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Presente e Futuro della Terapia Anticorpale nel Mieloma Multiplo

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Disclosures of Monica Galli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen			x			x	
BMS			x			x	
GSK			x			x	
Janssen			x			x	
Menarini						x	
Sanofi			x			x	
Takeda			x			x	

Pivotal Randomized Phase 3 Trials of Monoclonal Antibody Therapy in Newly Diagnosed Multiple Myeloma

Clinical trial	Patient population	Arm (n=number of patients)	Overall response (%)	Median progression-free survival (months)	Hazard ratio (*P* value)
ALCYONE[12]	Transplant-ineligible NDMM	D-VMP (n=350)	91	36.4	0.42 (*P*<.001)
		VMP (n=356)	74	19.3	
MAIA[11]	Transplant-ineligible NDMM	D-Rd (n=368)	92.9	61.9	0.53 (*P*<.001)
		Rd (n=369)	81.6	34.4	
CASSIOPEIA[9]	Transplant-eligible NDMM	D-VTd (n=543)	93	NR	0.47 (*P*<.001)
		VTd (n=542)	90	NR	

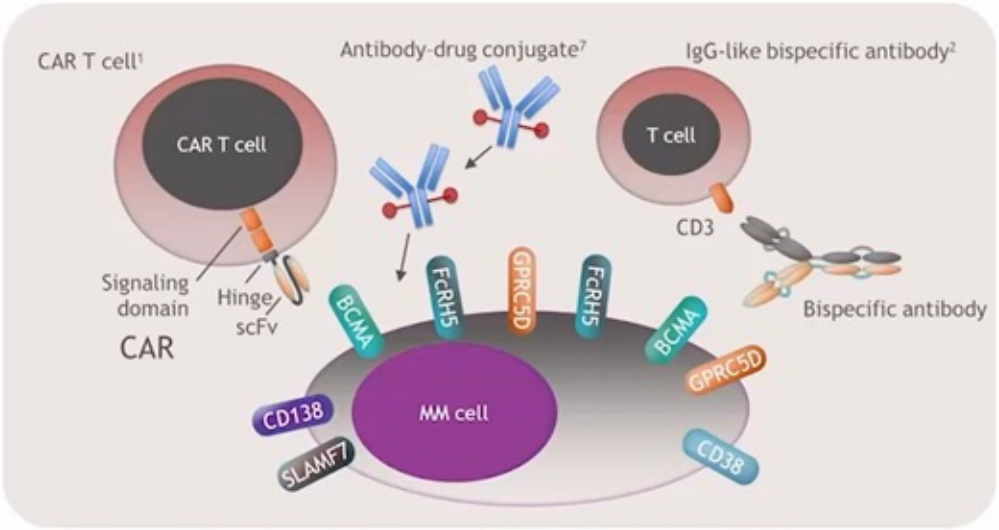
Modified from Cipkar C et al. ASH Educational 2022

Pivotal Randomized Phase 3 Trials of Monoclonal Antibody Therapy in Relapsed/Refractory Multiple Myeloma

Clinical trial	Patient population	Arm (n=number of patients)	Overall response (%)	Median progression-free survival (months)	Hazard ratio (*P* value)
ELOQUENT 3[21]	RRMM, at least 2 prior lines	E-Pd (n=60)	53	10.3	0.54 (*P*=.008)
		Pd (n=57)	26	4.7	
APOLLO[7]	RRMM, at least 1 prior line	D-Pd (n=151)	69	12.4	0.63 (*P*=.0018)
		Pd (n=153)	46	6.9	
ICARIA-MM[17]	RRMM, at least 2 prior lines	I-Pd (n=154)	63	11.5	0.6 (*P*=.001)
		Pd (n=153)	32	6.5	
POLLUX[6]	RRMM, at least 1 prior line	D-Rd (n=286)	93	44.5	0.44 (*P*<.001)
		Rd (n=283)	76	17.5	
ELOQUENT 2[20]	RRMM, 1–3 prior lines	E-Rd (n=321)	79	19.4	0.71 (*P*<.001)
		Rd (n=325)	66	14.9	
CANDOR[8]	RRMM, 1–3 prior lines	D-Kd (n=312)	84	NR	0.62 (*P*=.003)
		Kd (n=154)	75	15.8	
IKEMA[18]	RRMM, 1–3 prior lines	I-Kd (n=179)	87	NR	0.53 (*P*<.001)
		Kd (n=123)	83	19.2	
CASTOR[5]	RRMM, at least 1 prior line	D-Vd (n=251)	83	16.7	0.31 (*P*<.001)
		Vd (n=247)	63	7.1	

Cipkar C et al.
ASH Educational 2022

Immunotherapeutic Approaches & Targets in MM



- **ADC:**
  - Belantamab
  - MEDI2228
- **Bispecifics:**
  - AMG701
  - Teclistamab, talquetamab
  - Elranatamab
  - REGN5458
  - TNB-383B
  - CC-93269
  - Cevostamab
- **CAR T:**
  - Ide-cel
  - Cilta-cel
  - p-BCMA-101
  - CT053
  - ALLO-715

BCMA:[3]
- Selectively overexpressed in plasma cells
- Promotes proliferation and survival of MM cells

GPRC5D:[4,5]
- Highly and selectively expressed in MM
- Distribution is similar to but independent of BCMA

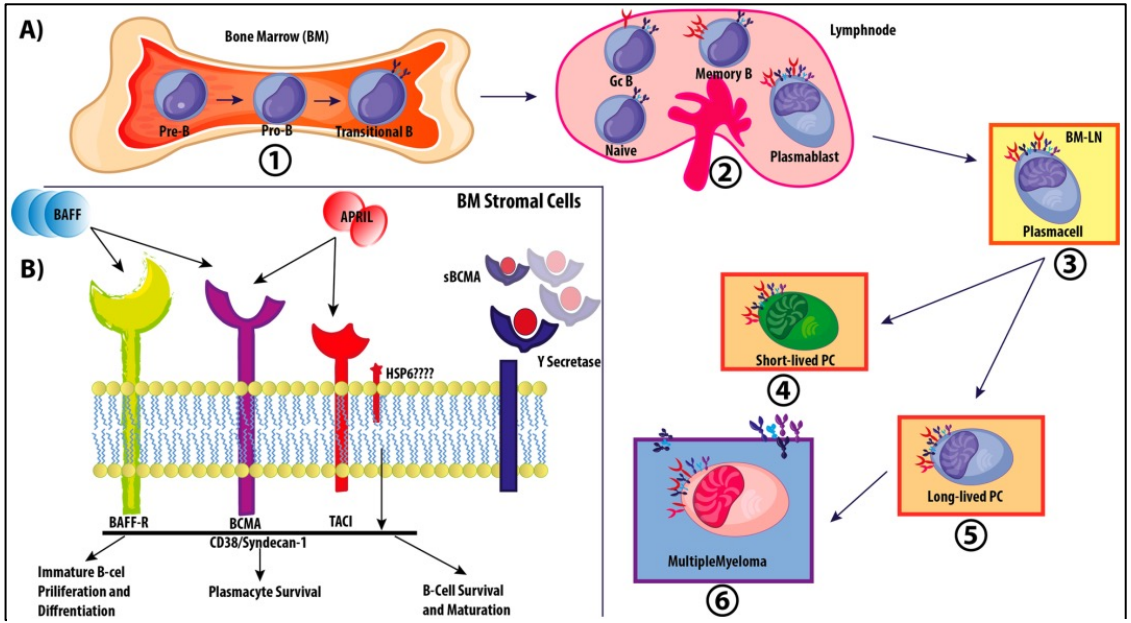
FCRH5:[6]
- High levels of expression on MM cells
- Normally expressed in plasma cells only

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; FcRH5, Fc receptor-like 5; GPRC5D, ide-cel, idecabtagene vicleucel; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; scFv, single chain variable fragment.

1. Rodriguez-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 et al. Blood Advances, 2020;5(8);2195-2
5. Smith EL, et al. Sci Transl Med. 2020;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31;383-395. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155.

Images adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.

BCMA Expression in Plasma Cells



BCMA is a non-tyrosine kinase receptor surface GP, expressed on normal & malignant plasma cells.

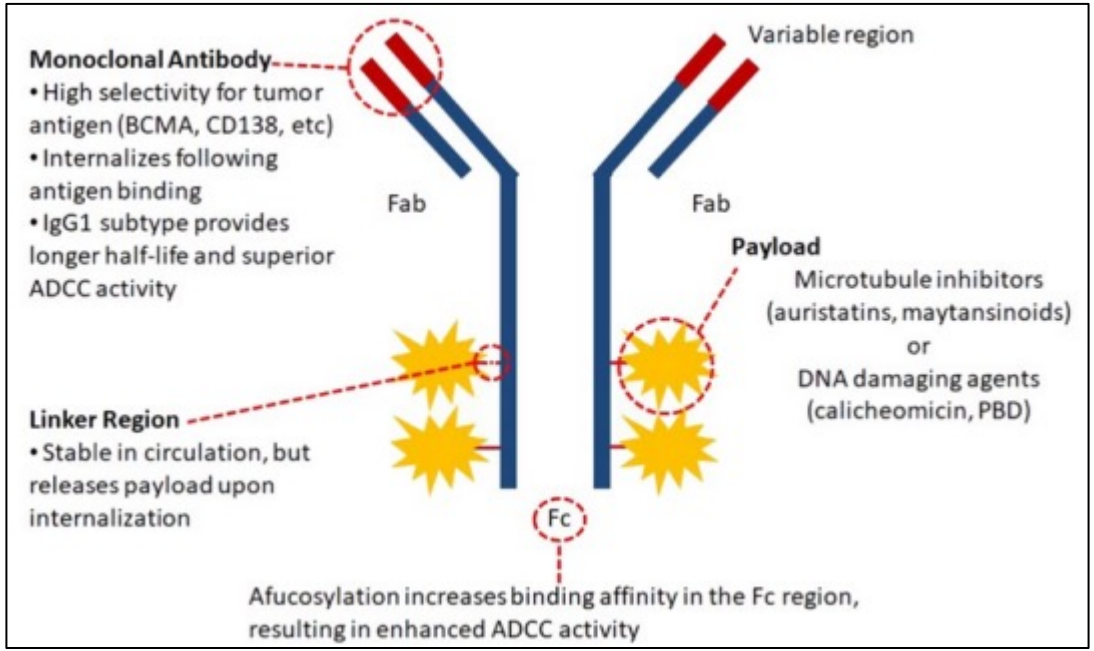
By its ligand, APRIL, BCMA increases survival and long-lived plasma cells.

BCMA can be regarded as a relatively exclusive MM marker.

BCMA expression is maintained through disease recurrence, extramedullary spread and residual disease

Lee et al. BJH 2016;174:911; Nobari et al. J Translat Med 2022;20:82

Characteristics of Antibody Drug Conjugates



ADCC: antibody-dependent cellular cytotoxicity

The components of the ADC and its target antigen influence the efficacy and safety profile.

The cytotoxic drug (payload or warhead) is the ultimate effector component, inducing direct cell killing either by inhibiting microtubule formation or directly damaging cellular DNA.

The conjugation chemistry of the linker determines the drug:antibody ratio, which critically influences the ADC potency.

Cipkar C et al. ASH Educational 2022

Belantamab mafodotin (GSK2857916): Humanized, afucosylated, IgG1 BCMA-targeted ADC that neutralizes soluble BCMA

Preclinical studies demonstrate selective, potent activity

Cytotoxic agent MMAF (non-cell permeable highly potent auristatin)

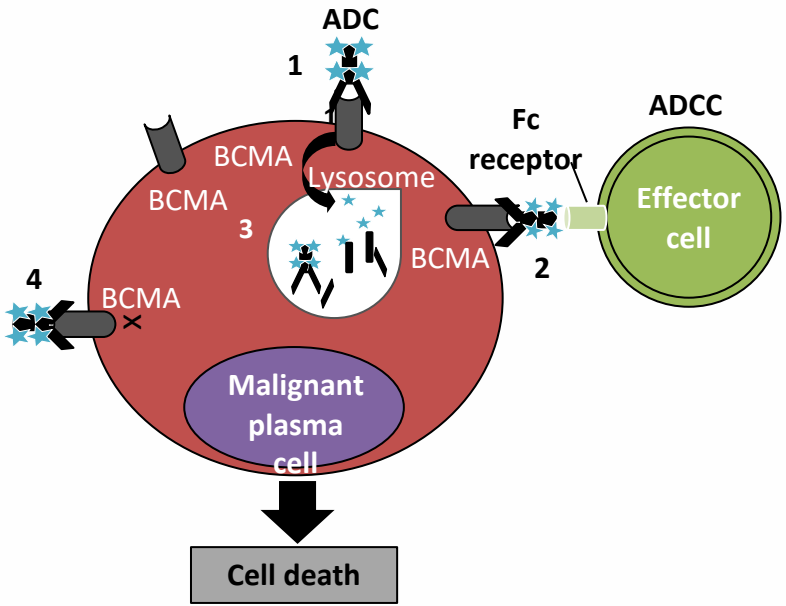
Afucosylation-enhanced ADCC

Linker is stable in circulation

- **Belantamab mafodotin was granted accelerated FDA approval in August 2020 as therapy for patients with R/R MM who have received ≥ 4 therapies, including a PI, and IMiD, and an anti-CD38 monoclonal antibody**

Four mechanisms of action:

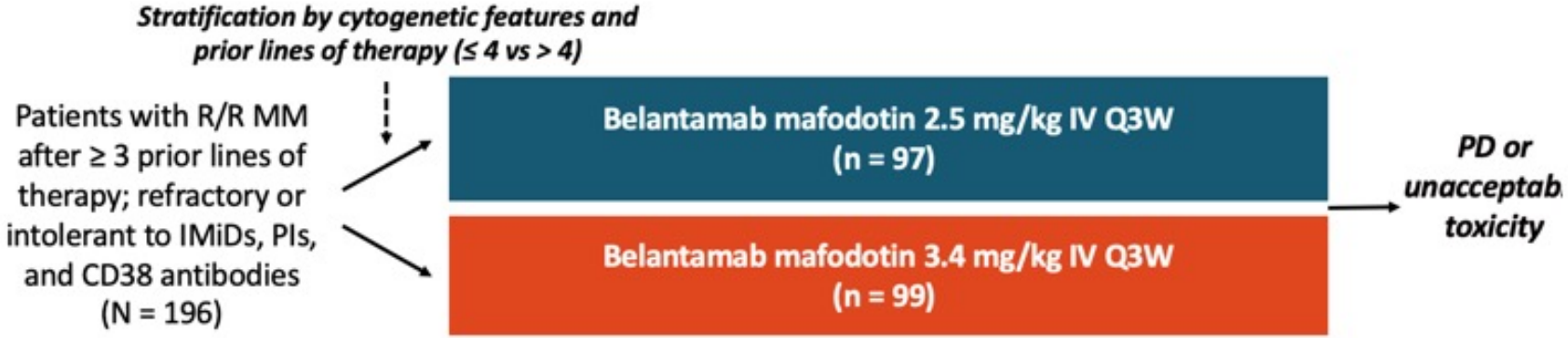
1. ADC
2. ADCC
3. Immunogenic cell death
4. BCMA receptor signaling inhibition



Tai. Blood. 2014;123:3128. Trudel. Lancet Oncol. 2018;19:1641.
Trudel. Blood Cancer J. 2019;9:37.

DREAMM-2: a two-arm, randomised, open-label, phase 2 study

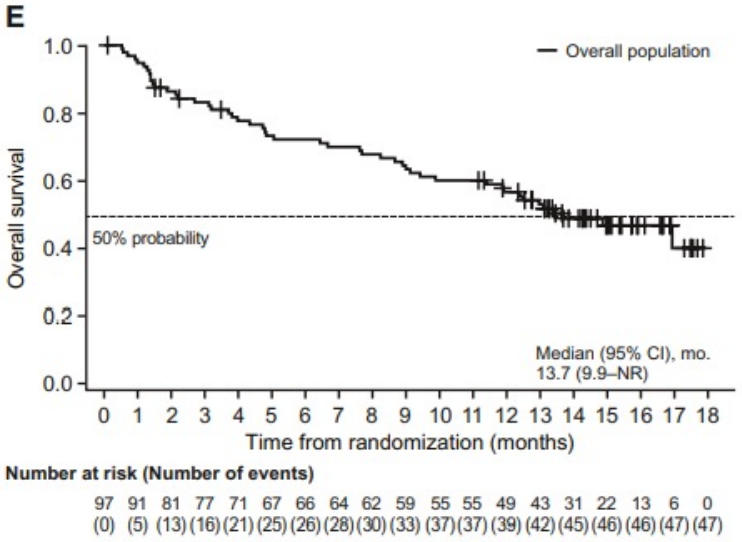
- Open-label, randomized phase II trial

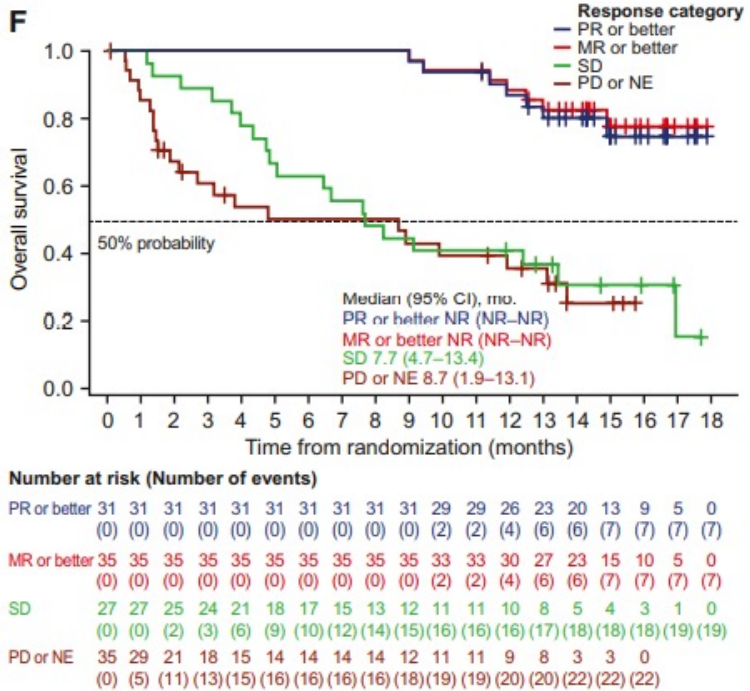


- Primary endpoint: ORR
- Results: ORR: 30% at 2.5 mg/kg vs 34% at 3.4 mg/kg; PFS: 2.9 mos at 2.5 mg/kg, 4.9 mos in 3.4 mg/kg; OS not yet reached in either group
- Select grade 3/4 AEs with 2.5 and 3.4 mg/kg: keratopathy (27%, 21%), thrombocytopenia (20%, 33%), anemia (20%, 25%)

Lonial S et al. Lancet Oncol 2020;21:207-221

DREAMM-2: 13-Month F-U Analysis of Pts Receiving 2.5 mg/kg





Lonial S et al. Cancer; 2021:Nov 15

DREAMM-3: Phase 3, open label, randomized study of single-agent Belamaf vs Pomalidomide/Dexamethasone

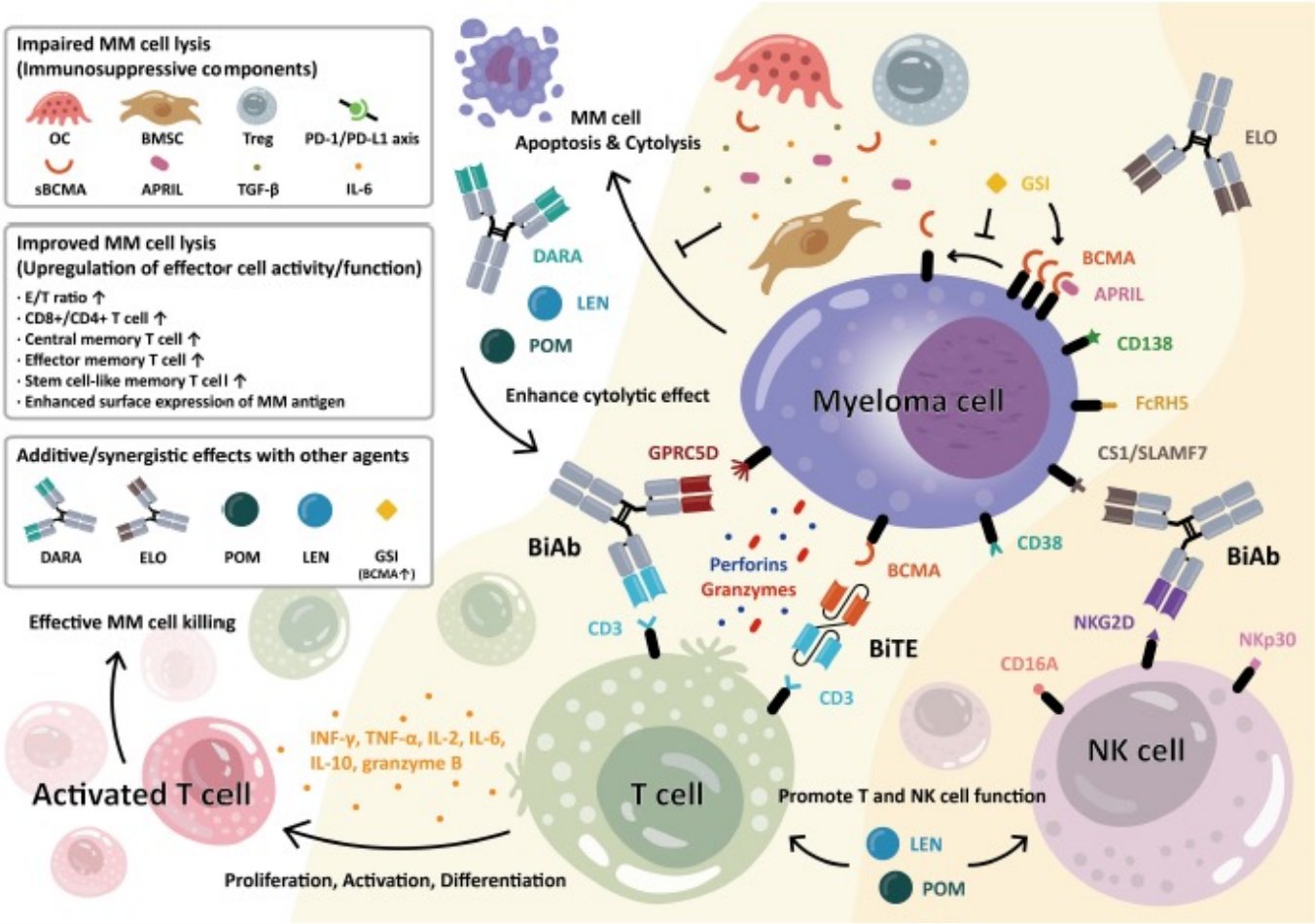
Efficacy and safety.

	Belamaf (ITT n=218, safety n=217)	Pd (ITT n=107, safety n=102)
ORR, n (%)	89 (41)	38 (36)
≥VGPR, n (%)	55 (25)	9 (8)
MRD- ≥VGPR, n (%)	15 (7)	0
DoR, months, median (95% CI)	NR (17.9, NR)	8.5 (7.6, NR)
Any AE, n (%)	211 (97)	95 (93)
Serious AEs, n (%)	94 (43)	40 (39)
Fatal AEs, n (%)	16 (7)	11 (11)
Grade 3–4 AEs, n (%)	164 (76)	71 (70)
AEs leading to discontinuation, n (%)	33 (15)	17 (17)

Belamaf monotherapy did not demonstrate PFS superiority when compared to Pd.
Belamaf monotherapy, however, showed longer mPFS and induced deeper, more durable responses than Pd.
No new safety signals were observed.

Weisel K et al. ASCO 2023; oral presentation

BiTEs & Bi-Specific Antibodies



Shih-Feng Cho et al. Front Oncol; 2022

Summary of BiTEs & Bispecific T-cell antibodies for MM

antiBCMAxCD3 →

antiFcRH5xCD3 →

antiGPRC5DxCD3 →

Name	Target	Antibody construct	Triple-class refractory (median LoT)	Trial phase	Schedule	Preliminary response/ activity	Safety	Current status (ClinicalTrials .gov)
AMG 420[38]	BCMA-CD3	BiTE®	N/A (29% prior anti-CD38, median 5 LoT)	Phase 1	Continuous infusion for 4 wk (out of 6)	ORR=31% ORR MTD=70%	38% CRS (6.25% ≥ gr 3) 5% ≥ gr 3 polyneuropathy 24% ≥ gr 3 infection	Active, not recruiting NCT03836053
AMG 701[39]	BCMA-CD3	HLE-BiTE®	68% (median 6 LoT)	Phase 1/2	Weekly IV	ORR=36% ORR=83% at 9 mg	75% CRS (10.5% ≥ gr 3) 8% neurotoxicity (gr 1–2) 13% ≥ gr 3 infection	Recruiting NCT03287908
Elranatamab[41]	BCMA-CD3	Humanized IgG2a Fc	91% (median 6 LoT; 22% prior anti-BCMA)	Phase 1	Weekly or every 2 wk Sc	ORR=64% for doses ≥215 µg/kg	67% CRS (gr 1–2)	MagnetisMM-1 Recruiting NCT03269136
REGN5458[42]	BCMA-CD3	Fc Fab arms	97.1% (median 5 LoT)	Phase 1/2	Weekly IV	ORR=73.3% at 96–200-mg doses	38.2% CRS (gr 1–2) 4% neurotoxicity (gr 1–2) 23% pneumonia (11% ≥ gr 3)	Recruiting NCT03761108
Teclistamab[40]	BCMA-CD3	Humanized IgG4 Fc	77.8% (median 5 LoT; prior anti-BCMA not permit-ted)	Phase 1/2	Weekly Sc	ORR=63%	72.1% CRS (gr 3, 0.6%; no gr 4) 14.5% neurotoxicity (1 gr 4 event) 44.8% ≥ gr 3 infection	MajestTEC-1 Recruiting NCT03145181
CC-93269[44]	BCMA-CD3	Asymmetric 2-arm IgG	66.7% (median 6 LoT)	Phase 1	Weekly IV	ORR=83.3% in 10 pts with doses ≥6 mg	89.5% CRS (1 gr 5 event) 26.3% infection	Recruiting NCT03486067
TNB-383B[44]	BCMA-CD3	IgG4 Fc CD3 activating T effector cells	62% (median 5 LoT)	Phase 1	Q21d IV	ORR=79% at doses ≥40 mg	52% CRS (3% ≥ gr 3 at RP2D) 28% infection	Recruiting NCT03933735
Cevostamab[45]	FcRH5-CD3	Humanized IgG1 Fc	85% (median 6 LoT; 33.5% prior anti-BCMA)	Phase 1	Q21d IV	ORR=54.5% at 160-mg-dose level	80.7% CRS (1.3% ≥ gr 3) 18.8% ≥ gr 3 infection 14.3% neurotoxicity (0.3% ≥ gr 3)	Recruiting NCT03275103
Talquetamab[46]	GPRC5D-CD3	Humanized IgG4 Fc	Weekly: 77% (median 6 LoT; 30% prior anti-BCMA) Biweekly: 65% (median 5 LoT; 17% prior anti-BCMA)	Phase 1/2	Weekly or biweekly Sc	Weekly: ORR=70% Biweekly: ORR=71%	Weekly: 73% CRS (1 gr 3) Biweekly: 78% CRS (gr 1–2)	MonumenTal-1 Recruiting NCT03399799

Cipkar C et al. ASH Educational 2022

Teclistamab in 165 RRMM (MajesTEC-1)

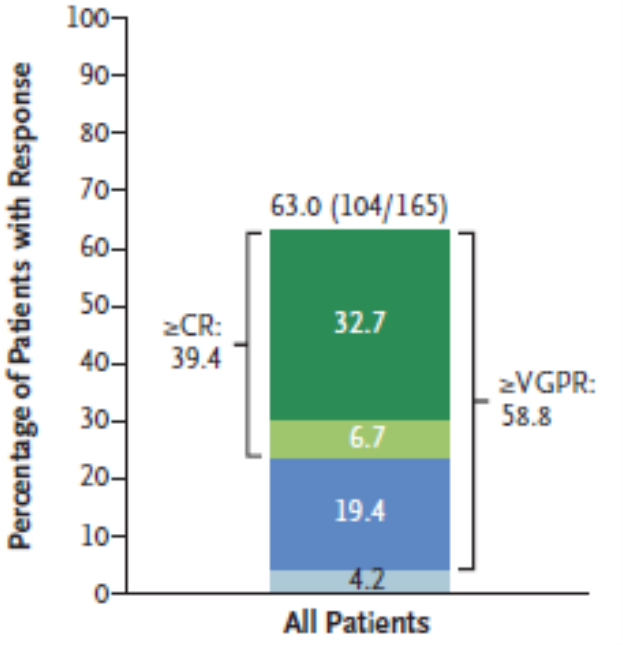
Extramedullary disease: 17%
High-risk cytogenetics: 25.7%
Previous therapy lines: median 5
Triple-class refractory: 77.6%
Penta-drug refractory: 30.3%

Characteristic	Phase 1 (N=40)	Phase 2 (N=125)	Total (N=165)
Age			
Median (range) — yr	62.5 (39.0–84.0)	64.0 (33.0–83.0)	64.0 (33.0–84.0)
≥75 yr — no. (%)	5 (12.5)	19 (15.2)	24 (14.5)
Sex — no. (%)			
Male	26 (65.0)	70 (56.0)	96 (58.2)
Female	14 (35.0)	55 (44.0)	69 (41.8)
Race — no. (%)*			
White	34 (85.0)	100 (80.0)	134 (81.2)
Black	1 (2.5)	20 (16.0)	21 (12.7)
Asian	0	3 (2.4)	3 (1.8)
Other	5 (12.5)	2 (1.6)	7 (4.2)
Median time since diagnosis (range) — yr	5.6 (0.8–17.4)	6.2 (0.9–22.7)	6.0 (0.8–22.7)
≥1 Extramedullary plasmacytoma — no. (%)†	8 (20.0)	20 (16.0)	28 (17.0)
≥60% Plasma cells in bone marrow — no./total no. (%)	3/38 (7.9)	15/122 (12.3)	18/160 (11.2)
ECOG performance-status score — no. (%)‡			
0	17 (42.5)	38 (30.4)	55 (33.3)
≥1	23 (57.5)	87 (69.6)	110 (66.7)
International Staging System class — no./total no. (%)			
I	24/39 (61.5)	61/123 (49.6)	85/162 (52.5)
II	11/39 (28.2)	46/123 (37.4)	57/162 (35.2)
III	4/39 (10.3)	16/123 (13.0)	20/162 (12.3)
High-risk cytogenetic profile — no./total no. (%)	12/37 (32.4)	26/111 (23.4)	38/148 (25.7)
del(17p)	9/37 (24.3)	14/111 (12.6)	23/148 (15.5)
t(4:14)	4/37 (10.8)	12/111 (10.8)	16/148 (10.8)
t(14;16)	1/37 (2.7)	3/111 (2.7)	4/148 (2.7)
Median no. of lines of previous therapy (range)	5 (2–11)	5 (2–14)	5 (2–14)
Previous stem-cell transplantation — no. (%)	34 (85.0)	101 (80.8)	135 (81.8)
Previous therapy exposure — no. (%)			
Triple-class§	40 (100.0)	125 (100.0)	165 (100.0)
Penta-drug¶	26 (65.0)	90 (72.0)	116 (70.3)
Refractory status — no. (%)			
Immunomodulatory agent‖	38 (95.0)	114 (91.2)	152 (92.1)
Proteasome inhibitor**	34 (85.0)	108 (86.4)	142 (86.1)
Anti-CD38 monoclonal antibody††	39 (97.5)	109 (87.2)	148 (89.7)
Triple-class§	32 (80.0)	96 (76.8)	128 (77.6)
Penta-drug¶	16 (40.0)	34 (27.2)	50 (30.3)
Refractory to last line of therapy	33 (82.5)	115 (92.0)	148 (89.7)

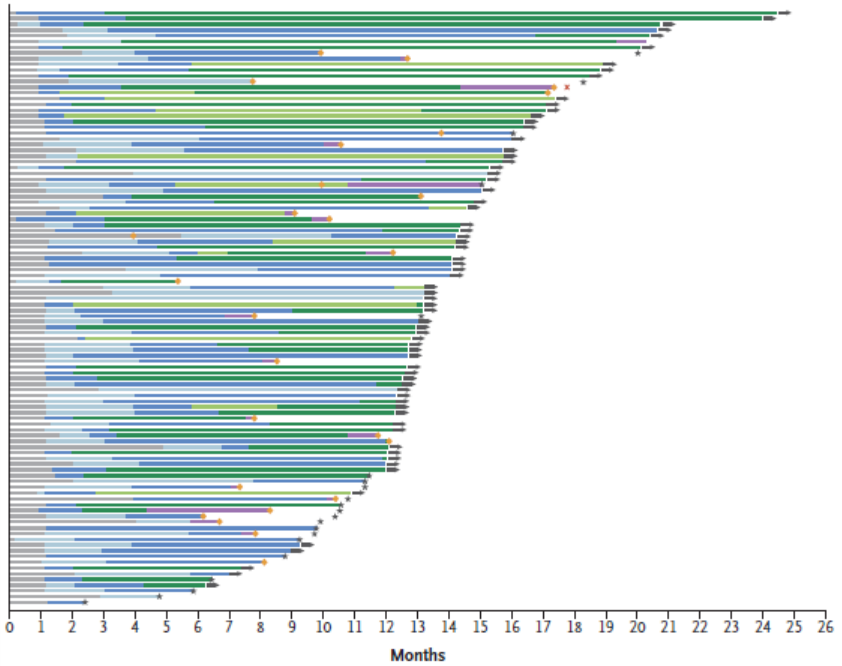
Moreau P et al. NEJM 2022;387:495

Teclistamab in RRMM (MajesTEC-1)

Response Rate in 165 Pts

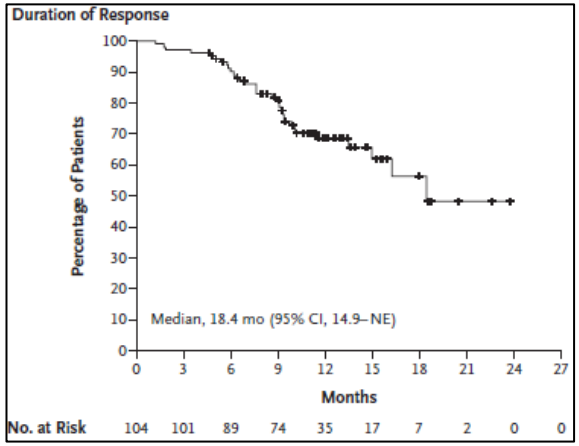


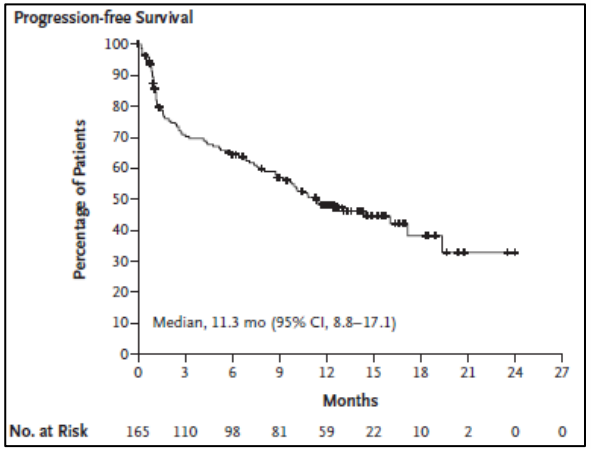
Treatment Response in 104 Pts

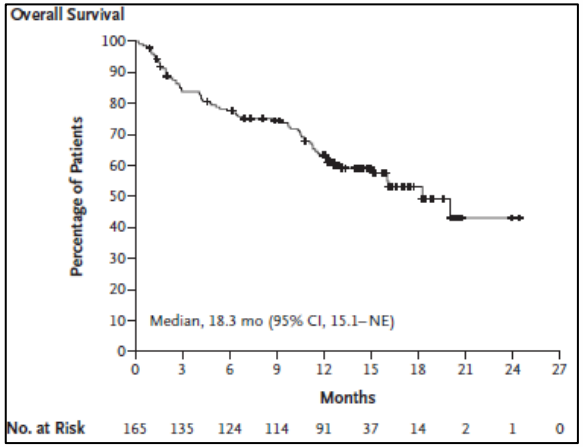


Moreau P et al. NEJM 2022;387:495

Teclistamab in RRMM (MajesTEC-1)







Moreau P et al. NEJM 2022;387:495

Teclistamab in RRMM (MajesTEC-1)

Table 2. Adverse Events in 165 Patients (Safety Population).*

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	165 (100)	156 (94.5)
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site erythema	43 (26.1)	0
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

CONCLUSIONS

Cytopenias and infections were common; toxic effects that were consistent with T-cell redirection were mostly grade 1 or 2.

Teclistamab resulted in a high rate of deep and durable response in pts with triple-class–exposed RRMM.

Moreau P et al. NEJM 2022;387:495

Talquetamab in 232 RRMM (MonumenTAL-1)

Extramedullary disease: 24.6%
High-risk cytogenetics: 16%
Previous therapy lines: median 6
Triple-class refractory: 79.3%
Penta-drug refractory: 29.7%

Table 1. Characteristics of the Patients at Baseline.

Characteristic	Subcutaneous Talquetamab, 405 μg Weekly (N=30)	Subcutaneous Talquetamab, 800 μg Every 2 Wk (N=44)	Subcutaneous Talquetamab, All Doses* (N=130)	Intravenous Talquetamab, All Doses* (N=102)
Age				
Median (range) — yr	62 (46–80)	64 (47–84)	64 (39–84)	65 (33–79)
≥70 yr — no. (%)	7 (23)	15 (34)	37 (28)	32 (31)
Sex — no. (%)				
Male	19 (63)	21 (48)	75 (58)	57 (56)
Female	11 (37)	23 (52)	55 (42)	45 (44)
Race or ethnic group — no. (%)†				
White	25 (83)	35 (80)	107 (82)	82 (80)
Black	4 (13)	4 (9)	13 (10)	14 (14)
Asian	0	3 (7)	4 (3)	2 (2)
Other or not reported	1 (3)	2 (5)	6 (5)	4 (4)
Median time since diagnosis (range) — yr	5.6 (1.7–19.6)	6.4 (0.8–21.3)	6.1 (0.8–21.3)	6.6 (0.9–27.0)
≥1 Extramedullary plasmacytoma — no. (%)	11 (37)	15 (34)	42 (32)	15 (15)
≥60% Plasma cells in bone marrow — no./total no. (%)	6/29 (21)	5/41 (12)	21/121 (17)	22/100 (22)
International Staging System class — no./total no. (%)				
I	12/29 (41)	16/43 (37)	44/124 (35)	33/100 (33)
II	13/29 (45)	18/43 (42)	56/124 (45)	43/100 (43)
III	4/29 (14)	9/43 (21)	24/124 (19)	24/100 (24)
High-risk cytogenetic abnormalities — no./total no. (%)‡	3/27 (11)	9/40 (22)	18/112 (16)	14/88 (16)
del(17p)	1/27 (4)	7/40 (18)	12/112 (11)	7/88 (8)
t(4;14)	2/27 (7)	3/40 (8)	9/112 (8)	7/88 (8)
t(14;16)	0	0	0	1/88 (1)
Median no. of lines of previous therapy (range)	6 (2–14)	5 (2–17)	6 (2–17)	6 (3–20)
Previous stem-cell transplantation — no. (%)	27 (90)	33 (75)	111 (85)	87 (85)
Previous therapy exposure — no. (%)				
Triple-class exposure§	30 (100)	43 (98)	129 (99)	101 (99)
Penta-drug exposure¶	24 (80)	30 (68)	100 (77)	79 (77)
Refractory status — no. (%)				
Immunomodulatory drug‖	28 (93)	42 (95)	121 (93)	98 (96)
Proteasome inhibitor**	25 (83)	36 (82)	106 (82)	92 (90)
Anti-CD38 monoclonal antibody††	30 (100)	39 (89)	119 (92)	97 (95)
Triple-class refractory‡‡	23 (77)	33 (75)	97 (75)	87 (85)
Penta-drug refractory§§	6 (20)	9 (20)	33 (25)	36 (35)
Refractory to last line of therapy	26 (87)	39 (89)	111 (85)	91 (89)

Chari A et al. NEJM 2022;387:2232

Talquetamab in 232 RRMM MonumenTAL-1)

Response Rate

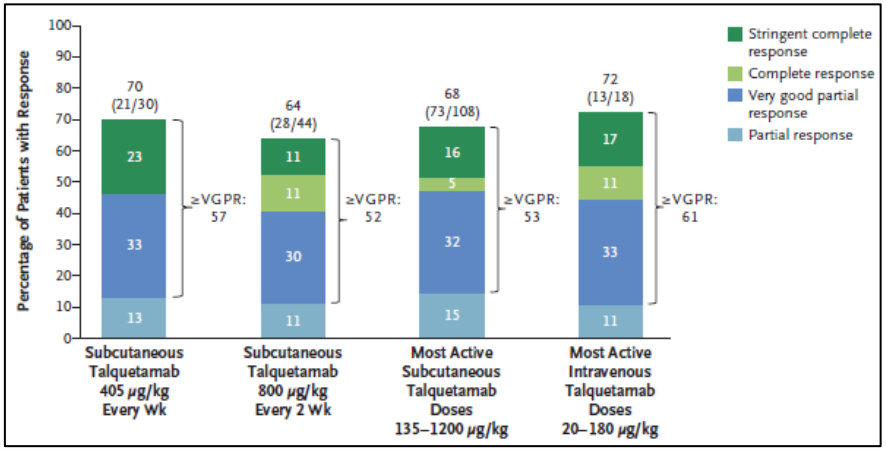


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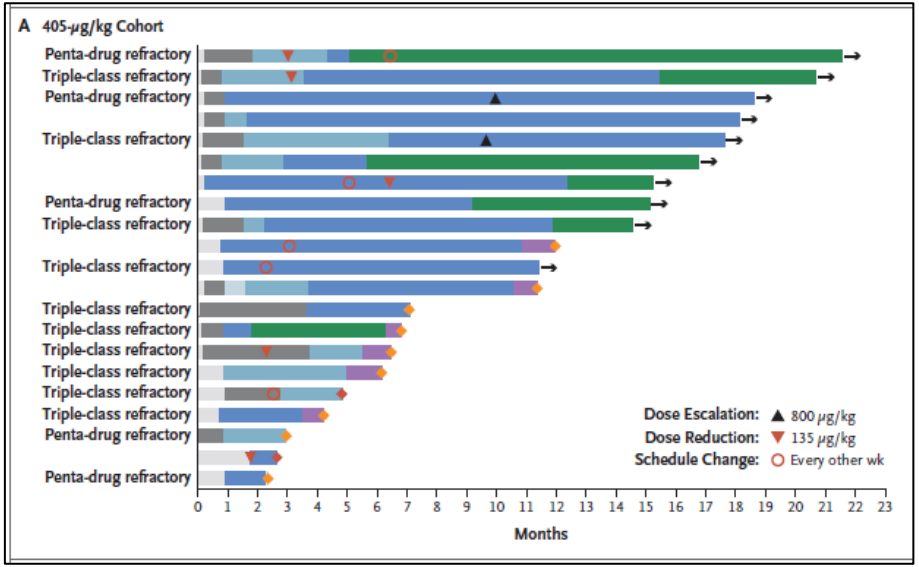
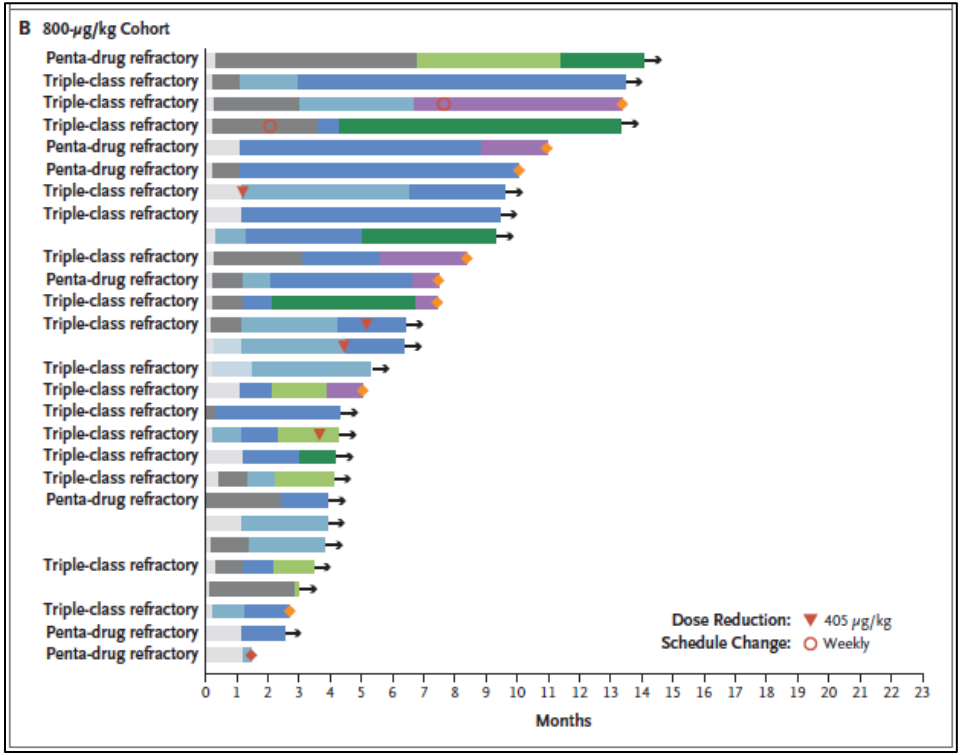
Table 2. Adverse Events.*

Event	Subcutaneous Talquetamab, 405 μg Weekly (N=30)		Subcutaneous Talquetamab, 800 μg Every 2 Wk (N=44)		Intravenous Talquetamab, All Doses (N=102)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)					
Any adverse event	30 (100)	26 (87)	44 (100)	38 (86)	102 (100)	92 (90)
Hematologic event						
Anemia	18 (60)	9 (30)	19 (43)	10 (23)	59 (58)	34 (33)
Neutropenia	20 (67)	18 (60)	16 (36)	14 (32)	48 (47)	27 (26)
Lymphopenia	12 (40)	12 (40)	17 (39)	17 (39)	53 (52)	48 (47)
Thrombocytopenia	11 (37)	7 (23)	10 (23)	5 (11)	36 (35)	13 (13)
Leukopenia	12 (40)	9 (30)	8 (18)	6 (14)	38 (37)	16 (16)
Nonhematologic event						
Cytokine release syndrome	23 (77)	1 (3)	35 (80)	0	50 (49)	5 (5)
Skin-related event†	20 (67)	0	31 (70)	1 (2)	24 (24)	0
Dysgeusia	19 (63)	NA	25 (57)	NA	38 (37)	NA
Fatigue	10 (33)	1 (3)	12 (27)	0	37 (36)	1 (1)
Nail-related event‡	17 (57)	0	12 (27)	1 (2)	20 (20)	0
Pyrexia	10 (33)	0	8 (18)	0	32 (31)	0
Headache	6 (20)	0	11 (25)	0	35 (34)	2 (2)
Rash-related event§	14 (47)	0	13 (30)	7 (16)	15 (15)	1 (1)
Diarrhea	9 (30)	0	7 (16)	0	29 (28)	4 (4)
Cough	6 (20)	0	5 (11)	0	36 (35)	0
Dry mouth	9 (30)	0	25 (57)	0	7 (7)	0
Nausea	9 (30)	0	7 (16)	0	23 (23)	0
Arthralgia	7 (23)	0	4 (9)	0	33 (32)	3 (3)
Decreased weight	9 (30)	0	14 (32)	1 (2)	12 (12)	0
Increased alanine aminotransferase	6 (20)	1 (3)	13 (30)	3 (7)	13 (13)	2 (2)
Increased aspartate aminotransferase	3 (10)	0	15 (34)	3 (7)	14 (14)	2 (2)
Back pain	3 (10)	0	9 (20)	0	22 (22)	1 (1)
Hypophosphatemia	8 (27)	5 (17)	8 (18)	3 (7)	19 (19)	14 (14)
Dysphagia	11 (37)	0	12 (27)	0	5 (5)	0
Decreased appetite	6 (20)	1 (3)	9 (20)	0	15 (15)	1 (1)
Constipation	2 (7)	0	6 (14)	0	18 (18)	2 (2)
Increased γ-glutamyltransferase	6 (20)	1 (3)	10 (23)	3 (7)	14 (14)	3 (3)

Talquetamab in 232 RRMM (MonumenTAL-1)





Response: Stringent complete response; Complete response; Very good partial response; Partial response; Minimal response; Stable disease; Progressive disease

End-of-Treatment Status: Discontinued — progressive disease; Discontinued — other reason; Continued treatment

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Talquetamab in 232 RRMM (MonumenTAL-1)

Conclusions

Talquetamab, a new, off-the-shelf bispecific antibody against the novel target GPRC5D, had substantial antitumor effects in patients with heavily pretreated RRMM.

The recommended doses of 405 µg per kilogram weekly and 800 µg per kilogram every other week that were administered subcutaneously had similar safety profiles and similar efficacy.

Cytokine release syndrome, skin-related events, and dysgeusia were common with talquetamab treatment but were primarily low-grade.

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Cevostamab

N. of pts: 160 (males: 58,1%)
Median age: 64 years, range: 33-82 years
Extramedullary disease: 21.3% of pts
N. of prior lines of therapy: 6 (range: 2-18)
Triple-class refractory: 85.0%
Prior anti-BCMA targeting agent: 33.8%
Prior CAR-T: 17.5%
Prior Bispecific antibody: 8.1%
Prior ADC: 16.9%

Table. Adverse event summary

N (%) of pts	Any AE (N=160)	Any Gr 3–4 AE (N=160)
Any AE*	159 (99.4)	94 (58.8)
Cytokine release syndrome	128 (80.0)	2 (1.3)†
Infections (SOC)	68 (42.5)	30 (18.8)
Neurological/Psychiatric (SOC)	65 (40.6)	6 (3.8)†
Anemia	51 (31.9)	35 (21.9)‡
Diarrhea	42 (26.3)	1 (0.6)†
Cough	37 (23.1)	0
Nausea	35 (21.9)	0
Neutropenia	29 (18.1)	26 (16.3)
Infusion-related reaction	28 (17.5)	0
Fatigue	26 (16.3)	3 (1.9)†
Aspartate aminotransferase increased	25 (15.6)	10 (6.3)
Hypomagnesaemia	25 (15.6)	1 (0.6)†
Pyrexia	25 (15.6)	0
Neutrophil count decreased	24 (15.0)	22 (13.8)
Alanine aminotransferase increased	24 (15.0)	11 (6.9)‡
Any serious AE	89 (55.6)	
Any TR serious AE†	40 (25.0)	
Any Gr 5 (fatal) AE	24 (15.0)§	
Any TR Gr 5 (fatal) AE†	1 (0.6)¶	
Any AE leading to withdrawal of cevostamab	16 (10.0)	
Any TR AE leading to withdrawal of cevostamab†	7 (4.4)	

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Cevostamab

RESULTS

At data cut-off, 158/160 pts were efficacy evaluable.
In dose-escalation, responses were observed at the 20-198 mg target dose levels, and data suggested a target dose-dependent increase in clinical efficacy.
Median time to response was 29 days (range: 20-179 days).
Two dose-expansion cohorts were opened: ORR was higher at the 160 mg dose level (54.5%, 24/44 pts) than at the 90 mg dose level (36.7%, 22/60).
At target dose levels >90 mg, ORRs in pts with prior exposure to CAR-Ts, BsAbs, ADCs, and anti-BCMA targeting agents were 44.4% (4/9 pts), 33.3% (3/9), 50.0% (7/14), and 36.4% (8/22) respectively.
Median follow-up among all responders (n=61) was 8.1 months;
Estimated median duration of response was 15.6 months (95% CI: 6.4, 21.6).

CONCLUSIONS

Cevostamab monotherapy continues to show clinically meaningful activity in a large cohort of pts with heavily pre-treated RRMM, with a target dose-dependent increase in ORR, but no increase in CRS rate.
Responses appear durable, and are observed in pts with prior exposure to CAR-Ts, BsAbs, and ADCs.
Compared with single-step dosing, double-step dosing at the 0.3/3.6mg level appears to be associated with a trend for an improved safety profile.

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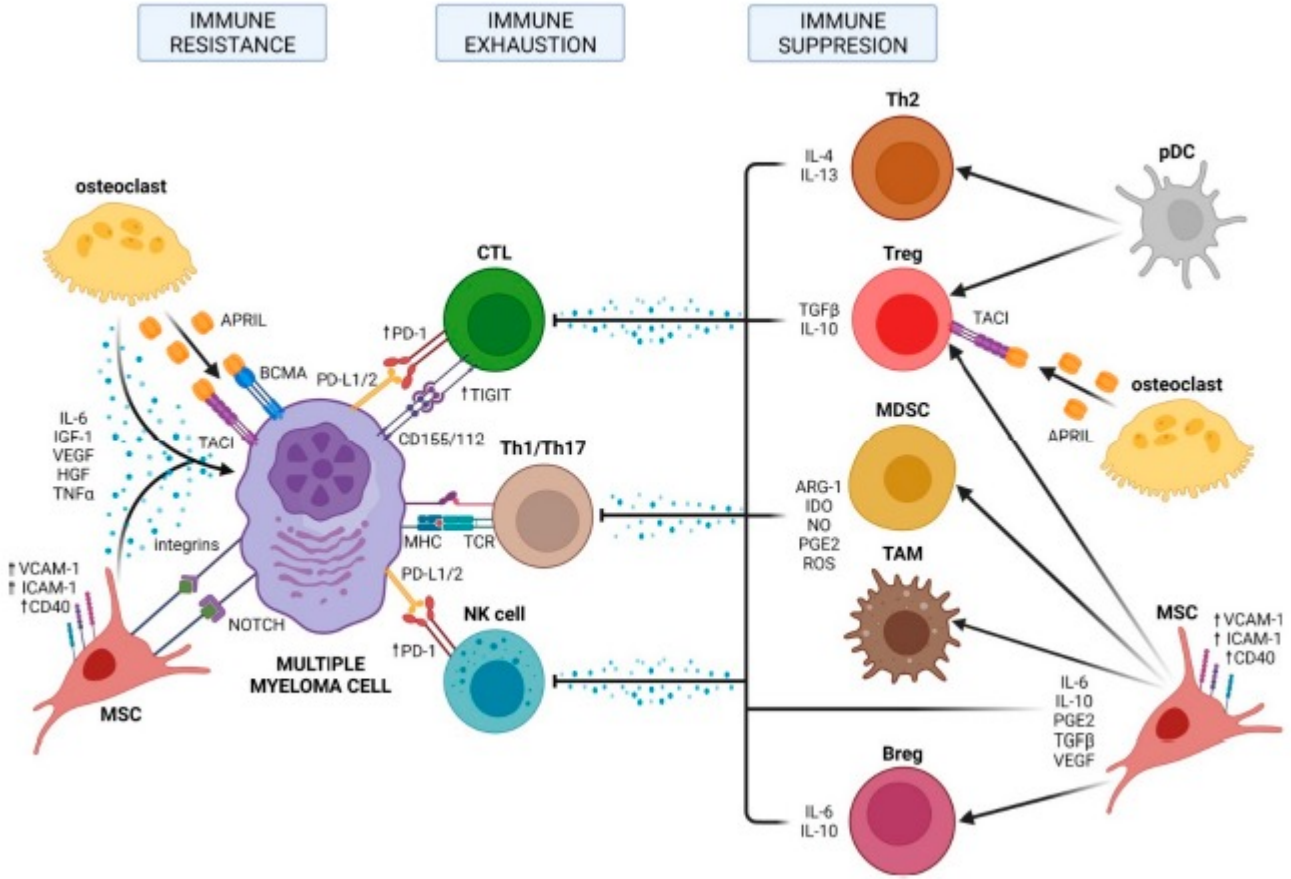
Major mechanisms of immune evasion mediated by bone marrow microenvironment in MM



Neumeister P et al. Int J Mol Sci 2022;23:7627

Strategy 1: Combination with other anti-myeloma agents

Rationale: Potential synergistic effect, reduced tumor burden.

Trial No.	Agents
NCT03287908 (Phase 1)	Pavurutamab (AMG 701) monotherapy Pavurutamab + pomalidomide Pavurutamab + pomalidomide + dexamethasone
NCT04108195 TriMM-2 (Phase 1)	Talquetamab + daratumumab Teclistamab + daratumumab Then ± pomalidomide
NCT05090566 MagnetisMM-4 (Phase 2)	Sub-study B Elranatamab + lenalidomide + dexamethasone
NCT05020236 MagnetisMM-5 (Phase 3)	Elranatamab vs daratumumab+ pomalidomide+ dexamethasone Elranatamab + daratumumab vs daratumumab+ pomalidomide+ dexamethasone
NCT05137054 (Phase 1)	Linvoseltamab (REGN5458) + daratumumab + dexamethasone Linvoseltamab + carfilzomib + dexamethasone Linvoseltamab + lenalidomide + dexamethasone Linvoseltamab + bortezomib + dexamethasone

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Strategy 2: Combination of 2 bispecific molecules targeting various MM antigens	
Rationale: To reduce the risk of antigen loss related disease relapse.	
NCT04586426 (Phase 1)	Part 2: Dose expansion cohort Talquetamab + teclistamab Talquetamab + teclistamab + daratumumab
Strategy 3: Combined agent which enhances expression of target antigen	
Rationale: Enhanced antigen expression increased anti-MM activity of bispecific molecules	
NCT04722146 (Phase 1)	Talquetamab + nirogacestat
NCT05090566 MagnetisMM-4 (Phase 2)	Sub-study A Elranatamab + nirogacestat

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Conclusions

Bispecific antibodies targeting BCMA, GPRC5D & FcRH5 have demonstrated high activity with a manageable toxicity profile in heavily pretreated MM.

Novel combination strategies and earlier use of these agents may lead to further improvements in depth & duration of response.

Great efforts are ongoing to understand how to best sequence the immunotherapeutic strategies which soon will be made available by AIFA.

TRIspecific antibodies targeting two different tumor antigens (BCMA & GPRC5D; CD38 & CD28) on plasma cells hold great promise.

Grazie per l'attenzione