Anticorpi bispecifici anti-BCMA

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Disclosures, Roberto Mina

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Scientific Advisory Board	Janssen, Celgene, Takeda, BMS, Amgen, Sanofi

T-cell engagers: redirecting T cells against myeloma cells

Bispecifics

BCMA	GPRC5D	FcRH5
Teclistamab	Talquetamab	Cevostamab
Elranatamab	Forimtamig	
Linvoseltamab (REGN5458)		
ABBV-383 (TNB-383B)		
Alnuctamab (CC-93269)		

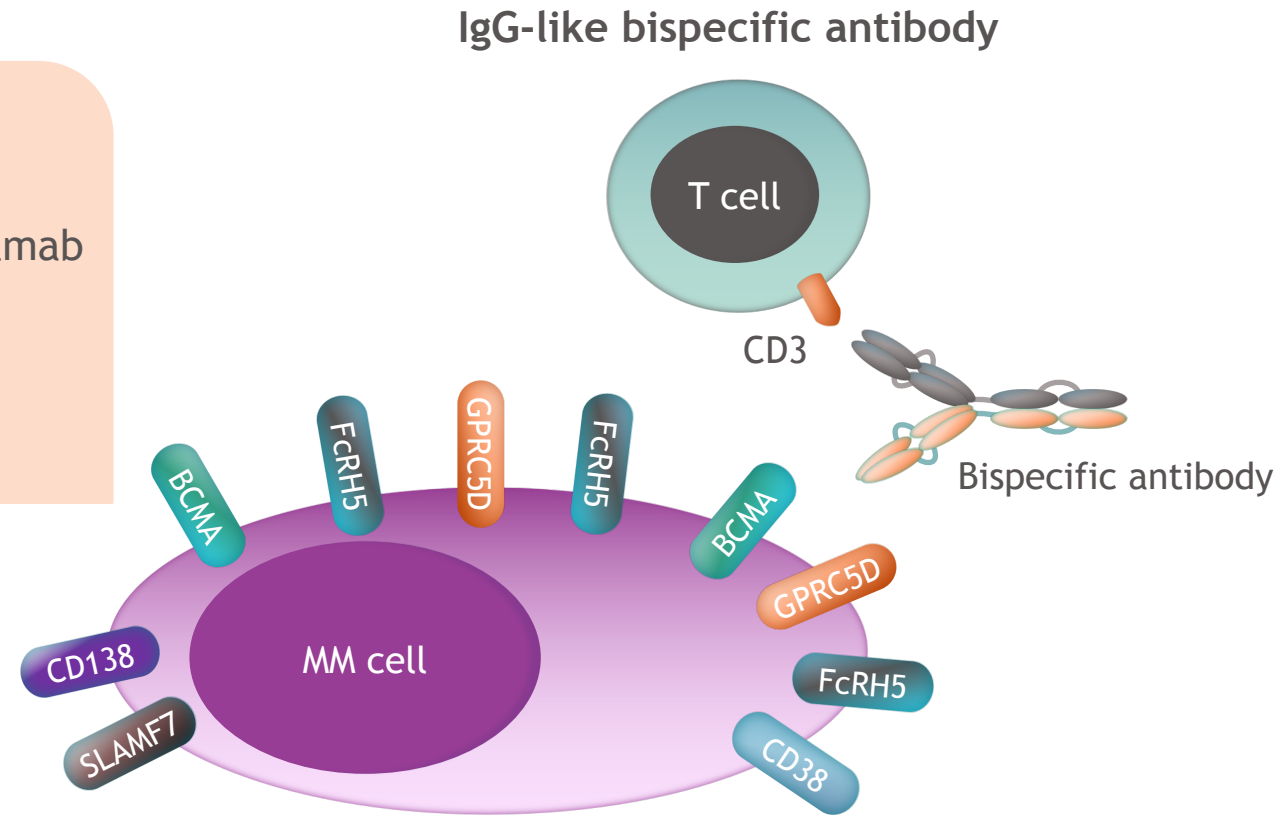

Image adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71; Rodriguez-Lobato LG, et al. Front Oncol. 2020;10:1243; and van de Donk NWCJ, et al. Lancet Haematol. 2021;8:e446-61.

BCMA-targeting bispecific antibodies

1. Efficacy and safety data of anti-BCMA bispecific antibodies
2. Bispecific antibodies targeting BCMA for triple-class refractory myeloma: where do we stand?
3. Targeting BCMA with a bispecific antibody in BCMA-exposed patients: what do we know?
4. How to improve the efficacy of bispecific antibodies?

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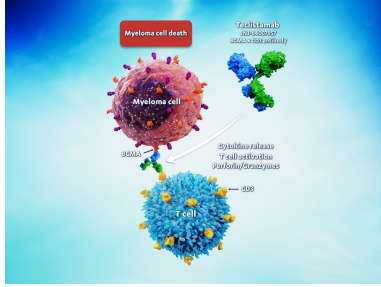
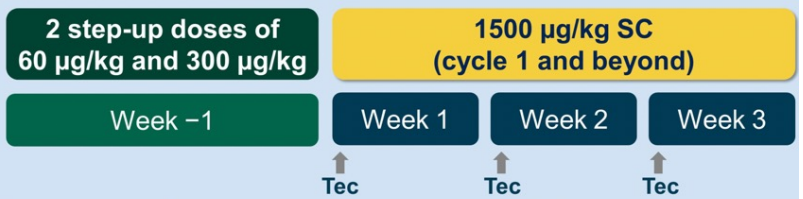
Teclistamab, a BCMA × CD3 T-Cell Redirecting Bispecific Antibody: MajesTEC-1 study



- Teclistamab (JNJ-64007957) is an off-the-shelf, T-cell redirecting, bispecific antibody that binds to CD3 on T cells and BCMA on plasma cells to mediate T-cell activation and subsequent lysis of BCMA-expressing MM cells
- The phase 1 portion of the MajesTEC-1 study identified the RP2D for teclistamab monotherapy: 1.5 mg/kg subcutaneous (SC) QW with step-up doses of 0.06 and 0.3 mg/kg[3]
- Teclistamab has been approved by the FDA and EMA for the treatment of RRMM patients who have received at least 3 prior lines including an IMiD, a PI and an anti-CD38 monoclonal antibody.

Dosing Schedule at RP2D



- Premedications[b] were limited to step-up doses and first full dose
  - No steroid requirement after first full dose

Characteristic	Safety Analysis N=165
Age (years), median (range)	64.0 (33–84)
Age ≥75 years, n (%)	24 (14.5)
Male, n (%)	96 (58.2)
Race, n (%)	
White	134 (81.2)
African-American/Black	21 (12.7)
Other[a]	10 (6.1)
Extramedullary plasmacytomas ≥1[c], n (%)	28 (17.0)
High-risk cytogenetics[d], n (%)	38 (25.9)
Prior lines of therapy, median (range)	5.0 (2–14)
Refractory status, n (%)	
Triple-class refractory[f]	128 (77.6)
Penta-drug refractory[g]	50 (30.3)
Refractory to last line of therapy	148 (89.7)
Exposure status, n (%)	
Triple-class exposed[f]	165 (100)
Penta-drug exposed[g]	116 (70.3)
Selinexor	6 (3.6)

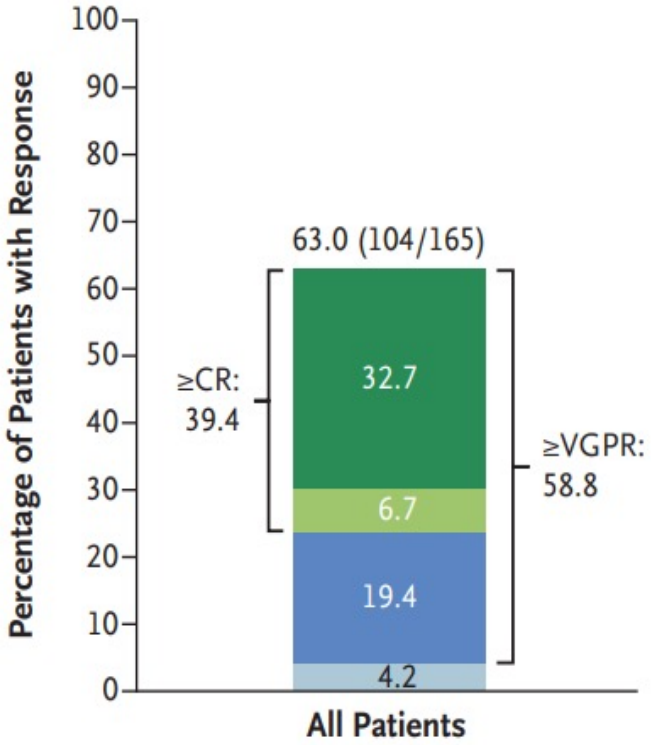
BCMA, B-cell maturation antigen; IFN, interferon; IL, interleukin; MM, multiple myeloma; QW, once weekly; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; TNF, tumor necrosis factor

1. Mateos MV, et al. *J Clin Oncol* 2021; 39 (suppl): 8041. 2. Costa L et al. *J Clin Oncol* 2021; 39 (suppl): 8030. 3. Usmani SZ, et al. *Lancet* 2021; 398(10301): 665-74.

Philippe Moreau et al, Abs. n 896 Presented at ASH December 11-14, 2021; Atlanta, GA/Virtual.

MajesTEC-1: teclistamab for RRMM

Overall response rates

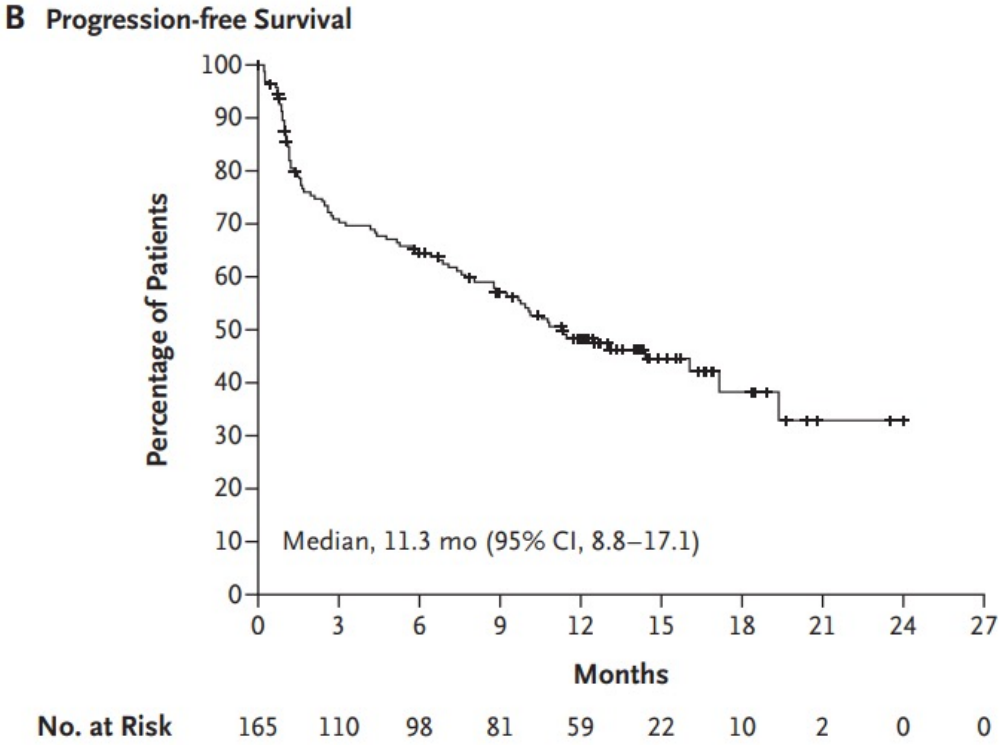


MRD negativity rate[b]

- ✓ 27% at a threshold of 10^{-5}
- ✓ 16.7% (25/150; 95% CI: 11.1–23.6) at a threshold of 10^{-6},[c]

- — Median DOR 18 months
- — Median PFS 11.3 months
- — Median OS 18.3 months

Progression-free survival



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)

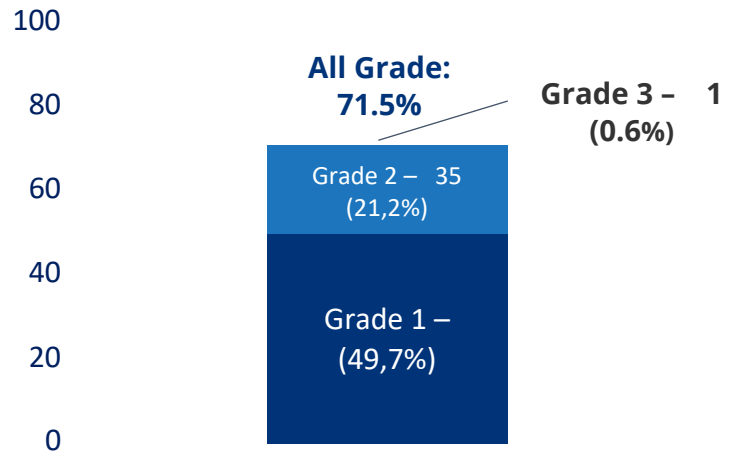
CR, complete response; DOR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; sCR, stringent partial response; VGPR, very good partial response

Moreau et al. NEJM 2022

MajesTEC-1: Cytokine Release Syndrome and neurotoxicity

Parameter	Safety Analysis Set N=165
Patients with CRS, n (%)	118 (71.5)
Patients with ≥2 CRS events	54 (32.7)
Time to onset (days), median (range)	2 (1–6)
Duration (days), median (range)	2 (1–9)
Patients who received supportive measures[a], n (%)	109 (66.1)
Tocilizumab	60 (36.4)
Low-flow oxygen by nasal cannula[b]	21 (12.7)
Steroids	13 (7.9)
Single vasopressor	1 (0.6)

Maximum CRS grade[c]



- All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that fully resolved, and 97% of events were confined to step-up and cycle 1
- Patients with neurotoxicity, n (%) 12.7%
- Headache 8.5%
- **ICANS[a] <5%**

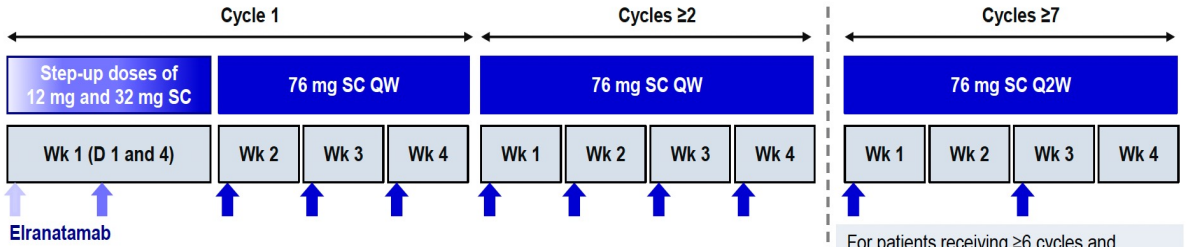
[a]A patient could receive >1 supportive therapy; [b]≤6 L/min; [c]CRS was graded using Lee et al *Blood* 2014 in the phase 1 portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al *Blood* 2014 criteria were mapped to ASTCT criteria for patients in the phase 1 portion.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome

Philippe Moreau et al, Abs. n 896 Presented at ASH December 11-14, 2021; Atlanta, GA/Virtual.

Efficacy and Safety of Elranatamab in Patients With Relapsed/Refractory Multiple Myeloma Naïve to B-cell Maturation Antigen (BCMA)-Directed Therapies: Results From Cohort A of the MagnetisMM-3 Study

Nizar Bahlis[1], Michael H. Tomasson[2], Mohamad Mohty[3], Ruben Niesvizky[4], Ajay Nooka[5], Salomon Manier[6], Christopher Maisel[7], Yogesh Jethava[8], Joaquin Martinez-Lopez[9], H. Miles Prince[10], Bertrand Arnulf [11], Paula Rodriguez-Otero[12], Guenther Koehne[13], Cyrille Touzeau[14], Noopur Raje[15], Shinsuke Iida[16], Marc-Steffen Raab[17], Eric Leip[18], Sharon Sullivan[18], Umberto Conte[19], Andrea Viqueira[20], Alexander Lesokhin[21]

MagnetisMM-3: Elranatamab Dosing Schedule



Premedication:

60 min (±15 min) prior to the first 3 doses of elranatamab

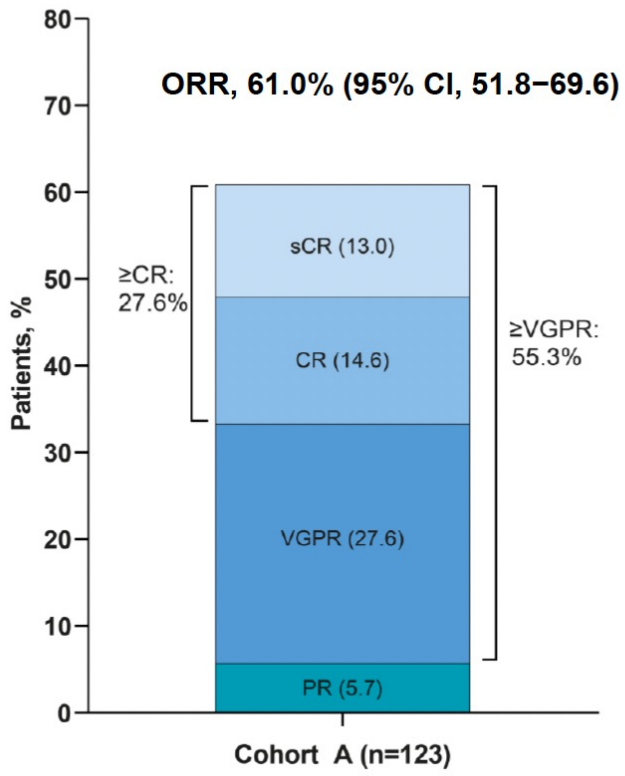
- Acetaminophen 650 mg (or paracetamol 500 mg)
- Diphenhydramine 25 mg (or equivalent), oral or IV
- Dexamethasone 20 mg (or equivalent), oral or IV

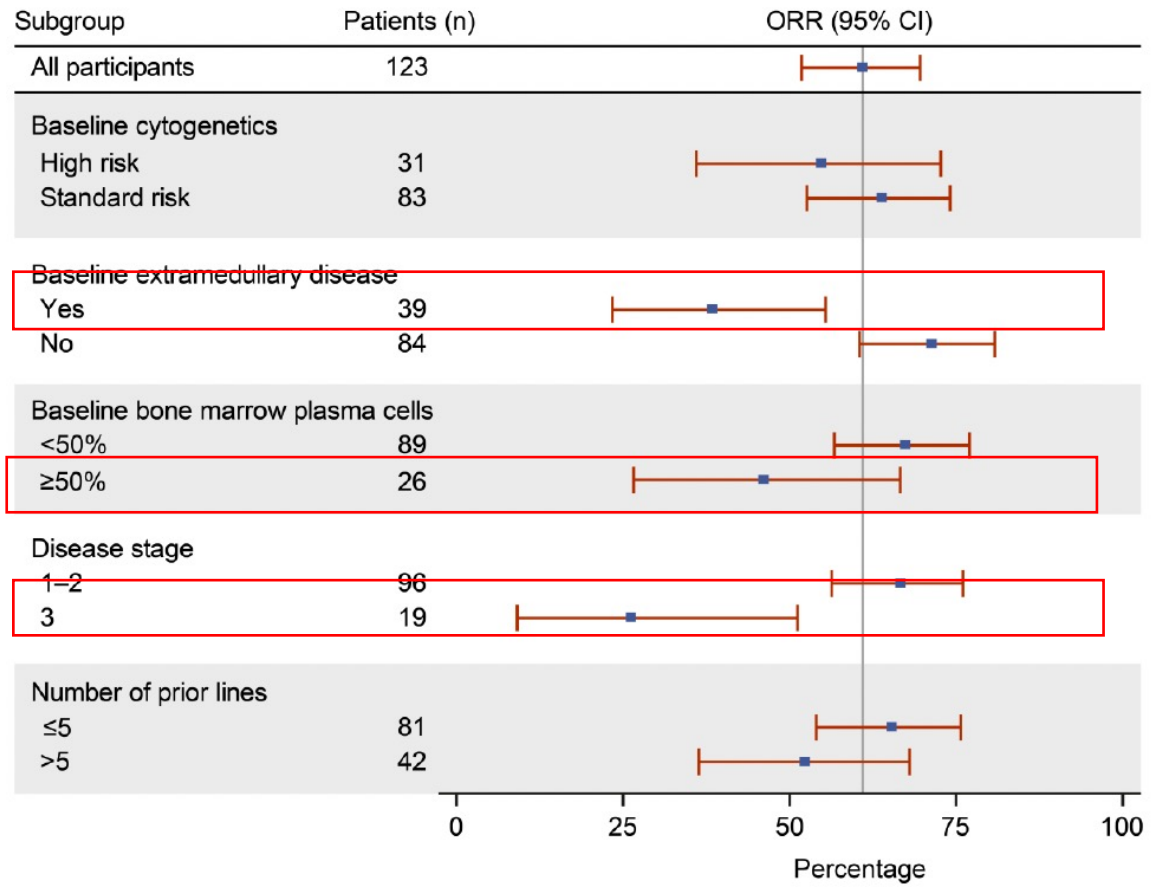
Baseline characteristics

	Cohort A (N=123)[a]
Extramedullary disease by BICR, n (%)[d]	39 (31.7)
Bone marrow plasma cells, n (%)	
<50%	89 (72.4)
≥50%	26 (21.1)
Missing	8 (6.5)
Prior lines of therapy, median (range)	5 (2–22)
Prior stem cell transplant, n (%)	87 (70.7)
Exposure status, n (%)	
Triple-class[e]	123 (100)
Penta-drug[f]	87 (70.7)
Refractory status, n (%)	
Triple-class[e]	119 (96.7)
Penta-drug[f]	52 (42.3)
Refractory to last line of therapy, n (%)	118 (95.9)

Elranatamab for RRMM: efficacy from cohort A of the magnetismm-3 study

Overall response rate



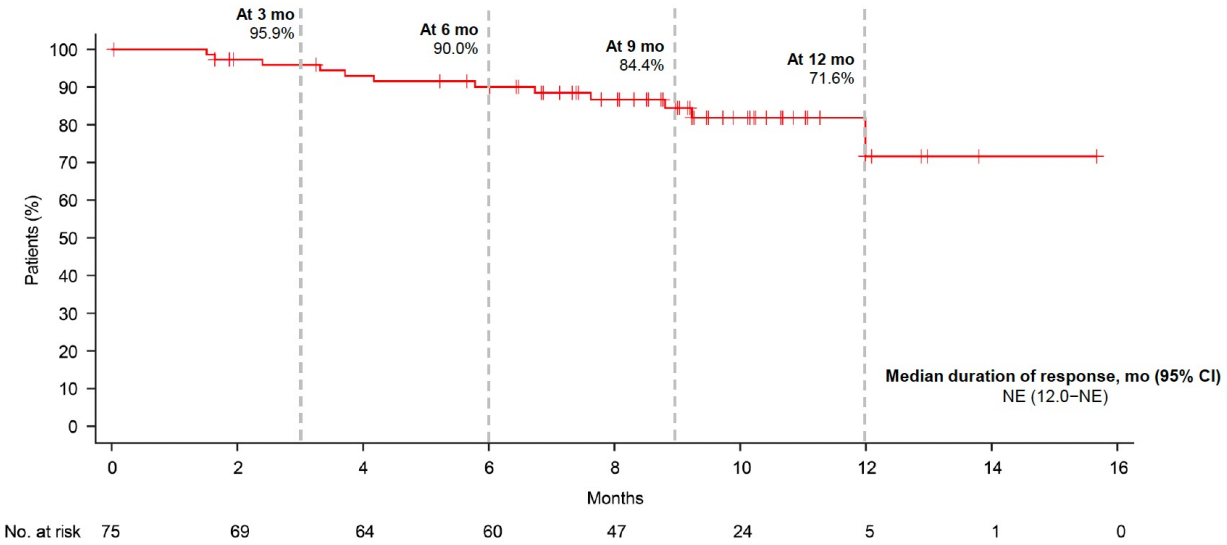


MRD negativity 91%
(10^5, n=22 patients tested)

Bahlis N. et al, ASH 22

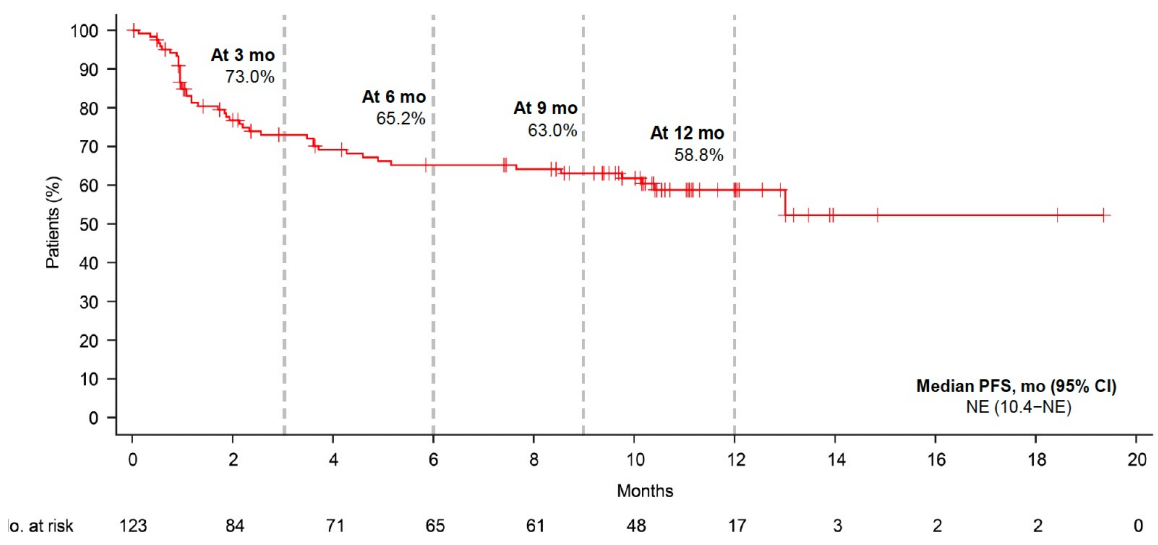
Elranatamab for RRMM: efficacy from cohort A of the magnetismm-3 study

Duration of response
(responder patients only)



BICR=blinded independent central review; CI=confidence interval; NE=not evaluable

Progression-free survival



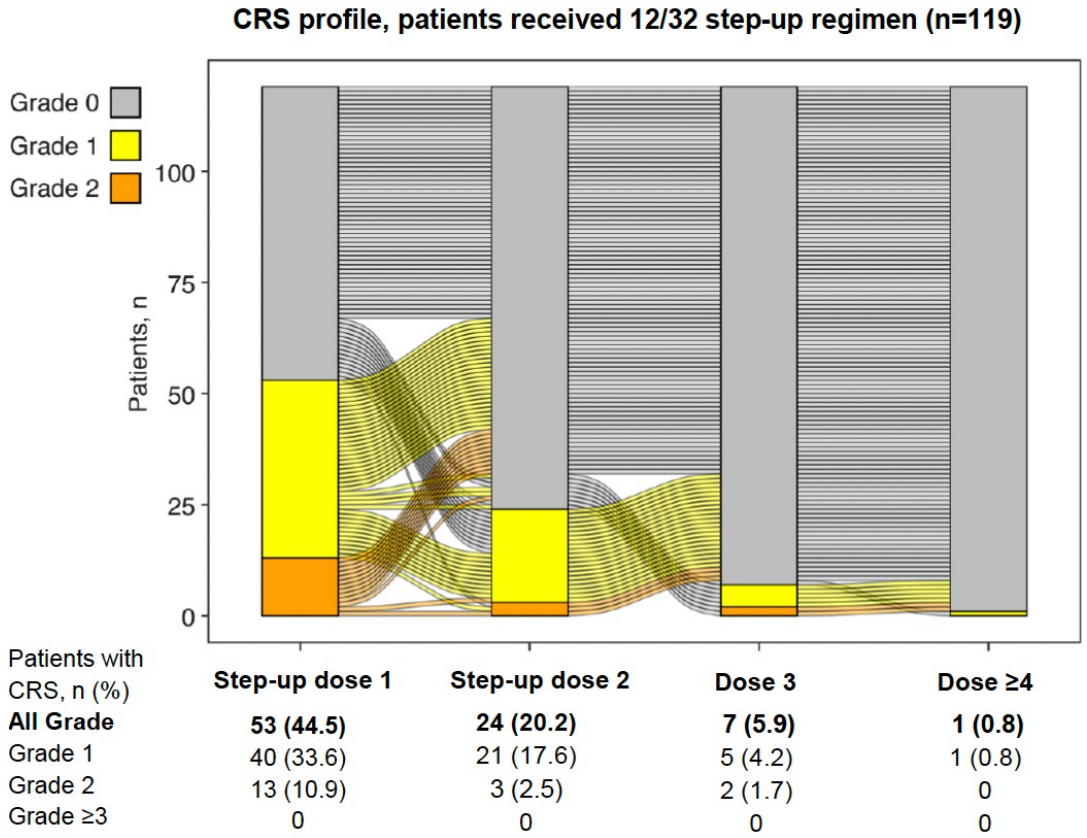
ICR=blinded independent central review; CI=confidence interval; NE=not evaluable; PFS=progression-free survival

Bahlis N. et al, ASH 22

Elranatamab for relapse and refractory, anti-BCMA treatment naive mutliple myeloma patients: safety from cohort A of the magnetismm-3 study

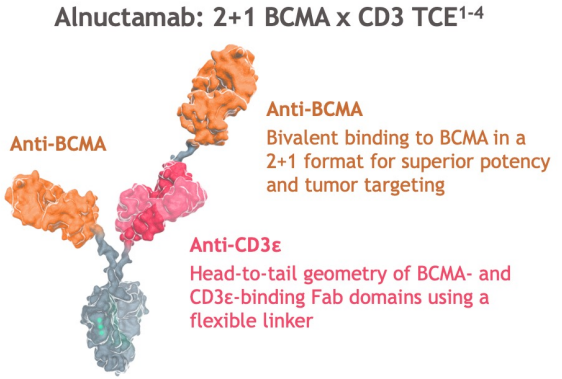
TEAE of special interest	12/32 mg step-up regimen (n=119)[a] CRS	ICANS
Patients with TEAE, n (%)	67 (56.3)	4 (3.4)
Maximum Grade 1	50 (42.0)	1 (0.8)
Maximum Grade 2	17 (14.3)	3 (2.5)
Maximum Grade ≥3	0	0
Patients with >1 TEAE, n (%)	18 (15.1)	1 (0.8)
Median time to onset of TEAE, d (range)	2.0 (1.0–9.0)	2.5 (1.0–4.0)
Median time to resolution of TEAE, d (range)	2.0 (1.0–19.0)	2.0 (1.0–6.0)
Patients who received tocilizumab[b] or steroids, n (%)		
Tocilizumab	27 (22.7)	2 (1.7)
Steroids	10 (8.4)	2 (1.7)
Permanent discontinuation due to AE, n (%)	0	0

Infections were reported in 66.7% (Grade 3/4, 35.0%) of patients



Bahlis N. et al, ASH 22

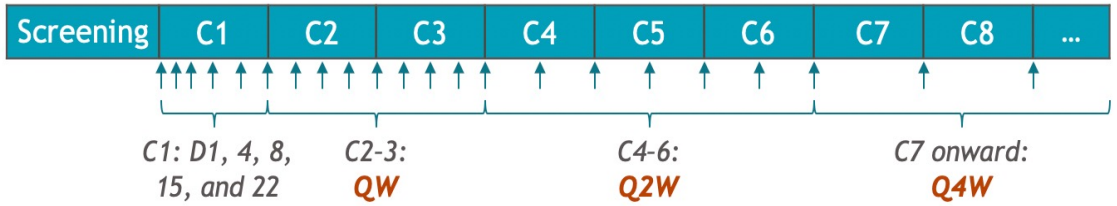
Alnuctamab, a BCMA × CD3 T-cell engager, in patients with relapsed/ refractory multiple myeloma: results from a phase 1 first-in-human study



Key eligibility criteria

- RRMM after ≥ 3 prior regimens, including an immunomodulatory drug (IMiD®), PI, and anti-CD38 therapy
- Progressive disease within 60 days of last regimen
- No prior BCMA-directed therapy

SC alnuctamab dose schedule (28-day cycles)



SC dose escalation

- All cohorts: 2 step-up doses (3 mg on C1D1 and 6 mg on C1D4)
- Target dose (10 mg, 15 mg, 30 mg, or 60 mg) on C1D8 and thereafter

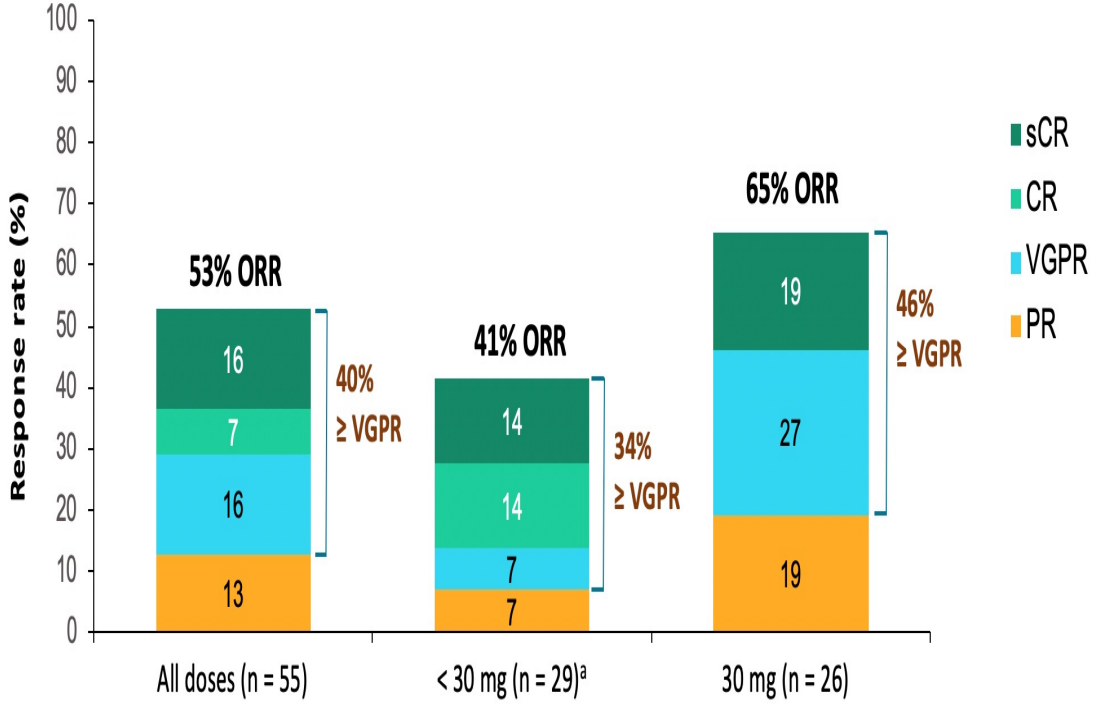
SC cohort expansion – multiple cohorts

Exposure status, n (%)	
Triple-class[b] / Penta-drug[c] exposed	68 (100) / 43 (63)
Refractory status, n (%)	
Triple-class[b] / Penta-drug[c] refractory	43 (63) / 19 (28)

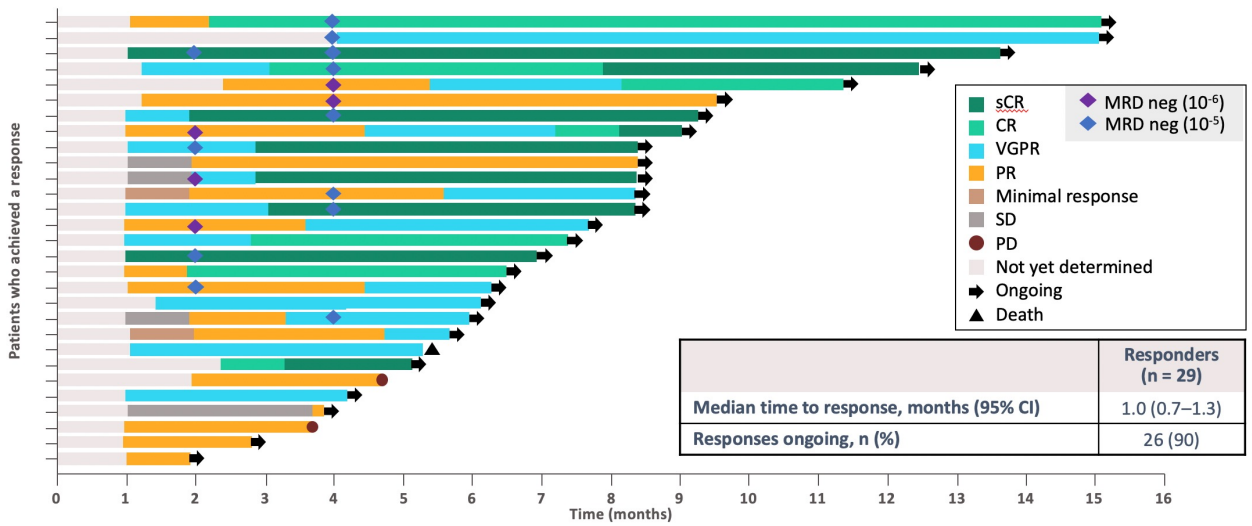
Wong SW et al, ASH 2022

Alnuctamab, a B-cell maturation antigen × CD3 T-cell engager for RMMM

Overalll response rate



Duration of response



	Responders (n = 29)
Median time to response, months (95% CI)	1.0 (0.7–1.3)
Responses ongoing, n (%)	26 (90)

Among 29 patients who achieved a response, 16 of 20 patients with evaluable[b] MRD samples (80%) were MRD negative at C2D1 or C4D1 (≥ 10^{-5} sensitivity)

Database cut-off: November 1, 2022. Data are shown for the efficacy-evaluable population, defined as patients who met eligibility criteria, received ≥ 1 dose, and had ≥ 1 post-baseline efficacy assessment or discontinued treatment for lack of efficacy. Patients receiving the 60-mg target dose were excluded due to limited follow-up.
[a]Patients who received 10- or 15-mg target doses. [b]Excludes patients (n=9) who did not have an evaluable MRD sample at either C2D1 or C4D1 because of inadequate sample quality or missing samples. CR, complete response; PD, progressive disease; P response; SD, stable disease; VGPR, very good partial response.

Wong SW et al, ASH 2022

Anti-BCMA T-cell engagers
Efficacy results

	Trial phase	Patients, n	Prior BCMA	Schedule	ORR, %	CR, %	Median DOR, months	Median PFS, months	Median OS, months
Teclistamab*	1-2	165	NO	Q1W s.c.	63[a]	39.4	18.4	11.3	18.3
Elranatamab (Cohort A)	2	123	NO	Q1W – Q2W s.c.	61[b]	28	NR	NR	NR
Linvoseltamab (REGN5458)[C]	1	73	-	Q1W i.v.	75[2]	43.2[2]	NR; 8-months: 90.2%**,[3]	NR	NR
ABBV-383 (TNB-383B)(≥40 mg cohort)	1	24	-	Q3W i.v.	79[3]	29[3]	NR	NR	NR
Alnuctamab (CC-93269)[C]	1	30	NO	C1–3: QW; C4–6: Q2W; C7+ Q4W s.c.	65	19	NR	NR	NR

Inter-trial comparisons should not be made because of differences in study design, patient populations, treatment interventions, and duration of follow-up, among others. We cannot make direct comparisons or draw conclusions from one trial to another. For descriptive purposes, efficacy results for each of the studies mentioned are listed. *Teclistamab has been granted conditional marketing authorization by the EC for the treatment of adult patients with RRMM, after ≥3 prior therapies, including an IMiD™, a PI, and an anti-CD38 MoAb and have demonstrated disease progression on the last therapy. **The Kaplan–Meier estimated probability of responders being in response for 8 months or more. [a]1.5mg/kg (RP2D) of Teclistamab. [b]76 mg (RP2D) of Elranatamab. [c]RP2D not yet reported
NR; not reported. s.c., subcutaneous.
1. Mailankody, S. N Engl J Med. 2022;387:558-61. 2. Zonder JA et al., abstract S189 at EHA 2022. 3. Kumar S. et al. abstract 900 presented at ASH 2021. 4. Costa LJ et al., oral presentation S205, presented at EHA 2020

Anti-BCMA T-cell engagers:
Safety results

	CRS, %		Neurotoxicities, %		Infections, %		Neutropenia, % (Grade 3-4)	Thrombocytopenia, % (Grade 3-4)
	All grade	Grade 3-4	All grade	Grade 3–4	All grade	Grade 3-4		
Teclistamab	72	1	14	1	76.4[2]	44.8[2]	64.2[2]	21.2[2]
Elranatamab (cohort A)	56	0	3	0	67	35	48	22
Linvoseltamab (REGN5458)	38	0	4	0	41[4]	NR[4]	22[4]	13[4]
ABBV-383 (TNB-383B)(60 mg),[5]	72[5]	2[5]	5	NR	32[6]	31[6]	37[5]	12[5]
Alnuctamab (CC-93269)[7]	53	0	3	0	34	9	32	9

Inter-trial comparisons should not be made because of differences in study design, patient populations, treatment interventions, and duration of follow-up, among others. We cannot make direct comparisons or draw conclusions from one trial to another. For descriptive purposes, efficacy results for each of the studies mentioned are listed. 1. Mailankody S. N Engl J Med. 2022;387:558-61. 2. Moreau P, N Engl J Med, 2022;387:495-505. 3. Lesokhin AM et al., abstract 8006, oral presentation at ASCO 2022 4. Zonder JA et al., abstract S189, oral presentation at EHA 2022. 5, Voorhees et al. abstract OAB-055, oral presentation at IMS 2022. 6. Kumar S. et al. abstract 900 presented at ASH 2021. 7. Costa LJ et al., Abstract S205, oral presentation at EHA 2020.

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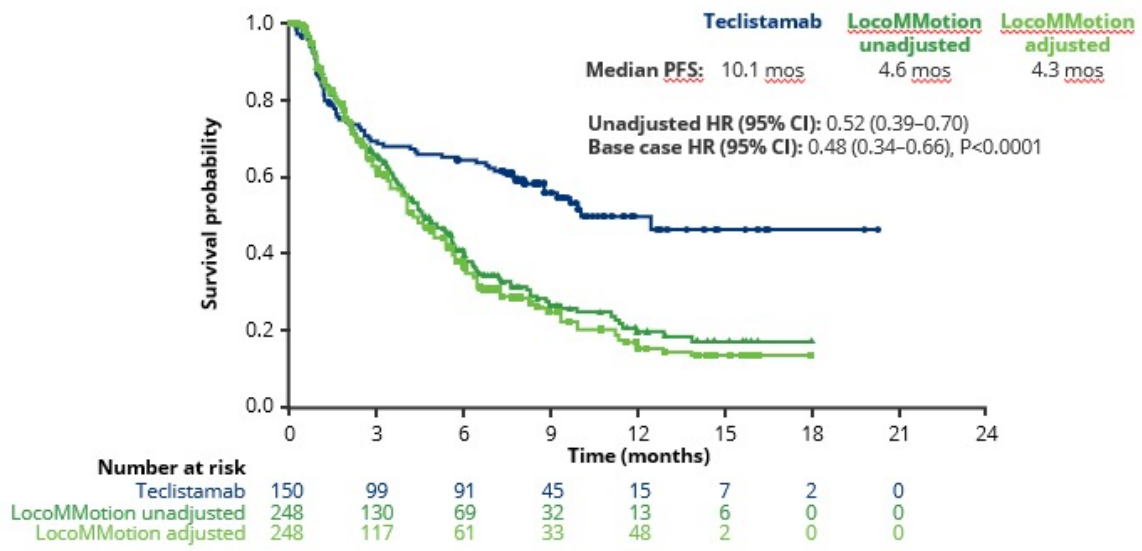
Bispecific antibodies for triple-class refractory myeloma:

Teclistamab vs Real world clinical practice

Progression-free survival



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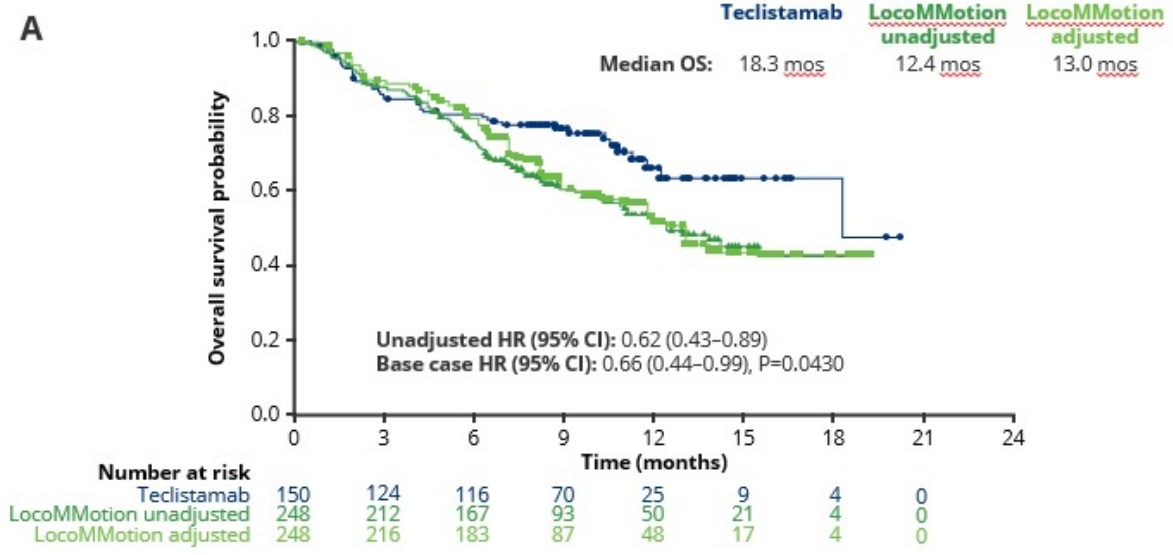
Overall survival



BCMA, B-cell maturation antigen; IMiD, immunomodulatory drug; PI, proteasome inhibitor; ORR, overall response rate; CR, complete response;

Van De Donk N. et al. ASCO2022. Abs 8016

ADC, bispecific antibodies, CAR T-cell: how to pick a BCMA-targeting agent?

	ADC[1]	Bispecific antibody[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]

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.

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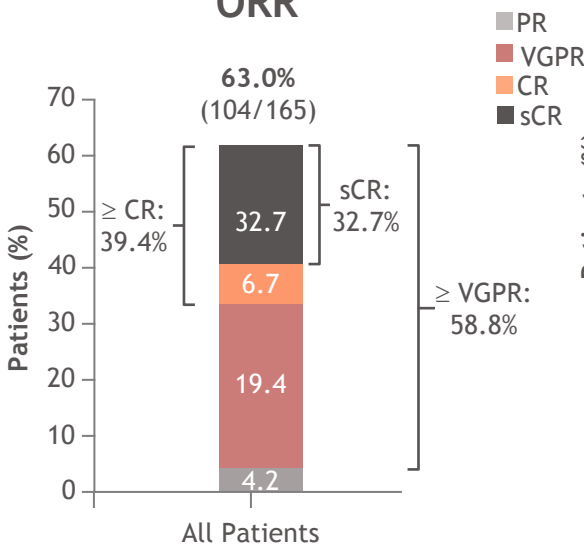
Can we plan sequential ADC, TCE and CAR T?

Teclistamab, MAJESTEC-1

No prior BCMA

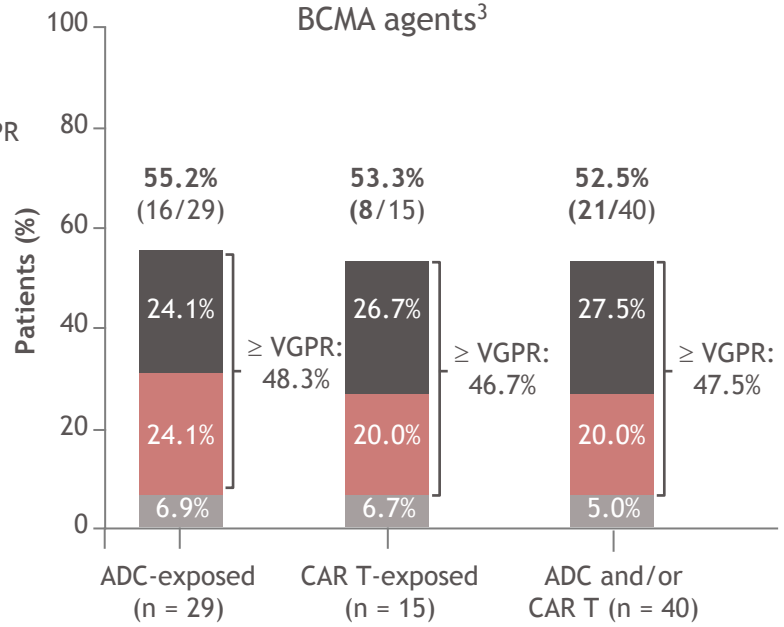
MAJESTEC-1, cohort A: no prior anti-BCMA agents[2]



Prior BCMA

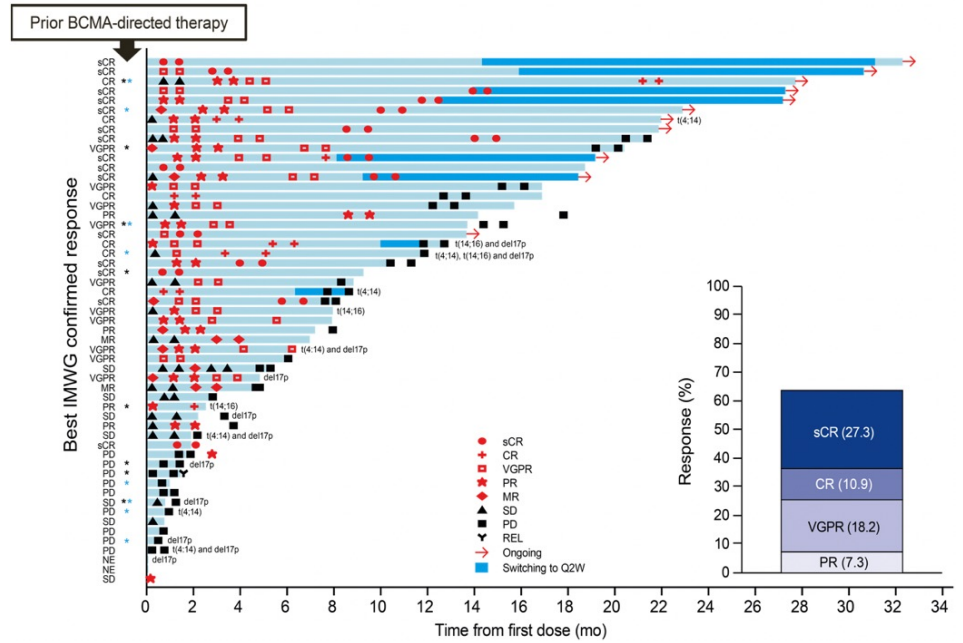
ORR[a] in cohort C

MAJESTEC-1, cohort C: Teclistamab for RRMM patients previously exposed to anti-BCMA agents[3]



Elranatamab, MAGNETISMM-1

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



[a]PR or better, IRC assessed, per IMWG 2016 criteria.

ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee.

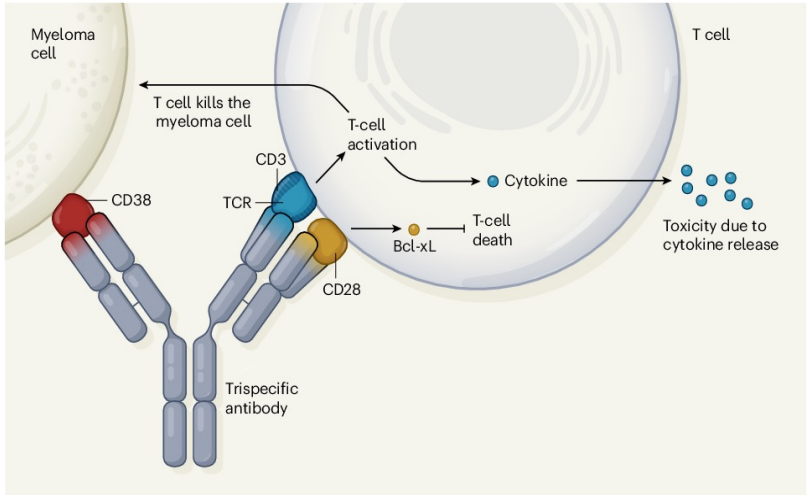
1. Hansen DK, et al. Poster presented at ASCO 2022. J Clin Oncol. 2022;40:abstract 8042. 2. Moreau P, et al. N Engl J Med. 2022;387:495-505. 3. Touzeau C, et al. Poster presented at ASCO 2022; J Clin Oncol. 2022;40;abstract 8013.

BCMA-targeting bispecific antibodies

1. Efficacy and safety data of anti-BCMA bispecific antibodies
2. Bispecific antibodies for triple-class refractory myeloma: where do we stand?
3. Targeting BCMA with a bispecific antibody in BCMA-exposed patients: what do we know?
4. How to improve the efficacy of bispecific antibodies?

Improving the efficacy of bispecific antibodies:

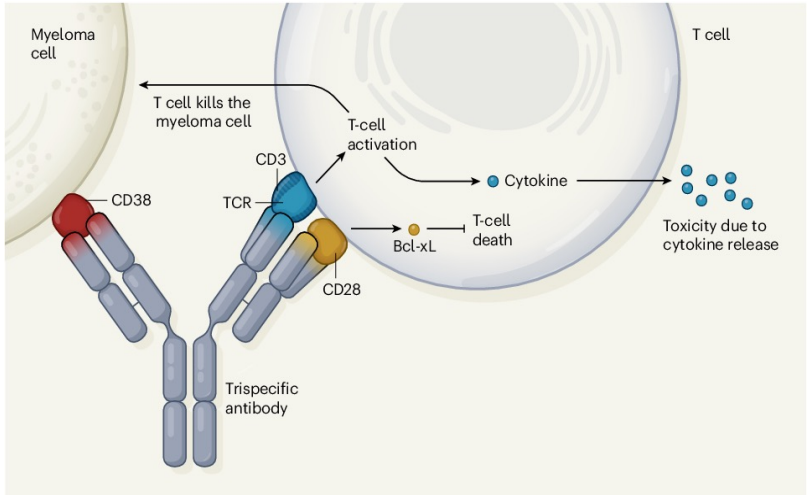
Constructs



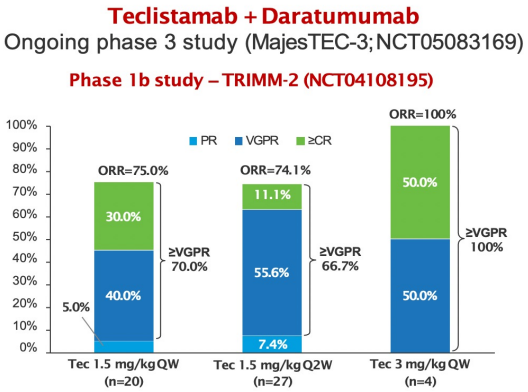
Wu Nature Cancer 2020

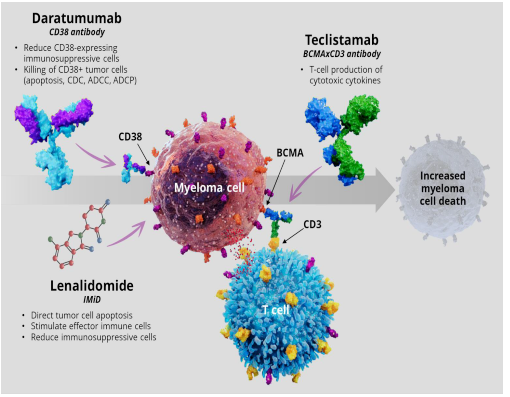
Improving the efficacy of bispecific antibodies:

Constructs



Partnership: anti-CD38 MoAb, ImiD, anti-PD1





Wu Nature Cancer 2020; Rodriguez-Otero ASCO 2022

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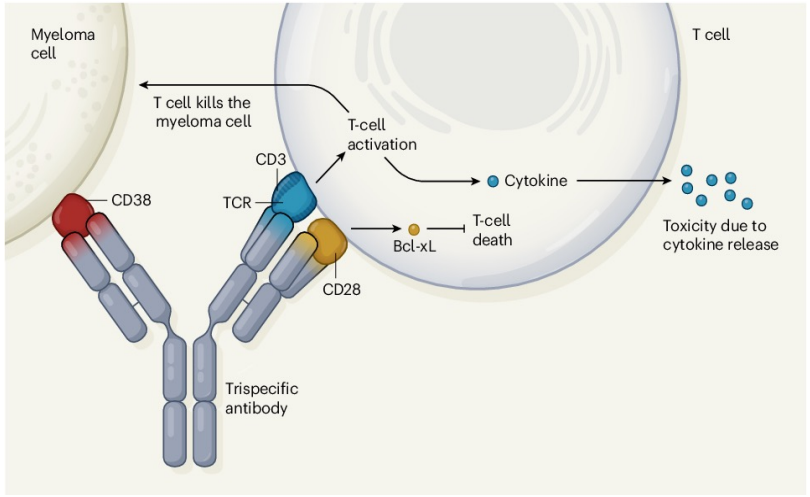

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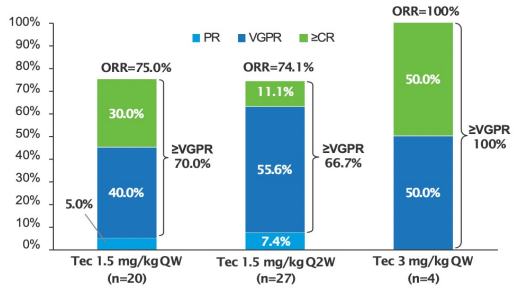
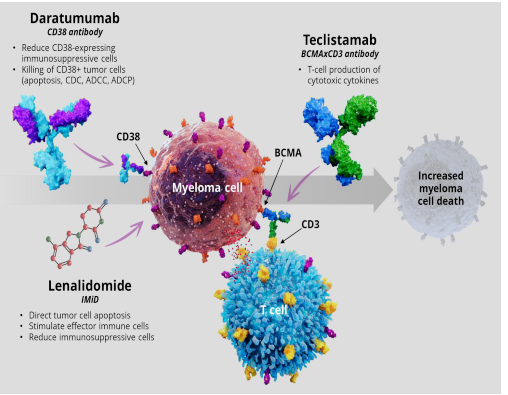
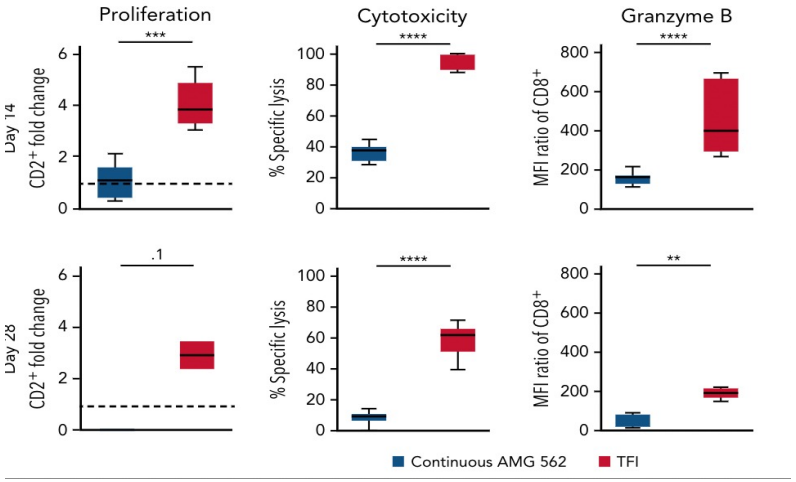




Treatment strategy: fixed duration



Wu Nature Cancer 2020; Rodriguez-Otero ASCO 2022; Philipp N. et al Blood 2022;

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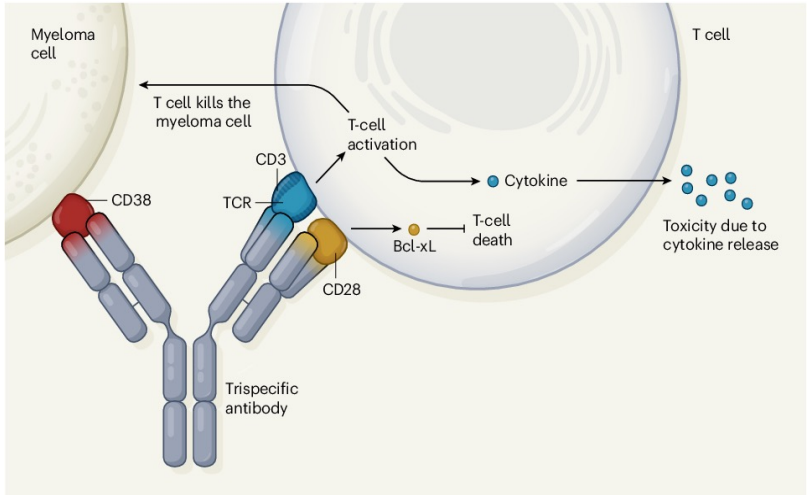

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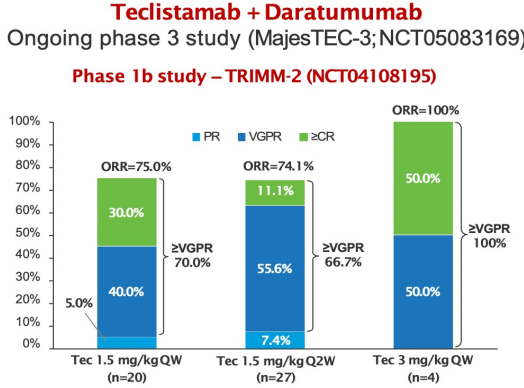

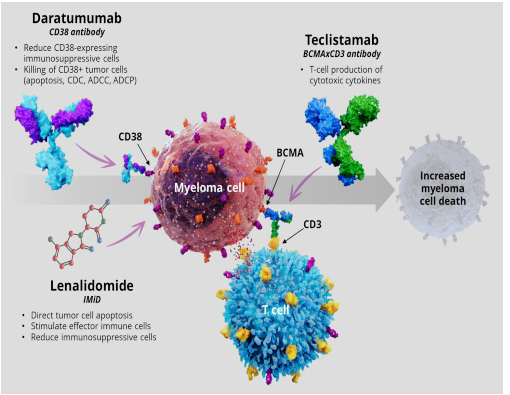

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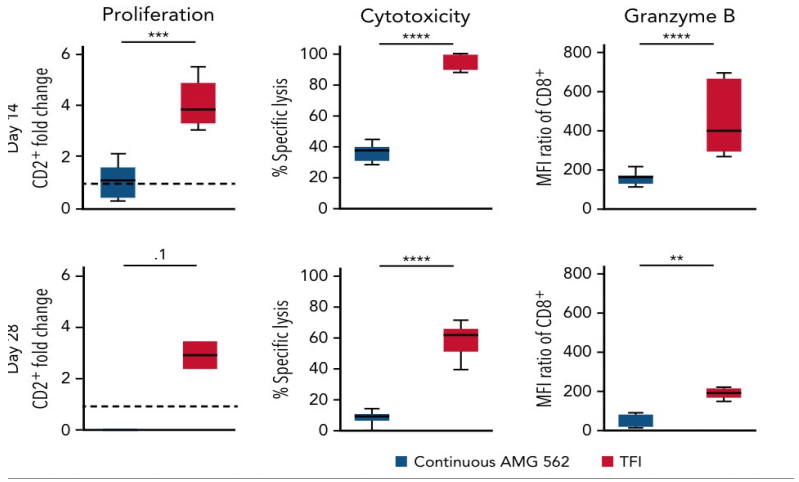
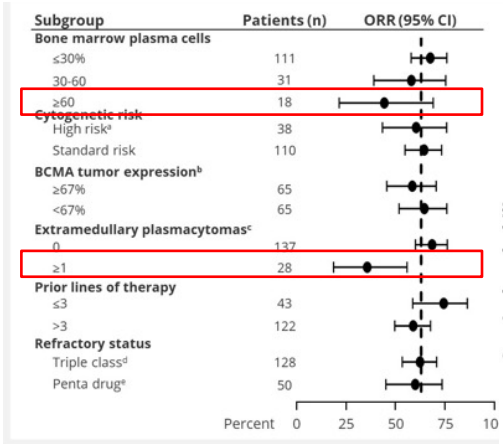
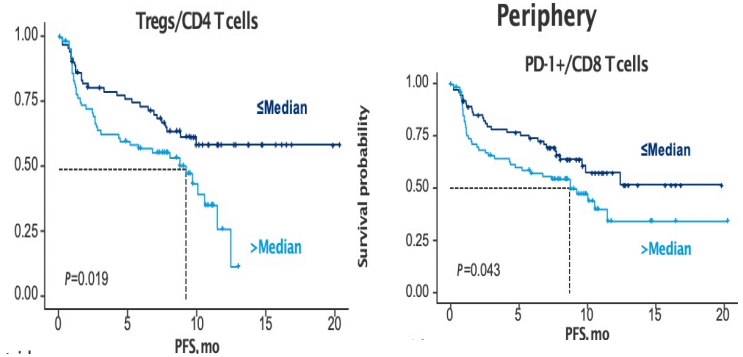




Patient and disease selection



Wu Nature Cancer 2020; Rodriguez-Otero ASCO 2022; Philipp N. et al Blood 2022; Lesokhin ASCO 2022; Cortes-Selva D. et al ASH 2022

Conclusions

Promises:

- Anti-BCMA bispecific antibodies showed great efficacy in heavily pre-treated RRMM patients: ORR and CR rates up to 80% and 40% and durable responses (>12 months).
- Bispecific antibodies are associated with lower rates and grades of CRS and ICANS as compared to CAR T-cells, thus allowing older patients to be treated.

Hurdles:

- Grade 3-4 infections up to 45%: data about type and timing of infections and mitigation strategies are warranted.
- Mitigation strategies to reduce the risk of CRS and ICANS to allow oupatient administration

Future perspectives:

- Partners: IMiDs, anti-CD38 MoAbs and anti-PD1 could improve efficacy; caution with toxicity (infections?)
- Alternative strategies (e.g. fixed duration) to improve safety and incorporate bispecific in currrent treatments (post-ASCT consolidation, MRD driven therapy)

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