POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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Terapia di Salvataggio con anticorpi Monoclonali/Bispecifici

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Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen,Sanofi, BMS, GSK, Takeda, Roche, Amgen, Pfizer, Menarini, Abbvie, Regeneron, Astrazeneca						x	x

Treatment landscape for triple-class exposed MM patients in 2025

1° line	2° line	3° line	4° line	5° line and beyond
Anti-CD38 MoAbs				
Bortezomib and lenalidomide				
	Carfilzomib/ixazomib/ pomalidomide, elotuzumab/selinexor			

- Ide-cel
- Cilta-cel

- **Teclistamab**
- **Elranatamab**
- **Talquetamab**

- Selinexor

- Melflufen

Approved for pts that have received at least 3 prior lines, includung anti-CD38 MoAbs, PIs and IMIDs

BCMA, B-cell maturation antigen; MoAb, monoclonal antibody; IMiD, immunomodulatory drug; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor

New targets on myeloma cells and New drugs

BCMA

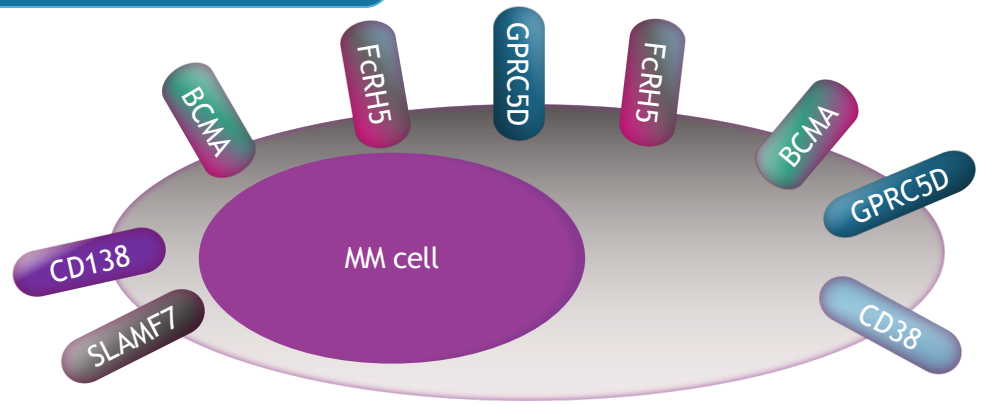
- BCMA is a member of the TNF receptor superfamily
- APRIL and BAFF are known ligands, leading to activation of the NF-κB pathway
- BCMA promotes plasma cell survival, growth, resistance to apoptosis, adhesion, and angiogenesis
- γ-secretase cleaving causes shedding of soluble BCMA
- BCMA is expressed on **malignant PCs, at low levels on normal PCs and mature B lymphocytes** and is absent in non-hematological tissues

FcRH5

- FcRH5 is a surface protein in the Ig superfamily
- It is expressed only in B cells, with increasing expression in **mature B cells and plasma cells**
- FcRH5 is involved in proliferation and isotype expression

GPRC5D

- GPRC5D is a member of the G protein-coupled receptor family with an **unknown function**
- It is highly expressed on **malignant PCs,** as well as hard **keratinized structures** (hair shaft, nail, and central region of the tongue)



Modality of targeting: ADC, Bispecific antibodies, CAR-T cells

Image adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.
APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CD, cluster of differentiation; FcRH5, Fc receptor-like 5; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; MM, multiple myeloma; NF-κB, nuclear factor Bs; PC, plasma cell; SLAMF7, signaling lymphocytic activation molecule family member 7; TNF, tumor necrosis factor.
1. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 2. Pillarisetti K, et al. Blood Adv. 2020;4:4538–49. 3. Yu B, et al. J Hematol Oncol. 2020;13:125. 4. Verkleij CPM, et al. Blood Adv. 2020;5;2196-215. 5. Smith EL, et al. Sci Transl Med. 2019;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31;383-95. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155. 8. Lancman G, et al. Blood Cancer Discov. 2021;2:423-33.

Outline

Bispecific Antibodies anti-BCMA

Bispecific Antibodies anti-GPRC5D

Bispecific Antibodies anti-FcRH5

Novel Constructs

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Bispecific Antibodies anti-BCMA

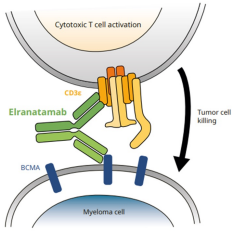
Bispecific Antibodies anti-GPRC5D

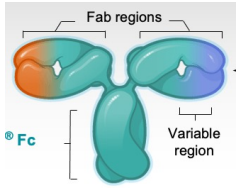
Bispecific Antibodies anti-FcRH5

Novel Constructs

BCMA-targeting bispecific antibodies

	Teclistamab MajesTEC-1[1] (n=165)	Elranatamab Magnetismm3[2] (n=123)	ABBV-383B[3] (n=118)	Linvoseltamab LINKER-MM1[4] (n=117)
Phase	I/II	I/II	I	II
Target	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3
scFv	Humanized	Humanized	Human	Human
Ig	IgG4	IgG2a	IgG4	IgG4
Administration	SC	SC	IV	IV
# prior lines	5 (2-14)	5 (2-12)	5 (1-15)	5 (2-14)
Age	64 (33-84)	69 (44-89)	68 (35-88)	70 (37-91)



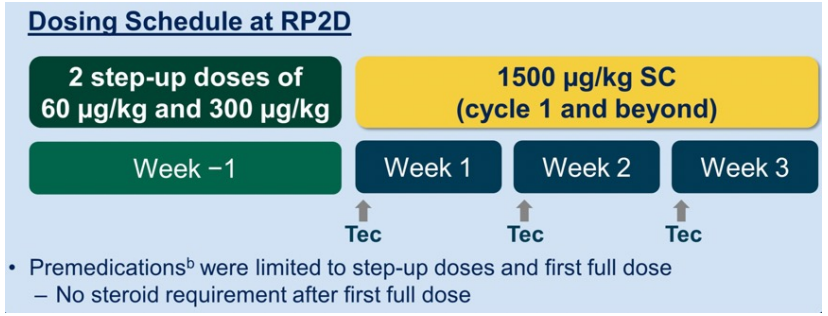


[1] Nooka et al. ASCO 2022; [2] Bahlis et al. ASH 2022; [3] Voorhees et al. IMS 2022; [4] Hans L. et al. ASCO 2023;

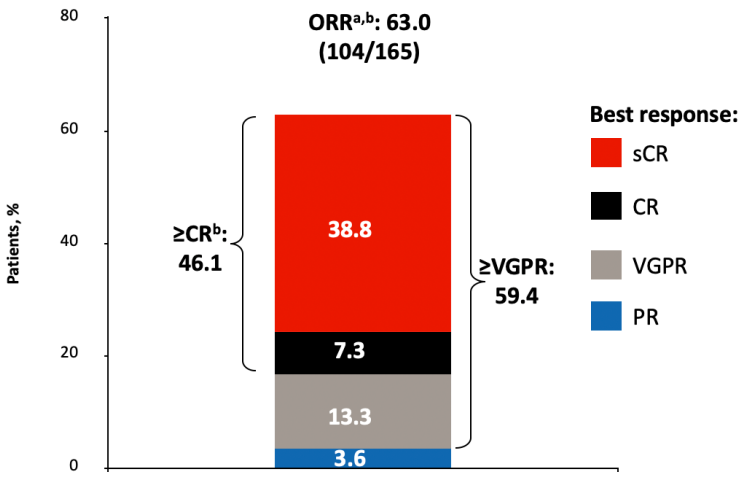
MajesTEC-1: teclistamab for RRMM

Median N of prior lines: 5

Triple Class Exposed 100%, Triple class Refractory 77%



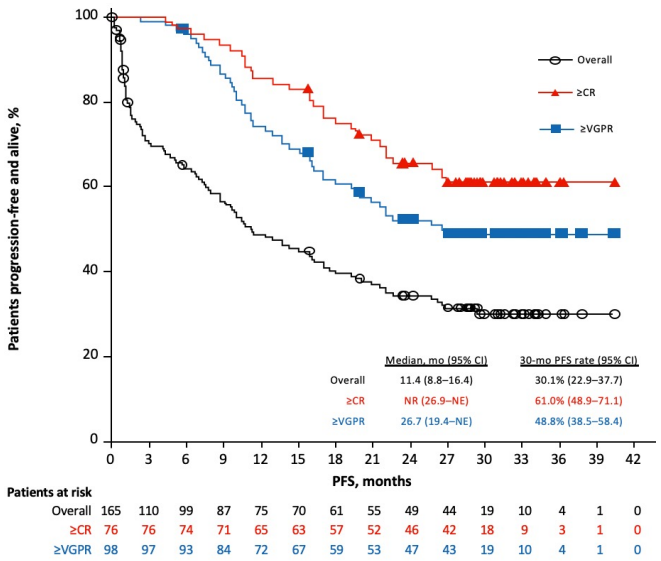
Overall response rates



ITT MRD negativity rate (10^{-5}): 27%

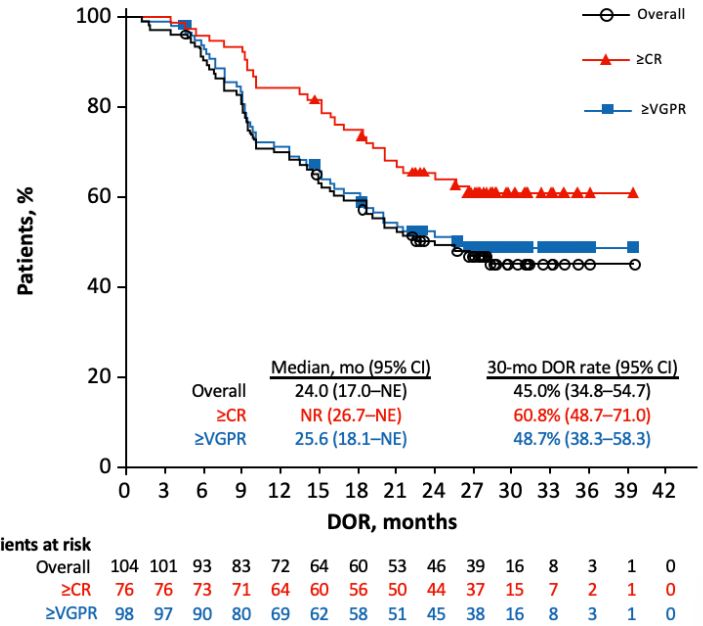
- 86% MRD-evaluable patients were MRD neg at any point

Progression-free survival



Median PFS: ≤3 prior LOT: 18.1 months; >3 prior LOT: 9.7 months

Duration of response



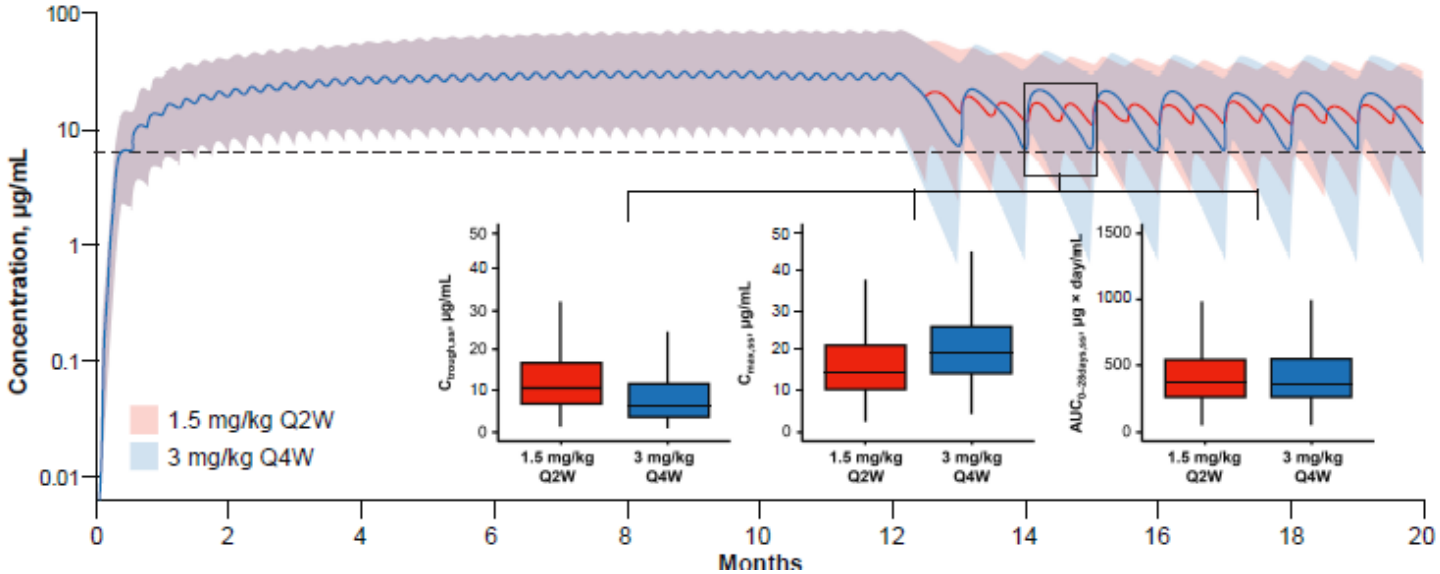
Garfall A. et al. EHA 24

aPR or better, IRC assessed; ORR in efficacy analysis population, which includes all patients who received their first dose on or before March 18, 2021 (n=150)

CR, complete response; DOR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; sCR, stringent partial response; VGPR, very good partial response

Less frequent dosing in responders: modelling and simulation data from the MajesTEC-1 study

Comparable estimated steady-state Teclistamab PK with 1.5 mg Q2W vs 3 mg/kg Q4W



- **Modelling and simulation results from MajesTEC-1 support the approved switch to Teclistamab 1.5 mg/kg Q2W in patients maintaining a response for ≥6 months, and indicate comparable PK between the 1.5 mg/kg Q2W and 3 mg/kg Q4W Teclistamab doses**
- **Exposure-response trends suggest that switching from QW to Q2W dosing did not affect maintenance of response to Teclistamab**
- **Maintenance of tumor volume reduction and DoR were comparable between virtual patients who switched to Q2W dosing after maintaining a response for ≥6 months and those who remained on QW dosing, based on QSP modeling**
- **Results from Teclistamab population PK modeling suggest that the 3mg/kg Q4W schedule may provide maintenance of response comparable with the 1.5 mg/kg Q2W schedule**
- **Teclistamab 3 mg/kg Q4W dosing will be evaluated in 3 phase 3 studies (MajesTEC-3, MajesTEC-9, and MonumenTAL-6) and in MajesTEC-10 (Phase I)**

AUC, area under the curve; Cmax, maximum concentration; DoR, duration of response; MajesTEC, MajesTEC study series; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; QSP, quantitative systems pharmacology; TAL, talquetamab; Teclistamab, bispecific T-cell engager targeting BCMA; tumor, abnormal growth of tissue.

Guo Y, et al. ASH 2024 (Abstract No. 1989).

Teclistamab single agent data at ASH 2024: Insights from real-world experiences

- ***Can we use Teclistamab in elderly patients?***[1]
  - Real-world analysis from US Multiple Myeloma Immunotherapy consortium (n= 385, 83 aged 75 or older)
    - **Elderly** patients had lower % of EMD and trend towards lower incidence of HR-CA and lower proportion of triple-class refractory patients (>> **selection** bias)
    - Comparable safety with better survival likely related to better **patient selection** (mPFS 10.72 vs 5.2 m, p-value 0.005 and mOS NR vs 16.1 m, p-value 0.00479)
  - IMF database (N=81): frail older adults showed a trend towards higher rates of ≥ grade 2 CRS, ≥ grade 2 ICANS as well as ≥3 grade infections. Efficacy was maintained.

- ***Can we do the step-up dosing of Teclistamab in community hospitals?***[2] (n=156, 45 pts in community cohort)
  - High % of patients with prior BCMA-therapy in the academic setting (34.2% vs 22.2%).
  - Higher proportion of ISS1, slightly higher ECOG, lower renal impairement (34.2 vs 17.8%), lower disease burden in community cohort (EMD 38.7% vs 26.7%)
  - Comparable safety: similar incidence of infections, hospitalization due to infections (9.9% vs 6.7%).
  - Higher efficacy (ORR 62.1% vs 81.3%) in the community likely related to better **patient selection**

- ***Tocilizumab prophylaxis in real-world (Teclistamab-Erlanatamab-Talquetamab)***[3] (n=72)
  - Tocilizumab IV 1h prior to SUD1. Overall incidence of CRS with tocilizumab 14%.

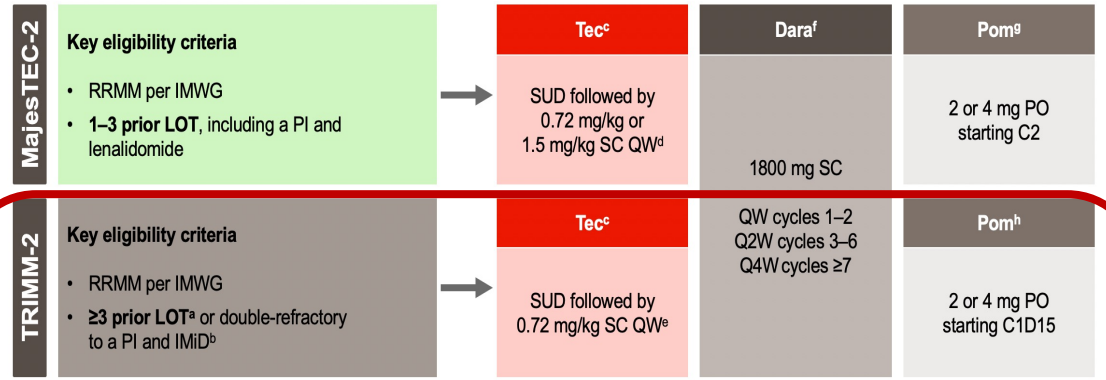
- ***Teclistamab after anti BCMA***[4] (n=193)
  - Lower ORR, VGPR and PFS (4.6 vs 8.2); better PFS if treatment free interval > 8 months

CRS, cytokine release syndrome; ECOG, Eastern Cooperative Oncology Group; EMD, extra medullary disease; HRCA, high-risk cytogenetic abnormalities; ISS, international staging system; IV, intravenous; m, months; mOS, median overall survival; mPFS, median progression free survival; NR, not reached; ORR, objective response rate; US, United States.

1. Pasvolsky O et al, ASH 2024 (Abstract No.0934 - oral presentation); 2. Khan A et al, ASH 2024 (Abstract No. 0933 - oral presentation); 3. Kowalski A et al, ASH 2024 Abstract No. 0932 - oral presentation).4; Dima D at al ASH 2024 Abstract No. 0897

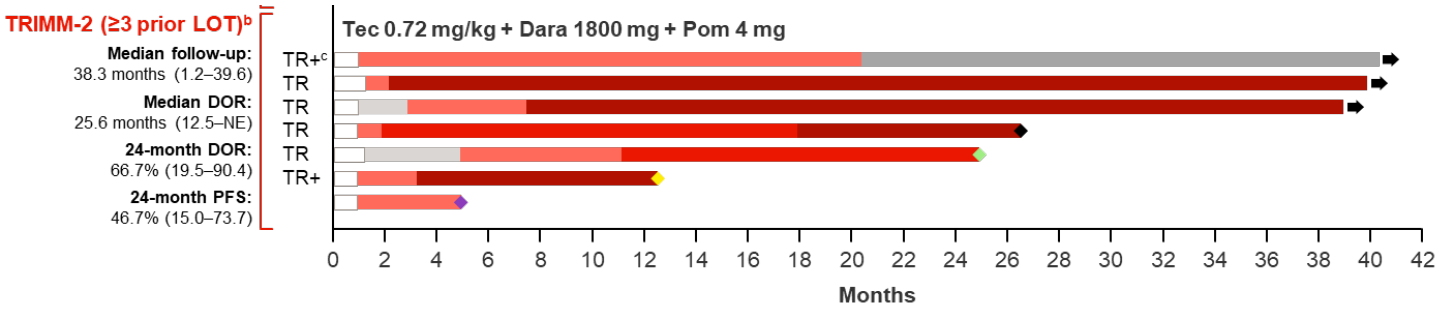
Teclistamab based Combinations: TRIMM-2 study
Teclistamab + daratumumab + pomalidomide

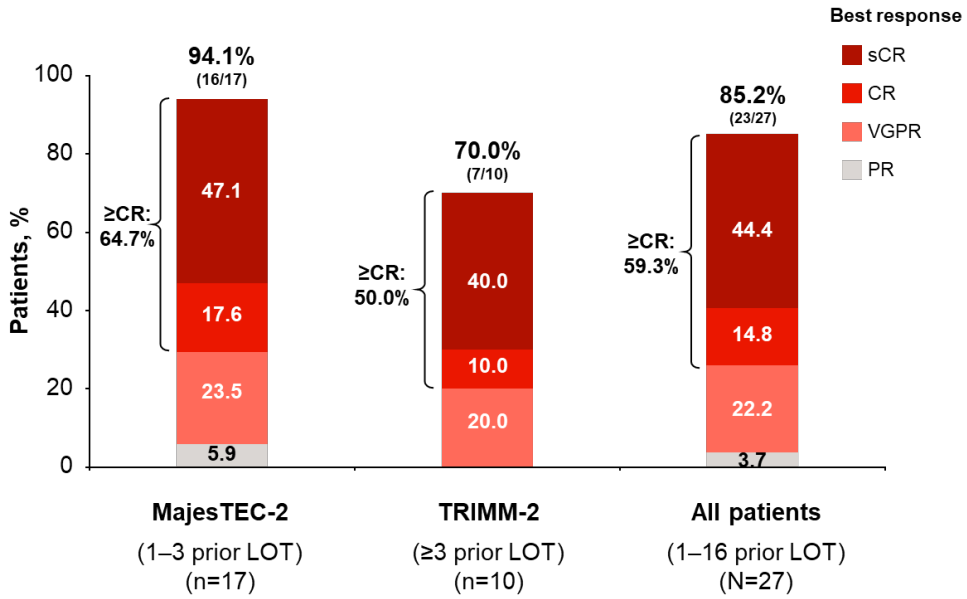
Study design



TRIMM-2: *≥3 PL or double-refractory.[a,b]*
N=10. Median of 4 PL.
70% Triple-class refractory. 30% prior BCMA

	TRIMM-2 (≥3 prior LOT); n=10	
	Any Grade	**Grade 3/4**
Any infection	9 (90.0)	6 (60.0)
Infections[a]		
Upper respiratory tract infection	4 (40.0)	0
Pneumonia	4 (40.0)	4 (40.0)
Sinusitis	4 (40.0)	1 (10.0)
COVID-19	4 (40.0)	1 (10.0)
COVID-19 pneumonia	1 (10.0)	1 (10.0)
Hypogammaglobulinemia		
Hypogammaglobulinemia[b]	10 (100)	
Received IVIG[c]	8 (80.0)	





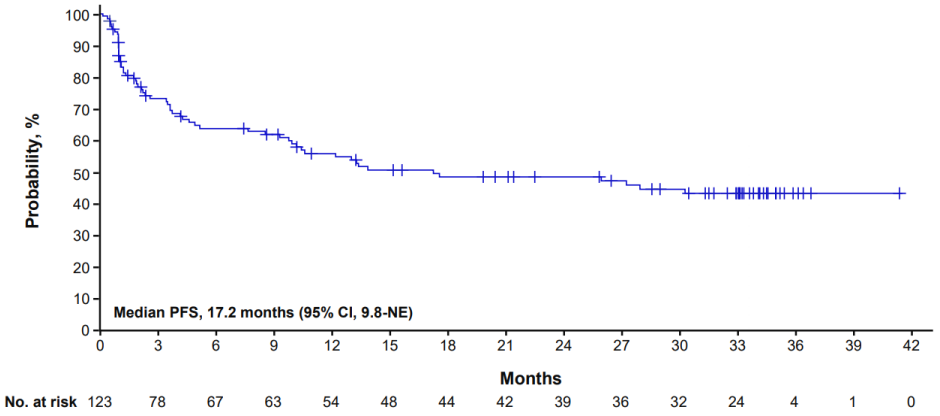
D'Souza A. et al ASH2024

Elranatamab: Phase 2 MagnetisMM-3 trial

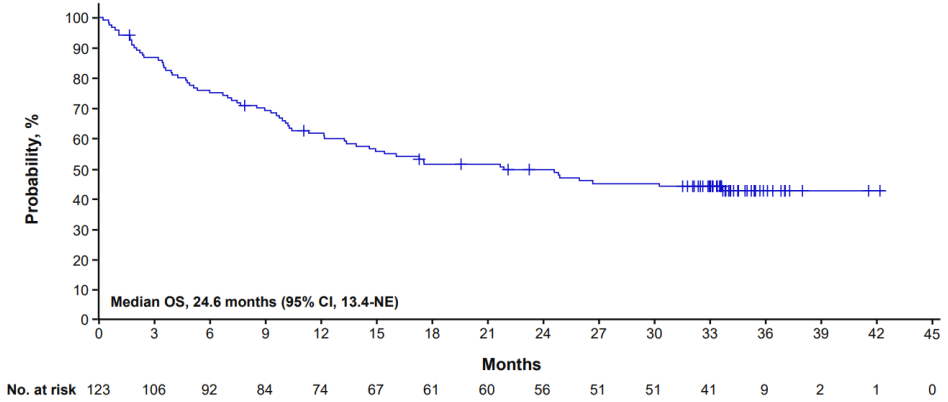
Median FUP 33.9 m

Key inclusion: RRMM ≥ 3 PL, Triple-class refractory (97%); Penta-ref: 41.5%[a] Median age 68 y (36.0-89.0). Median nºPL: 5 (2.0-22.0).

PFS [mPFS 17.2m (9.8 – NE)]



OS [mOS 24.6 m (13.4 –NE)]

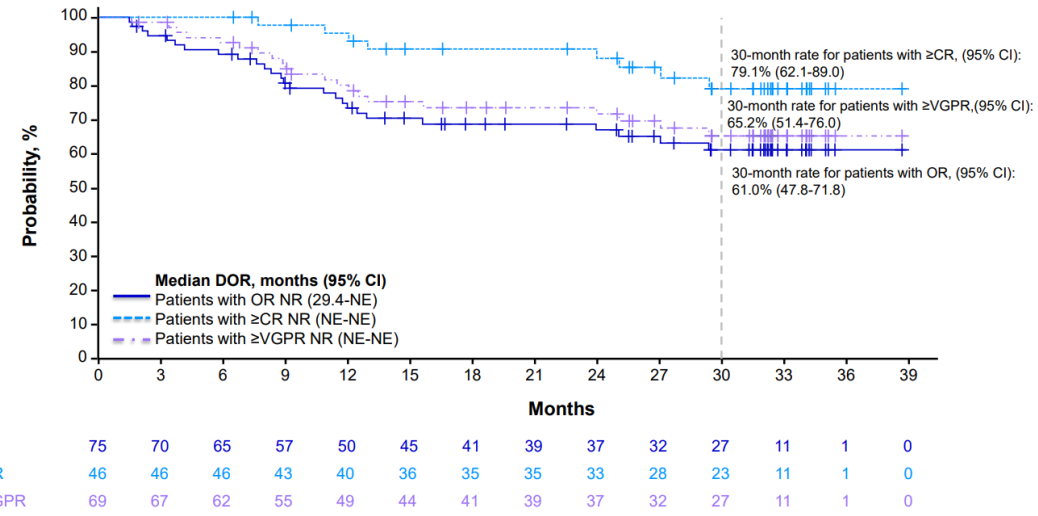


Response

ORR 61.0%, ≥ CR 37.4%; ≥VGPR 47.2%

MRD-negativity at the threshold of 10^{-5} was achieved by 90.3% of those pts in CR/sCR (n=31)

Duration of response



No. at risk													
OR	75	70	65	57	50	45	41	39	37	32	27	11	1	0
Pts with ≥CR	46	46	46	43	40	36	35	35	33	28	23	11	1	0
Pts with ≥VGPR	69	67	62	55	49	44	41	39	37	32	27	11	1	0

Safety:

No new safety signals were observed

[a]Penta-drug refers to ≥2 proteasome inhibitors, ≥2 immunomodulatory drugs, and ≥1 anti-CD38 antibody.

CI, confidence interval; (s)CR, (stringent) stable complete response; DOR, duration of response; mFUP, median follow up; mo, months; NE, not evaluable; NR, not reached; OR, objective response; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; PL, prior lines; pts, patients; Q4W, every 4 weeks; RR, relapsed/refractory; TCE, triple-class exposed; VGPR, very good partial response; .

1. Prince HM, et al. ASH 2024 (Abstract No. 4738 – poster).

Elranatamab Combination: MagnetisMM-20 trial (Erla-Kd)

Median FUP: 8.9m

Key inclusion: RRMM 1-3 PL, K-sensitive. If prior K wash-out at least 6 months. No prior BCMA.
Median nºPL 2 (1-3); TCE 50%, only 1 prior K.
N=12

DL1 Elranatamab 12, 32 and 44mg QW until C7 then Q2W
DL2 12, 32 and 76mg QW until C7 then Q2W
+ Carfilzomib (K) 70mg/m2 weekly*

Safety

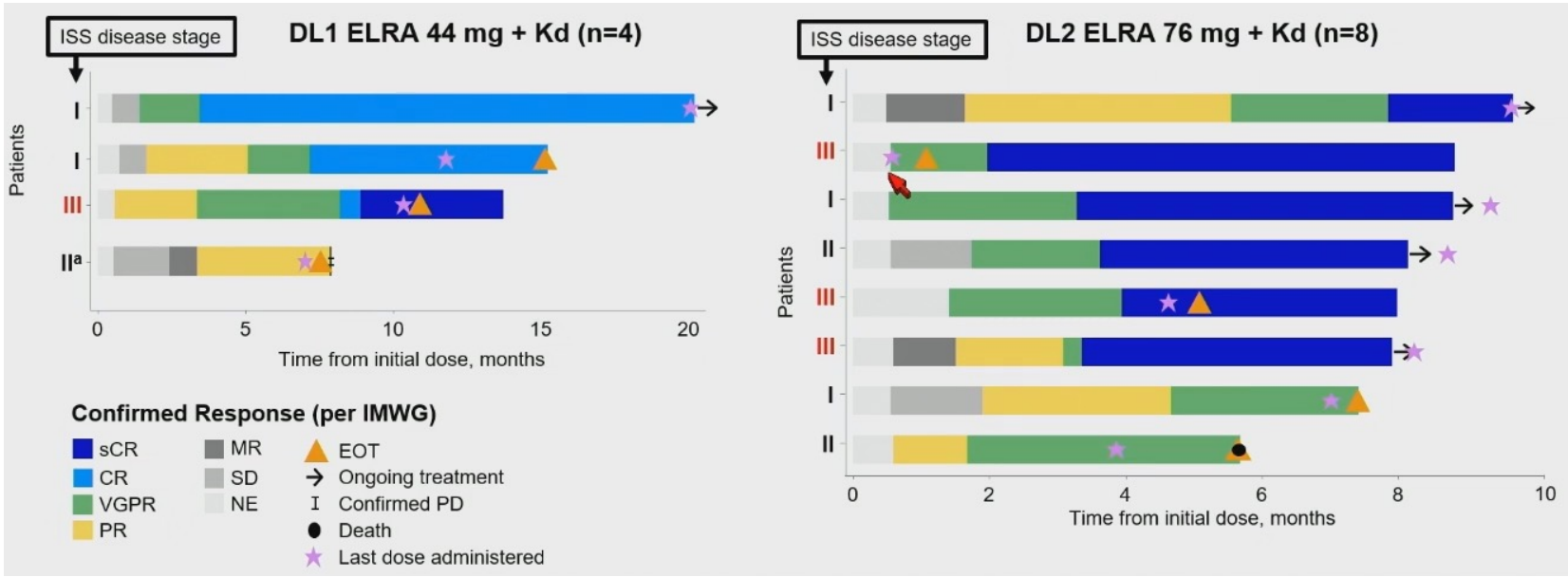
TEAEs	All grade	G3-4
Neutropenia	9 (75%)	9 (75%)
Thrombocytopenia	9 (75%)	5 (41.7%)
Infections	11 (91.7%)	2 (16.7%)
CRS	9 (75%)	0
Diarrhea	6 (50%)	1 (8.3%)
CMV reactivation	6 (50%)	1 (8.3%)

No ICANS was reported
No DLT in 10 evaluable patients

Response

ORR 100%; ≥CR 75%; ≥VGPR 91.7%

Swimmer plot of response per investigator

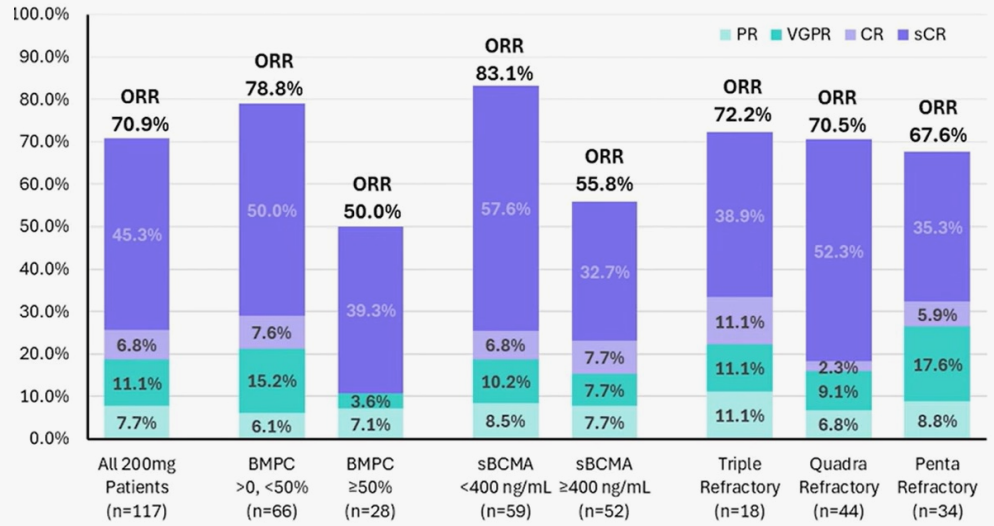


*If patients received 6 or more months of QW ELRA and achieved PR or better (lasting 2 or months), the could change to Q2W dosing at the same DL.
BsAbs, bispecific antibodies; (s)CR, (stringent) stable complete response; CMV, cytomegalovirus; CRS, cytokine release syndrome; D, dexamethasone; DL, dose level; DLT, dose-limiting toxicity; Elra, elranatamab; EOT, end of trial; G, grade; K, carfilzomib; ICANS, immune cell associated neurotoxicity syndrome; IMWG, International Myeloma Working Group; ISS, international staging system; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PL, prior lines; (VG)PR, (very good) partial response; QW, weekly; Q2W, every other week; SD, stable disease; TCE, triple class exposed; TEAE, treatment emergent adverse event.
Tomasson MH, et al. ASH 2024 (Abstract No. 1024 – oral presentation).

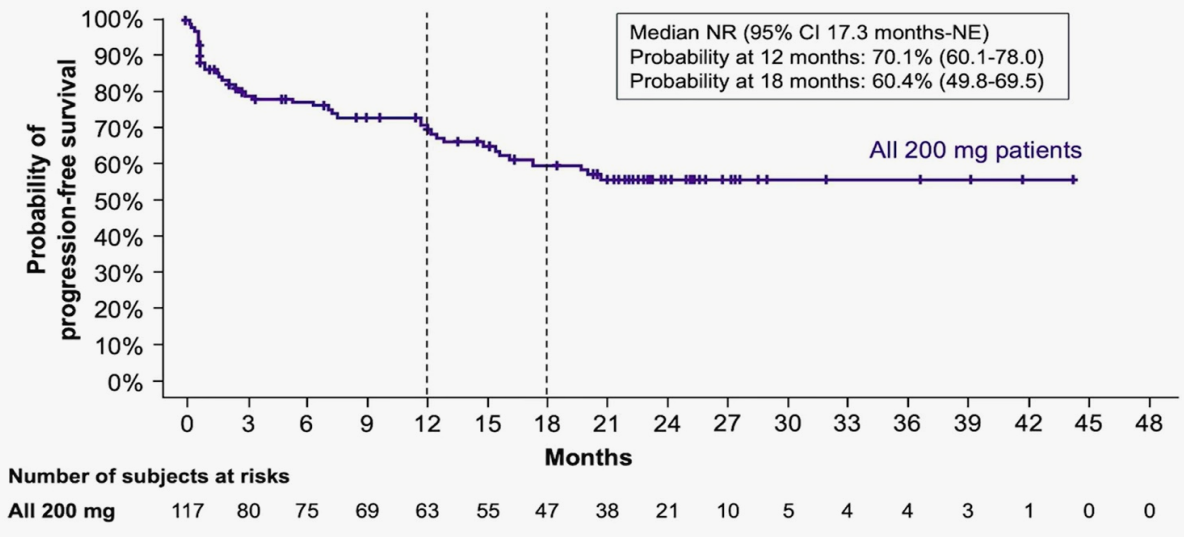
Linvoseltamab Phase 1/2 FIH study in RRMM

Patient characteristics: Median age 70y; ISS III in 17.9%; EMD 14.5%; Median nº PL: 5 (2-19); (N=117; median FU 21.3 months)

ORR in overall population and key selected groups

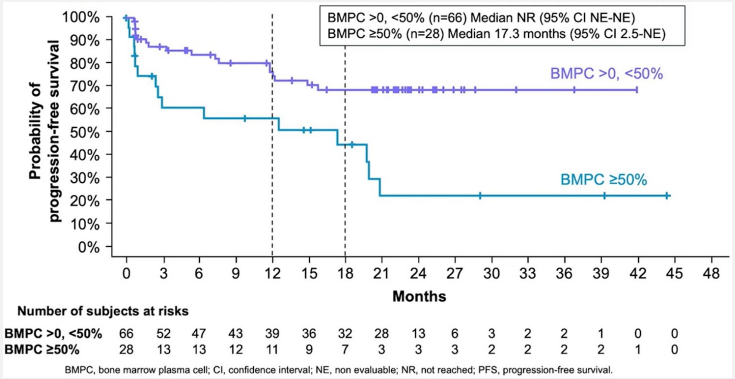


PFS at 200 mg



CI, confidence interval; NE, non evaluable; NR, not reached; PFS, progression-free survival.

BMPC



BMPC, bone marrow plasma cell; CI, confidence interval; NE, non evaluable; NR, not reached; PFS, progression-free survival.

Shorter PFS among pts with high-tumor burden

No new safety signal
Infections 75.2; Grade 3-4 36.8%

CI, confidence interval; (s)CR, (stringent) stable complete response; EMD, extra medullary disease; FIH, first in human; ISS, international staging system; mFUP, median follow up; m/mo, months; NE, not evaluable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; PL, prior lines; (VG)PR, (very good) partial response; RR, relapsed/refractory; TCE, triple class exposed.

Shah M, et al. ASH 2024 (Abstract No. 3369 – poster).

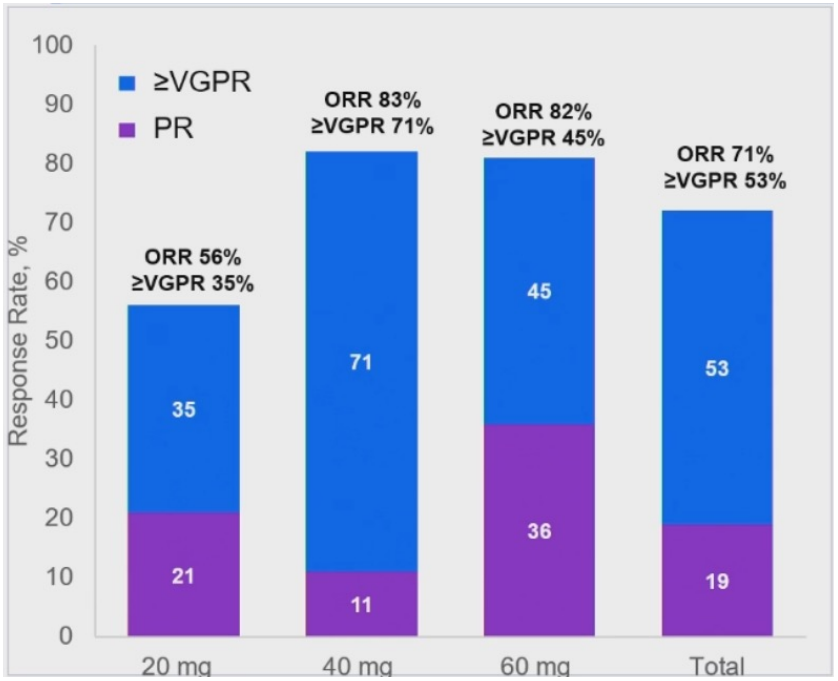
ABBV-383 (etentamig) combination + Dara + Dex

Phase 1b dose escalation and safety expansion study

Median nº PL: 4 (3-10); Prior AntiCD38 was allowed with > 90 days wash-out; AntiCD38-refractory 56%. Triple-class exposed 70%. N=86

ABBV-383 is composed of a ***bivalent BCMA-binding domain with high avidity, a low-affinity CD3-binding domain*** designed to mitigate cytokine release with potential for minimal T-cell exhaustion, and a present but silenced Fc tail resulting in an extended half-life and convenient dosing interval (every 4 weeks [Q4W]).

Efficacy



	Etentamig + Daratumumab-Dexamethasone			
	20 mg n=34[a]	40 mg n=35[a]	60 mg n=11	Total N=80
Median follow-up, months[b] (range)	4 (0–17)	8 (1–13)	8 (1–10)	7 (0–17)
Median time to first response, months (range)	1.1 (1–6)	1.0 (1–4)	1.0 (0–1)	1.0 (0–6)
Depth of response				
sCR/CR	5 (15)	14 (40)	3 (27)	22 (28)
MRD neg ($<10^{-5}$) among evaluable sCR/CR	1/2 (50)	12/12 (100)	3/3 (100)	16/17 (94)

Safety

Adverse events	*All grades*	*Grade 3-4*
Neutropenia	48%	44%
CRS	**29%**	**4%**
ICANs	4%	1%
Infections	67%	26%

- 10 patients (12%) discontinued due to AEs
- 12 TEAE leading to death (none deemed related to the study drug)

[a]Data combined for dose-escalation and safety expansion cohorts. [b]Based on N=86 total patients in the full analysis set. Median follow up is 16 months (1–17) and 4 months (0–5) for 20 mg dose-escalation and –expansion cohorts, respectively, and 13 months (9–13) and 7 months for 40 mg dose-escalation and –expansion cohorts, respectively.

(s)CR, (stringent) stable complete response; CRS, cytokine release syndrome; ICANS, immune cell associated neurotoxicity syndrome; MRD, minimal residual disease; ORR, objective response rate; (VG)PR, (very good) partial response; TEAE, treatment emergent adverse event.

1Rodriguez C, et al. ASH 2024 (Abstract No. 496 – oral presentation).

Outline

Bispecific Antibodies anti-BCMA

Bispecific Antibodies anti-GPRC5D

Bispecific Antibodies anti-FcRH5

Novel Constructs

GPRC5D × CD3 T-cell bispecific antibody: Talquetamab

MonumenTAL-1, Phase I/II study

Trial design[2]

RP2D 0.4 mg/kg QW SC
- Prior BCMA-targeting ADC treatment allowed
- Prior T-cell redirecting therapy-naïve

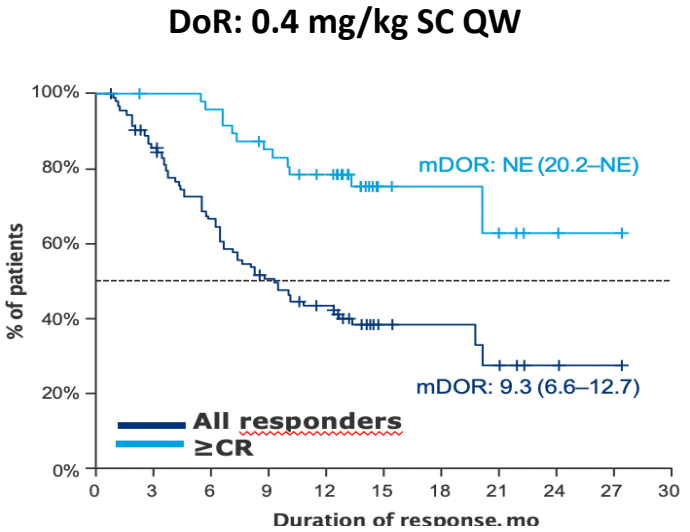
(n=143; n=21 Phase I and n=122 Phase II)

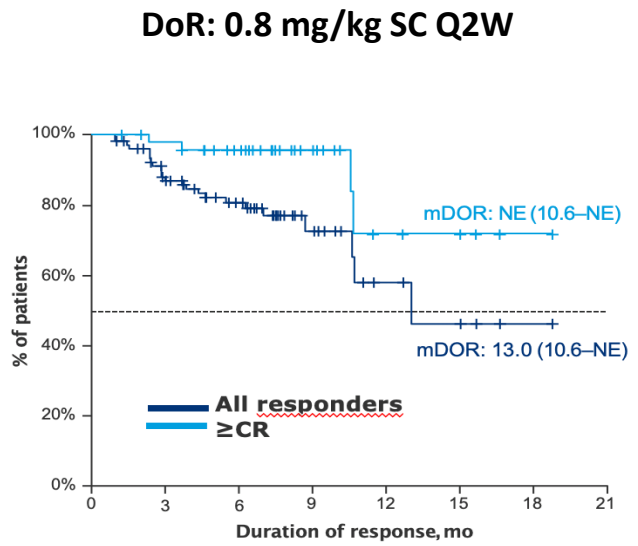
RP2D 0.8 mg/kg Q2W SC
- Prior BCMA-targeting ADC treatment allowed
- Prior T-cell redirecting therapy-naïve

(n=145; n=36 Phase I and n=199 Phase II)

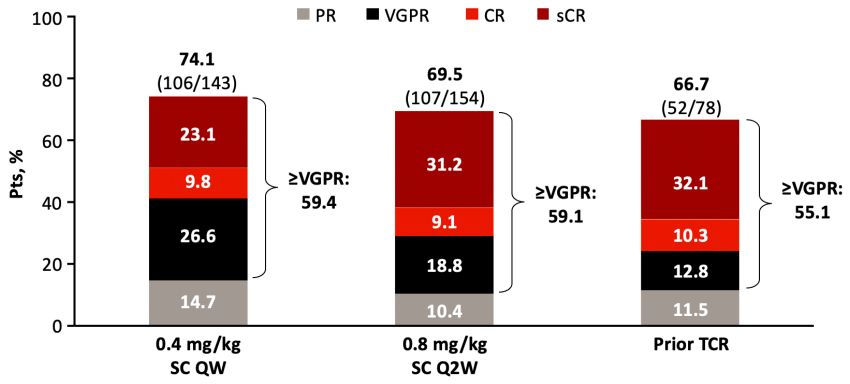
100% triple-class exposed
69–74% triple-class refractory

Duration of response[3]





Response rates[2]



Efficacy Outcomes	0.4 mg/kg QW (n = 143)	0.8 mg/kg Q2W (n = 154)	Prior TCR (n = 78)
Median follow-up, mo	29.8	23.4	20.5
Median DOR, mo (95% CI)†	9.5 (6.7–13.4)	17.5 (12.5–NR)	NA‡
Median PFS, mo (95% CI)	7.5 (5.7–9.4)	11.2 (8.4–14.6)	7.7 (4.1–14.5)
24 mo OS rate (95% CI)	60.6 (51.7–68.4)	67.1 (58.3–74.4)	57.3 (43.5–68.9)

AE, adverse event; BCMA, B-cell maturation antigen; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; ICANS, immune cell effector cell-associated neurotoxicity syndrome; mPFS, median progression-free survival; PR, partial response; NA, not applicable; NR, not reported; Q2W, every 2 weeks; QW, weekly; RP2D, recommended Phase II dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

1. Chari A, et al. N Engl J Med 2022;387:2232-2244; 2. Schinke CD, et al. ASCO 2023 (Abstract No. 8036 – oral presentation); 3. Chari A, et al. ASH 2022 (Abstract No. 157 – presentation); Rasche L. et al, EHA24.

Targeting GPRC5D after anti-BCMA treatment: Real word data

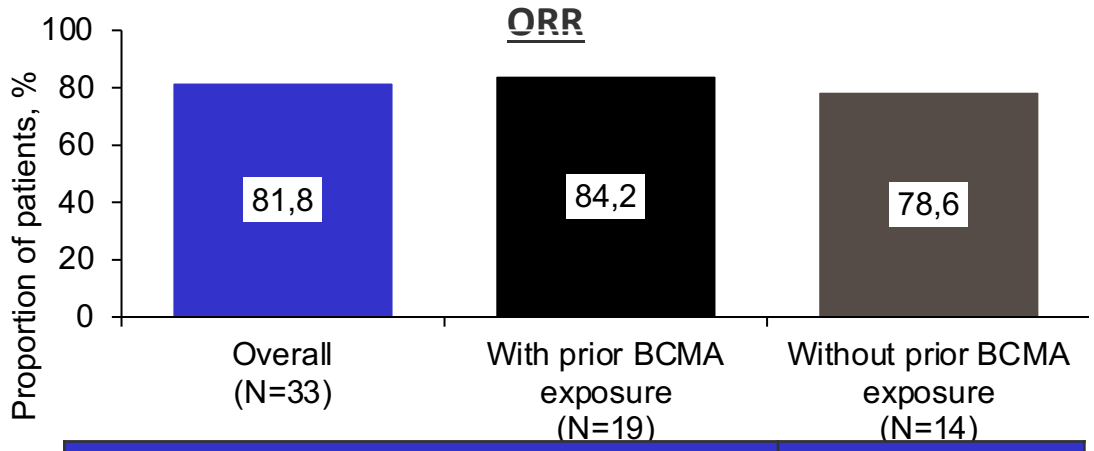
Talquetamab, GPRC5DxCD3 :
US Single Center[1]

	BCMA CAR-T naïve (n=19)	BCMA CAR-T exposed (n=18)	BCMA BsAb exposed (n=6)	BCMA CAR-T and BsAb exposed (n=12)
ORR, n (%)	13 (68)	14 (78)	3 (50)	6 (50)
CR, n (%)	2 (11)	11 (61)	1 (17)	4 (33)

Talquetamab, GPRC5DxCD3 :
US Retrospective 5 Centers[2]

Subgroup	ORR, n/N (%)	P value
BDT as immediate prior line		
Yes	12/25 (48.0)	<0.01
No	29/38 (80.6)	
Time from BDT		
<6 months	21/37 (56.8)	0.02
≥6 months	22/26 (84.6)	

Talquetamab, GPRC5DxCD3 :
Real word Acentrus STUDY[3]



AEs of Interest	N=50
Dysgeusia, n (%)	34 (68.0)
Improvement	
Yes	21 (61.8)
Days to improvement, mean [median]	79.0 [77.5]
No	6 (17.6)
Missing/unknown	7 (20.6)
Decrease in weight, n (%)	24 (48.0)
Change from baseline (median, %)	-6.5%
<5	9 (37.5)
5 - <10	12 (50.0)
10 - <20	3 (12.5)
≥20	0 (0.0)

1. Graeter A, et al. ASH 2024 (Abstract No. 5168 – poster); 2. Shakih H, et al. ASH 2024 (Abstract No. 5170 – poster). 3. Rodriguez C, et al. ASH 2024 (Abstract No. 5157 – poster)

Outline

Bispecific Antibodies anti-BCMA

Bispecific Antibodies anti-GPRC5D

Bispecific Antibodies anti-FcRH5

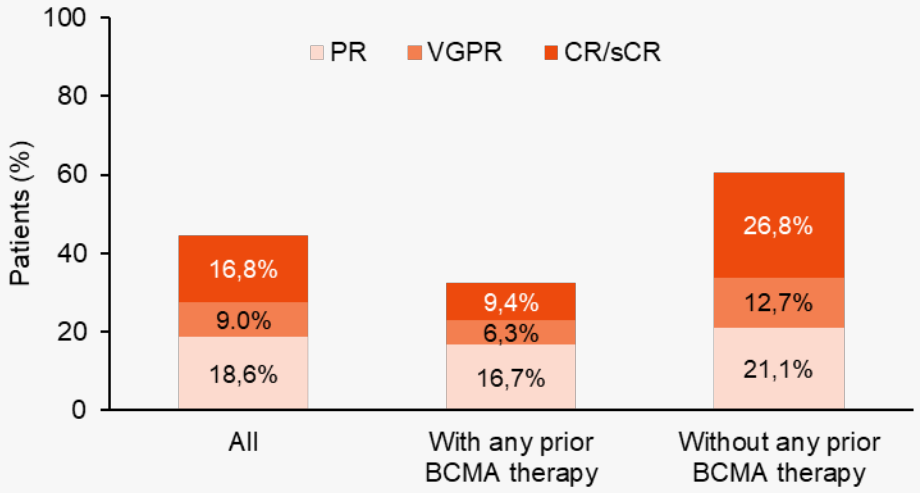
Novel Constructs

Cevostamab (FcRH5-CD3 BsAbs)_GO39775 phase 1 trial

Key inclusion: RRMM for which no stablised therapies is available. Prior BCMA or GPRC5d were allowed.
Median nº PL 6 (2-18); 57.5% prior BCMA, 35.9% prior CAR, 24% prior BSAbs, 20.4% prior ADC
N=324

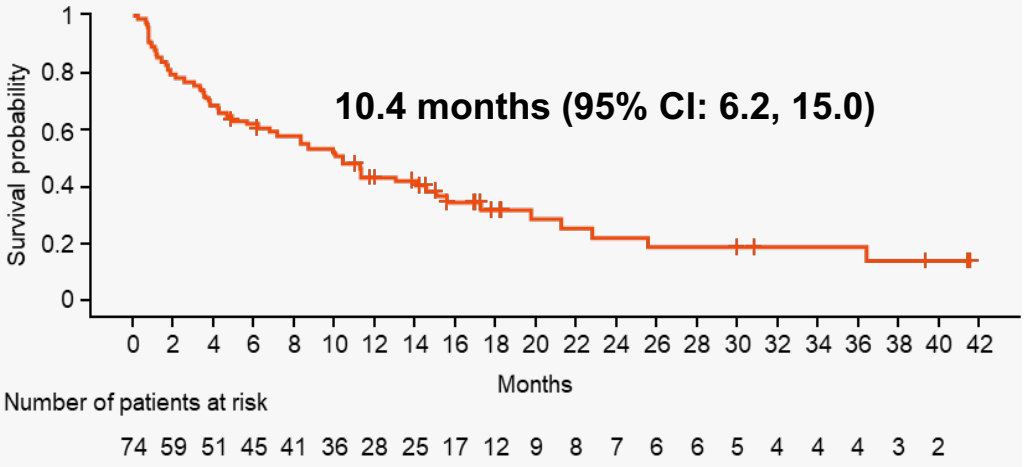
Fixed duration (17 cycles = 12 m) Several cohorts evaluated
167 patients were treated at 160mg full dose with different SUD
0.3/1.2/3.6/160mg Q3W TS cohort >> Schedule moving forward

ORR at the 160 mg TD level in all patients and in patient subgroups by prior BCMA therapy



- median time to first response: 1.4 m (range: 0.5–4.6)
- median time to best response: 2.6 m (range: 0.5–13.4)

DoR at the 160 mg TD level among patients in PR+ (n=74)



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

DoR after completion of therapy (17 cycles)

- 28 patients completed 17 cycles of treatment at the 160mg TD level
- 9 patients had responses ≥6 months from completion (8/9 in CR/sCR at completion)
- 6 patients had ongoing responses of <6 months
- 1 patient in sCR withdrew from study

Time on study in months, median (range): 14.8 (0.5-48.8).†
*Unvalidated analysis; data cut-off: Aug 22, 2024; †Includees time after completion and/or discontinuation of treatment when AE reporting was limited to 90 days after the last dose of study drug of another anti-cancer therapy, whichever occurred first, and to treatment-related SAEs thereafter.
ADC, antibody-drug conjugate; BsAbs, bispecific antibodies; CAR, chimeric antigen receptor; CI, confidence interval; (s)CR, (stringent) stable complete response; (m)DoR, (median) duration of response; mFUP, median follow up; m, months; ORR, objective response rate; PFS, progression-free survival; PL, prior lines; (VG)PR, (very good) partial response; Q3W, every 3 weeks; RR, relapsed/refractory; SAE, serious adverse event; SUD, step-up dose; TD, total dose.
Richter J, et al. ASH 2024 (Abstract No. 1021 – presentation).

Cevostamab (FcRH5-CD3 BsAbs)_GO39775 phase 1 trial

Adverse events at the 160mg TD level (n=167)

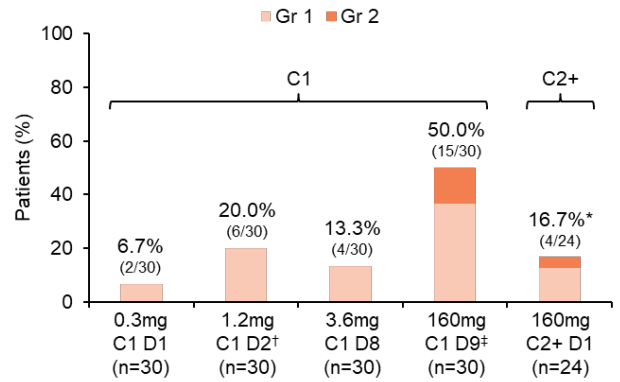
N (%) unless stated	Any	Any related
Time on study in months, median (range)*	14.8 (0.5–48.8)	
AE	167 (100)	154 (92.2)
Gr 3–4	96 (57.5)	72 (43.1)
Gr 5 (fatal) excluding PD	10 (6.0)†	3 (1.8)‡
SAE	96 (57.5)	47 (28.1)
AE leading to treatment discontinuation	30 (18.0)	13 (7.8)

- Most Gr 3–4 AEs were reversible cytopenias
- Almost all CRS was Gr 1–2, with the profile influenced by the step-dosing regimen

CRS Events at the RP2D dose (n=30)

	C1 0.3/1.2/3.6/160mg TS
N (%) of patients with:	n=30
CRS	19 (63.3)
Gr 1	14 (46.7)
Gr 2	5 (16.7)
Gr 3+	0
CRS leading to discontinuation	0
N (%) of patients receiving:	n=30
Tocilizumab	9 (30.0)
Steroids	4 (13.3)
Tocilizumab and steroids	2 (6.7)
N (%) of CRS events:	n=35
Resolved at data cut-off	35 (100)

CRS in the C1 0.3/1.2/3.6/160mg TS cohort by dose and Gr



Infections at 160 mg (n=167)

N (%) of patients	n=167
AE of infection	91 (54.5)
Gr 3–5 AE of infection	32 (19.2)
Gr 3	24 (14.4)
Gr 4	2 (1.2)
Gr 5 (fatal)	6 (3.6)
SAE of infection	37 (22.2)
AE of infection leading to treatment discontinuation	10 (6.0)

N (%) of patients	n=167
Pneumonia	16 (9.6)
URI	14 (8.4)
UTI	12 (7.2)
Rhinovirus infection	9 (5.4)
COVID-19	8 (4.8)
Sinusitis	6 (3.6)
Viral URI	6 (3.6)
Pneumonia viral	4 (2.4)
Conjunctivitis	4 (2.4)
Oral candidiasis	4 (2.4)
Skin infection	4 (2.4)

AE, adverse event; BsAbs, bispecific antibodies; Cx, cycle x; CRS, cytokine release syndrome; Dx, day x; Gr, grade; PD, progressive disease; RP2D, recommended Phase II dose; SAE, serious adverse event; URI, upper respiratory tract infection; UTI, urinary tract infection; TD, total dose.

Richter J, et al. ASH 2024 (Abstract No. 1021 – presentation).

Outline

Bispecific Antibodies anti-BCMA

Bispecific Antibodies anti-GPRC5D

Bispecific Antibodies anti-FcRH5

Novel Constructs

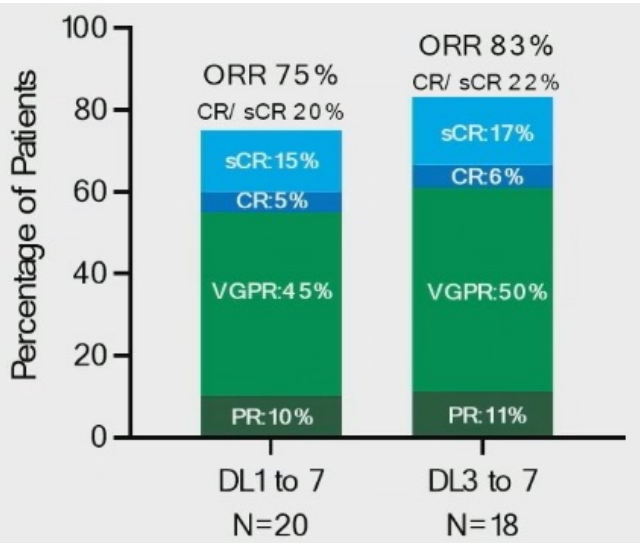
ISB 2001 (BCMAxCD38xCD3 trispecific antibody)
FIH Dose escalation Ph1 trial

Key inclusion: TCE RRMM. Prior CAR, BSABs and BCMA allowed. N=20
Median nº PL 6 (3-11); Triple-class refr 5 (25%). AntiBCMA CAR n=2, AntiBsABs n=9 [4 GPRC5d, 6 FcRH5, 1 BCMA]. 5 patients with prior BCMA-ADC. EMD in 30%.

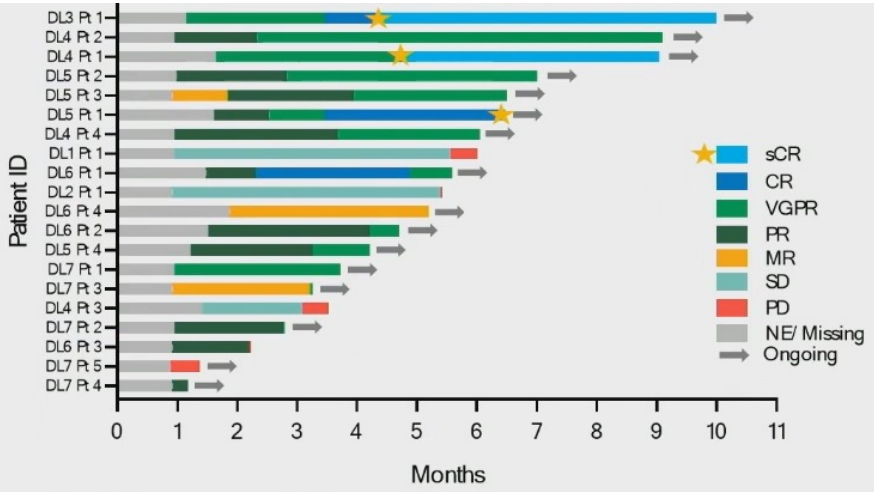
ISB2001 SUD 1 (C1D1), C1D4 SUD2 and weekly dosing

Response

ORR



DoR



Median follow up 6 months (range: 2-10)

First objective response observed at DL3 (sCR, MRD negative at 10^{-5} level)

Median time to first response was 36 days (range: 29-57)

Safety

TEAEs	All grade	Grade 3	Grade 4
Neutropenia	7 (35%)	3 (15%)	3 (15%)
Related infections	9 (45%)	3 (15%)	0
CRS	15 (75%)	0	0
Median time to CRS 3 days (1-118) Median duration of CRS: 2 (1–8) days			
No neurological AEs or ICANS			

- Responses were maintained in patients refractory to antiCD38 MoAb
- Responses in patients without **any prior CAR/BsAbs (n=10): ORR 90%; sCR 30%.**
- ORR in patients with **prior CAR or BsAbs (n=8) 75%, sCR 13%**
- ORR in patients with **prior BCMA therapy (n=7) 86%, CR 14%.**

ADC, antibody drug conjugate; AE, adverse event; BsAbs, bispecific antibodies; C, cycle; CAR, chimeric antigen receptor; (s)CR, (stringent) stable complete response; CRS, cytokine release syndrome; D, day; DL, dose level; DoR, duration of response; EMD, extra medullary disease; FIH, first in humans; ICANS, immune cell associated neurotoxicity syndrome; mAb, monoclonal antibody; MRD, minimal residual disease; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PL, prior lines; (VG)PR, (very good) partial response; SD, stable disease; SUD, step-up dose; TCE, triple class exposed; TEAE, treatment emergent adverse event.

1. Quach H, et al. ASH 2024 (Abstract No. 1026 – oral presentation).

EMB06 (2+2 BCMAxCD3 BsAbs): Ph1 dose escalation study

Novel 2+2 BCMA×CD3 features tetravalent binding domains in cis-configuration and optimized anti-CD3 arms.

Key eligibility: RRMM ≥2 prior lines. Prior PI and IMIDs exposure. AntiCD38 if accesible. N=40 , median 3 prior lines

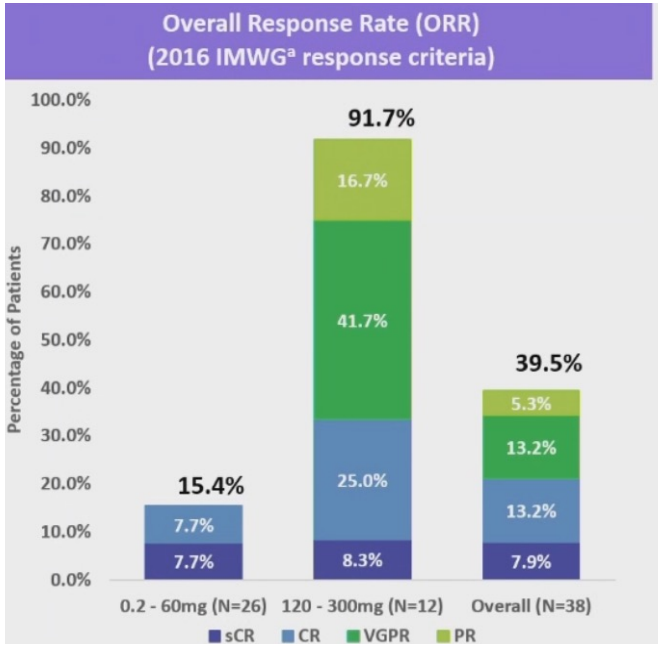
Dosing Schedule: 1-2 SUD followed by weekly dosing

Safety

TEAEs	All grade	G3-4
Neutropenia	17 (42.5%)	10 (25%)
Thrombocytopenia	13 (32.5%)	8 (20%)
Fever	14 (35%)	1 (2.5%)
Infections	28 (70%)	15 (37.5%)
Opportunistic infections	3 (7.5%)	1 (2.5%)

- No ≥G3CRS
- **4 deaths from TEAEs included: 3 PD and 1 cardiac failure.**
- TEAEs leading to dose interruption 23 (57.5%)

Response



Response	0.2-60mg (N=27)	120-300mg (N=13)	Overall (N=40)
Response-evaluable patients,[b] n	26	12	38
ORR, n (%)	4 (15.4)	11 (91.7)	15 (39.5)
Rate of MRD negativity, n/m* (%)	3/4 (75)	4/4 (100)	7/8 (87.5)
Time to response (months), median (range)	1.2(1.2-2.1)	1.2 (1.1-2.1)	1.2 (1.1-2.1)
DOR (months), median (95% CI)†	NR (22.1, NE)	NR	NR (22.1, NE)
DOR Rate % (95% CI) @ 9 months†	100 (100, 100)	100 (100, 100)	100 (100, 100)
PFS (months), median (95% CI)†	2.1 (1.2, 3.0)	NA	3.0 (1.9, NA)

AE, adverse event; BsAbs, bispecific antibodies; CI, confidence interval; (s)CR, (stringent) stable complete response; CRS, cytokine release syndrome; DLT, dose limiting toxicity; DoR, duration of response; EMD, extra medullary disease; IMID, immunomodulatory drug; MRD, minimal residual disease; ORR, objective response rate; PFS, progression free survival; PI, proteasome inhibitor; (VG)PR, (very good) partial response; RR, relapsed/refractory; SUD, step-up dose; TEAE, treatment emergent adverse event.

Tan PT, et al. ASH 2024 (Abstract No. 498 – presentation).

Conclusions

Bispecific Antibodies anti-BCMA:

-Teclistamab and Erlanatamab single agent in late lines ORR ～60%, mPFS 11-17 months;

-Tec real life: importance of pt selection? Dose Optimization?

Bispecific Antibodies anti-GPRC5D:

-Talquetamab ORR ～ 70%; mPFS 7-11 months.

- Role for sequencing after BCMA? Dose/Schedule optimization?

Bispecific Antibodies anti-FcRH5

-Cevostamab ORR ～ 45%; mduration of response 10 months ; fixed duration

Future Development

- Novel Constructs under development

- Combo under evaluation → is there a role for combo in late lines?

Thank you

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