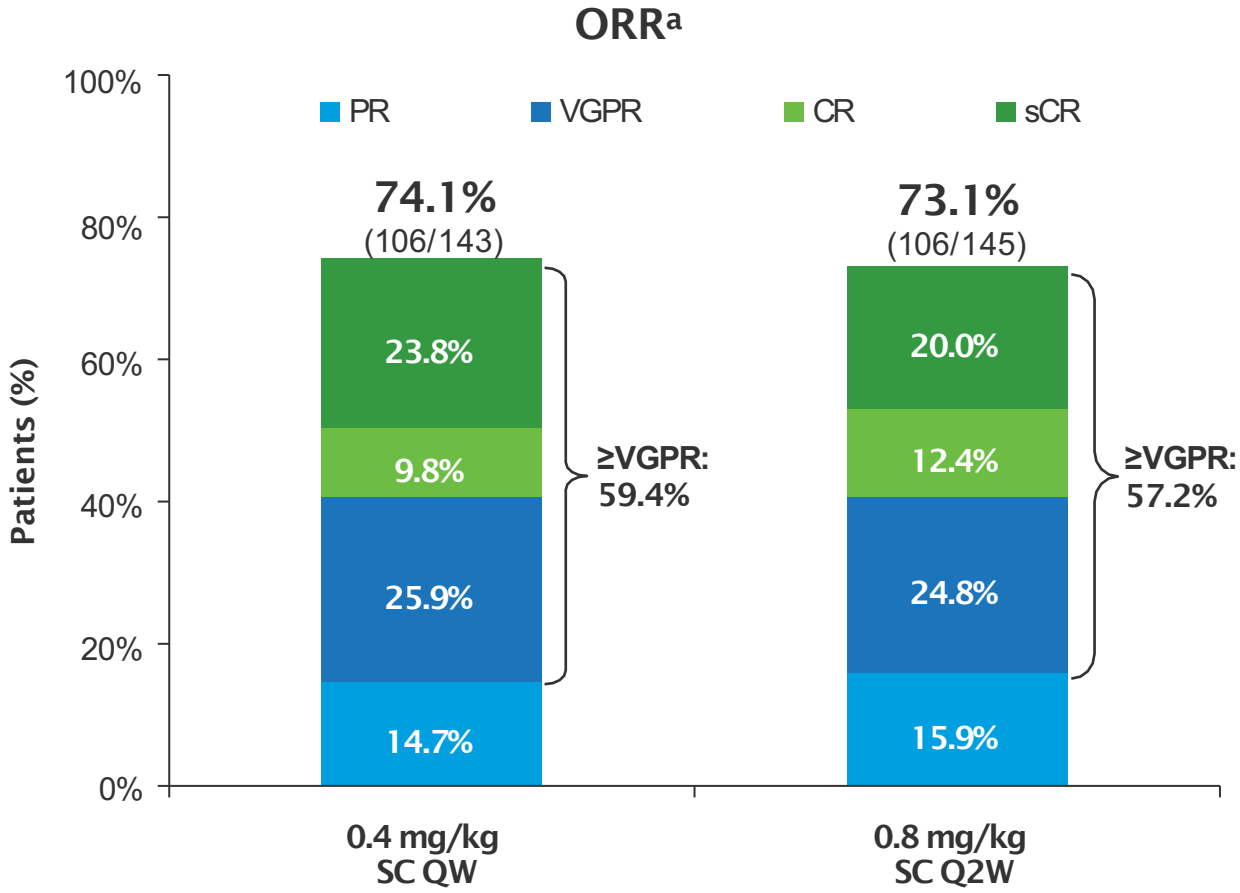
(Phase 1 [n=21] + Phase 2 [n=122]: N=143)

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)



Data cut-off date: September 12, 2022.
[a]Independent review committee assessment of evaluable patients per 2011 IMWG response criteria; due to rounding, individual response rates may not sum to the ORR. [b]Denotes patients who died.
[c]Calculated from n=106 responders in each group. CR, complete response; IMWG, International Myeloma Working Group; PR, partial response; ORR, overall response rate; Q2W, every other week; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

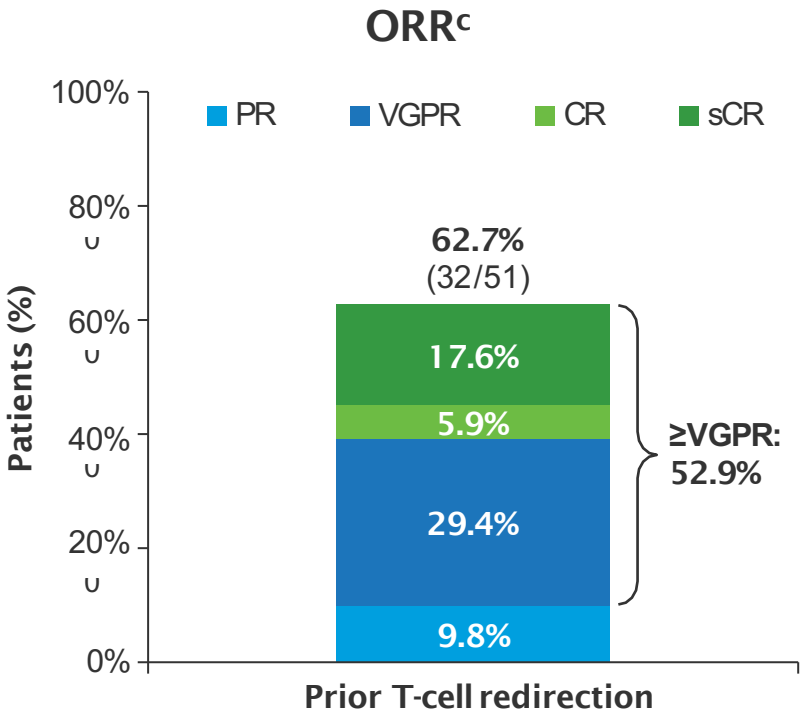
1. Chari et al, ASH 2022

Anti-GPRC5D in anti-BCMA exposed/refractory

TALQUETAMAB: MonumenTAL 1[1]

Median follow-up 14.9

- **Patients enrolled in cohort of prior T-cell redirection therapy:**
  - **Were younger** and had a **higher prevalence of high-risk cytogenetics**
  - **Median of 6 prior lines of therapy** (range, 3–15)
  - 70.6% (n=36) received prior CAR-T cell therapy and 35.3% (n=18) prior bispecific antibody therapy; 3 patients received both
  - 7.8% (n=4) were refractory to belantamab
  - Most patients received QW (n=43) vs Q2W (n=8) talquetamab dosing
- **62.7% ORR** at a median follow-up of 11.8 months (range, 1.0[a]–25.4)
  - Median DOR was 12.7 months[b] (range, 3.7–NE)
  - **72.2% ORR** (26/36; 95% CI, 54.8–85.8%) in patients with **prior CAR-T therapy**
  - **44.4% ORR** (8/18; 95% CI, 21.5–69.2%) in patients with **prior bispecific antibody treatment**
- Safety profile comparable in patients with and without prior T-cell redirection therapy



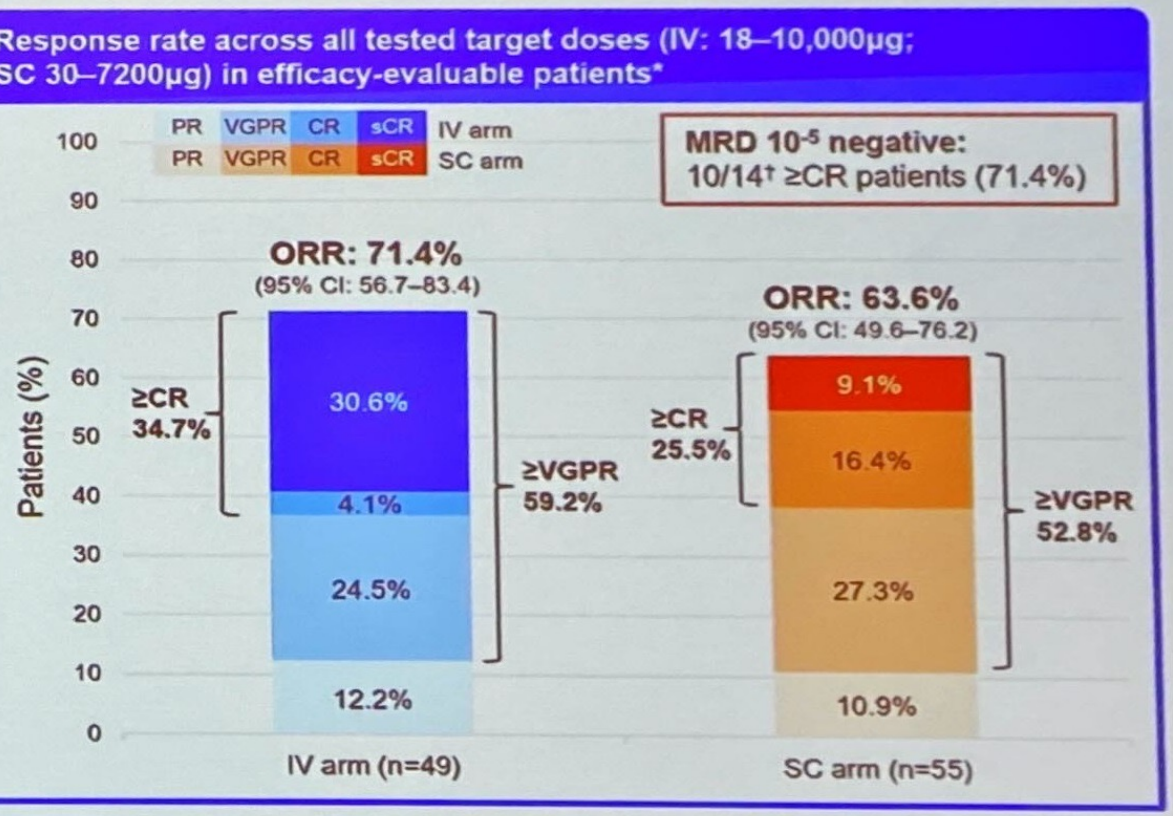
Data cut-off date: September 12, 2022 (efficacy), May 16, 2022 (safety).
[a]Denotes patient who died. [b]Data are still immature. [c]Independent review committee assessment of evaluable patients per 2011 IMWG response criteria; due to rounding, individual response rates may not sum to the ORR. CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; IMWG, International Myeloma Working Group; NE, not estimable; ORR, overall response rate; PR, partial response; QW, weekly; Q2W, every other week; sCR, stringent complete response; VGPR, very good partial response.

1. Chari et al, ASH 2022

Anti-GPRC5D in anti-BCMA exposed/refractory

Forimtamig[1]

	IV arm (n=49)	SC arm (n=55)
Median follow-up, months (range)	11.6 (0.5–20.6)	8.0 (1.1–15.0)
Median time to first response, months (95% CI)	1.4 (1.2–1.8)	1.6 (1.2–2.1)
Median duration of response, months (range)	10.8 (0.0–17.6)	12.5 (1.2–12.5)
Patients with ongoing response at data cut-off, n/N (%)	23/35 (65.7)	25/35 (71.4)
Patients with prior anti-BCMA and response, n/N (%)	5/10 (50.0)	6/11 (54.5)



Data cut-off: October 21, 2022; *patients who received ≥1 target dose of forimtamig and had at least one baseline and one on-treatment tumor assessment or discontinued due to clinical progression; †of 14 evaluable patients with available BMA at the time of response across all IV and SC doses so far, 10 had MRD-negative CR at 10^{-5}. BMA, bone marrow aspirate; CI, confidence interval; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

1. Carlo Stella et al, ASH 2022

Anti-FcRH5 in anti-BCMA exposed/refractory

Cevostamab[1]

Characteristic, % (unless otherwise stated)	Total (N = 161)
Median age (range), years	64 (33–82)
Male	58.4 %
High-risk cytogenetics†	
1q21 gain	70.5 %
t(4;14)	55.6 %
t(14;16)	13.5 %
del(17p)	2.2 %
Extramedullary disease	21.1 %
Median time since first MM therapy (range), years	6.1 (0.3–22.8)
Median number of prior lines of therapy (range)	6 (2–18)
Prior anti-CD38 antibody	88.2 %
Prior anti-BCMA	**33.8 %**
Prior ADC	**16.9 %**
Prior bispecific antibody	**8.1 %**
Prior CAR-T	**17.5 %**
Triple-class refractory‡	84.5 %
Penta-drug refractory§	68.3 %

In the overall population ORR was:

- **29% in the 90 mg cohort**
- **54.8% in the 160 mg cohort**

At target dose levels >90mg ORR was:

- **44.4% in prior CAR-T**
- **33.3% in prior TCE**
- **50% in prior ADCs**
- **36.4% in prior anti-BCMA targeting agents**

Trudel S et al ASH 2021

CAR-T reinfusion after PD with the same agent

Phase II KarMMa trial: retreated patients after first PD[1]

	Total Enrolled (N=140)	Total Retreated (N=28)
Best overall response—no. (%)	94 (67)	6 (21)
Stringent complete response	41 (29)	0
Complete response	1 (1)	0
Very good partial response	25 (18)	1 (4)
Partial response	27 (19)	5 (18)
Stable disease	22 (16)	5 (18)
Progressive disease	8 (6)	15 (54)
Not evaluable*	14 (10)	2 (7)
Median progression-free survival (95% CI)—mo	9.5 (6.9–12.5)	1.0 (1.0–2.1)

Progression-free survival is measured from time of enrollment in the total enrolled population and from time of ide-cel re-infusion in the retreated population.
*Patients who did not have response assessment data or whose only assessment was not evaluable for response.

- Durations of response ranged from 1.9 to 6.8 months;
- All the patients who had a response were retreated at a dose higher than their initial dose.

1. Munshi et al, nejm 2021

Anti-BCMA CAR T in anti-BCMA exposed/refractory

Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium[1]

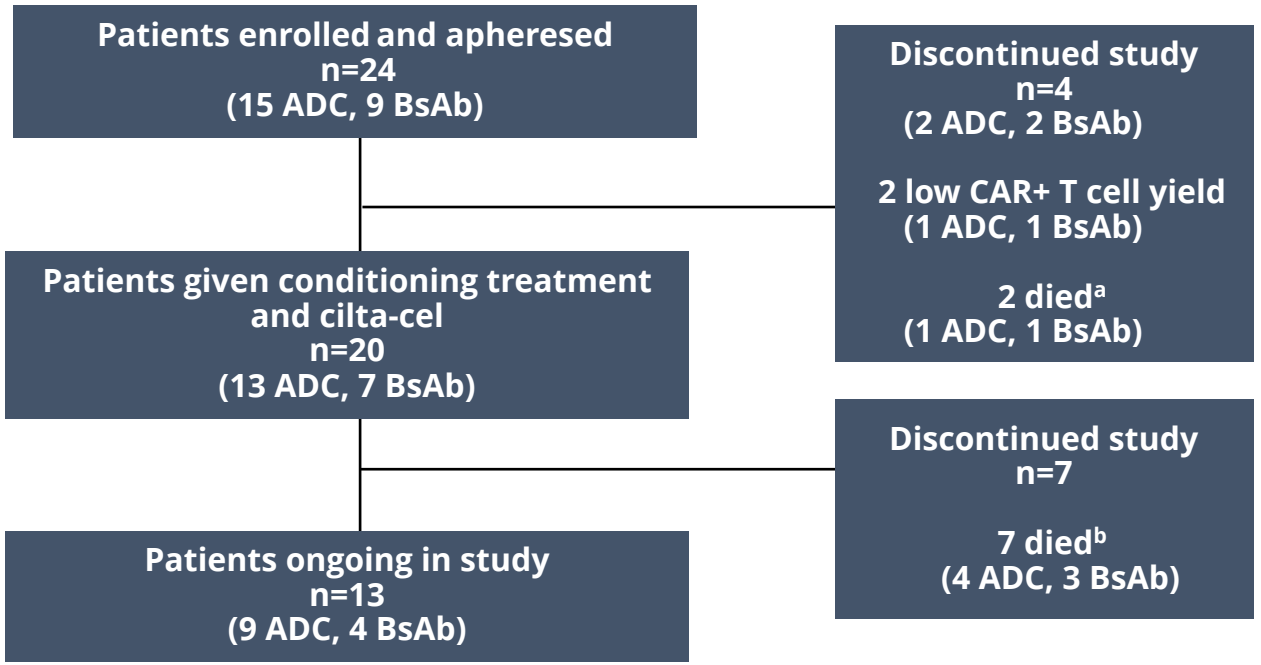
- Clinical outcomes with standard-of-care (SOC) ide-cel under the commercial Food and Drug Administration label at 11 US institutions
- 159 patients treated with Ide-cel (not eligible for KarMMa phase II clinical trial→ 25%; prior use of BCMA-targeted therapy →21%)
- After a median follow-up of 6.1 months →PFS 8.5 months (In KarMMa II 8.8 months)
- **Prior history of anti-BCMA therapy was associated with lower PFS: 3.2 months vs 9 months**
- If BCMA chimeric antigen receptor-T-cell treatment is planned, prior exposure to BCMA-targeted therapy should be avoided.

1. Hansen D K et al JCO 2023

Anti-BCMA CAR T in anti-BCMA exposed/refractory

Cartitude-2 cohort C[1]

- At the time of data cut-off (October 2021), the median follow-up for patients treated with prior ADC was 11.8 months, and 10.9 months for those treated with prior BsAbs



1. Cohen et al Blood 2023

Anti-BCMA CAR T in anti-BCMA exposed/refractory

Cartitude-2 cohort C[1]

Patient demographics and baseline characteristics (ADC exposed)

Characteristic	(N=13)
Age, y, median (range)	66 (44–81)
Male, n (%)	8 (61.5)
Bone marrow plasma cells[b] ≥60%, n (%)	4 (33.3)
Extramedullary plasmacytomas, n (%)	5 (38.5)
High-risk cytogenetic profile,[c] n (%)	2 (15.4)
Time from initial MM diagnosis, y, median (range)	6.4 (3.6–16.3)
Prior LOT, median (range)	8 (4–13)
Therapy in last line, n (%)	
Anti-BCMA	4 (30.8)
Other treatments	9 (69.2)
Refractory status, n (%)	
Triple-class[d]	11 (84.6)
Penta-drug[e]	7 (53.8)
Anti-BCMA treatment refractory	11 (84.6)
To last line of therapy	13 (100)

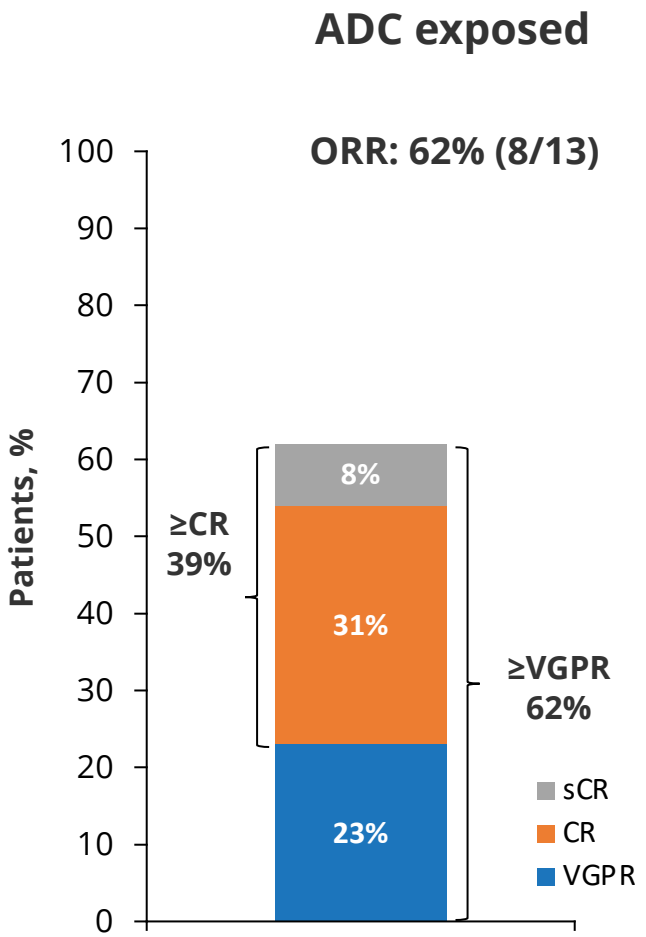
Patient demographics and baseline characteristics (bispecific exposed)

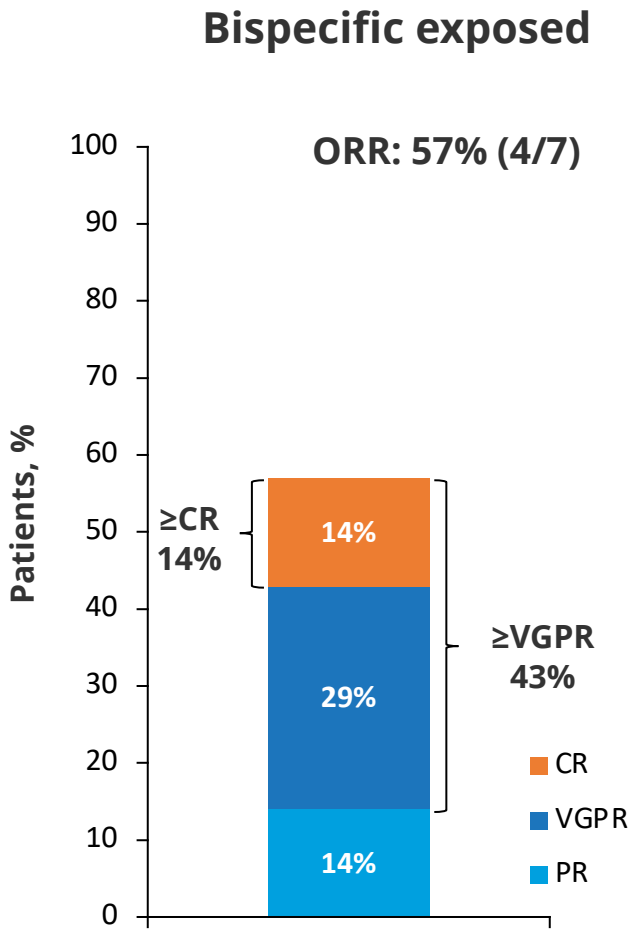
Characteristic	(N=7)
Age, y, median (range)	60 (49–71)
Male, n (%)	4 (57.1)
Bone marrow plasma cells[b] ≥60%, n (%)	2 (28.6)
Extramedullary plasmacytomas, n (%)	0
High-risk cytogenetic profile,[c] n (%)	1 (14.3)
Time from initial MM diagnosis, y, median (range)	5.0 (2.5–14.5)
Prior LOT, median (range)	8 (6–12)
Therapy in last line, n (%)	
Anti-BCMA	2 (28.6)
Other treatments	5 (71.4)
Refractory status, n (%)	
Triple-class[d]	7 (100.0)
Penta-drug[e]	4 (57.1)
Anti-BCMA treatment refractory	5 (71.4)
To last line of therapy	6 (85.7)

1. Cohen et al Blood 2023

Anti-BCMA CAR T in anti-BCMA exposed/refractory

Cartitude-2 cohort C[1]



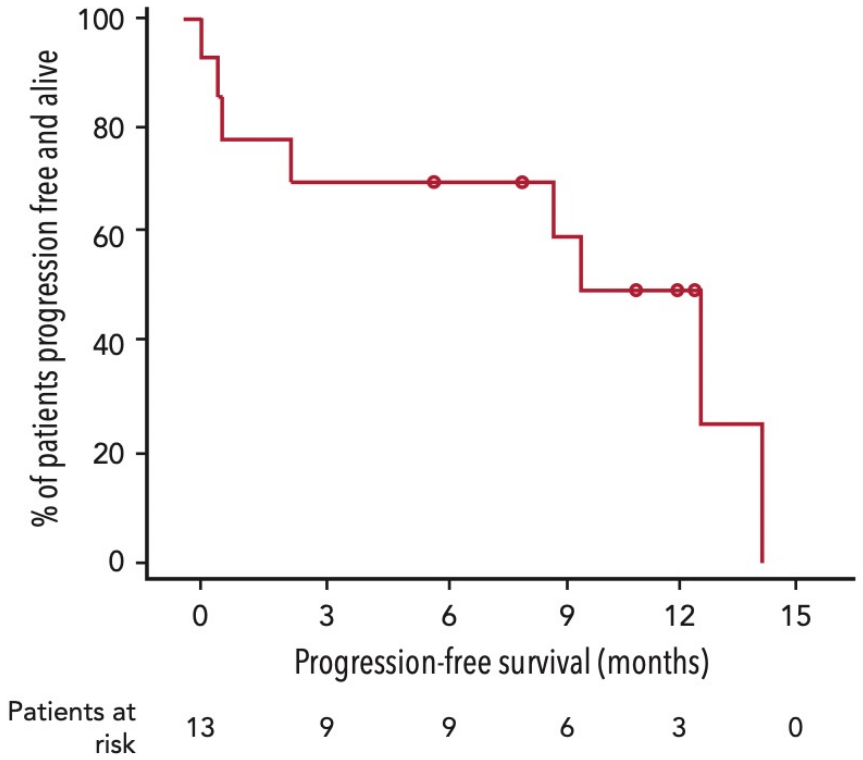


1. Cohen et al Blood 2023

Anti-BCMA CAR T in anti-BCMA exposed/refractory

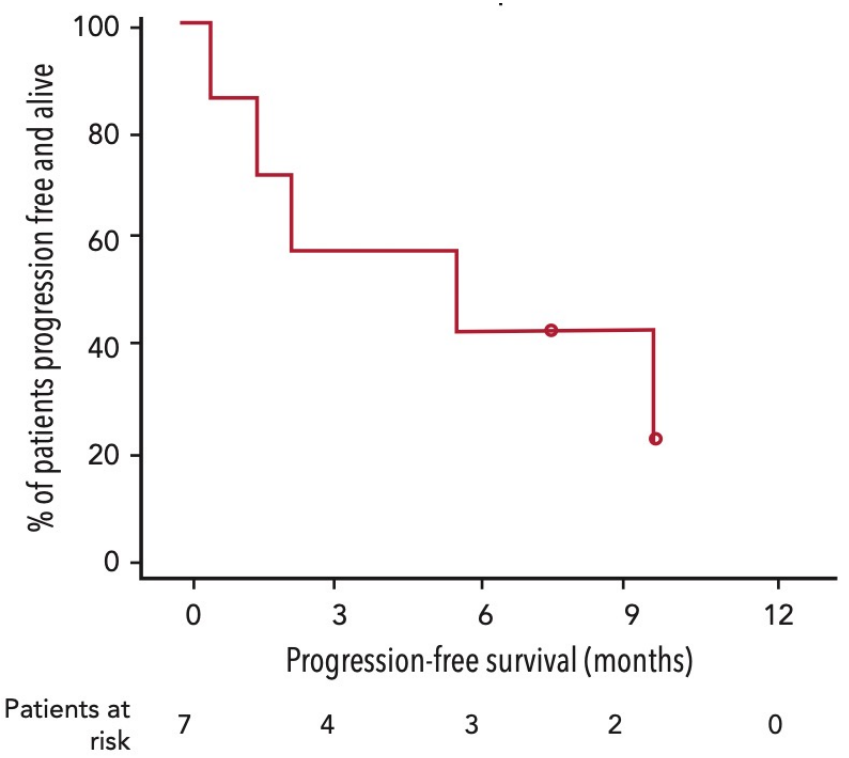
Cartitude-2 cohort C[1]

ADC exposed



Median PFS 9.5 months

Bispecific exposed



Median PFS 5.3 months

1. Cohen et al Blood 2023

Anti-BCMA CAR T in anti-BCMA exposed/refractory

Cartitude-2 cohort C[1]

Timing of BCMA-targeting after ADC treatment

Treatments	Responders (n=8)	Nonresponders (n=5)
Duration of last anti-BCMA ADC treatment, days		
Median	22.5	63.0
Range	1–277	22–527
Time from last anti-BCMA ADC treatment to apheresis, days		
Median	150.0	56.0
Range	26–695	40–895
Time from last anti-BCMA ADC treatment to cilta-cel infusion, days		
Median	226.5	116.0
Range	62–749	95–944

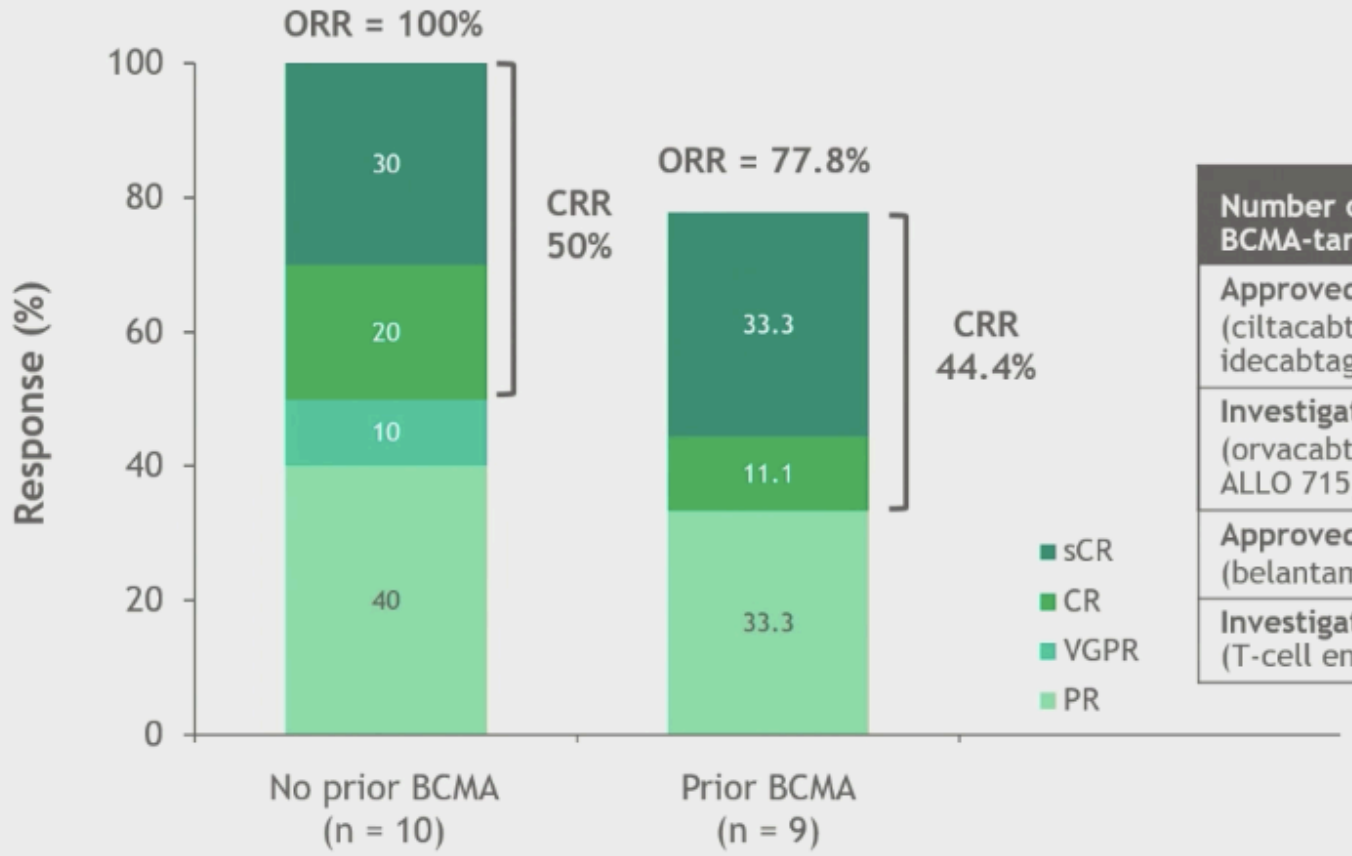
Timing of BCMA-targeting after BsAb treatment

Treatments	Responders (n=4)	Nonresponders (n=3)
Duration of last anti-BCMA BsAb treatment, days		
Median	53.5	130.0
Range	23–127	15–260
Time from last anti-BCMA BsAb treatment to apheresis, days		
Median	220.5	84.0
Range	28–281	77–251
Time from last anti-BCMA BsAb treatment to cilta-cel infusion, days		
Median	276.0	124.0
Range	84–329	119–307

1. Cohen et al Blood 2023

Anti-GPRC5D CAR T in anti-BCMA exposed/refractory

BMS-986393[1]



Number of patients with prior BCMA-targeted therapy, n (%)	n = 9
Approved CAR T cells (ciltacabtagene autoleucel, idecabtagene vicleucel)	2 (10.5)
Investigational CAR T cells (orvacabtagene autoleucel, ALLO 715, others not specified)	5 (26.3)
Approved non-CAR T cells (belantamab mafodotin)	1 (5.3)
Investigational non-CAR T cells (T-cell engager)	1 (5.3)

Data cutoff: September 7, 2022. [a]CC-95266 efficacy-evaluable population includes all patients who received conforming BMS-986393 cell product, had measurable disease at the last disease assessment prior to BMS-986393 infusion, and had ≥ 1 post-infusion disease-response assessment. The patient in the 450 x 10^6 CAR T cell group was not included in the efficacy-evaluable analysis set. Responses were assessed per International Myeloma Working Group criteria. CAR, chimeric antigen receptor; CR, complete response; CRR, complete response rate; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

9

1.Bal et al ASH 2022

Anti-GPRC5D CAR T in anti-BCMA exposed/refractory

MCARH109[1]

Response	All Patients		Previous BCMA Therapies		No Previous BCMA Therapies	
	All Dose Levels (N=17)	25×10^6–150×10^6 CAR T Cells (N=12)	All Dose Levels (N=10)	25×10^6–150×10^6 CAR T Cells (N=6)	All Dose Levels (N=7)	25×10^6–150×10^6 CAR T Cells (N=6)
	number (percent)					
Partial response or better	12 (71)	7 (58)	7 (70)	3 (50)	5 (71)	4 (67)
Very good partial response or better	10 (59)	5 (42)	6 (60)	2 (33)	4 (57)	3 (50)
Complete response or better	6 (35)	3 (25)	4 (40)	2 (33)	2 (29)	1 (17)

1.Mailankody S et al nejm 2022

Anti-GPRC5D CAR T in anti-BCMA exposed/refractory

	Patients (n=10)
Median age, years	64 (58–68)
Sex	
Female	5 (50%)
Male	5 (50%)
Race	
Chinese	10 (100%)
Other	0
Median time since diagnosis, months	39 (25–78)
International Staging System stage	
I	2 (20%)
II	5 (50%)
III	3 (30%)
Type of myeloma	
IgA	5 (50%)
IgG	5 (50%)
Extramedullary disease	4 (40%)
ECOG performance status score	
0	1 (10%)
1	3 (30%)
2	6 (60%)
High-risk cytogenetic profile	6 (60%)
del17p	3 (30%)
t(14;16)	0
t(4:14)	5 (50%)
GPRC5D expression≥50%	9 (90%)
Time between apheresis and OriCAR-017 infusion, days	24·5 (22·0–41·0)
Median lines of previous therapies	5·5 (4·0–10·0)
Previous therapies	
Proteasome inhibitors	
Bortezomib	10 (100%)
Ixazomib	5 (50%)
Carfilzomib	1 (10%)
Immunomodulatory drugs	
Lenalidomide	10 (100%)
Thalidomide	5 (50%)
Pomalidomide	4 (40%)
Anti-CD38 monoclonal antibodies	2 (20%)
Autologous haematopoietic stem-cell transplantation	2 (20%)
BCMA CAR T-cell therapy	5 (50%)

ORiCAR-017[1]

	Patients (n=10)
Overall response	10 (100%)
Best response	
Stringent complete response	6 (60%)
Complete response	0
Very good partial response	4 (40%)
Time to best response, months	3·1 (2·0–5·1)
Time to complete response or better, months	4·1 (2·0–5·9)
Minimal residual disease negativity at 10^{-5}	10 (100%)

- 5 patients previously exposed to BCMA-targeted CAR T-cell therapy (2 with BCMA-negative relapses)
- Responses→ 2 sCR and 3 VGPR

1. Zhang M et al Lancet haem 2023

Other agents in anti-BCMA exposed/refractory

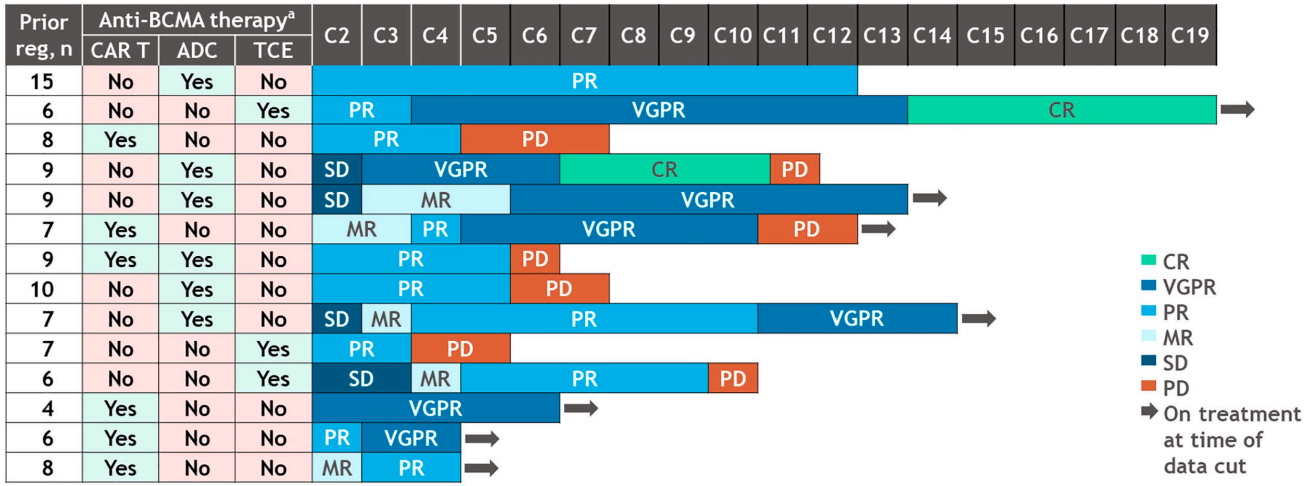
CC-220-MM-001 Trial: BCMA exposed patients[1]

Table. Summary of prior therapies

Prior therapies, n (%)	IBER + DEX Anti-BCMA-exposed cohort (N = 38)
ASCT	33 (86.8)
IMiD agent	38 (100)
Lenalidomide	37 (97.4)
Pomalidomide	37 (97.4)
PI	38 (100)
Anti-CD38 mAb	38 (100)
BCMA-targeted therapy	38 (100)[a]
CAR T cell therapy	14 (36.8)
Antibody-drug conjugate	13 (34.2)
T-cell engager	9 (23.7)
Other	4 (10.5)[b]

[a]Two patients received CAR T cell therapy and an antibody-drug conjugate; [b]All patients received SEA-BCMA (a naked anti-BCMA mAb).
ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; DEX, dexamethasone, IBER, iberdomide; mAb, monoclonal antibody; IMiD, immunomodulatory drug; PI, proteasome inhibitor; SEA, sugar-engineered antibody.

Figure. Responses over time



[a]None of the responding patients had received the "other" category of anti-BCMA therapy (SEA-BCMA).
ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; C, cycle; CAR, chimeric antigen receptor; CR, complete response; MR, minimal response; PR, partial response; PD, progressive disease; reg., regimen; SD, stable disease; TCE, T-cell engager; VGPR, very good partial response.

- ORR 36.8% (CR 5.3%; VGPR 13.2%).
- Median duration of response was 7.5 months
- Median PFS was 2.4 months
- Results similar to cohort D (triple-class refractory patients not exposed to anti-BCMA)

1. Lonial S et al ASH 2022

Conclusions

- Few data available on sequencing and re-treatment of ADC, TCE and CAR-T therapy in Myeloma
- Very few data on very few patients…….
- We have to pick the best (and available…) one, rather than to think about sequencing at the moment
- Anti-BCMA agents are the only approved agents, but TCE and CAR-T vs other targets will be available soon
- Reinfusion with the same CAR-T after PD do not seem to be a good option
- Changing the target in BCMA-negative relapses may be a better strategy
- Retreatment with BCMA targeting agents is indeed feasible
- Changing the target in BCMA-positive relapses may be a good option as well, especially immediately after PD from anti-BCMA agents.
- Changing mechanism of action in refractory patients may lead to better outcomes (e.g. TCE after CAR-T or ADC)

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