

ANTICORPI BISPECIFICI

Il futuro degli anticorpi bispecifici nel MM

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LE NUOVE FRONTIERE
DELL'IMMUNOTERAPIA
PER LA CURA DEL

MIELOMA MULTIPLO

dalla teoria alla pratica



TORINO 3-4 MARZO 2023

Disclosures of Paola Tacchetti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS/Celgene						X	X
Janssen						X	X
Amgen						X	X
Sanofi							X
Takeda							X
Pfizer							X
Abbvie							X
GSK							X



T-cell redirecting strategies in RRMM

	Bispecific antibody	“New generation”CAR T
Response	ORR: 43-79% CR: 19-43%	ORR: 73-100% CR: 33-83%
Safety	CRS all grade/grade $\frac{3}{4}$: 38-80%/ 0-3% ICANS all grade/grade $\frac{3}{4}$: 5-14%/ < 1% cytopenia and infections (up to 45% grade $\frac{3}{4}$)	CRS all grade/grade $\frac{3}{4}$: 60-80%/ 0-15% ICANS all grade/grade $\frac{3}{4}$: 6-18%/ 0-6% cytopenia, and infections
Dosing	Q1W/Q2W/Q4W, IV/SC until PD (starting fixed duration)	Single dose
Accessibility	Off the shelf	Turnaround time, reducing
Administration	Inpatient for first doses/outpatient Available in community setting	Inpatient Available in community setting

The intention of the graph is not comparative and is provided for ease of viewing information from various products. Direct comparison between products is not intended and should not be inferred.

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.

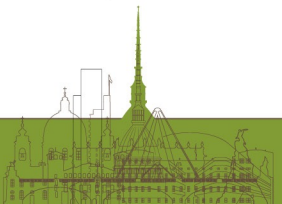


Are we using T-cell redirecting strategies optimally ?

Probably not....

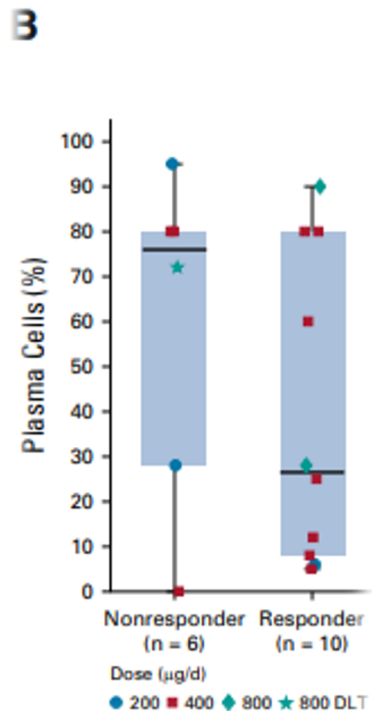
We must still learn how to optimally use them

- Combination strategies
- Earlier lines of therapy
 - Fitter T-cells
- Debulking → less T-cell exhaustion?
- Better knowledge on infectious prophylaxis, strategies to mitigate CRS/ICANS
- Treatment duration
- Sequencing

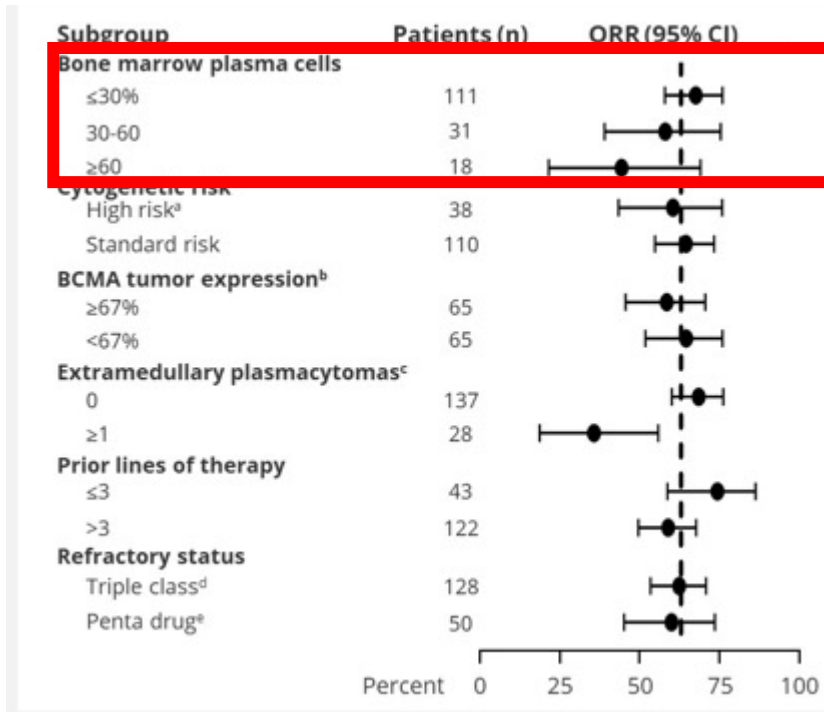


Impact tumor burden in BsAb studies

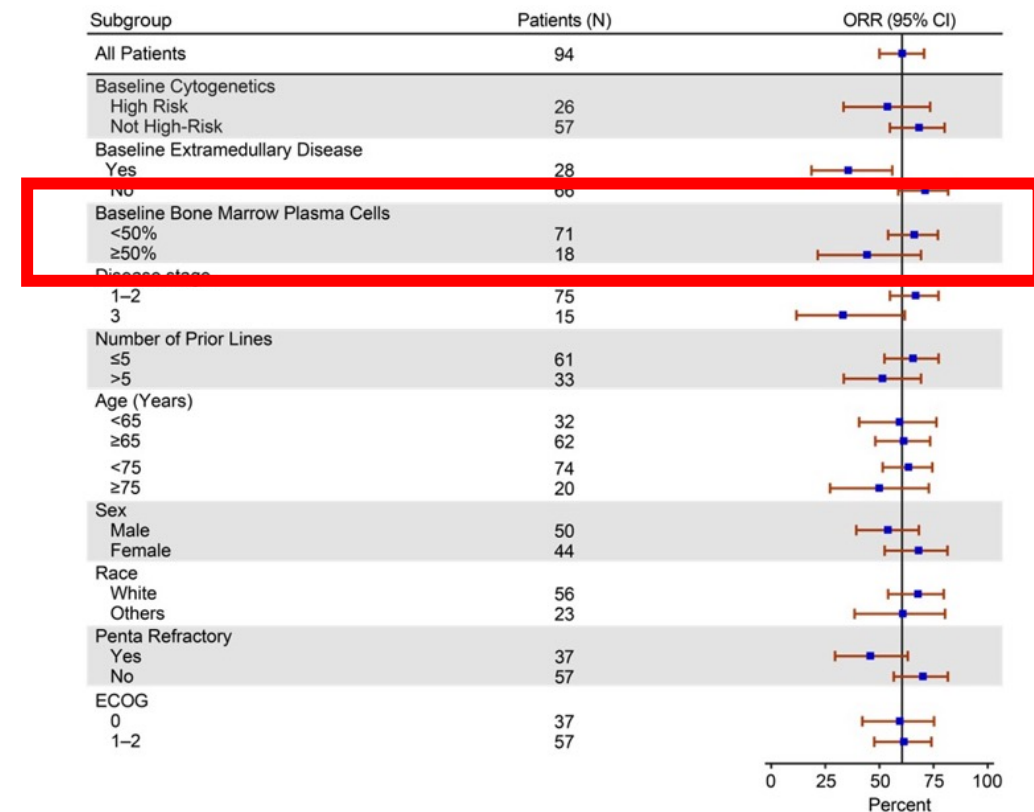
AMG420 study; responding vs non-responding patients



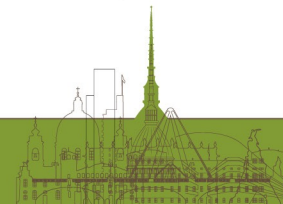
Teclistamab: Majestic-1 study



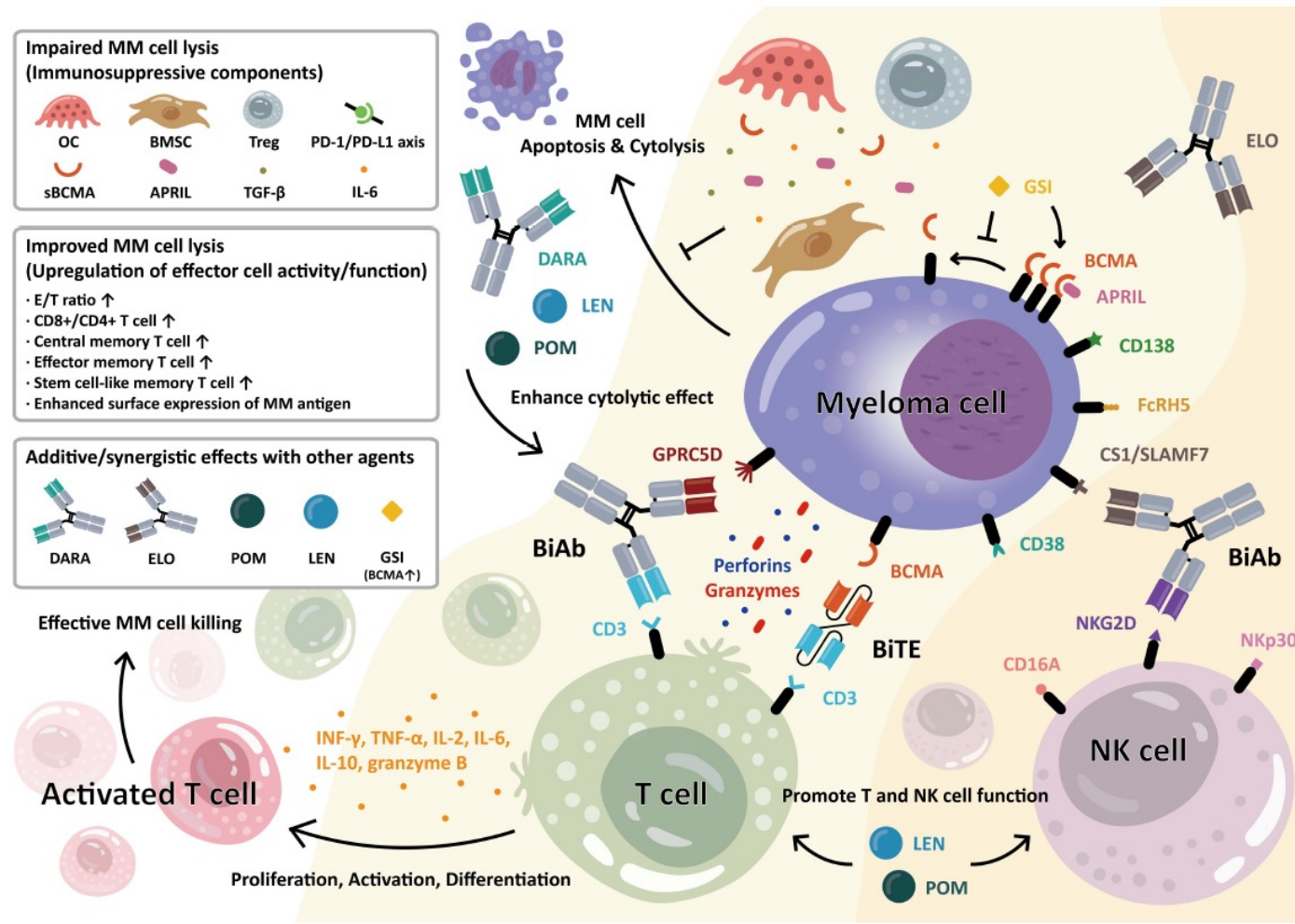
Elranatamb: MagnetisMM-1 study



Nooka AK et al. ASCO 2022; Lesokhin AM et al. ASCO 2022; Moreau P et al. ASH 2021; Topp J et al. Clin Oncol 2020



Anti-myeloma activity of bispecific antibody (BiAb) and bispecific T-cell engager (BiTE) molecules in the bone marrow MM microenvironment



Cho S et al., Frontiers in Oncology 2022



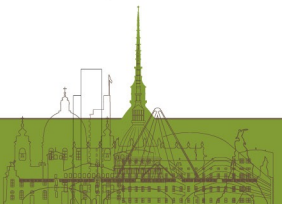
Combination with other anti-MM agents

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

Cho S et al., Frontiers in Oncology 2022



Combination of 2 bispecific molecules targeting various MM antigens or combination with agent which enhances expression of target antigen

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)

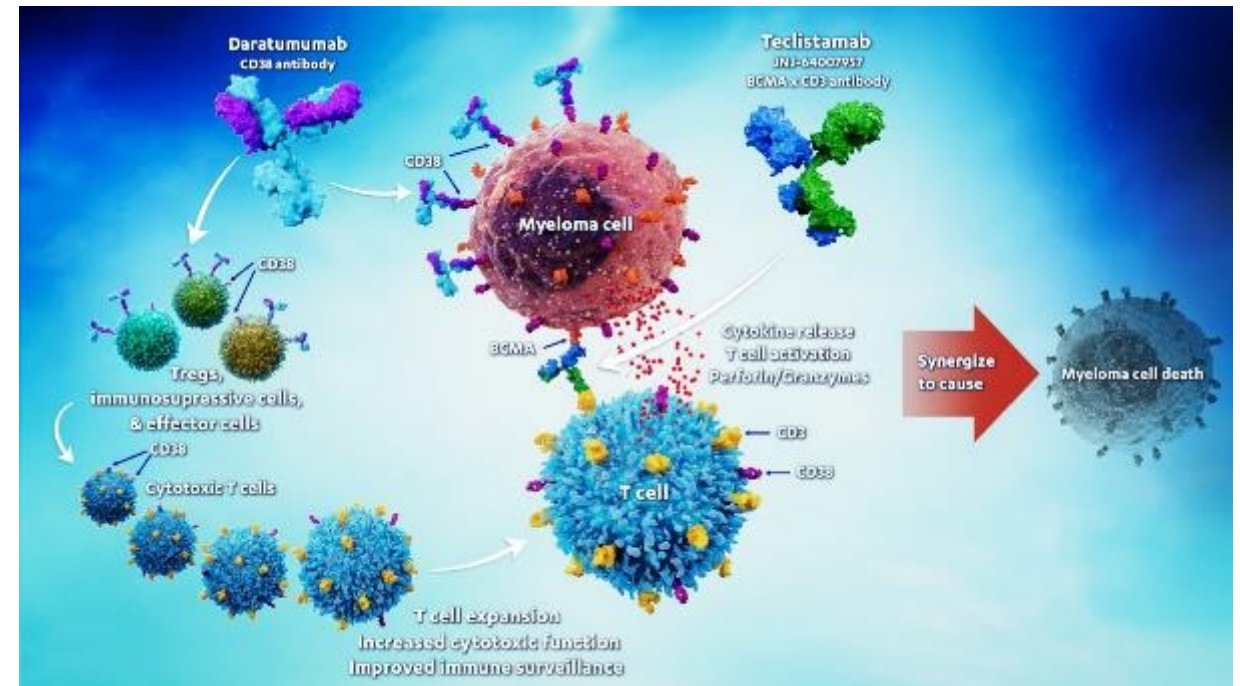
Sub-study A
Elranatamab + nirogacestat

Cho S et al., Frontiers in Oncology 2022



Teclistamab plus Daratumumab: A Rational, Immunotherapy-based Combination

- Teclistamab (tec; JNJ-64007957) is an off-the-shelf, BCMA x CD3 T-cell redirecting bispecific antibody under investigation in patients with RRMM¹
- Daratumumab (dara) is a human IgG1k anti-CD38 mAb with direct on-tumor and immunomodulatory actions²⁻³
- The combination of tec + dara has been shown to upregulate CD38+/CD8+ T cells and proinflammatory cytokines, suggesting the potential for synergistic efficacy⁴



BCMA, B-cell maturation antigen; Dara, daratumumab; mAb, monoclonal antibody; RRMM, relapsed/refractory multiple myeloma; Tec, teclistamab

1. Pillarisetti K, et al. Blood Adv 2020; 4(18):4538-49. 2. van de Donk N, et al. Immunol Rev 2016; 270:95-112. 3. Krejcik J, et al. Blood 2016; 128(3):384-94. 4. Frerichs KA, et al. Clin Cancer Res 2020; 26:2203-15.



Teclistamab + Daratumumab – TRIMM-2

- Ongoing **phase 1b**, open-label, multicenter, multicohort study in patients with RRMM

Key eligibility criteria

- Adults with measurable MM
- ≥3 prior LOT, including a PI and IMiD
- Prior anti-CD38 therapy allowed (90-day washout period)
- Prior BCMA-directed therapies were allowed

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

Among 51 response-evaluable pts, **ORR was 76.5%**

VGPR or better in 70.6% of all response-evaluable pts

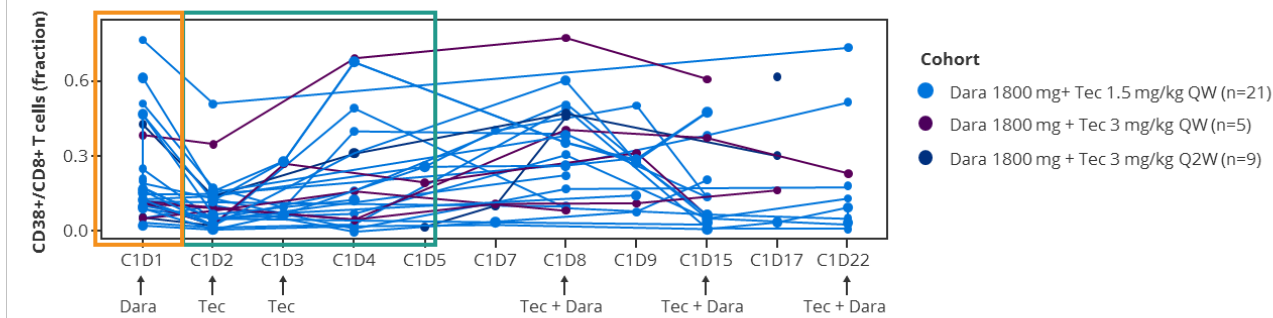
ORR of 73.7% (28/38) was achieved in pts with prior anti-CD38 exposure

Tec + dara dosing schedules

Dara	Tec SC	Patients enrolled
1800 mg SC (per approved schedule ¹) Cycles 1–2: QW Cycles 3–6: Q2W Cycles 7+: Monthly	1.5 mg/kg QW ^a	n=21
	3 mg/kg Q2W ^a	n=39
	3 mg/kg QW	n=5

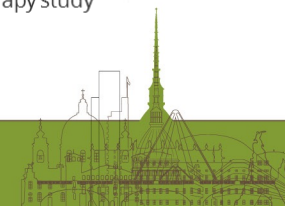
Characteristic	N=65
Prior lines of therapy, median (range)	5.0 (1-15)
Exposure status, n (%)	
IMiD ^e	63 (96.9)
Anti-CD38 mAb ^f	49 (75.4)
Triple-class ^g	49 (75.4)
Penta-drug ^h	36 (55.4)
BCMA-targeted therapy ⁱ	8 (12.3)
Refractory status, n (%)	
IMiD ^e	54 (83.1)
Anti-CD38 mAb ^f	41 (63.1)
Triple-class ^g	38 (58.5)
Penta-drug ^h	20 (30.8)
To last line of therapy	52 (80.0)

Pharmacodynamics of tec + dara administration



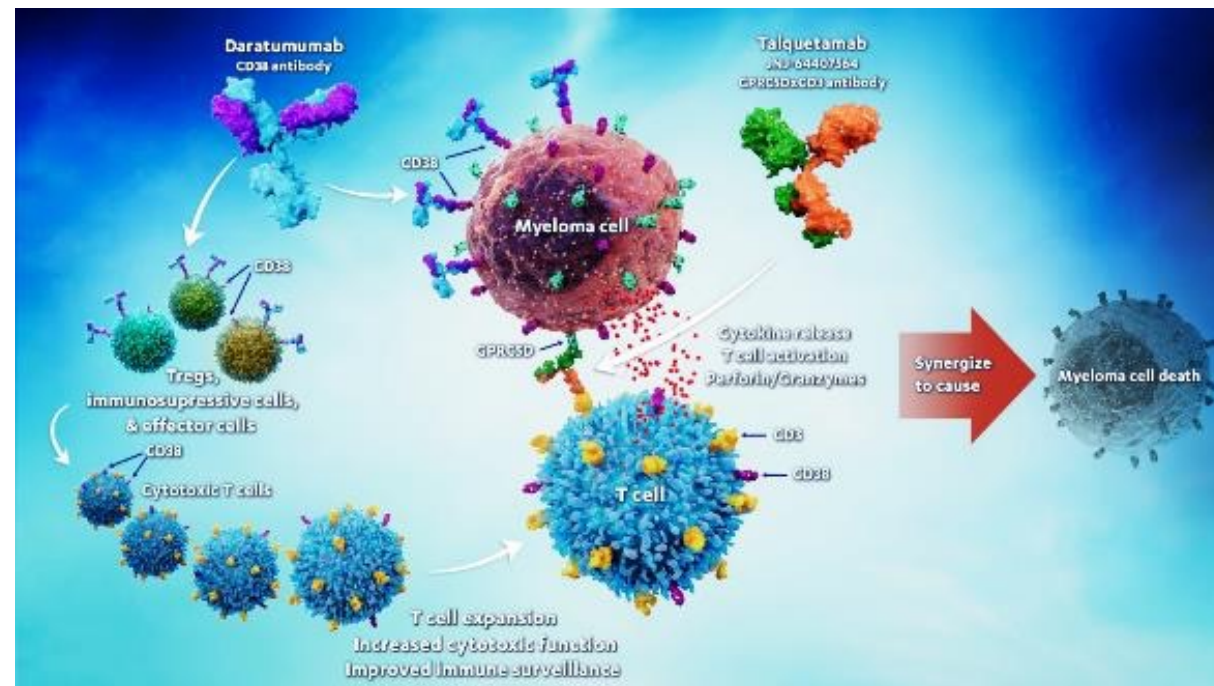
- The proportion of CD38+CD8+ T cells declined after initial dara dosing on C1D1 (orange box), consistent with previous data with dara
- Notably, tec administration led to induction of CD38+ CD8+ T cells after the first step up dose of tec (green box)
- Pharmacokinetic profile of tec in the presence of dara was consistent with the profile observed in the MajesTEC-1 monotherapy study
- As of March 9, 2022, all 41 evaluable patients did not have detectable anti-tec antibodies

Rodriguez Otero P et al., EHA 2022 Oral presentation S188



Talquetamab plus Daratumumab: A Rational, Immunotherapy-based Combination

- Talquetamab (tal; JNJ-64407564) is a first-in-class, off-the-shelf, T-cell redirecting, bispecific antibody targeting both GPRC5D and CD3 receptors¹
- Daratumumab (dara) is a human IgG1k mAb targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action²
 - Dara monotherapy leads to T-cell expansion and enhanced T-cell cytotoxic potential³
- The combination of tal and dara has the potential to yield synergistic clinical efficacy. Preclinical studies showed the addition of dara enhanced tal-mediated lysis of MM cells⁴
- Here we present updated results for patients with RRMM who received tal + dara in a phase 1b, open-label, multicenter, multicohort trial (TRIMM-2; NCT04108195), including additional patients and longer follow up



dara, daratumumab; GPRC5D, G-protein coupled receptor family C group 5 member D; IgG, immunoglobulin G; mAb, monoclonal antibody; RRMM, relapsed/refractory multiple myeloma; Treg, regulatory T cell

1. Pillarisetti K, et al. Blood. 2020;135(15):1232-43. 2. van de Donk N, et al. Immunol Rev 2016; 270:95-112. 3. Krejcik J, et al. Blood 2016; 128(3):384-94. 4. Verkleij CPM, et al. Blood Adv. 2021;5(8):2196-2215.



Talquetamab + Daratumumab – TRIMM 2

- Phase 1b, open-label, multicenter, multicohort study in patients with RRMM

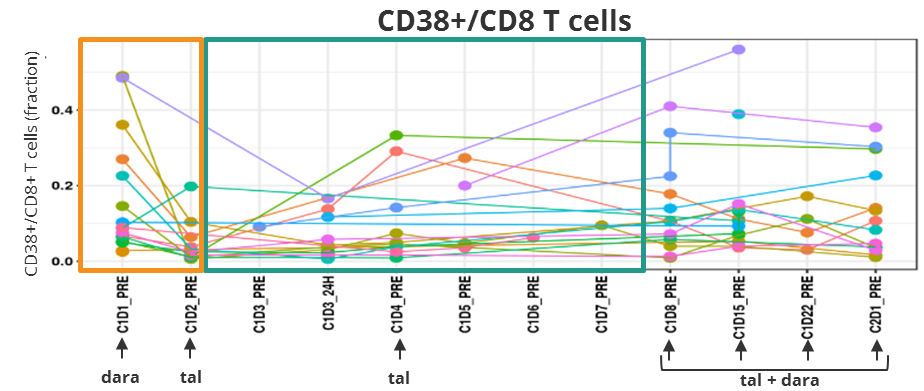
Key Study Eligibility Criteria
 Adults with diagnosis of MM per IMWG criteria
 ≥3 prior LOT or double refractory to PI and IMiD
 Tp with an anti-CD38 mAb >90 days prior allowed
 Includes pts who were refractory to anti-CD38 tp

Tal + Dara Dosing Cohorts

Tal	Dara SC	Patients enrolled to date (n)
800 µg/kg SC Q2W	1800 mg SC Cycles 1-2: QW Cycles 3-6: Q2W	44
400 µg/kg SC QW	Cycles 7+: monthly	14

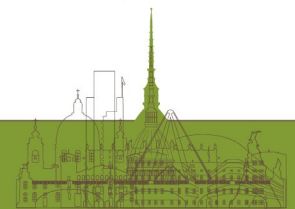
Characteristic	Tal 400 µg/kg QW + dara (n=14)	Tal 800 µg/kg Q2W + dara (n=44)
Prior lines of therapy, n, median (range)	6 (4–16)	5 (2–14)
Prior stem cell transplantation, n (%)	13 (92.9)	33 (75.0)
Exposure status, n (%)		
Anti-CD38 ^d	11 (78.6)	38 (86.4)
IMiD ^e	14 (100)	44 (100)
Triple-class ^f	11 (78.6)	37 (84.1)
Penta-drug ^g	10 (71.4)	27 (61.4)
BCMA-targeted therapy ^h	8 (57.1)	20 (45.5)
Refractory status, n (%)		
Anti-CD38 ^d	11 (78.6)	33 (75.0)
IMiD ^e	13 (92.9)	40 (90.9)
Triple-class ^f	8 (57.1)	28 (63.6)
Penta-drug ^g	5 (35.7)	12 (27.3)
To last line of therapy	12 (85.7)	31 (70.5)

Parameter	Evaluable patients ^a	
	Tal 400 µg/kg QW + dara (n=14)	Tal 800 µg/kg Q2W + dara (n=37)
Follow-up, median (range)	6.7 months (1.9–19.6)	4.2 months (0.2–12.3)
ORR ^b , n (%)	10 (71.4)	31 (83.8)
CR/sCR	4 (18.6)	11 (29.7)
VGPR	4 (28.6)	13 (35.1)
PR	2 (14.3)	7 (18.9)
SD	4 (28.6)	4 (10.8)
PD	0	2 (5.4)
Time to first confirmed response, median (range)	1.0 month (0.9–2.4)	1.0 month (0.9–6.5)



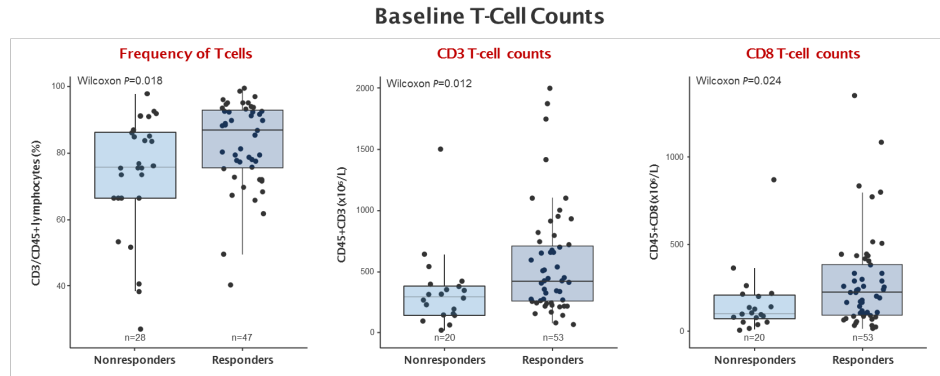
- The proportion of CD38+CD8+ T cells declined after initial dara dosing on C1D1 (orange box), consistent with previous data for dara
- Tal administration led to induction of CD38+ CD8+ T cells after the first step up dose of tec (green box)
- The PK of tal in the presence of dara was consistent with that observed with tal monotherapy in the phase 1 MonumentAL-1 study
- Anti-tal antibodies were detected in 2 of 44 immunogenicity-evaluable patients as of 9 March 2022
ADAs had no apparent effect on safety

Chari A et al ASH 2021; Van de Donk N et al. EHA 2022



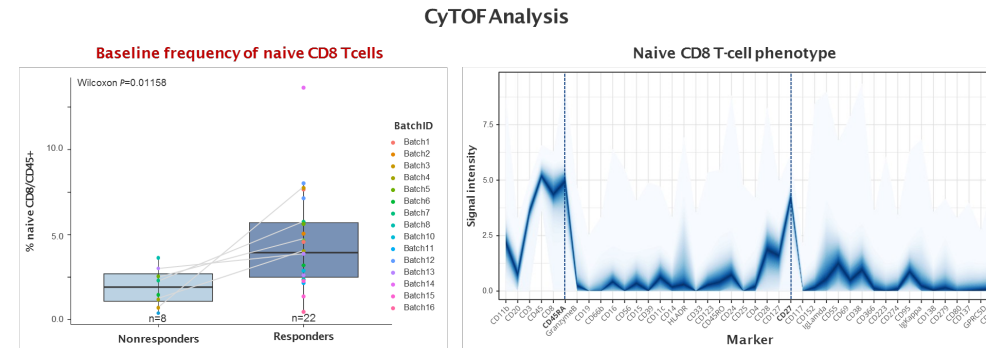
Importance of immune fitness

Clinical Response Is Associated With a Higher Frequency and Number of Peripheral T Cells at Baseline



- Higher frequency of T cells at baseline was significantly associated with clinical response
- Higher baseline CD3 and CD8 T-cell counts were seen in responding patients
- No significant differences were observed in CD4 T-cell counts in responders compared with nonresponders

Achievement of Clinical Response Is Associated With Frequency of Naive CD8 T Cells at Baseline



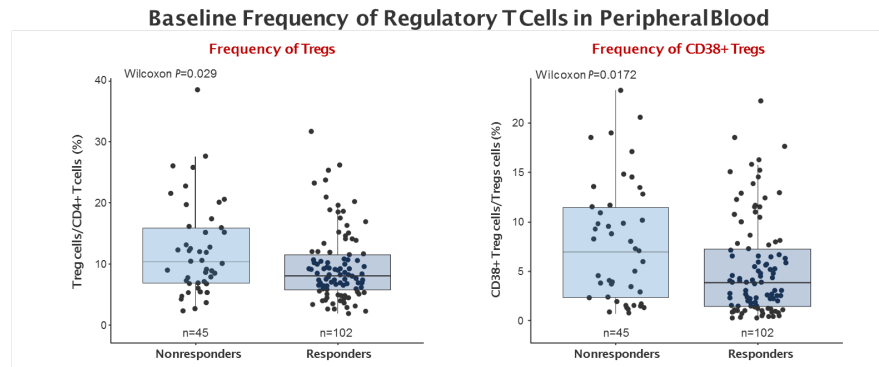
- Proportion of naive CD8 T cells at baseline was higher among responders
- At baseline, fan plot confirms CD8 T cells were CD45RA+CD27+, consistent with a naive phenotype

CytoF, cytometry by time of flight.

44

Teclistamab in Patients With RRRMM: Correlative Analyses From MajesTEC-1

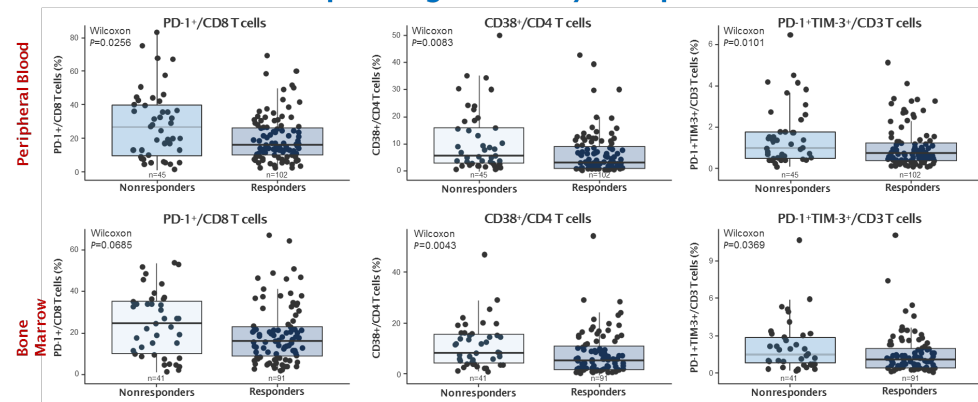
Clinical Response Is Associated With Baseline Frequency of Total Tregs and CD38+ Tregs in Periphery



- Tregs, which are key regulators of immune response, were found at a higher frequency in patients not achieving a clinical response

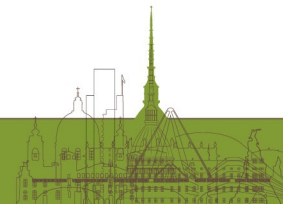
Treg, regulatory T cell.

Clinical Response Is Associated With Baseline Frequency of T Cells Expressing Inhibitory Receptors



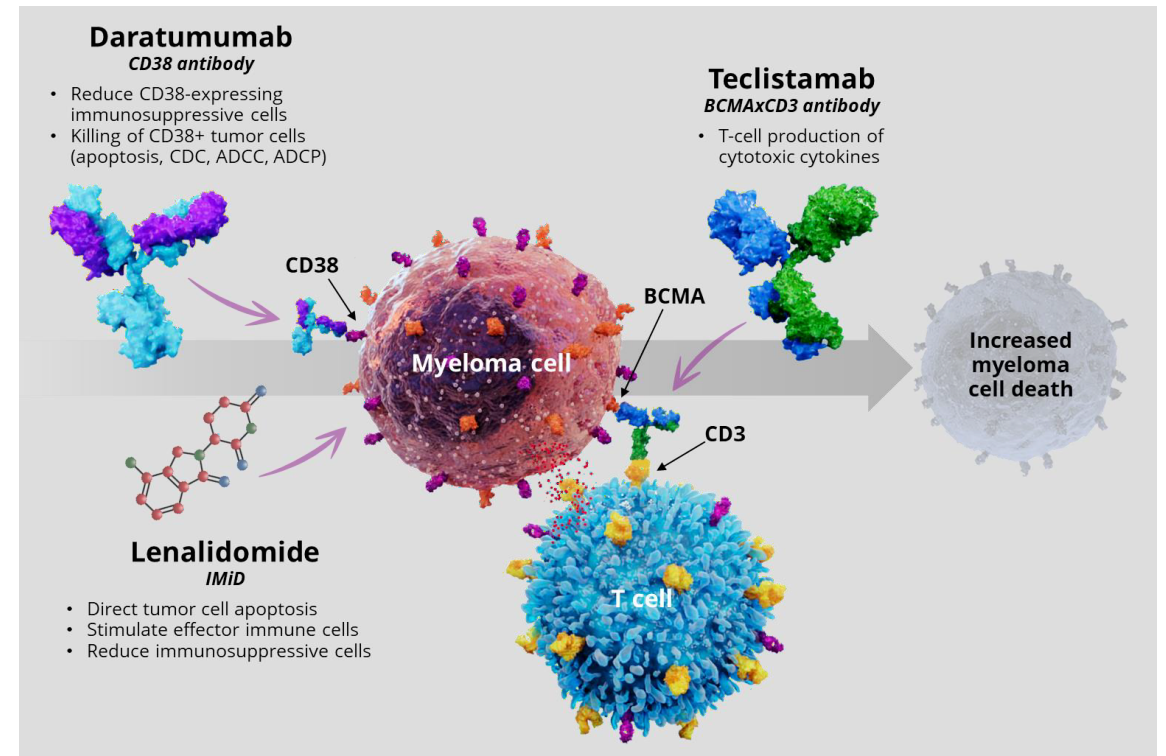
- PD-1, TIM-3, and CD38 markers can be associated with T-cell exhaustion or dysfunction

Cortes-Selva D et al. ASH 2022 Oral Presentation 98



Teclistamab in Combination With Daratumumab and Lenalidomide in RRMM treated with 1–3 prior LOT: the MajesTEC-2 trial

- **Teclistamab** is the first off-the-shelf **BCMA×CD3 bispecific antibody approved (ORR, 63%)** for patients with heavily pretreated RRMM¹⁻³
- **D-Rd** is an **established SOC** for RRMM⁴
- **Combining these may enhance efficacy**
 - Through the cytotoxic and immunomodulatory action of each drug in a **fully immune-based triplet**
 - **In earlier lines of treatment** where patients may have a more **favorable immune profile** (ASH 2022, Oral #97)⁵
- We present initial results from a **phase 1b** multicohort study (**MajesTEC-2**; NCT04722146) exploring the combination of **tec-dara-len in patients with RRMM**



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; CD38, cluster of differentiation 38; CDC, complement-dependent cytotoxicity; D-Rd, daratumumab, lenalidomide, and dexamethasone; IMiD, immunomodulatory drug; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma; SOC, standard of care; tec-dara-len, teclistamab, daratumumab, and lenalidomide.

1. TECVAYLI [summary of product characteristics]. Accessed October 26, 2022. https://www.ema.europa.eu/en/documents/product-information/tecvayli-epar-product-information_en.pdf. 2. TECVAYLI [prescribing information]. Accessed October 26, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022?761291s0001bl.pdf. 3. Moreau P, et al. *N Engl J Med* 2022; 387:495-505. 4. Bahlis NJ, et al. *Leukemia* 2020; 34:1875-84. 5. Cortes-Selva D, et al. Presented at ASH; December 10–13, 2022; New Orleans, LA. Oral presentation #97.

Searle E et al. ASH 2022 Oral Presentation 160



MajesTEC-2 Is an Ongoing, Phase 1b, Multicohort Study

Ongoing, Phase 1b, Multicohort Study



Key eligibility criteria

- Measurable MM
- 1–3 prior lines of therapy, including an IMiD and a PI



Primary endpoints

- Safety^a
- Dose-limiting toxicities

Key secondary endpoints

- ORR^b
- Rate of \geq VGPR and \geq CR^b
- Duration of response
- Time to response

Tec-Dara-Len Dosing Schedule:

Tec	Dara	Len
<p>Following step-up dosing</p> <p>0.72 mg/kg or 1.5 mg/kg SC QW, with transition to 3 mg/kg SC Q2W starting at cycle 3</p>	<p>1800 mg SC (per approved schedule)</p> <p>Cycles 1–2: QW</p> <p>Cycles 3–6: Q2W</p> <p>Cycles 7+: Q4W</p>	<p>25 mg PO daily for 21 days of a 28-day cycle, starting at cycle 2</p> <p>Cycles 2–4: dexamethasone 40 mg PO given QW</p>

^aAEs assessed per CTCAE v5.0, except for CRS and ICANS, which were graded per ASTCT guidelines. ^bAssessed per IMWG 2016 criteria.

\geq VGPR, very good partial response or better; \geq CR, CR or better; AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for AEs; ICANS, immune effector cell-associated neurotoxicity syndrome; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; PI, proteasome inhibitor; PO, by mouth; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week; SC, subcutaneous; tec-dara-len, teclistamab, daratumumab, and lenalidomide.

Characteristic	Dara 1800 mg SC Len 25 mg PO	
	Tec 0.72 mg/kg SC (n=13)	Tec 1.5 mg/kg SC (n=19)
Median (range) age, years	65 (38–71)	60 (46–75)
\geq 1 extramedullary plasmacytomas, n (%)	1 (7.7)	1 (5.3)
High-risk cytogenetics, ^a n (%)	3/12 (25.0)	7/15 (46.7)
ISS stage, n (%)		
I	8/11 (72.7)	9/16 (56.3)
II	2/11 (18.2)	4/16 (25.0)
III	1/11 (9.1)	3/16 (18.8)
Median (range) time since diagnosis, years	3.9 (0.4–7.8)	3.4 (1.1–6.3)
Median (range) prior LOT	2 (1–3)	2 (1–3)
Prior stem cell transplant, n (%)	8 (61.5)	18 (94.7)
Prior proteasome inhibitor, n (%)	13 (100)	19 (100)
Prior immunomodulatory drug, n (%)	13 (100)	19 (100)
Prior anti-CD38 mAb, n (%)	5 (38.5)	5 (26.3)
Refractory status, n (%)		
To lenalidomide	6 (46.2)	3 (15.8)
To an anti-CD38 mAb ^b	3 (23.1)	3 (15.8)

Searle E et al. ASH 2022 Oral Presentation 160



MajesTEC-2: Safety Profile of Tec-Dara-Len

Non-hematologic AEs

AE (any Grade: ≥25% and/or Grade 3/4: ≥10%), n (%)	N=32	
	Any Grade	Grade 3/4
CRS	26 (81.3)	0
Fatigue	15 (46.9)	2 (6.3)
Diarrhea	15 (46.9)	0
Cough	13 (40.6)	1 (3.1)
COVID-19	12 (37.5)	4 (12.5)
Insomnia	12 (37.5)	1 (3.1)
Hypophosphatemia	10 (31.3)	2 (6.3)
Pyrexia	10 (31.3)	1 (3.1)
Upper respiratory tract infection	10 (31.3)	0
Nausea	10 (31.3)	0
ALT increased	9 (28.1)	3 (9.4)
Pneumonia	8 (25.0)	5 (15.6)

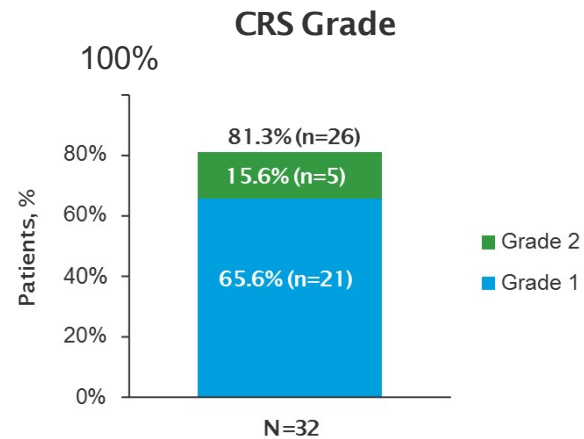
Grade 3/4 AEs occurred in 29 (90.6%) patients

– Most common were cytopenias and pneumonia

Hematologic AEs

AE (any Grade: ≥25% and/or Grade 3/4: ≥10%), n (%)	N=32	
	Any Grade	Grade 3/4
Neutropenia	27 (84.4)	25 (78.1)
Thrombocytopenia	8 (25.0)	5 (15.6)
Anemia	7 (21.9)	4 (12.5)
Febrile neutropenia	4 (12.5)	4 (12.5)
Lymphopenia	4 (12.5)	4 (12.5)

- All CRS events were low grade; no grade ≥3 events reported
- 97% (37/38) of CRS events occurred during C1
- Median (range) time to onset: 2 (1-8) days



13 (40.6%) of pts received tocilizumab

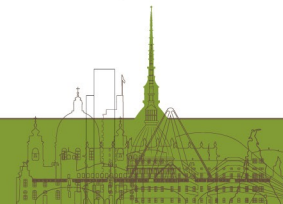
Infections With Tec-Dara-Len

AE (any Grade: ≥25% and/or Grade 3/4: ≥3.1%), n (%)	N=32	
	Any Grade	Grade 3/4
Patients with ≥1 infection, n (%)	29 (90.6)	12 (37.5)
COVID-19 ^a	12 (37.5)	4 (12.5)
Upper respiratory infection	10 (31.3)	0
Pneumonia	8 (25.0)	5 (15.6)
COVID-19 pneumonia	4 (12.5)	1 (3.1)
Sepsis	3 (9.4)	3 (9.4)
Pneumonia pseudomonal	2 (6.3)	2 (6.3)
Cytomegalovirus infection ^b	2 (6.3)	2 (6.3)

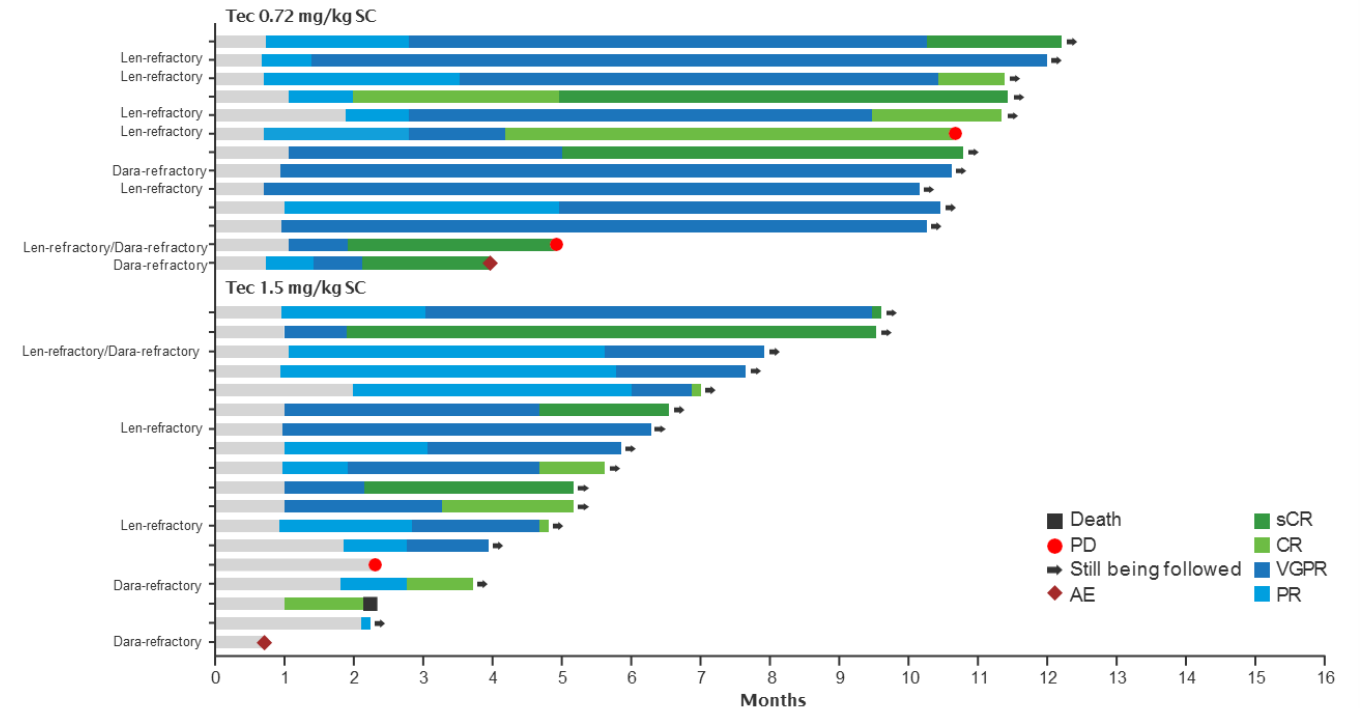
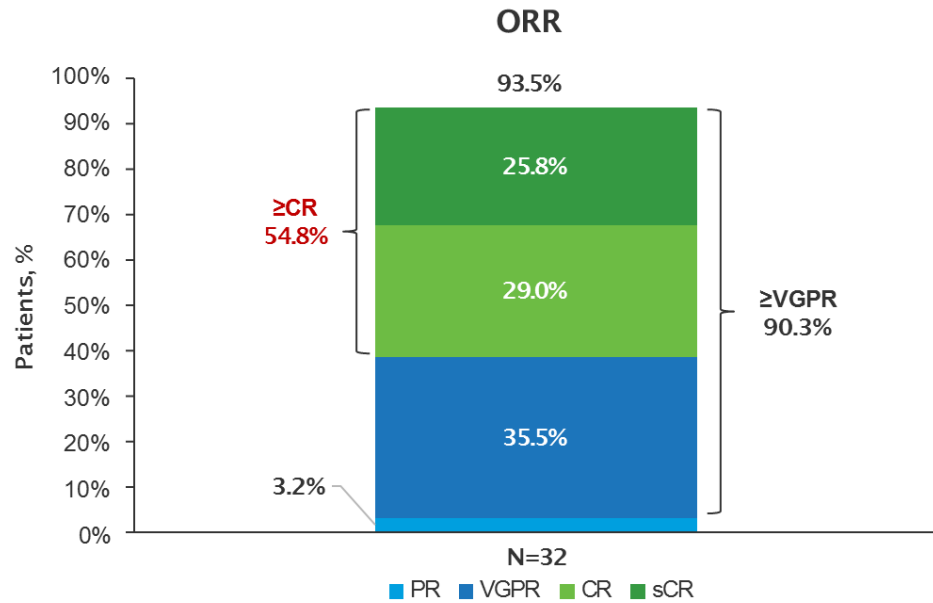
Infections were common but majority were low-grade

- Most common infections were COVID-19, upper respiratory infection, and pneumonia
 - 4 (33.3%) of 12 pts who had COVID-19 were unvaccinated
 - 2 (6.3%) pts discontinued due to an AE (COVID-19)
- 2 fatal AEs were reported
 - COVID-19 (77 days after last dose)
 - Multiorgan failure due to sepsis

Searle E et al. ASH 2022 Oral Presentation 160



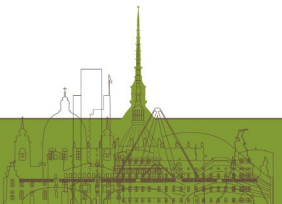
MajesTEC-2: Efficacy



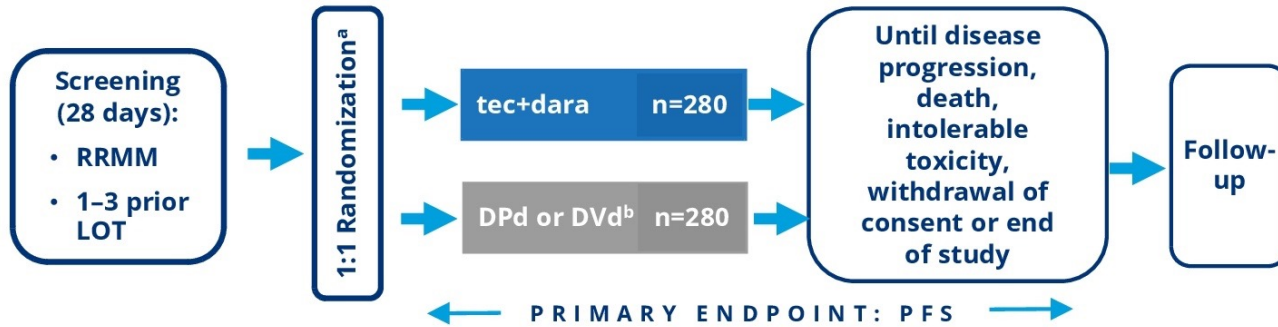
- Responses were observed in patients who were refractory to daratumumab and/or lenalidomide
- 25/31 (80.6%) patients remain progression-free and on treatment at data cut-off

Variable	Median (range)
Follow-up, months	8.4 (1.1–12.9)
Time to first response, months	1.0 (0.7–3.3)
Time to ≥CR, months	3.0 (1.0–10.4)

Searle E et al. ASH 2022 Oral Presentation 160



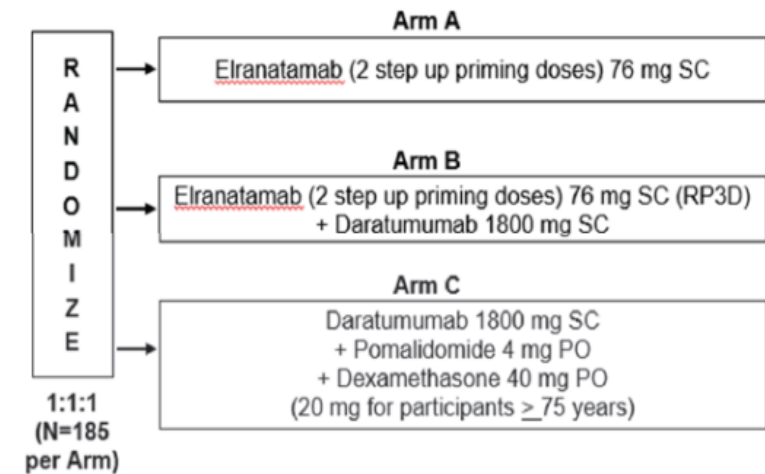
MajesTEC-3: Phase 3 Trial of Teclistamanb + Dara vs DPd or DVd in RRMM treated with 1-3 Prior LOT¹



^aAt randomization, patients will be stratified by investigator's choice of DPd or DVd, International Staging System stage, number of prior LOT, and prior anti-CD38 exposure. ^bPatients in this arm receive investigator's choice of either DPd or DVd. PFS, progression-free survival

Bi-specific as treatment of early relapse

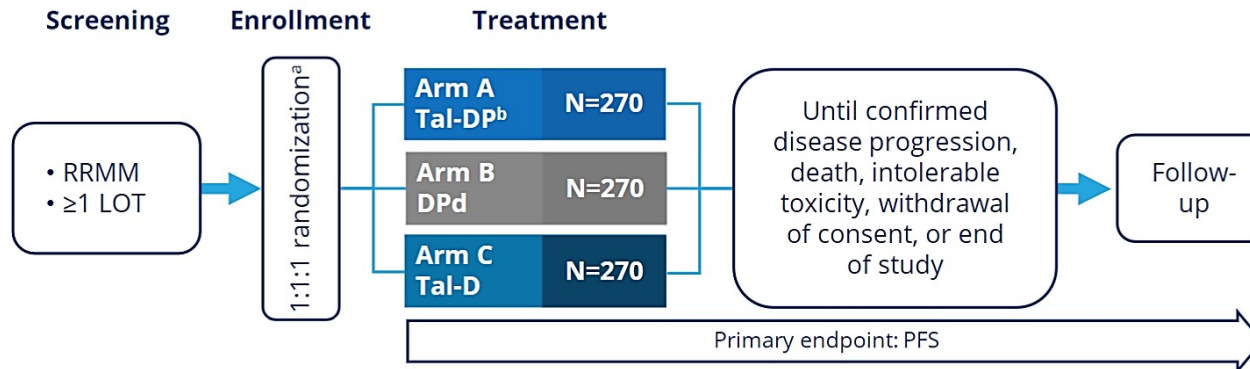
MagnetisMM-5: Phase 3 Trial of Elranatamab and Elranatamab + Dara vs DPd in RRMM Following ≥1 Prior LOT³



PART 2: Phase 3

RRMM ≥1 prior LOT, including len and PI

MonumentAL-3: Phase 3 Trial of Talquetamab + Dara ± Pom vs DPd in RRMM Following ≥1 Prior LOT²



^aPatients will be stratified during randomization according to International Staging System stage, prior Dara exposure, and number of prior LOT. ^bDexamethasone will also be administered in cycles 2-4 in arms A and C and in cycles 1-7+ in arm B. Tal and Dara will be administered subcutaneously, Pom will be administered orally, and dexamethasone can be delivered either orally or intravenously. All treatment arms will be given in 28-day cycles. PFS, progression-free survival.

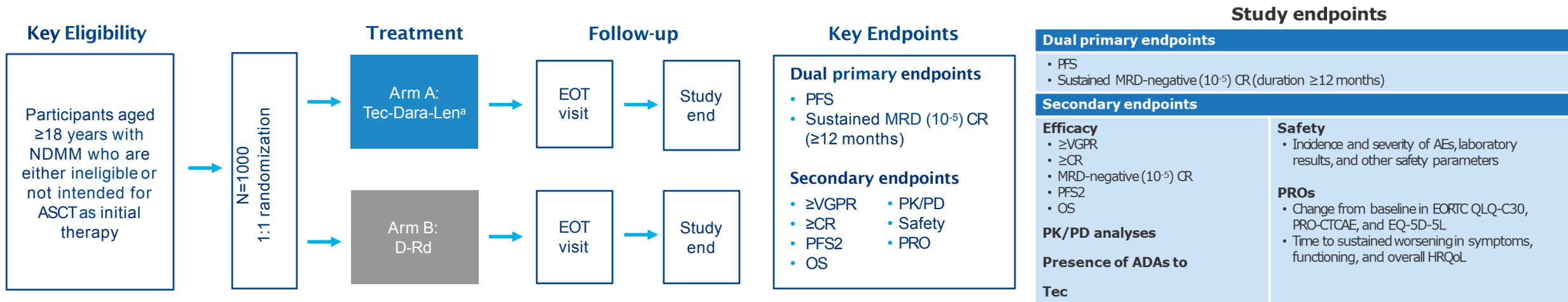
RRMM ≥1 prior LOT, including len and PI, pts with 1 prior tx line must be lena refractory

1. Mateos MV et al. ASCO 2022; TSP8072 (poster presentation); 2. Cohen YC et al. ASH 2022; 1925 (poster presentation); 3. Grosicki S et al. ASCO 2022; TPS8074 (poster presentation)



MajesTEC-7: Tec-Dara-Len vs D-Rd in NDMM

- MajesTEC-7 (NCT05552222) is a randomized, open-label phase 3 study that will compare tec-dara-len vs D-Rd in patients with NDMM who are transplant-ineligible or for whom ASCT is not intended



T-cell fitness is better in earlier lines of therapy

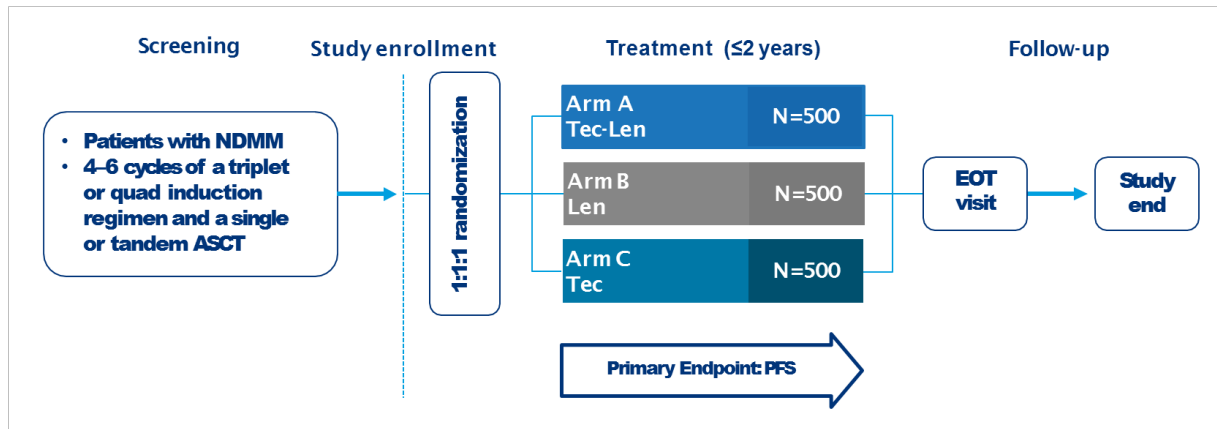
➔ Several trials with BsAbs will start or have started in newly diagnosed MM and early relapsed/refractory MM

Krishnan A et al. ASH 2022 Poster Presentation 4558



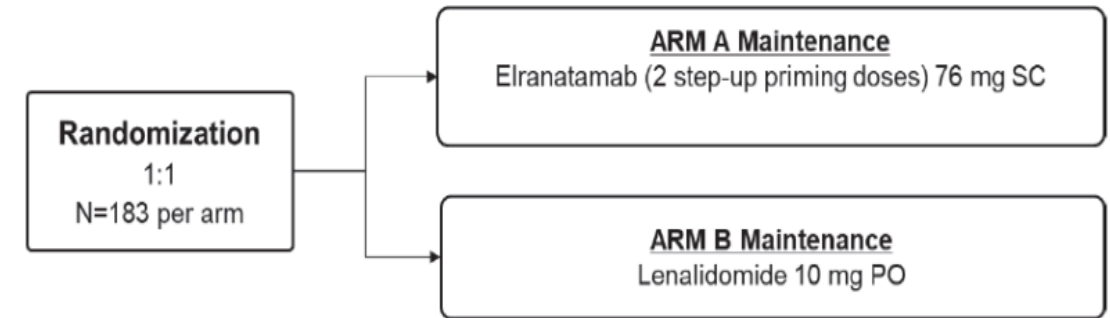
Bi-specific as Maintenance Therapy Following ASCT in NDMM

MajesTEC-4: Phase 3 Study Design



Teclistamab + Lenalidomide and Teclistamab Alone Versus Lenalidomide Alone as Maintenance Therapy Following ASCT in NDMM¹

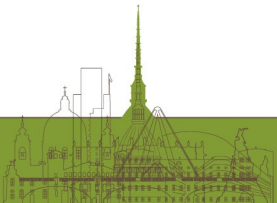
MagnetisMM-7



Elranatamab Versus Lenalidomide as Maintenance Therapy Following ASCT in NDMM²

Prior debulking to optimize effector: target ratio (rational sequencing)

1. Zamagni E et al. ASH 2022 Poster Presentation 3242; 2. ClinicalTrials.gov NCT05317416



Practical management of bispecific toxicities

Cytokine release syndrome

Timing differs between IV vs SC dosing

Mostly confined to step-up and first full dose

Mitigation with step-up dosing and premedication (steroids/paracetamol/clemastine), early intervention with Tocilizumab

ICANS/neurotoxicity events are rare

Hematologic toxicity

Neutropenia common during first 1-2 cycles

Neutropenia highly responsive to G-CSF, **wait 24 hours from bispecific dose**

On target/off tumor toxicity

Elimination of normal plasma cells

Infections

Prophylaxis with co-trimoxazole and valacyclovir

Consider IVIG in case of recurrent infections and development of hypogammaglobulinemia, despite prophylaxis, consider long-term infection risk, test for virus/fungal infection if clinically indicated

Specific toxicity by the target



New strategies to mitigate CRS/ICANS

Pre-treatment with tocilizumab prior to cevostamab FcRH5 × CD3 bispecific antibody

Key inclusion criteria

- RRMM for which no established therapy is available, appropriate or tolerable
- Prior CAR T-cells, ADCs, and bispecific antibodies allowed

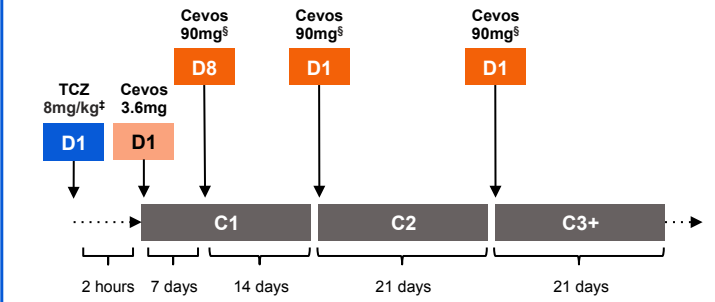
Cevostamab dosing in all patients

- Q3W IV infusions for up to 17 cycles*
- C1 single step dosing
- Premedication with acetaminophen, diphenhydramine, and corticosteroid

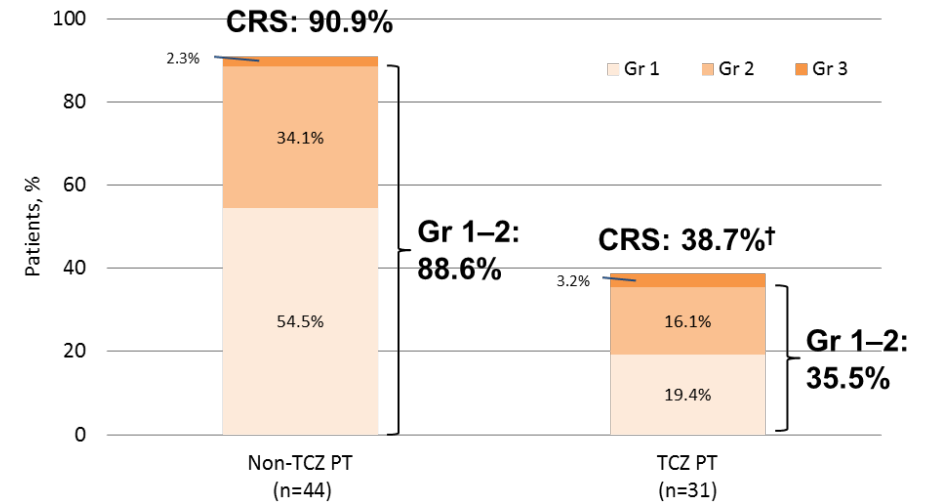
Treatment cohorts in this analysis

- Patients in the TCZ pre-treatment (PT) group received a single 8mg/kg dose of TCZ
- Patient data from the previously enrolled non-TCZ PT 3.6/90mg group served as a retrospective comparator
- Patients in the TCZ PT and non-TCZ PT groups were enrolled at different times, and were not randomized to treatment
- TCZ and/or corticosteroids were allowed in both groups for CRS treatment

Single step dosing regimen†



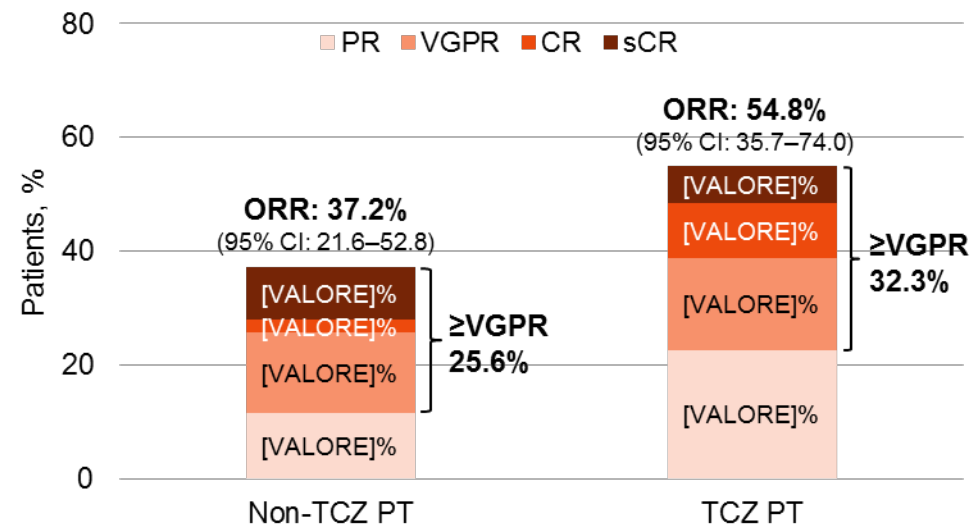
Patients (%) with CRS in the non-TCZ PT and TCZ PT groups*



- Median time to CRS onset from infusion of cevostamab was 1 day in both groups (range: non-TCZ PT, 0–3 days; TCZ PT, 1–3 days)
- In the non-TCZ PT group, 16 patients (36.4%) received TCZ treatment
- In the TCZ PT group, 6 patients (19.3%) received TCZ treatment

The overall rate of CRS was significantly lower in the TCZ PT group than in the non-TCZ PT group
No impact of TCZ on response rate and quality

Response rates among efficacy evaluable patients in the non-TCZ PT and TCZ PT arms



Enduring Responses after 1-Year, Fixed-Duration Cevostamab Therapy in Patients with Relapsed/Refractory Multiple Myeloma: Early Experience from a Phase I Study

P1924

Enduring Responses After 1-Year of Fixed-Duration Cevostamab Therapy in Patients with Relapsed/Refractory Multiple Myeloma: Early Experience from a Phase I Study

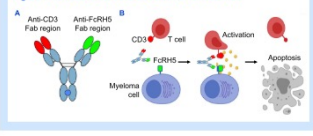
Alexander M Lesokhin,^{1,2} Joshua Richter,³ Suzanne Trudel,⁴ Adam D Cohen,⁵ Andrew Spencer,⁶ Peter A Forsberg,⁷ Jacob P Zaudsch,⁸ Sheeba K Thomas,⁹ Nizar Bohli,¹⁰ Luciano J Costa,¹¹ Paula Rodriguez-Oloro,¹² Maria-Victoria Mateos,¹³ Jesus G Berdeja,¹⁴ Rayan Kaedbey,¹⁵ Amrita Krishnan,¹⁶ Rafael Fonseca,¹⁷ Voleak Cheung,¹⁸ James Cooper,¹⁹ Teiko Sumiyoshi,¹⁸ Chihunt Wong,¹⁸ Simon J Harrison¹⁹

*e-mail: lesokhia@mskcc.org

Background

- Relapsed/refractory multiple myeloma (RRMM) remains an incurable disease. Most treatment regimens are continued until disease progression (PD).
- New treatments that are efficacious when given for a fixed duration and offer the potential for an extended treatment-free period, may decrease cumulative toxicities and the burden on patients and healthcare systems.
- Cevostamab (Figure 1A) is a T-cell engaging bispecific antibody that targets the membrane-proximal domain of FcRH5 on myeloma cells and the epsilon domain of CD3 on T cells. Dual binding results in T-cell directed killing of myeloma cells (Figure 1B).
- In an ongoing Phase I trial (GO39775, NCT03275103) in patients with heavily pre-treated RRMM, cevostamab demonstrated clinically meaningful activity and a favorable safety profile when given once every 3 weeks (Q3W) for a fixed-duration of 17 cycles (approximately 1 year) in per protocol.
- Here we report the duration of response data in the following groups:
 - Patients who remained in response at the time of completing 17 cycles of cevostamab and stopped treatment per protocol
 - Patients who were in response at the time of treatment discontinuation due to an adverse event (AE)
 - Preliminary retreatment experience

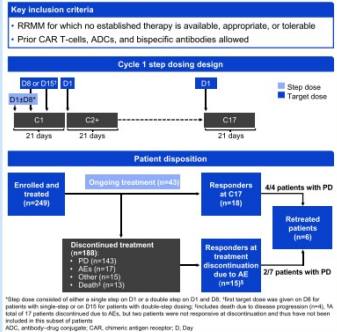
Figure 1. Structure and mode of action of cevostamab.



GO39775 is a Phase I dose-escalation and dose-expansion study evaluating the safety and efficacy of Q3W intravenous cevostamab in patients with RRMM (Figure 2).

- Cevostamab was given as a fixed-duration treatment for up to 17 cycles (C) or until unacceptable toxicity or PD
- Patients were eligible for retreatment if they:
 - Progressed after completion of C17
 - Were in response but discontinued cevostamab due to AE(s)
- Response was evaluated per International Myeloma Working Group criteria
- AEs were reported up to 90 days following the last dose of cevostamab
- Serious AEs (SAEs) were reported throughout follow-up

Figure 2. GO39775 study design.



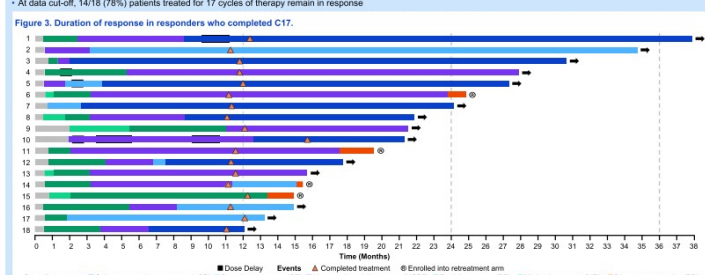
Most patients who completed 17 cycles of cevostamab had heavily pre-treated and highly refractory disease (Table 1).

Table 1. Baseline patient and disease characteristics.

No. (%) of patients, unless stated	Patients who completed 17 cycles (n=191)	Responders who discontinued due to AE (n=10)	All patients (n=249)
Median age, years (range)	67 (43–80)	66 (46–77)	64 (33–84)
High-risk cytogenetic*, n (%) of patients with available assay result	0/12 (0)	4/9 (44.4)	53/157 (33.8)
Extramedullary disease	1 (0.6)	1 (6.7)	59 (23.7)
Time since first multiple myeloma therapy in years, median (range)	5.8 (1.9–13.4)	7.5 (1.8–17.6)	6.3 (0.3–22.8)
Number of lines of prior therapy, median (range)	5.5 (2.0–11.0)	7.0 (3.0–11.0)	6.0 (2.0–18.0)
Prior anti-CD38	15 (83.3)	13 (86.7)	220 (88.4)
Prior anti-BCMA	5 (27.8)	2 (13.3)	88 (35.3)
Prior CAR-T	1 (0.6)	2 (13.3)	45 (18.1)
Prior ADC	4 (22.0)	2 (13.3)	47 (18.9)
Prior bispecific antibody	1 (0.6)	2 (13.3)	24 (9.6)
Triple-class refractory†	14 (77.8)	13 (86.7)	213 (85.6)
Penta-drug refractory‡	12 (66.7)	9 (60.0)	169 (67.9)

*Includes del(17p), t(14;16), and del(17q) chromosomal aberrations; †At least 1 PR, and 1 anti-CD38 antibody; ‡At least 1 PR, and 2 anti-CD38 antibody; BCMA, B-cell maturation antigen; ADC, antineoplastic drug; PD, progressive inhibitor

Most responders at C17 remain in response at the time of data cut-off (Figure 3). As of August 22, 2022, median follow-up post treatment was 9.6 months (range 1.2–26.2). Target cevostamab doses ranged from 40–160mg. At data cut-off, 14/16 (78%) patients treated for 17 cycles of therapy remain in response.



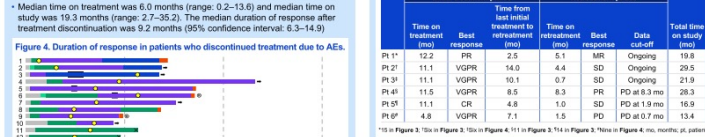
A VGPR or better was achieved in 17 of the 18 patients by the time of completion of therapy. At the time of completing C17, eight patients were in sCR, three were in CR, six were in PR, and one patient was in PR. Seven patients remained in response ≥12 months after completion. sCR in four patients, CR in one patient and VGPR in two patients.

No patients who achieved an sCR have relapsed. Four of 18 patients experienced PD, with best response and time to progression after the completion of treatment as follows: VGPR 12.9, VGPR 6.3, CR 4.2, and PR 1.4 months.

Two SAEs of pneumonia were reported after the completion of therapy. These occurred in two patients, with onsets of 1.3 and 3.8 months after the last dose of cevostamab. Both events resolved and both patients remained on study. No other SAEs were reported after completion of therapy.

Fifteen patients discontinued treatment due to AEs prior to C17 and continued in response. As of data cut-off, median follow-up for patients who remained in response upon discontinuation due to AEs was 11.0 months (range: 2.4–33.6). Target cevostamab doses ranged from 40–190mg with a median of eight (range: 1–16) cycles of cevostamab therapy.

Median time to progression was 6.0 months (range: 0.2–13.6) and median time on study was 19.3 months (range: 2.7–25.2). The median duration of response after treatment discontinuation was 9.2 months (95% confidence interval: 6.3–14.9).



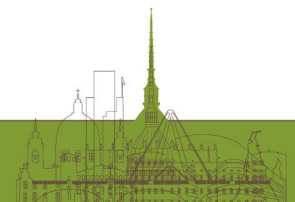
Conclusions: Early data from this Phase I study suggest that patients with heavily pre-treated RRMM can maintain durable responses (≥12 months) after completion of 17 cycles of cevostamab treatment. Responders who discontinued due to AEs were able to maintain their response. The data presented are an encouraging indicator that a fixed treatment duration can be efficacious and offer patients a treatment-free period. Most responders that received cevostamab retreatment therapy were able to exhibit disease control. Further data are needed to confirm the duration of response and associated correlates following completion of treatment.

Presented at the 2022 American Society of Hematology Annual Meeting | December 10–13, 2022

Cevostamab was administered by iv infusion in 21-d cycles with step-up dosing in C1 for CRS mitigation. Treatment was continued for 17 cycles (approximately 1 year) unless PD or unacceptable toxicity occurred. Patients who achieved ≥PR by C17 and maintained a response through C17 were included in the analysis.

At data cut-off (March 8, 2022), a total of 16 pts completed C17 and were eligible for analysis. Median prior LOT: 6 (range: 2–11)

- Best overall response (BOR): 7 sCR, 3 CR, 5 VGPR, 1 PR
- 13 of the 16 pts remained in remission
- 8 pts maintaining a response ≥6 mos after completion of tp
- 3 pts maintaining a response ≥12 mos after completion of tp



Open questions and future directions

Can we plan sequential ADC, TCE and CAR T?

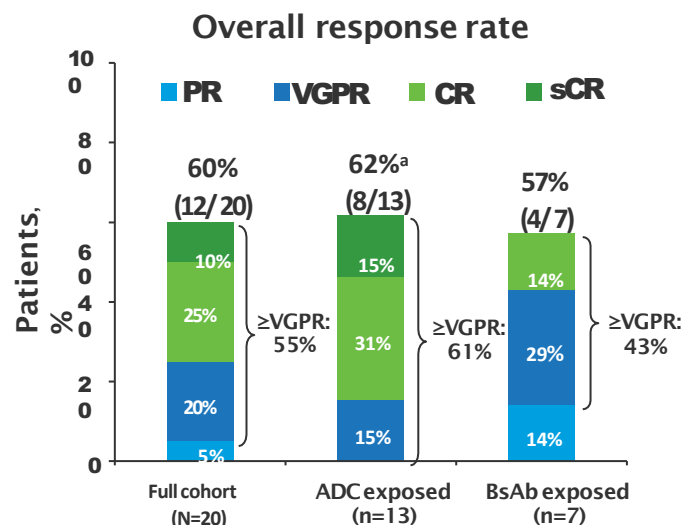
Ide-cel in pts with prior anti-BCMA

Ide-cel: ≥4 prior lines - real world data¹

Characteristic	Best response of ≥ CR			PFS		
	OR	95% CI	p	HR	95% CI	p
Prior anti-BCMA	0.30	0.10, 0.79	0.02	2.51	1.21, 5.24	0.014
High-risk cytogenetics	0.79	0.35, 1.75	0.6	2.39	1.18, 4.85	0.016
Extramedullary disease	1.66	0.77, 3.66	0.2	1.39	0.70, 2.78	0.3
ECOG PS ≥ 2	0.54	0.18, 1.51	0.3	1.91	0.79, 4.58	0.15
Penta-refractory	1.43	0.66, 3.16	0.4	0.93	0.46, 1.87	0.8
Cell dose ≥400 ×10 ⁶ CAR T-cells	0.90	0.41, 1.97	0.8	0.55	0.27, 1.10	0.09
Patient age, years	0.99	0.95, 1.04	0.7	1.00	0.97, 1.04	0.8

Cilta-cel with prior anti-BCMA

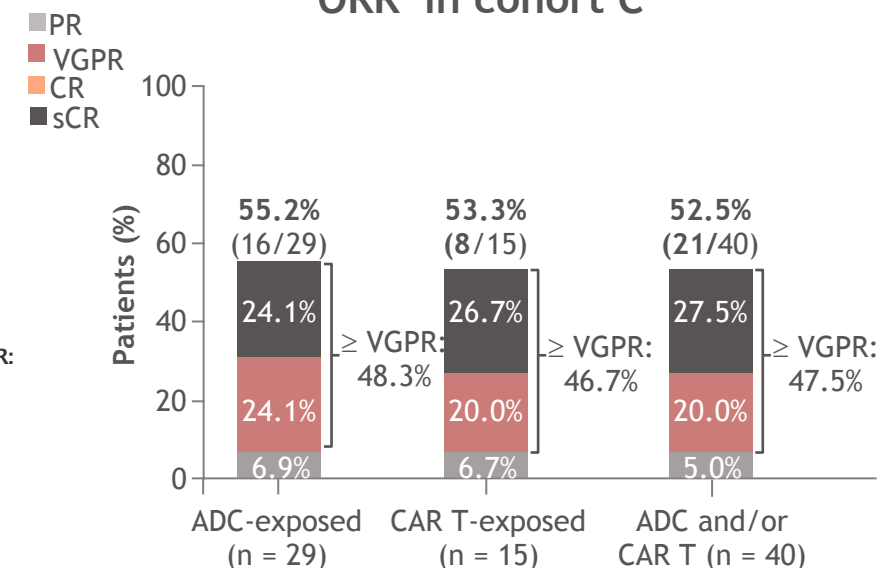
Cartitude-2, Cohort C
18 months follow-up



- Median DOR: 123 months (8.2 after BsAb)
- Median FFS: 9.1 months (5.3 after BsAb)

Teclistamab with prior anti-BCMA

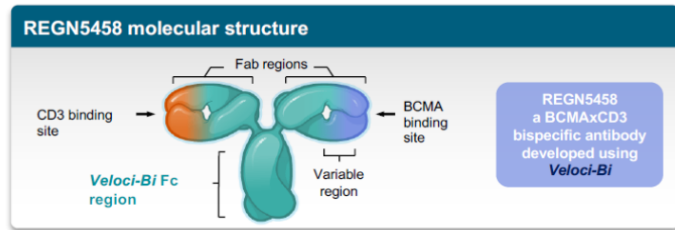
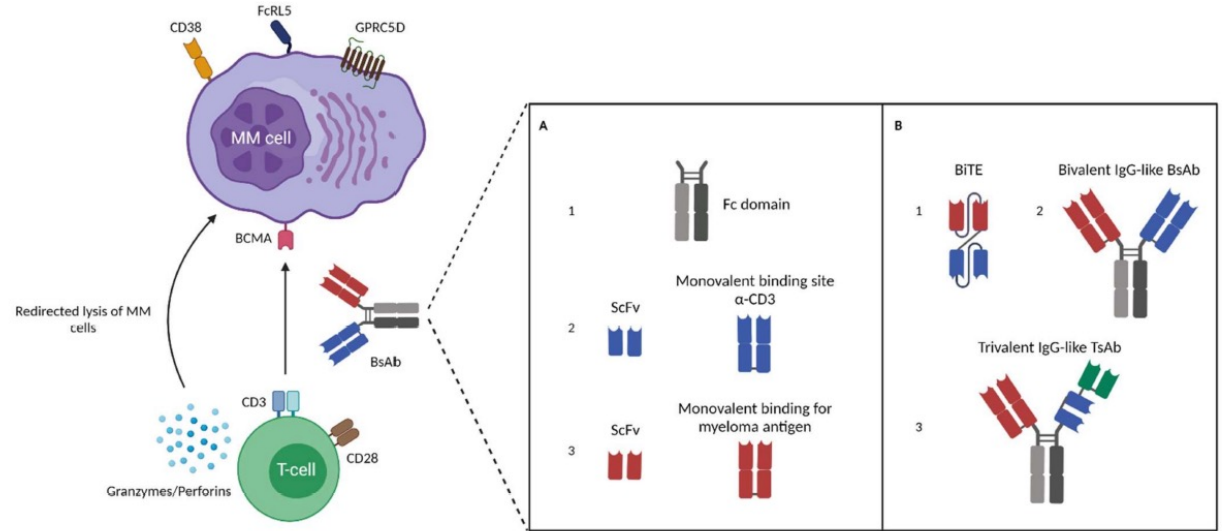
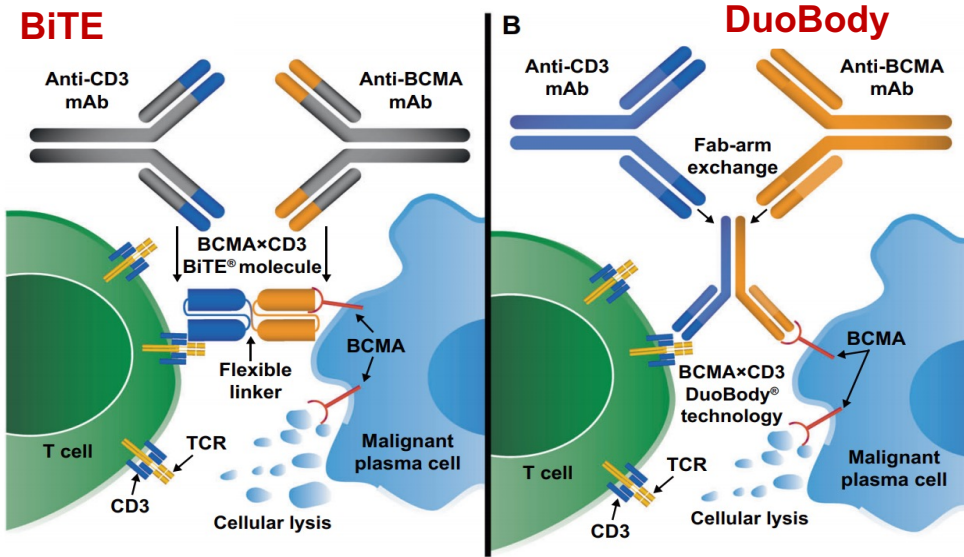
MAJESTEC-1, Cohort C
ORR^a in cohort C



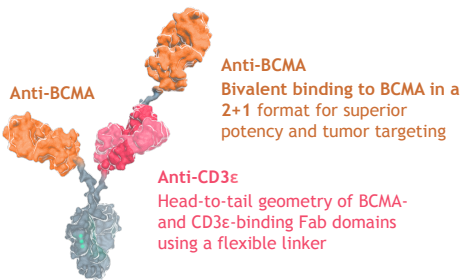
Hansen DK, et al. JCO 2022; Cohen AD et al, ASH 2022 poster presentation; Touzeau C, et al. Poster presented at ASCO 2022; J Clin Oncol. 2022;40;abstract 8013



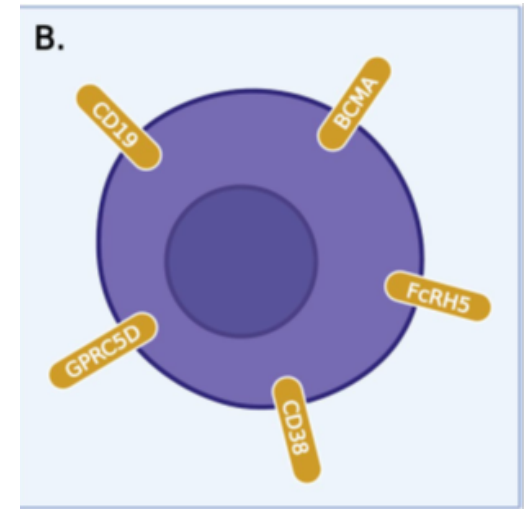
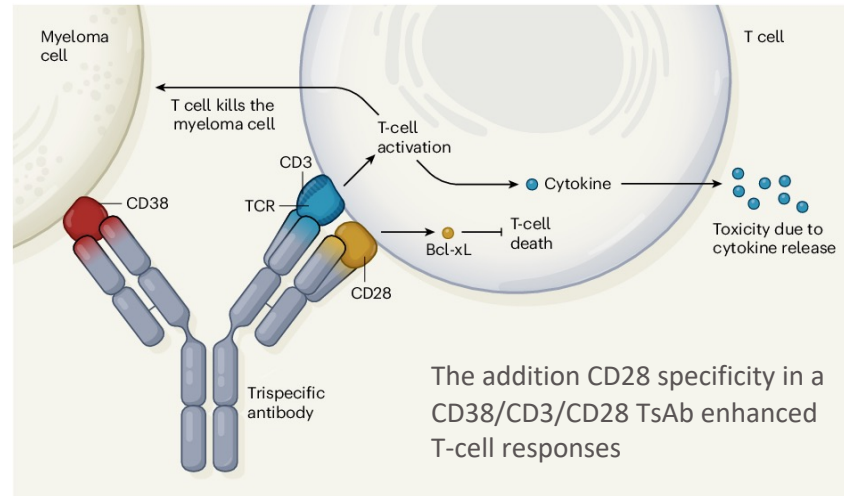
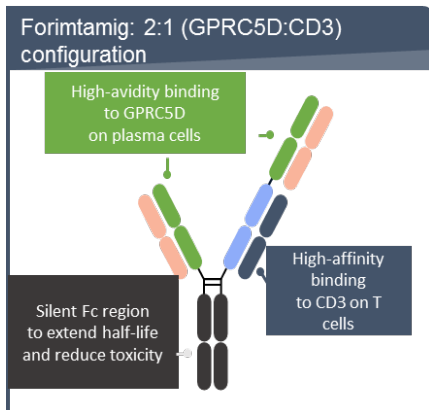
Different BsAbs Formats and Target Antigens



Alnuctamab: 2+1 BCMA x CD3 TCE



Fc γ R-silent Fc
No binding to Fc γ R and C1q to minimize infusion-related reactions



Hosny M et al. Journal of Clinical Medicine 2021; Kegyes et al. Journal of Hematology & Oncology 2022



Conclusions

- Bispecific antibodies are being integrated in the future **treatment algorithms**
- The **immune profile** is of main importance
- **Optimal use** of T-cell redirecting approaches can include
 - Combination strategies
 - Earlier lines of therapy
 - Better control of toxicities
 - Fixed duration of treatment?
- The «**sequencing issue**» of these newer treatment modalities is currently under investigation
- More bispecific molecules will enter clinical development



Thanks!

Seràgnoli Institute of Hematology



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