Highlights from IMS 20th meeting 2023

Anticorpi bispecifici anti-BCMA in fase di sviluppo (e di combinazione con altri agenti)

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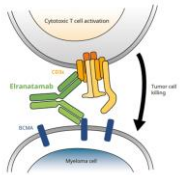
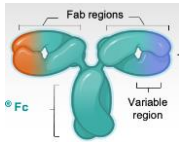
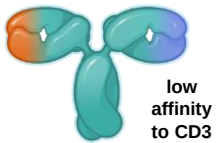
BOLOGNA, Royal Hotel Carlton

BCMA-targeting bispecific antibodies

	Approved BsAb		IV infusion		2:1 binding	CD3 low affinity
	Teclistamab MajesTEC-1[1] (n=165)	**Elranatamab Magnetismm3[2] (n=123)**	**ABBV-383B[3] (n=118)**	**Linvoseltamab LINKER-MM1[4] (n=117)**	**Alnuctamab[5] CC-93269 (n=68)**	**REGN5459[6] (n=43)**
Phase	I/II	I/II	I	II	I/II	I/II
Target	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3
scFv	Humanized	Humanized	Human	Human	Humanized	Human
Ig	IgG4	IgG2a	IgG4	IgG4	IgG1-based	IgG4
Administration	SC	SC	IV	IV	SC	IV
# prior lines	5 (2-14)	5 (2-12)	5 (1-15)	5 (2-14)	4 (3-11)	5 (2-9)
Age	64 (33-84)	69 (44-89)	68 (35-88)	70 (37-91)	64 (36-79)	67 (26-85)







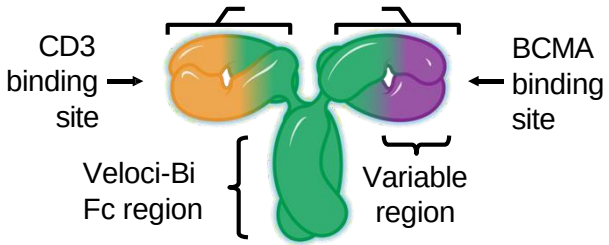
[1] Nooka et al. ASCO 2022; [2] Bahlis et al. ASH 2022; [3] Voorhees et al. IMS 2022; [4] Hans L. et al. ASCO 2023; [5] Wong et al. ASH 2019; [6] Suvannasankha et al. AACR 2023

Structure and MOA of Linvoseltamab (REGN5458)[1]

- Linvoseltamab: a BCMA x CD3 bispecific antibody
- Targets T-cell effector function to induce cytotoxicity of BCMA-expressing MM cells
- **Fully human**
- **Veloci-bi platform**

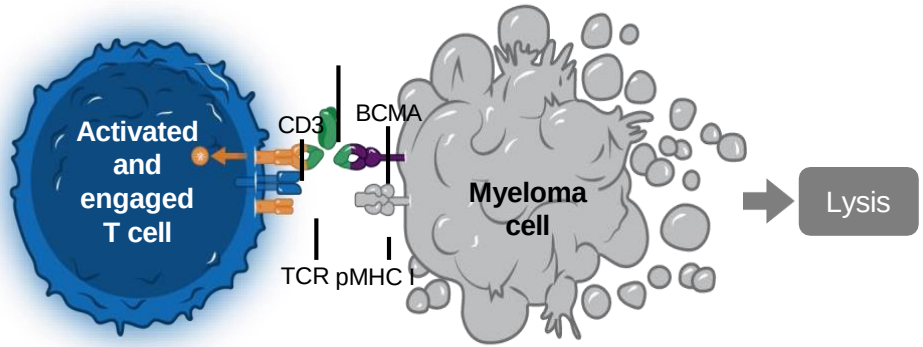
Linvoseltamab Molecular Structure

Fab regions



Linvoseltamab MOA

REGN5458
(BCMA x CD3 bispecific)



1. Zonder JA et al. EHA 2022. Abstract S189.

Preparing for Linvoseltamab Step-Up Dosing[1]

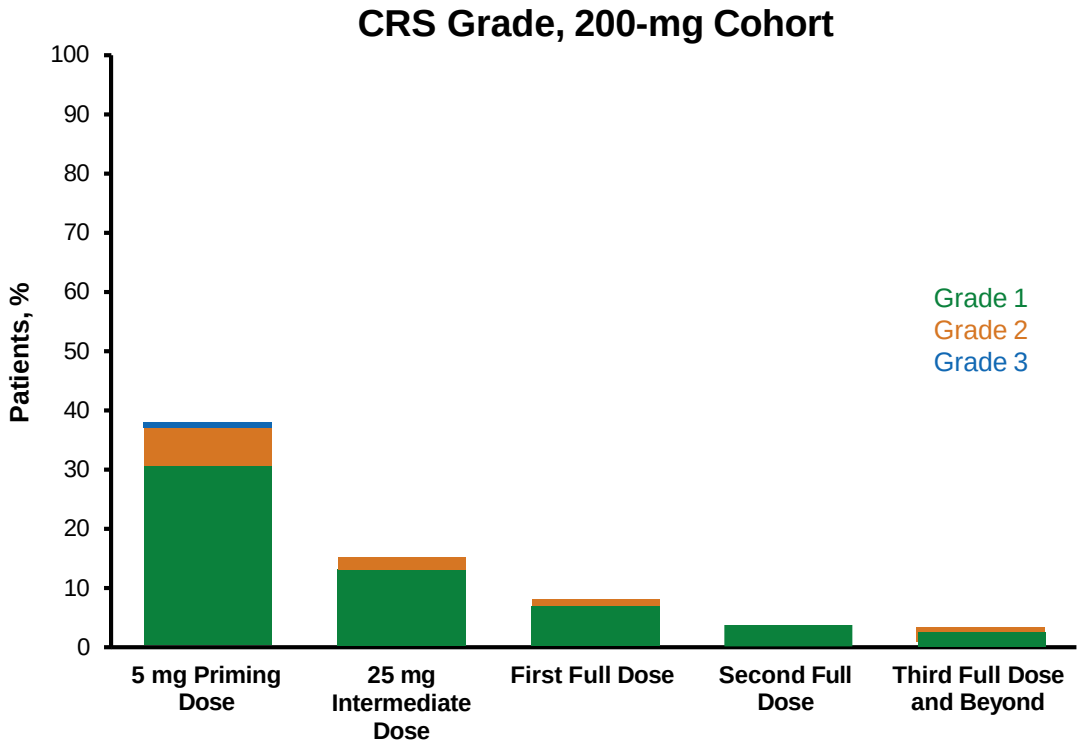
- **LINKER-MM1:** step-up IV dosing schedule was used in the 200-mg cohort

	Wk 1-2	Wk 3-6	Wk 7-14	Wk 16-23	Wk 24+
	Step-Up Doses	**Cycle 1**	**Cycles 2-3**	**Cycles 4-5**	**Cycle 6 Onwards**
200-mg cohort	5/25 mg	200 mg QW	200 mg QW	200 mg Q2W	≥ VGPR: 200 mg Q4W < VGPR: 200 mg Q2W

24 hr hospitalization after first 2 step-up doses

1. Bumma N et al. ASH 2022. Abstract 4555.

LINKER-MM1: Characterizing CRS in the 200-mg Linvoseltamab Cohort[1]



- Analysis on 117 patients treated at the RP2 dose of 200 mg
- Most CRS occurred in the step-up dosing period
- No grade 3 or higher CRS occurred after the step-up dosing period
- No grade 4 or 5 CRS reported
- CRS onset usually occurred on the day of dosing with resolution within 1 day
- Of those patients with CRS, the majority were grade 1

1. Lee HC et al. ASCO 2023. Abstract 8006.

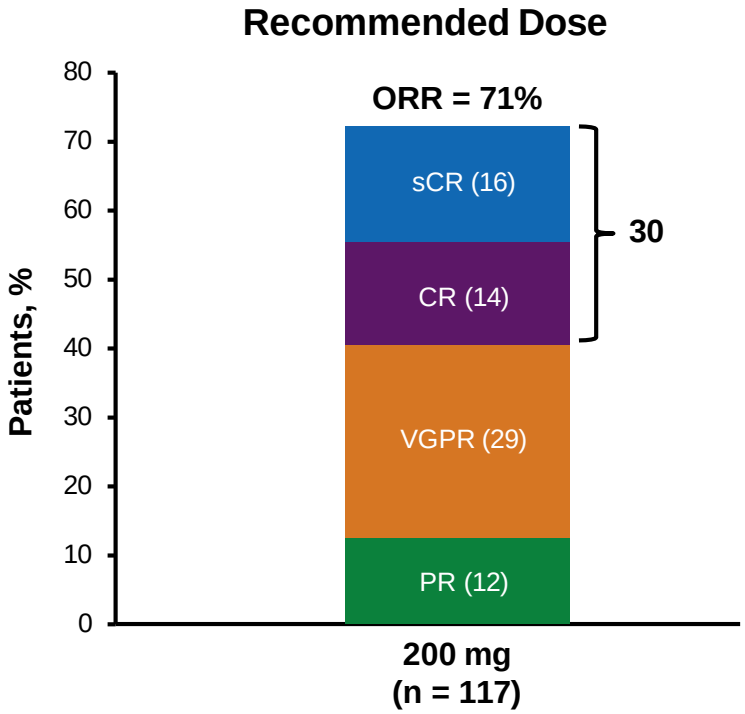
Activity of Linvoseltamab in Pretreated MM[1]

- **LINKER-MM1:** linvoseltamab was tested at the recommended 200-mg dose in patients with RRMM (N = 117)
- Median of 5 prior lines of therapy, 74% were at least TCR

After median follow-up of 6 months, patients receiving the 200-mg dose showed

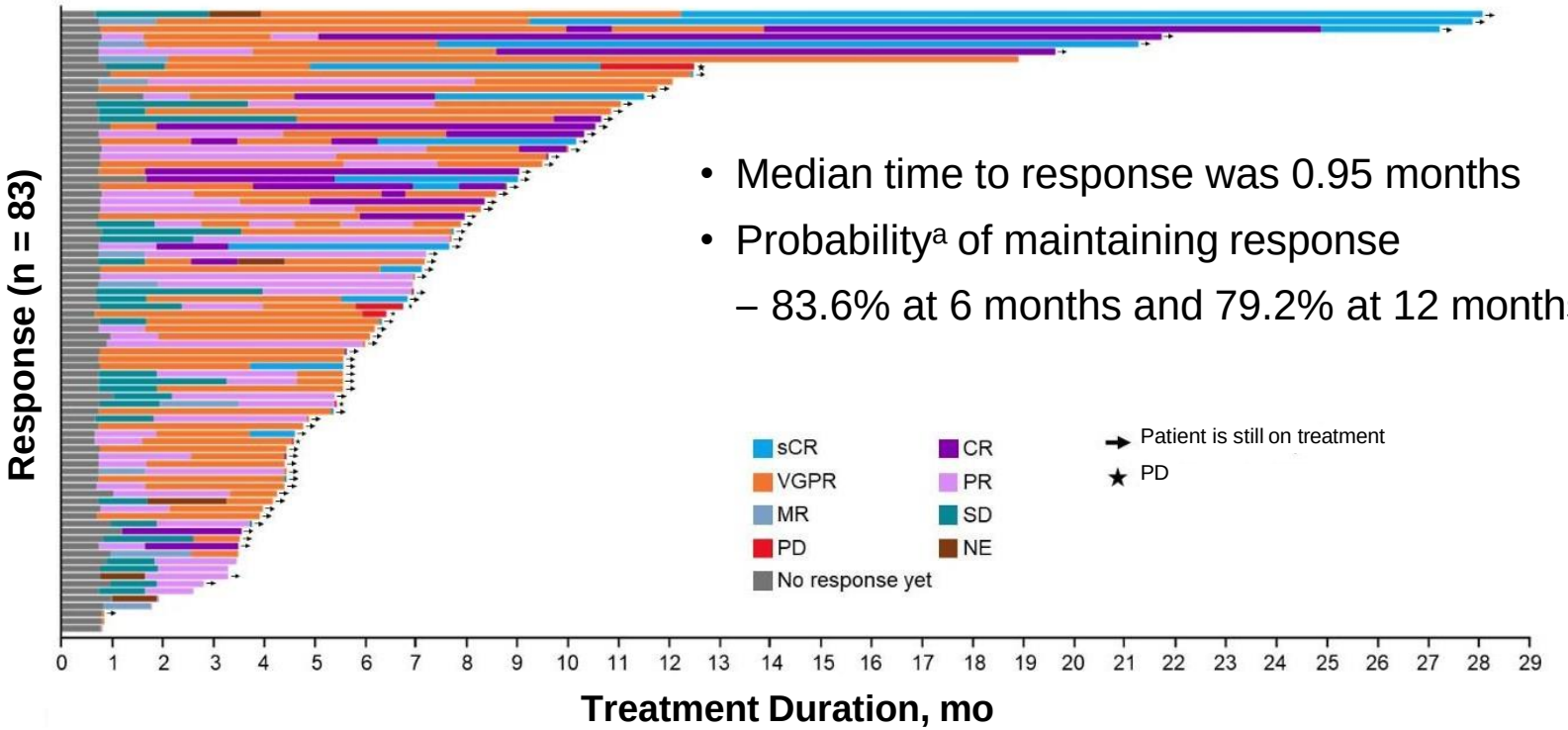
- ORR of 71%
- 59% achieved ≥VGPR

Among patients with CR or sCR with available MRD data (N = 46), 54.3% were MRD negative at 10^{-5}



1. Lee HC et al. ASCO 2023. Abstract 8006.

LINKER-MM1: Responses Are Durable and Deepen Over Time[1]



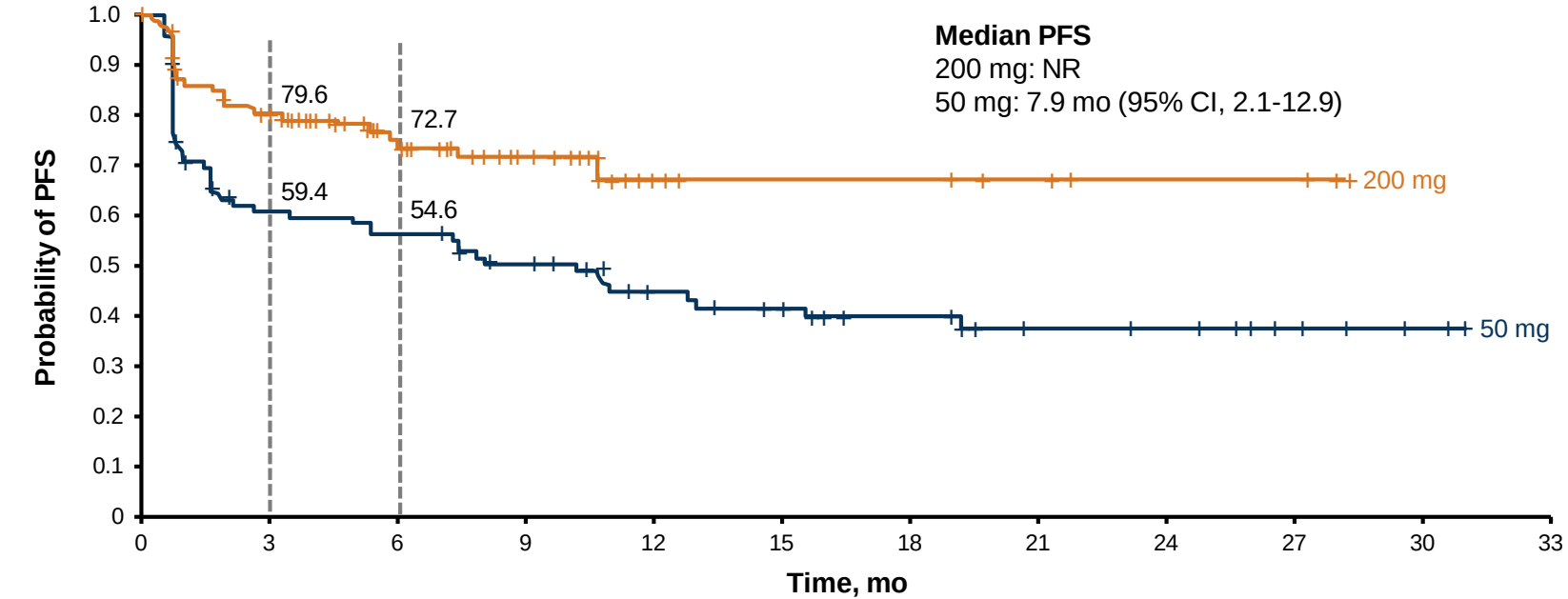
- Median time to response was 0.95 months
- Probability[a] of maintaining response
  - 83.6% at 6 months and 79.2% at 12 months

Data cut-off: February 28, 2023.

[a]Estimated Kaplan-Meier method. Median duration of follow-up: 5.6 months (range 0.2-28.2).

1. Lee HC et al. ASCO 2023. Abstract 8006.

LINKER-MM1: Median PFS Not Reached in 200-mg Linvoseltamab Cohort[1]

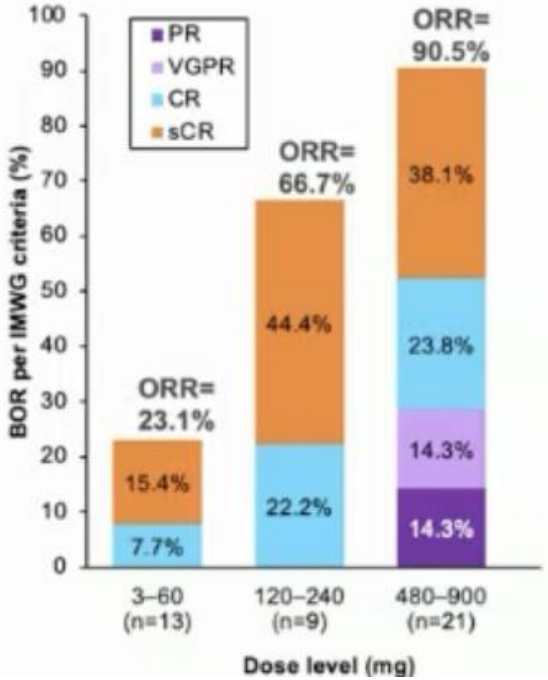


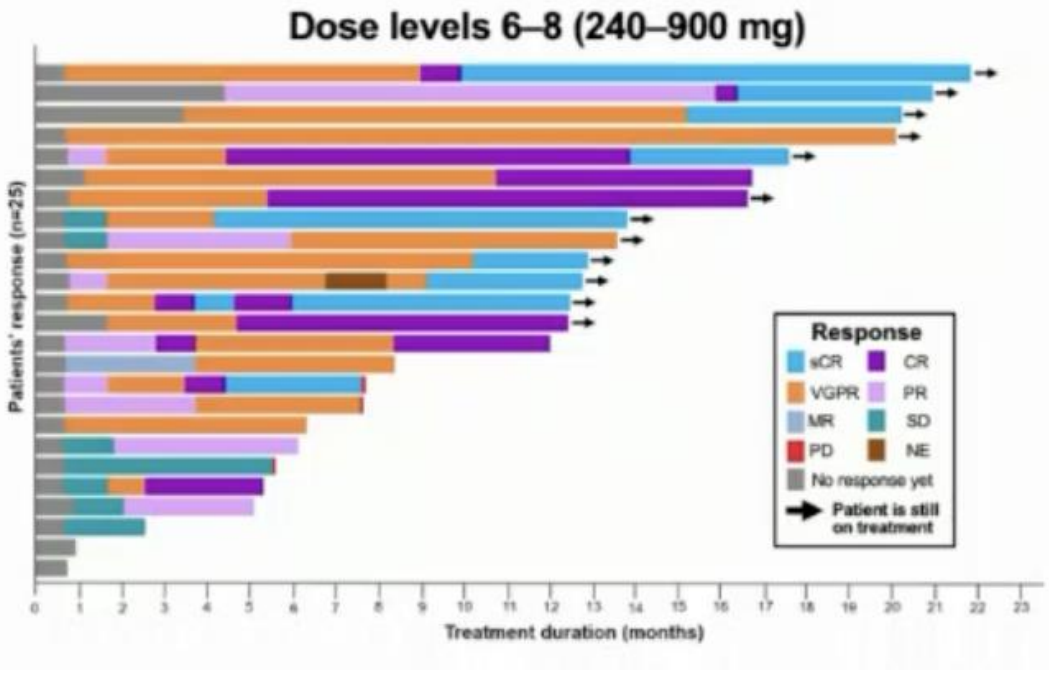
LINKER-MM3 will test linvoseltamab versus EPd in RRMM (NCT05730036)

1. Lee HC et al. ASCO 2023. Abstract 8006. 2. Jagannath S et al. ASH 2023. Abstract 4746.

REGN5459: low CD3 affinity

Rational = decrease T cell exhaustion

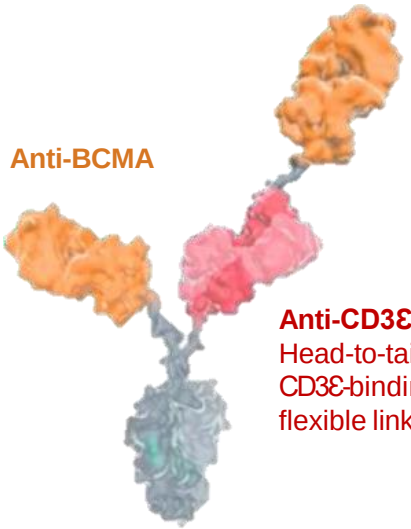




Suvannasankha A al. AACR 2023

Alnuctamab in RRMM

Alnuctamab: 2 + 1 BCMA X CD3 TCE



Anti-BCMA
Bivalent binding to BCMA in a 2 + 1 format for superior potency and tumor targeting

Anti-CD3Ɛ
Head-to-tail geometry of BCMA- and CD3Ɛ-binding Fab domains using a flexible linker

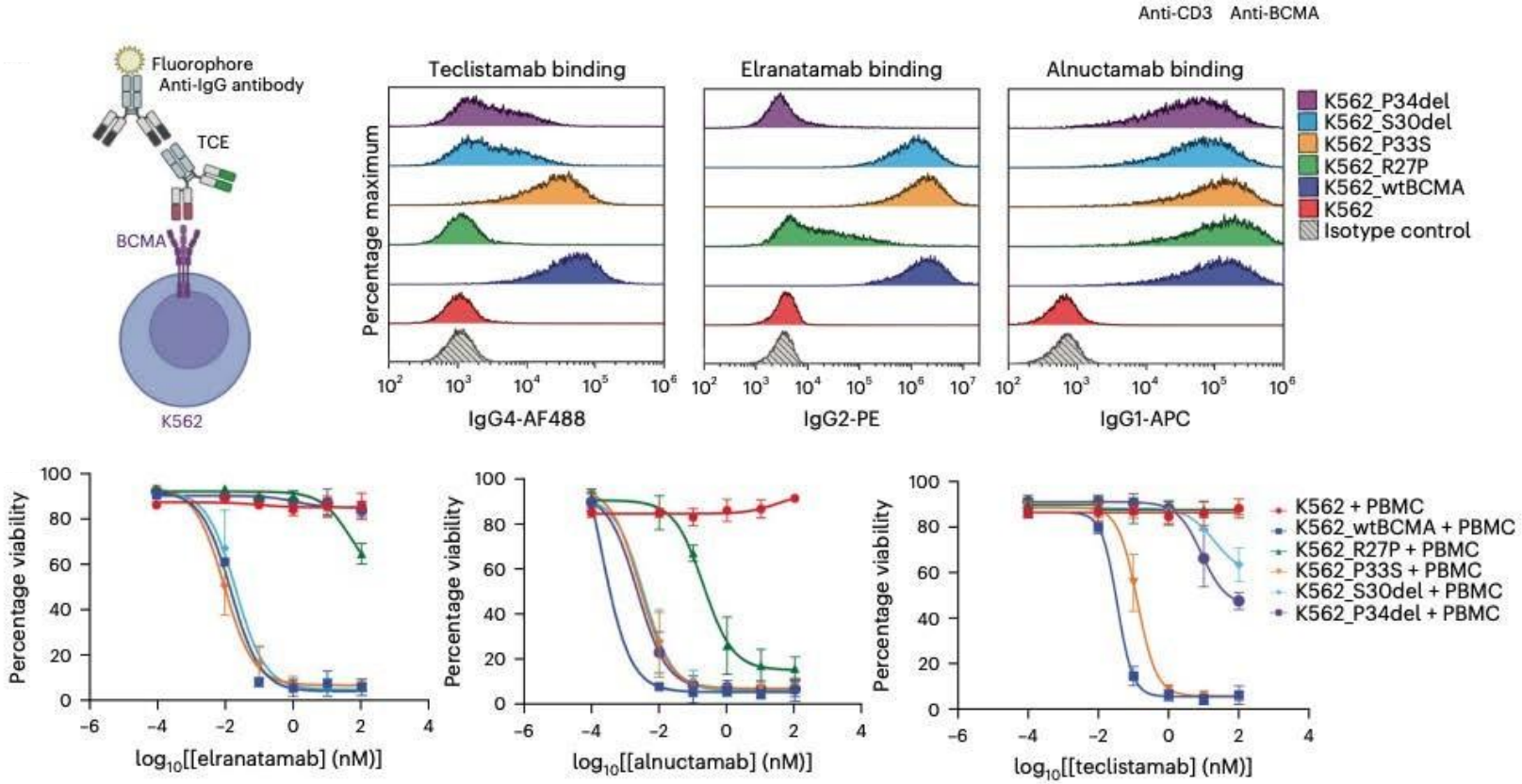
FcγR-silent Fc
No binding to FcγR and C1q to minimize infusion-related reaction

Alnuctamab: 2 + 1 BCMA x CD3 TCE with bivalent binding to BCMA[1,2]

- Clinical activity in patients with RRMM treated with ≥3 prior LOT in phase 1 trials (initial IV then SC administration)

1. Costa LJ et al. *Blood*. 2019;134[suppl 1]:143. 2. Wong SW et al. ASH 2022. Abstract 162. 3. Wong SW et al. IMS 2023.

Higher binding potency vs other BsAbs



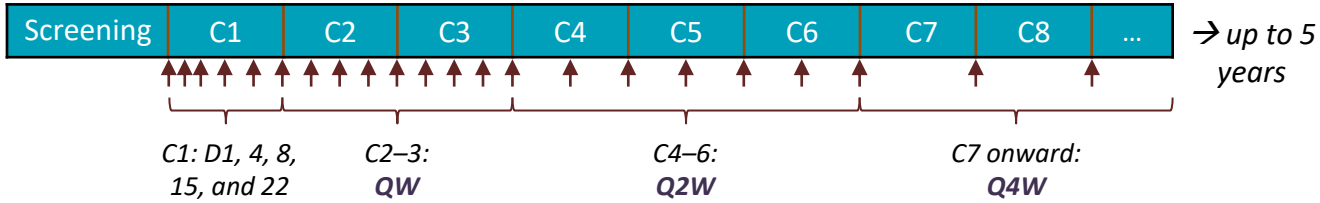
1. Lee H et al. *Nat Med*. 2023;29:2295-2306.

Phase 1 study design in patients with RRMM who received SC alnuctamab

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

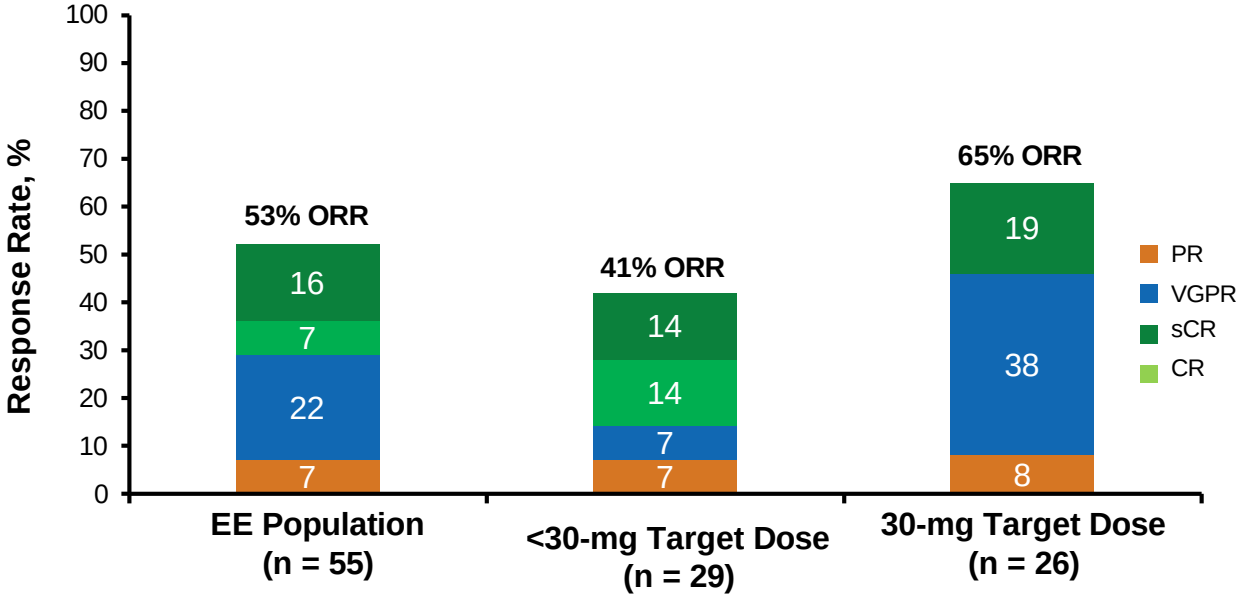
SC cohort expansion – multiple cohorts

Endpoints

Primary: Safety and tolerability, NTD, MTD, and RP2D
Secondary: Preliminary efficacy and PK
Exploratory: MRD negativity, PD parameters

Activity of SC Alnuctamab in RRMM

In 55 Efficacy-Evaluable Patients Treated With SC Alnuctamab, ORR Was 53% Across All Doses and 65% at the 30-mg Target Dose[1]

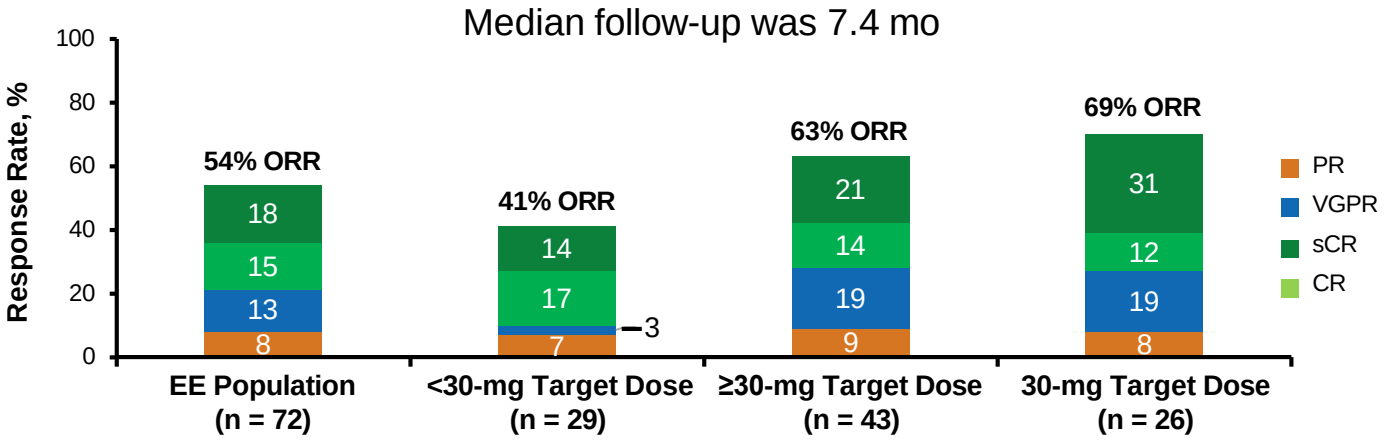


Safety	
Grade ≥3	**N = 73 (%)**
CRS	0
ICANS	0
Infections	10
Hematologic	
Neutropenia	42
Anemia	25
Thrombocytopenia	14

1. Wong SW et al. EHA, IMS 2023.

Updated Results With SC Alnuctamab[1]

73 patients treated with SC alnuctamab
- Patients had median of 4 prior regimens
- 96% were refractory to last LOT
- 100%/78% had triple-class/penta-drug exposed MM
- **63%/19% had triple-class/penta-drug refractory MM**

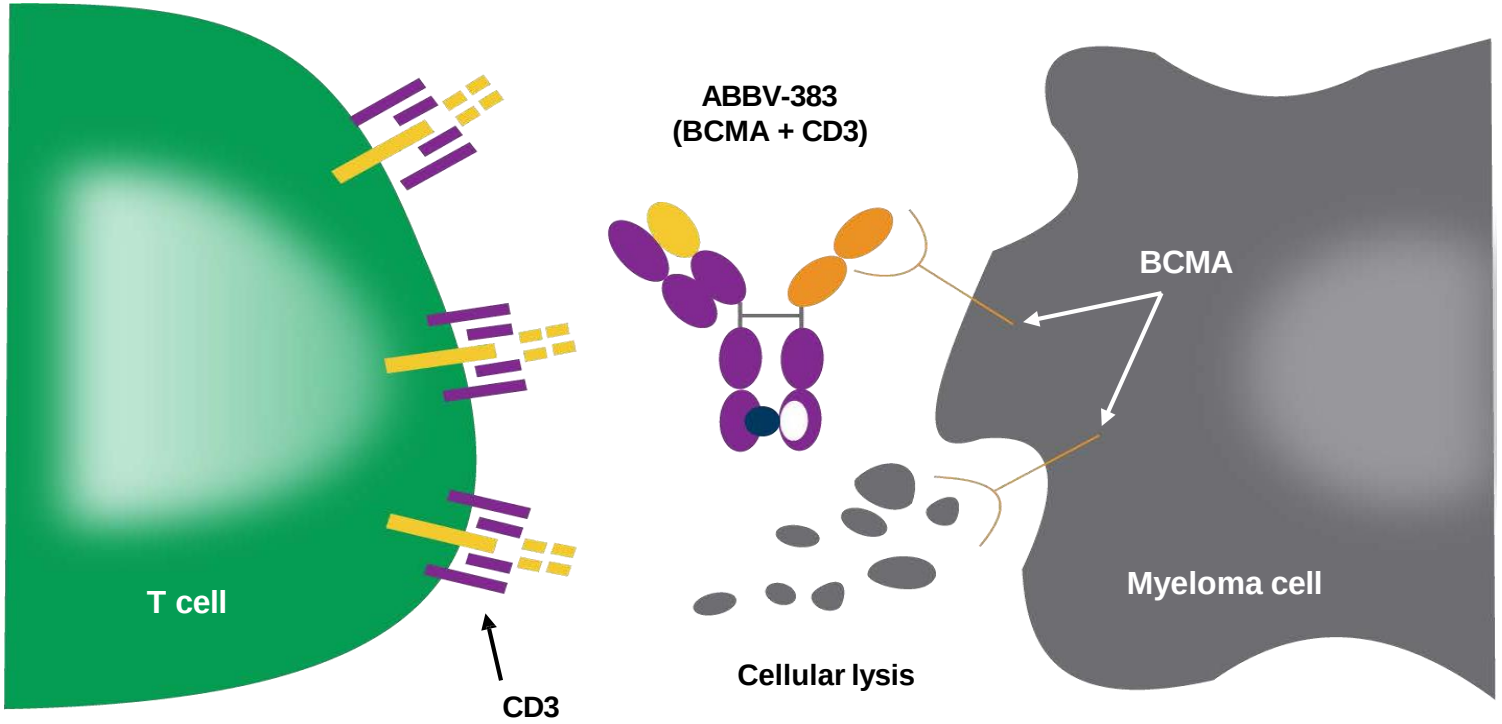


ASH23: Responses were durable and deepened over time, with a high proportion of responders achieving MRD negativity; high antitumor activity was observed at doses ≥ 30 mg and specifically at the 30-mg dose

1. Barr N et al. ASH 2023. Abstract 2011.

ABBV-383 Is a Next-Generation, Fully Human, Monoclonal, IgG4 T-BsAb, BCMA-Targeted Therapy

- Incorporates a **low activating CD3** that preclinically decouples T-cell activation from cytokine release and **preferentially activates effector over regulatory T cells**

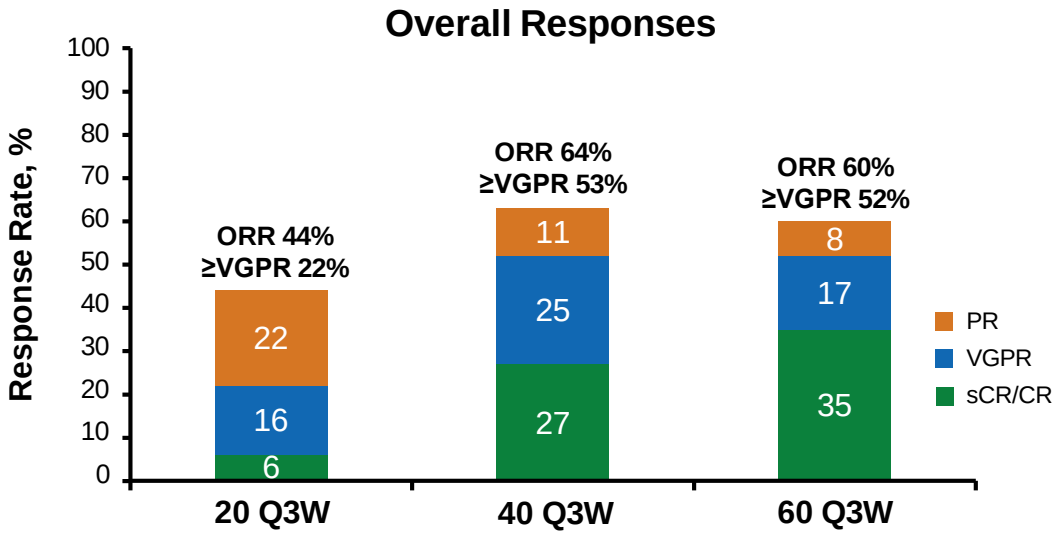


ABBV-383 in RRMM

- Durable responses previously reported at 40 mg and 60 mg dose levels, including in patients with triple-refractory RRMM; median DOR and PFS were NR[1]

- ABBV-383 IV Q3W at 20 mg, 40 mg and 60 mg dose levels in 174 pts[2]
- Median prior LOT: 5; 80% TCR

- Safety: CRS 60% (grade ≥ 3 1%)
- **Neutropenia 26%**
- **Infections grade 3-4 22%**



1. Voorhees P et al. ASH 2022. Abstract 1919. 2. Vij R et al. ASH 2023. Abstract 3378.

BCMA-targeting BsAbs: summary of efficacy

Bispecific Antibody	Teclistamab	Elranatamab	Linvoseltamab (REGN5458)	ABBV-383	Alnuctamab (BMS-93269)
Structure/Function	Humanized antibody	Humanized antibody	Veloci-Bi® platform **fully human antibody**	Low CD3 affinity **fully human antibody**	Humanized antibody **Bivalent binding**
Treatment	Weekly SC	Weekly SC	Weekly IV	**IV q3w**	**Qwk -> Q4wk SC**
Patients	n= 165	n= 123	n= 252	n= 174	n= 68
Median prior lines	5	5	5	5	4
Triple-class refractory	**78%**	**97%**	**81%**	**80%**	**63%**
ORR at RP2d	**63%**	**61%**	**64%**	**58-61%**	**65%**
RP2D (n)	1.5 mg/kg SC (n=165)	76 mg SQ (n=123)	200 mg IV (n=58)	40 to 60 mg IV (n=52; n=59)	30 mg SQ (n=26)
PFS	11.3 mos (8.8-17.1)	NE @ 12 mos; 51% @ 15 mos	NR	13.7 or 11.2 mos	NR
DOR	18.4 mos (14.9-NE)	NE @12 mos	89% @ 6 mos	NE	NE
Median f/u	14.1 mos	10.4 mos	3.2 mos	6.8	4.6 mos

Most BCMA×CD3 bispecific antibodies have been evaluated in **TCR MM patients.**
ORR ranges from 50–71% and covers the unmet need. PFS is approx 1 year for most bsAbs

Moreau P et al. *N Engl J Med.* 2022;387(6):495-505. Bahlis NJ et al. 2022 ASH. Abstract 97. Bumma N et al. 2022 ASH. Abstract 1936. Voorhees PM et al. 2022 ASH. Abstract 1919. Wong SW et al. 2022 ASH. Abstract 162. Abdallah AO et al. 2022 ASH. Abstract 3240. D'Souza A et al. *J Clin Oncol*. 2022;40(31):3576-3586.

BCMA-bispecific mAbs: summary of Safety profile

	Alnuctamab	Teclistamab	Elranatamab	Linvoseltamab	ABVV-3883
CRS (G 3-4)	50% (0%)	71.5% (0.6%)	56.3% (0%)	44% (0%)	60% (1%)
Median onset	3	2(1-6)	2	11 hours	1(1-2)
Duration	2	2(1-9)	2	15 hours	1(1-8)
Tocilizumab	56%	36.4%	40%	18%	NR
NTS	15%	14.5%	NR	NR	NR
ICANS	3% (G1)	3%	4%	5.6%	3%
Grade 3-4	0	0	0	1.2%	0.5%
Median onset	NR	3 days	2.5 days	NR	NR
Duration	3 and 5 days	7 days	2 days	NR	NR
Treatment required	NR	8.5%	3%	NR	NR
Cytopenias Grade 3-4					
Neutropenia	32%	64%	48%	22%	26%
Anemia	25%	37%	36%	23%	18%
Thrombopenia	9%	21%	22%	13%	11%
Infections	34%	76%	66%	54%	NR
Grade 3-4	9%	44%	35%	29%	22%

Hypogammaglobulinemia as AEs observed in most patients treated with BCMA-CD3 mABs along the therapy

1. Wong ASH 2022 Abstract 162; 2.Moreau et al.. NEJM 2022; 3. Bahlis N et al. ASH 2022: Abstr 158; 4. Bumma et al. ASH 2022; Abstract 4555; 5. Voorhes et al. ASH 2022;Absttract 1919

Are we using T-cell redirecting therapies optimally ?

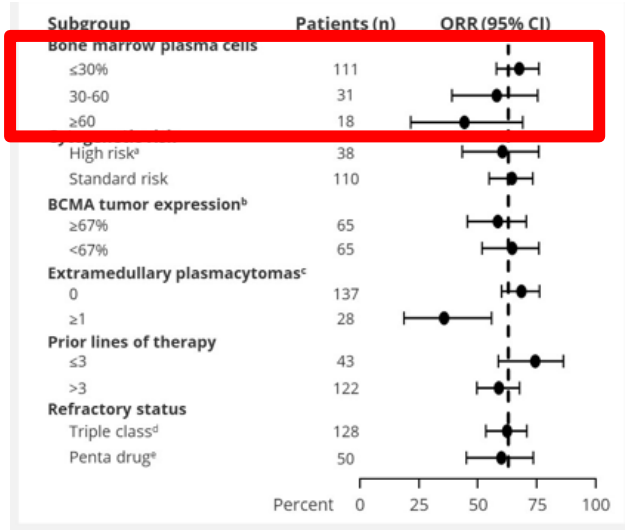
➢ **Strategies to enhance their potency**

- Combination strategies
- Earlier lines of therapy

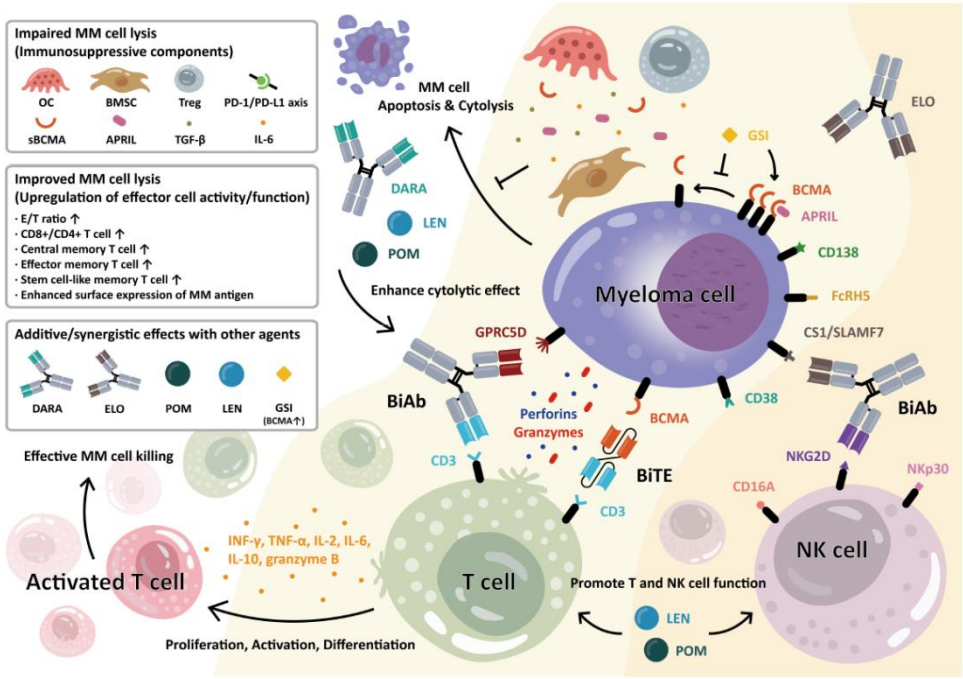
} Importance of tumor burden and immune fitness

Importance of tumor burden and immune fitness

Teclistamab: Majestec-1 study



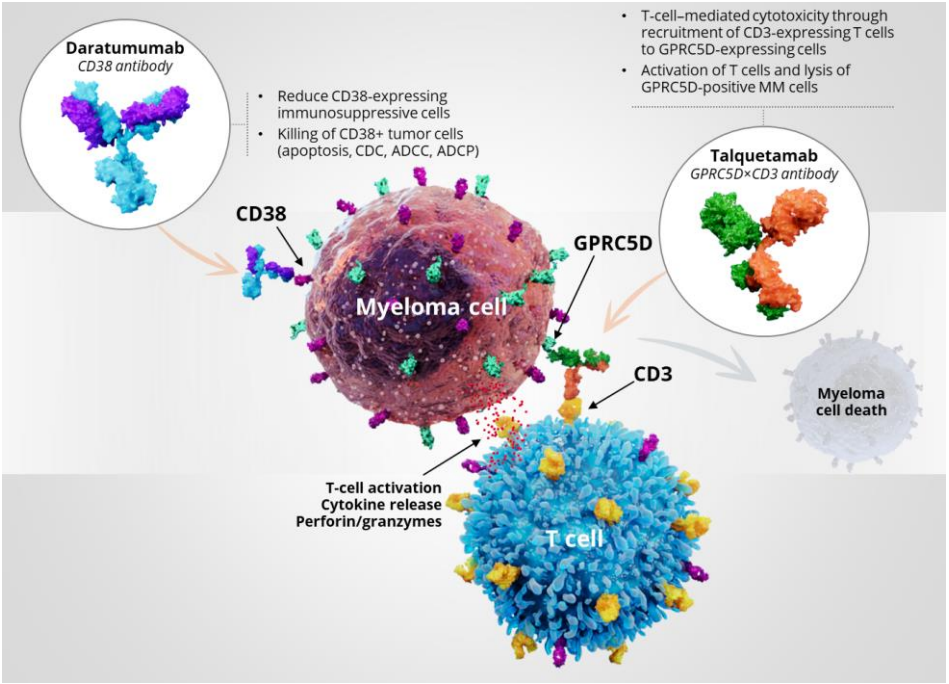
Moreau P et al. ASH 2021



Cho S et al. Frontiers in Oncology 2022

TRIMM-2: rationale to combine Teclistamab + Daratumumab

- Teclistamab is a first-in-class bispecific antibody targeting /BCMA
- Daratumumab is a foundational therapy in RRMM and NDMM that has direct on-tumor and immunomodulatory actions
  - **Daratumumab depletion of CD38-expressing Tregs may potentiate teclistamab-mediated killing of myeloma cells**
  - **Warning on infections!**



Dholaria B, et al. ASCO 2023. Poster 8003

Teclistamab/Elranatamab + Daratumumab

Teclistamab + Daratumumab (TRIMM-2 study)

65 pts, 5 median prior LOT

- 75% triple-refractory; 55% penta-refractory
- 12% prior anti-BCMA
- 63% anti-CD38 mAb refractory

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

Tec + Dara SC (n=37)		
AE (≥20%), n (%)	Any Grade	Grade 3/4
Hematologic		
Neutropenia	19 (51.4)	17 (45.9)
Anemia	17 (45.9)	11 (29.7)
Thrombocytopenia	12 (32.4)	12 (32.4)
Nonhematologic		
CRS	24 (64.9)	0 (0)
Diarrhea	13 (35.1)	1 (2.7)
Nausea	11 (29.7)	0 (0)
Asthenia	11 (29.7)	1 (2.7)
Fatigue	10 (27.0)	2 (5.4)
Pyrexia	9 (24.3)	0 (0)
Headache	9 (24.3)	0 (0)

- **ORR 76.5%, ≥VGPR 70.6%**
- **ORR of 73.7% in pts with prior anti-CD38 exposure**

Rodriguez Otero P et al. EHA 2022

Elranatamab + Daratumumab (MAGNETISMM-5)

Dara SC 1800 mg + Elra44 or 76 mg QW SC -> Q2W C7+

n = 34

Median prior LOT: 4

TCR 18%

ORR at RP2d 71%

CRS all(gr 3+) 41% (0%)

Neutropenia 47% (47%)
Pyrexia 21%

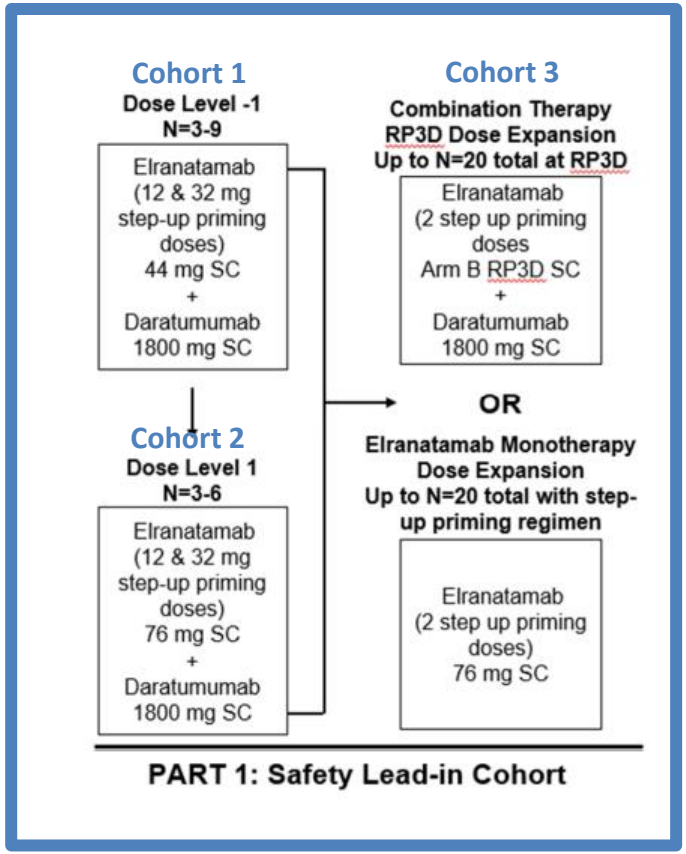
Analysis of the 34 pts enrolled in the safety-run-in phase

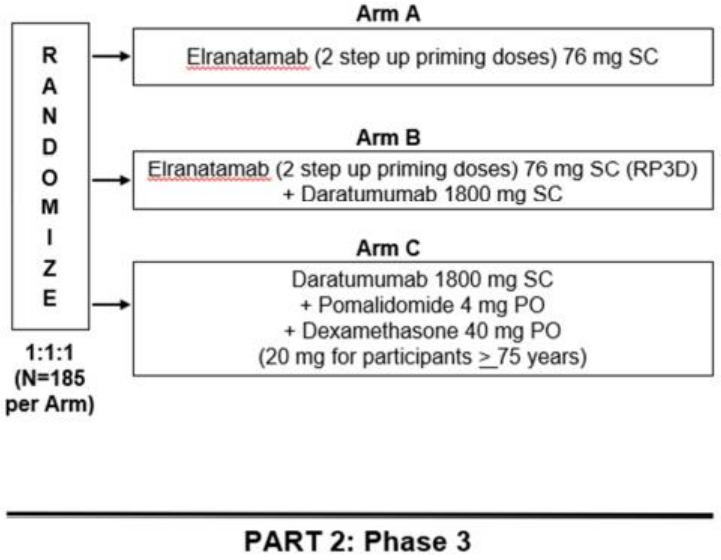
Grosicki et al, ASH 2022

MagnetisMM-5 Study

Safety lead-in designed to evaluate both a 2 step elranatamab priming regimen, and the combination of elranatamab + daratumumab

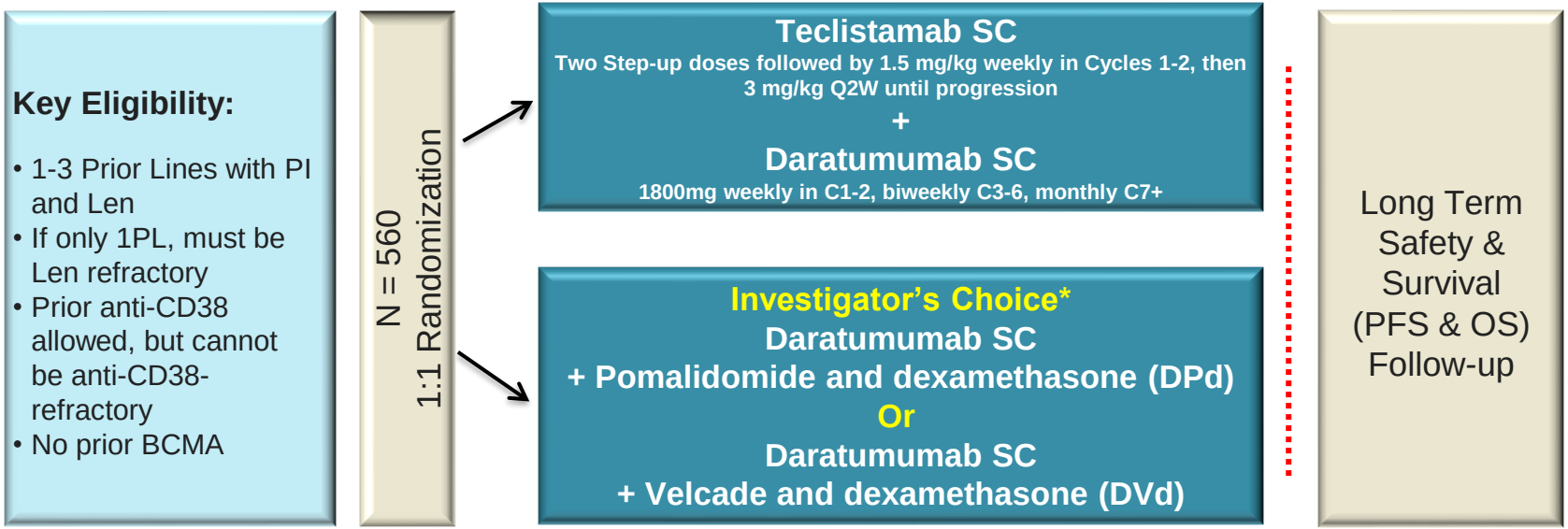
- Patients with 1-4 prior LOT
- **Primary end-point: PFS**
- **Fully enrolled**





- **Weekly elra C1-8, then Q2W if ≥ PR**

MajesTec-3 trial



- Primary end point – PFS
- ~ 560 patients will be 1:1 randomized

- Trial on held/re-analysis for **high rate of infections/deaths** in the Tec-Dara combination if **fixed dose** used

Combination strategies of anti- BCMA BsAbs in Ph 1-2 clinical trials

Study	Agents
Combination with other anti-myeloma agents	
NCT04108195_TriMM-2 (Phase 1)	Teclistamab + **daratumumab;** Talquetamab + **daratumumab;** then ± **pomalidomide**
MNCT04722146_MajesTEC-2 (Phase 1b)	Teclistamab + **lenalidomide;** Teclistamab + **daratumumab** + **lenalidomide;** Teclistamab + **daratumumab + lenalidomide** + bortezomib; Teclistamab + **daratumumab + pomalidomide**
NCT05090566_MagnetisMM-4 (Phase 2, Sub-study B**)**	Elranatamab + **lenalidomide +** dexamethasone
NCT05137054 (Phase 1)	Linvoseltamab + **daratumumab** + dexamethasone; Linvoseltamab + **carfilzomib** + dexamethasone Linvoseltamab + **lenalidomide** + dexamethasone; Linvoseltamab + **bortezomib** + dexamethasone
NCT05338775_TriMM-3 (Phase 1)	Teclistamab + **PD-1 inhibitor**; Talquetamab + PD-1 inhibitor
NCT05675449_MagnetisMM-20 (Phase 1b)	Elranatamab + **carfilzomib** + dexamethasone; Elranatamab + **maliparcept**
NCT05259839 (Phase 1, Sub-study A-B-C**)**	ABBV-383 **+ pomalidomide** + dexamethasone; ABBV-383 + **lenalidomide** + dexamethasone; ABBV-383 + **daratumumab** + dexamethasone
Combination of 2 bispecific molecules targeting various MM antigens	
NCT04586426 (Phase 1, Part 2: Dose expansion cohort**)**	Talquetamab + Teclistamab; Talquetamab + Teclistamab + daratumumab
NCT05927571 (Phase 1)	Cevostamab + Elranatamab
Combined agent which enhances expression of target antigen (γ secretase inhibitor)	
NCT04722146 (Phase 1)	Teclistamab + **nirogacestat**
NCT05090566_MagnetisMM-4 (Phase 2, Sub-study A**)**	Elranatamab + **nirogacestat**
NCT05259839 (Phase 1, Sub-study D**)**	ABBV-383 + **nirogacestat**

New advances with anti-BCMA CARTs and Bispecific Antibodies:

Anti- BCMA bispecific antibodies in early relapse

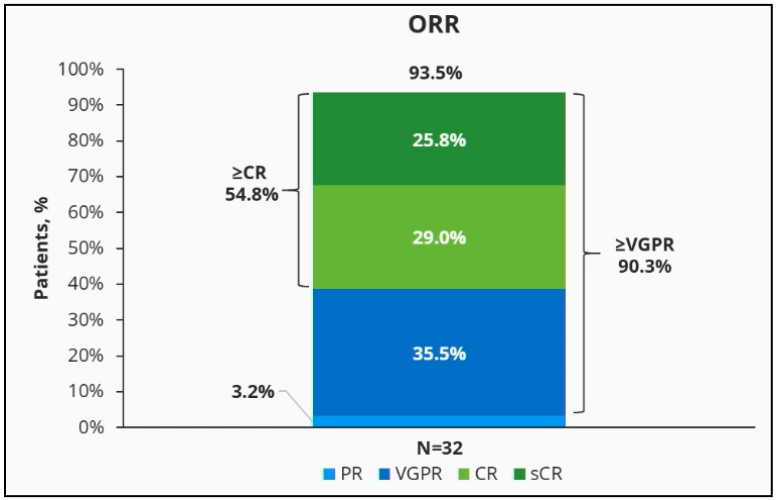
Key eligibility criteria
- Measurable MM
- 1–3 prior lines of therapy, including an IMiD and a PI

Primary endpoints
- Safety[a]
- Dose-limiting toxicities

Key secondary endpoints
- ORR[b]
- Rate of ≥VGPR and ≥CR[b]
- Duration of response
- Time to response

Tec-Dara-Len Dosing Schedule:

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



Majestec-2 phase 1b trial

AE, n (%)	Any Grade	Grade ≥3
Neutropenia	27 (84.4)	25 (78.1)
Thrombocytopenia	8 (25.0)	5 (15.6)
Anemia	7 (21.9)	4 (12.5)
CRS	26 (81.3)	0
Fatigue	15 (46.9)	2 (6.3)
Diarrhea	15 (46.9)	0
Cough	13 (40.6)	1 (3.1)
Hypophosphatemia	10 (31.3)	2 (6.3)
Pyrexia	10 (31.3)	1 (3.1)
Nausea	10 (31.3)	0
Pneumonia	8 (25.0)	5 (15.6)
COVID-19	12 (37.5)	4 (12.5)
Upper respiratory tract Infection	10 (31.3)	0
Sepsis	3 (9.4)	3 (9.4)

Most common Grade ¾ events, that occurred 90.6% patients were cytopenia and pneumonia
Pts with ≥1 infections were 29 (all grade; 90.6%) and 12 G3-4 (37.5%)
2 fatal AEs were reported (COVID-19 and sepsis)

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Ongoing phase 3 studies with anti-BCMA bispecific antibodies as treatment of RRMM at early relapse or NDMM

Study	Regimen	Condition
MajesTEC-3 NCT05083169	Tec-Dara vs DaraPd or DaraVd (on held)	RRMM 1-3 prior LOT (including len and PI)
MajesTEC-9 NCT05572515	Tec vs PVd or Kd (open for enrollment)	RRMM 1-3 prior LOT (including len and antiCD38 mAb)
MagnetisMM-5 NCT05020236	Elranatamab vs Elra-Dara vs DaraPd (fully enrolled)	RRMM ≥ 1 prior LOT (including len and PI)
MajesTEC-7 NCT05552222	Tec-Dara-Len vs DaraRd (open) Tal-Dara-Len vs DaraRd	NDMM ineligible or not intended for ASCT
MagnetisMM-6 NCT05623020	Elra-Dara-Len vs DaraRd (open)	NDMM not candidates for ASCT
MajesTEC-4 NCT05243797	Tec-Len vs Len vs Tec (safety-run-in analysis)	NDMM maintenance following ASCT
MagnetisMM-7 NCT05317416	Elranatamab vs Len (open)	NDMM maintenance following ASCT

Conclusions

- **2 anti-BCMA BsAb** are currently FDA and EMA approved and represent a **new standard of care after four/three lines of therapy**, where they significantly improved survival outcomes
- 3 new anti-BCMA BsAb, with different constructs, characteristics and schedules of administration are under investigation in phase I/II clinical trials, mostly in TCR patients
- **ORR ranges from 50–71%** and covers the unmet need**. PFS is approximately 1 year** for most BsAbs
- Newer anti-BCMA Bs Abs, with **less intense schedules** of administration and different constructs, together with **improved patient' management**, seem to reduce **the risk of severe neutropenia and infections**

- Multiple on-going programs include **combinations and earlier lines of treatments**
- **Combination programs** showed significantly **improved efficacy** but also **toxicity**, which needs caution and appropriate management