POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
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Terapie di salvataggio con anticorpi monoclonali

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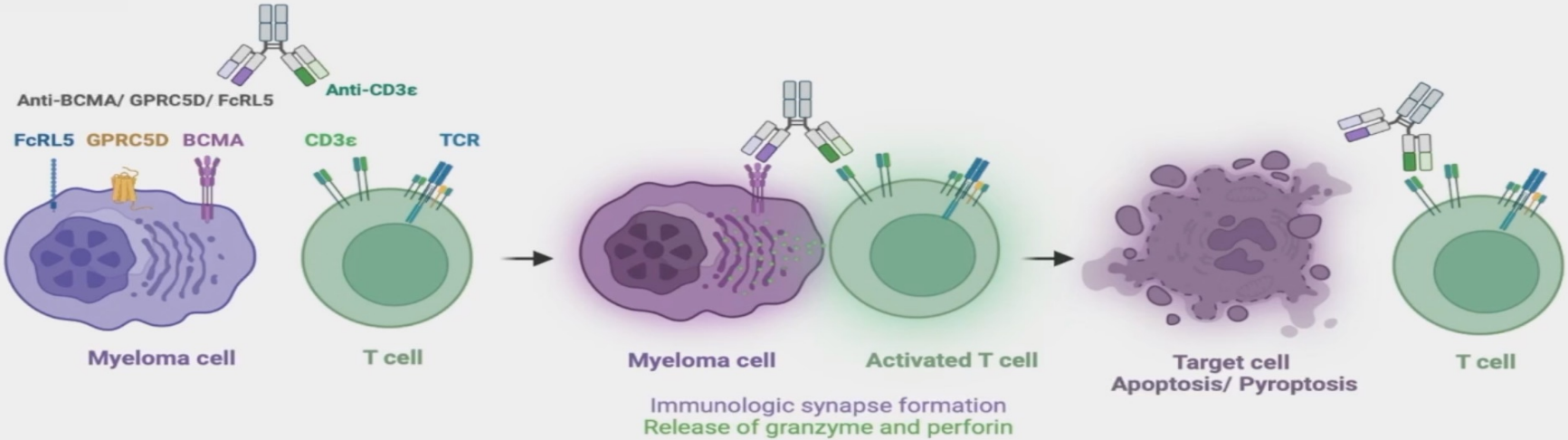
Disclosures of Renato Zambello

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

T cell engaging BsAb in Multiple myeloma

Targeted myeloma surface antigens in advanced clinical development include:

- BCMA: B-cell maturation antigen, (expression on B and plasma cells)
- GPRC5D: G protein– coupled receptor class C group 5D, (expression on plasma cells and keratinized tissues)
- FcRH5 fragment crystallizable receptor- like 5 (expression on B and plasma cells)



Fiigure produced by Dr Holly Lee with Biorender

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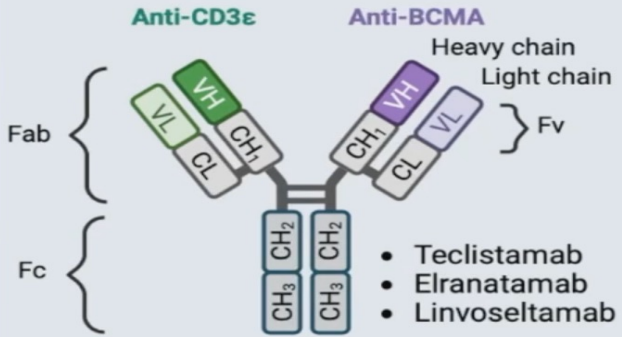
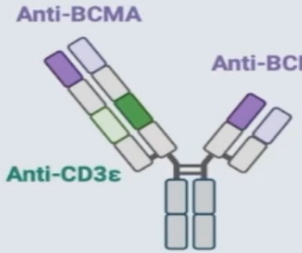
IgG-like BsAb design with monovalent BCMA Fab



- Teclistamab
- Elranatamab
- Linvoseltamab

IgG-like BsAb design with bivalent BCMA Fab



- Alnuctamab

- TNB-383B

Non-IgG BsAb Tandem scFv

- AMG420

Fiigure produced by Dr Holly Lee with Biorender

BCMA targeting bispecific antibodies in RRMM

	Teclistamab[1,2]	Elranatamab[3]	Elranatamab[4]	Linvoseltamab[5]	Alnuctamab[6,7]	ABBV-383[8]
Patients (n)	165	55	123	117	73	124
Dosing schedule	weekly /q2w SC	weekly / q2w SC	weekly/q2w IV	weekly/ q2 or 4 w IV	weekly/ q2-4w IV/SC	q3 weeks IV
med Prior LOT	5	6	5	5	4	5
ISS III / ↑↑PC (%)	12.3 / 11.2	20 / --	15.4 /21.1	18.8 /22.2	16 / --	31 / --
HR / EMD (%)	25.7 / 17	29.1/ 30.9	25.2 / 31.7	35.9/ 13.7	26 / 21	18 / --
TCR (%)	77.6	90.9*	100	73.5	63	82
ORR / ≧ CR (%) @ RP2D	63 / 45.5 1500 µg/kg SC	64 / 38.2 76 mg SC	61 / 35 76 mg SC	71 / 30 200 mg IV	69/ 43 30 mg SC	57 17 40-60 mg IV
mDOR	21.6 mos	17.1 mos	71.5% @ 15 mos	--	--	72.2 % @ 12 mos†
mPFS	11.3 mos ≦ 3 LOT 18.1 mos	11.8 mos	50.9% @ 15 mos	72.7% @ 6 mos	53% @ 12 mos	10.4 mos 57.9% @ 12 mos†
mOS	21.9 mos	21.2 mos	56.7% @ 15 mos	--	--	--
CRS (%)	72.1 (0.6 G3)	87.3 (0 G3)	56.3 (0 G3)	45.3 (0.9 G3)	56 (0 G3)	57 (2 G3)
Infections (%)	80 (55.2 G3-4)	74.5 (27.3 G3-4)	69.9 (39.8 G3-4)	59.8 (36.8 G3-4)	62 (16 G3-4)	41 (5 G3-4)

LOT = lines of therapy, HR = high risk cytogenetics, EMD = extramedullary disease, ↑↑PC = > 50-60% bone marrow plasma cells, TCR = triple class refractory, ORR = overall response rate, DOR = duration of response, PFS = progression free survival, OS = overall survival, SC = subcutaneous, IV = intravenous, mos = months, * = 23.6% prior anti-BCMA, -- = not reported, †mPFS at ≥ 40 mg dose level

1. Moreau et al NEJM 2022.; 2. Van de Donk et al ASCO 2023, 3. Bahlis et al Nat Med 2023; 4. Lesokhin et al Nat Med 2023; 5. Lee et al J ASCO 2023 ; 6 Wong et al ASH 2022 ; 7. Barr ASH2023, abstract # 2011; 8. D'Souza A J Clin Oncol 2022

GPRC5D or FcRH5 targeting BsAb in multiple myeloma

	Anti-GPRC5d Talquetamab[1,2]			Anti-GPRC5d Forimtamig[3]		Anti-FcRH5 Cevostamab[4,5]
Patients (n)	143 T-cell redirecting Rx naïve Anti-BCMA ADC allowed	145 T-cell redirecting Rx naïve Anti-BCMA ADC allowed	51 Prior anti-BCMA CAR/BsAb allowed	51 Prior anti-BCMA ADC/ CAR/BsAb allowed	57 Prior anti-BCMA ADC/ CAR/BsAb allowed	161
Dosing schedule	405 µg/kg SC QW	800 µg/kg SC Q2W	5-1600 µg/kg SC	18-10000 µg IV Q2-3W	1200-7200 µg SC Q2-3w	20-198 mg IV q3w
med Prior LOT	5	5	6	5	4	6
ISS III / ↑↑PC (%)	19.6 / 12.3	24.3 / 22.7	17.6 / 17	--	--	--
HR / EMD (%)	31.1 / 23.1	28.9 / 25.5	40.9 / 31.4	46.7 / 27.5	47.7 / 31.6	39.8 / 21.1
TCR / Penta-refr. (%)	74.1 / 29.4	69/ 23.4	84.3 / 41.2	62 / 36	71.9 / 42.1	84.5 / 68.3
ORR / ≧ CR (%) ORR prior BCMA (%)	74.1 / 33.6	71.7 / 38.7	64.7 / 35.3	71.4 / 34.7 50	63.6 / 25.5 54.5	56.7 /8.4 ×
mDOR	9.5 mos	NR	11.9 mos	10.8 mos	12.5 mos	11.5 months
12-month PFS (%)	34.9	54.4	38.1	--	--	--
12-month OS (%)	76.4	77.4	62.9	--	--	--
CRS (%)	79 (2.1 G3)	74.5 (0.7 G3)	76.5 (2.0 G3)	82.4 (2.1 G3)	78.9 (1.8 G3)	79.5 (2.3 G3)*
Infections (%)	58.7 (19.6 ≧G3)	66.2 (14.5 ≧G3)	72.5 (27.5 ≧G3)	60.8 (21.5 ≧G3)	45.6 (26.4 ≧G3)	43
Dysgeusia (%) Skin/Nail (%)	72 55.9 / 54.5	71 73.1 / 53.8	76.5 68.6 / 62.7	72.5 23.5	77.2 28.1	na

* 2-step-up 0.3/3.6/target dose 60-160 mg, × at the132-198 mg dose level, na not reported

1. Schinke at al ASCO 2023 , 2. Chari et al NEJM 2023; 3. Carlo-Stella et al. ASH 2022; 4. Trudel et al. ASH 2021; Harrison et al IMS2023

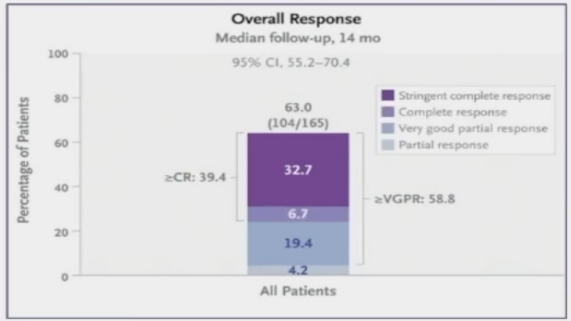
ASH 2023 oral abstracts

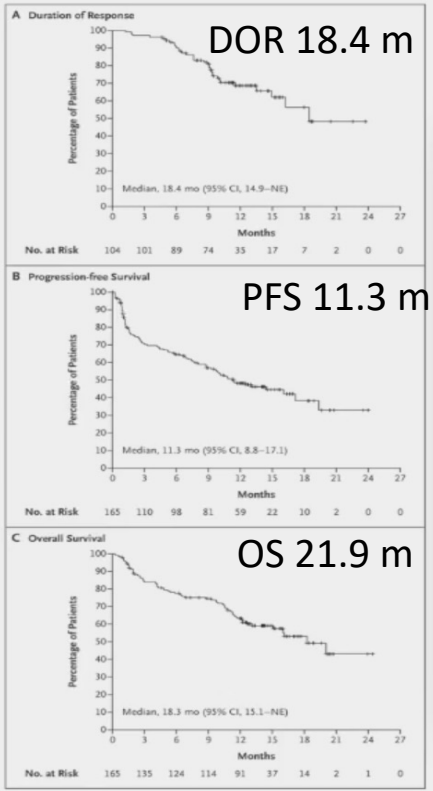
- **Real Word data, Teclistamab** (D. Dima et al, abs 91)
- **Antibodies with increased binding sites, tri specific construct** (S. Madan et al, abs 1012; K. Pillarisetti et al. abs 456)
- **Combination therapy (Talquetamab and Pomalidomide:** J. Matous et al, abs 1014)
- **Further on Bispecific Antibodies** (**Teclistamab:** D. Vishwamitra et al abs 455; **Talquetamab:** A. Chari et al, abs 1010; **Elranatamab:** M. Tomasson et al abs 3385; I. Mol et al abs 2015; **Alnuctamab**: N. Bar et al abs 2011)
- Snapshot on **sequencing**

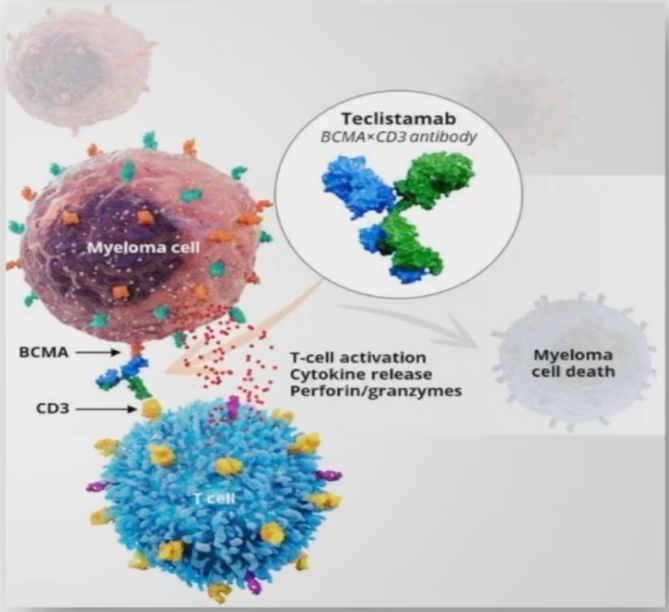
Background

- Teclistamab: T-cell redirecting bispecific antibody that binds to **CD3** on T cells and **BCMA** on plasma cells.
- Approved in October 2022 by the FDA based on the results of the phase 2 MajesTec-1 trial.
- RP2D for Teclistamab monotherapy: 1.5 mg/kg SC weekly with step-up doses of 0.06 (d1) and 0.3 (d4) mg/kg

MajesTEC-1 phase 2 trial (N=165)







Dima et al ASH 2023 abs 1012

Results: Patient Characteristics

Patients Characteristics	N = 106	MTec-1 (N=165)
Age, years, median (range)	66.5 (35–87)	64 (33-84)
Age >70 years, n (%)	34 (32)	
Median time since diagnosis, years (range)	5.5 (0.5-20)	6.0 (0.8-22.7)
Number of prior lines of therapy (median, range)	6 (4–17)	5 (2-14)
>4 prior LOT, n (%)	80 (75)	
Non-Hispanic White, n (%) Non-Hispanic Black, n (%)	72 (68) 28 (26)	134 (81) 21 (13)
R-ISS stage III, n (%)	25/80 (31)	20/162 (12)
ECOG Performance Status ≥2, n (%)	35 (33)	–
High-risk cytogenetics, n (%)	56/95 (59)	38/148 (26)
Extramedullary disease (EMD), n (%)	45 (42)	28 (17)
Refractory status: **• Triple Refractory, n (%)** **• Penta refractory, n (%)**	97 (92) 68 (64)	128 (78) 50 (30)
Prior BCMA-directed Therapy	56 (53)	–
Prior autologous stem cell transplant, n (%)	61 (58)	135 (82)
Prior allogeneic stem cell transplant, n (%)	3 (3)	

High risk cytogenetics: dele17p, t(4;14), t(14;16) and/or amp/gain 1q on FISH
EMD: defined as bone-independent (only) tumors

Reasons for MajesTEC-1 ineligibility

No. of patients who met exclusion criteria	N = 88 (83)
1 criterion	45 (42)
≥2 criteria	43 (41)
Prior anti-BCMA Therapy	56 (53)
Poor performance status (ECOG ≥2)	35 (33)
Any baseline cytopenia	33 (31)
Neutropenia ANC < 1000 cells/uL)	2 (2)
Anemia (Hemoglobin < 8 g/dL)	27 (25)
Thrombocytopenia (Platelets < 75K cells/uL)	21 (20)
Renal dysfunction (CrCl < 40 mL/min)	14 (13)
Liver dysfunction	5 (5)
Cardiac dysfunction: LVEF < 45%	4 (4)
Plasma Cell Leukemia	2 (2)
Amyloidosis	1 (1)
Central Nervous System Involvement	4 (4)
Autologous Stem Cell Transplant ≤12 weeks	1 (1)

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Results: Response to Teclistamab

Response (Full Cohort) N (%)	RWE cohort N=104	MajesTec-1 N=165
Overall response rate	**70 (66)**	**104 (63)**
Complete response or better	**31 (29)**	**65 (39.4)**
Very good partial response	18 (17)	32 (19.4)
Partial response	21 (20)	7 (4.2)
Minimal response	0	2 (1.2)
Stable disease	10 (9.5)	27 (16.4)
Progressive disease	**26 (24.5)**	**24 (14.5)**
Not evaluable	0	8 (4.8)

Subgroups of Interest	ORR, N (%)
Age>70 (n=34)	24 (71)
Non-Hispanic Black (n=28)	20 (71)
Pts ineligible for MajestEC-1 trial (n=88)	53 (60)
High-risk cytogenetics (n=56)	35 (63)
Triple Refractory (n=97)	62 (64)
Penta refractory (n=68)	46 (68)
Prior BCMA therapy	33 (59)
R-ISS III (n=25)	13 (52)
EMD (n=45)	21 (47)
Four or less prior LOT (n=26)	21 (81)
>4 lines of prior therapy (n=80)	49 (61)

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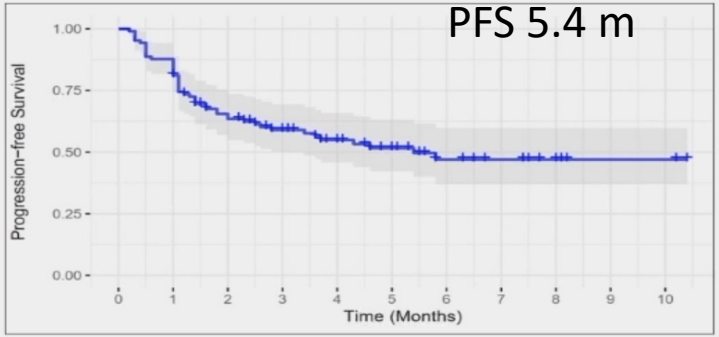
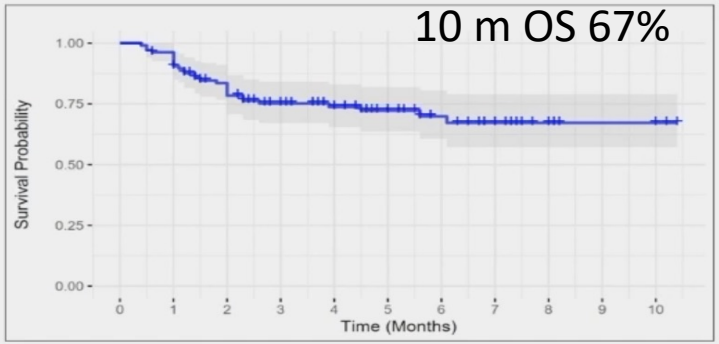
Results: Survival Outcomes

- After a median follow up of 3.8 months, a total of 46 patients progressed while on teclistamab.
- The **median PFS** for the entire cohort was **5.4 months** (95% CI, 3.4 months – not reached).
- At data cut off, a total of 29 patients had died; most (86%) from disease progression.

Cause of Death	Total deaths = 29
MM progression while on Teclistamab	21
Severe infection while on Teclistamab	3
Later MM progression while on next line of therapy	4
Myocardial infarction while on next line of therapy	1

- The **median OS** was **not reached**
- The **6-month** and **10-month OS** rates were **70%** (95% CI, 61-80%) and **67%** (95% CI, 57-79%), respectively.





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Safety: CRS, ICANS & Cytopenias

Adverse Events	N=106
CRS Any Grade	68 (64)
G3-4	1 (1)
Median time to Onset, days (range)	3.5 (range 1-8)
Median Duration, days, (range)	1 (range 1-6)
ICANS Any Grade	15 (14)
G3-4	3 (3)
Median time to Onset, days (range)	5 (range 1-10)
Median Duration, days, (range)	2 (range 1-30)
Tocilizumab	43 (41)
>1 dose of Toci	5 (5)
Recurrent CRS after Toci	2 (2)
Corticosteroids	35 (33)
Hospitalization for step-up dosing	
Length, days, median (IQR)	9 (8-11)
Intensive care unit stay	7 (7)

All with step up and first full dose; none with full doses in the outpatient setting

One G3 event at C1D22

Dosing schedules: **Day 1, 3, 5** (n=45) vs **Day 1, 4, 7** (n=61):

- Incidence of CRS after the 2nd step up dose- was significantly higher for the condensed group (51% vs 31%, **p=0.038**).

Hematologic toxicity on Day 30	N=99
Leukopenia Any	62 (63)
G3-4	19 (19)
Neutropenia Any	47 (47)
G3-4	21 (21)
Anemia Any	70 (71)
G3-4	16 (16)
Thrombocytopenia Any	60 (61)
G3-4	19 (19)
Hematologic toxicity on Day 90	**N=60**
Leukopenia Any	25 (42)
G3-4	4 (7)
Neutropenia Any	25 (42)
G3-4	9 (15)
Amenia Any	30 (50)
G3-4	6 (10)
Thrombocytopenia Any	28 (47)
G3-4	5 (8)
Supportive care	
G-CSF	22 (21)
TPO agonist	3 (3)
IVIG	44 (42)

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Safety: Infections

No. of patients who developed infection	N=33 (31)
Total Number of Infections	39
Severe infections	18 (46)
Infections of the respiratory system	27 (69)
Bacterial infections	16 (41)
Viral infections	20 (51)
Fungal Infections	3 (3)
Onset, days, median	46 (1-218)

Subsequent Hospitalizations while on Teclistamab:

Cause of Hospitalization	Total Hospital Admissions = 28
Infection	16
Cytopenia	3
Symptom control	6
Neurotoxicity	2
Acute Kidney Injury	1

Severe Infections	Total =18
Unspecified bacterial pneumonia	2
Unspecified bacterial colitis	1
Unspecified bacterial sepsis	1
Enterobacter cloacae bacteremia	1
Parainfluenza	**1**
Respiratory syncytial virus	**2**
Metapneumovirus	**2**
Rhino & adenovirus pneumonia	**1**
Covid-19 infection	**4**
Unspecified viral respiratory infection	**1**
Aspergillus pneumonia	1
Candida guilliermondii fungemia	1

Three pts died from severe infection while on TEC:
1 from COVID-19 pneumonia, 1 from rhino/adenovirus pneumonia and 1 from sepsis

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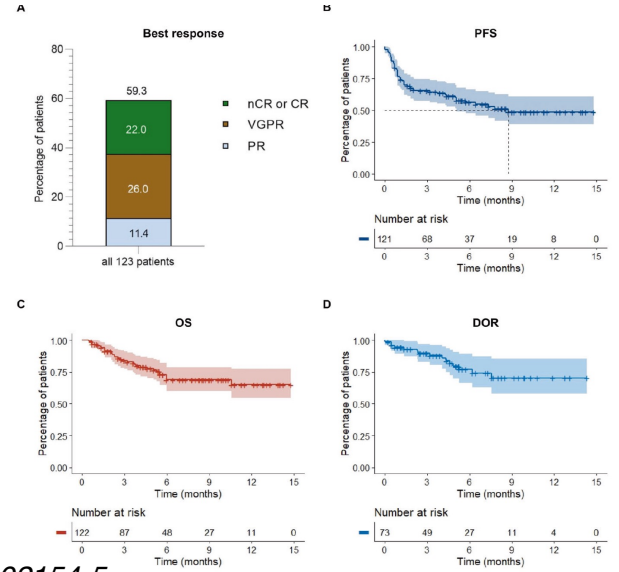
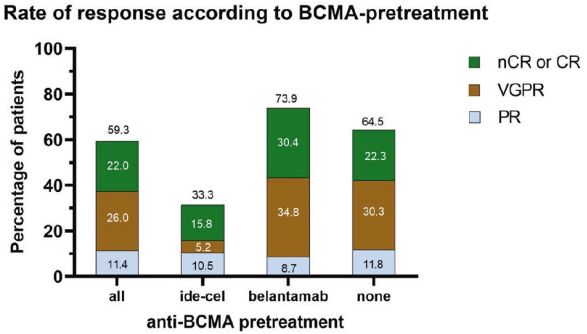
Real-world analysis of teclistamab in 123 RRMM patients from Germany

C. Riedhammer[1], F. Bassermann[2], B. Besemer[3], M. Bewarder[4], F. Brunner[5], A. Carpinteiro[6], H. Einsele[1], J. Faltin[7], J. Frenking[8], D. Gezer[9,10], S. Goldman-Mazur[11], M. Hänel[12], M. Hoegner[2], K. M. Kortuem[1], J. Krönke[13], M. Kull[14], T. Leitner[15], C. Mann[16], R. Mecklenbrauck[17], M. Merz[11], A. Morgner[12], A. Nogai[13], M. S. Raab[8], R. Teipel[18], R. Wäsch[19] and L. Rasche[1] ✉

Mean follow up 5.5.m

Characteristic	MAJESTEC-1	Real-world
Median age (range) - yr	64.0 (33.0–84.0)	67.0 (35.0–87.0)
Gender: male/female - %	58.2/41.8	56.9/43.1
Median time since diagnosis - yr (range)	6.0 (0.8–22.7)	6.5 (0.5–18.7)
Median no. of lines of previous therapy (range)	5 (2–14)	6 (3–14)
Extramedullary disease - no./total no. (%)	28/165 (17.0)	43/119 (36.1)
≥60% plasma cells in bone marrow no./total no. (%)	18/160 (11.2)	21/59 (35.6)
ISS no./total no. (%)		
I	85/162 (52.5)	25/92 (27.1)
II	57/162 (35.2)	35/92 (38.0)
III	20/162 (12.3)	31/92 (33.7)
High risk cytogenetic profile no./total no. (%)	38/148 (25.7)	39/106 (36.8)
Refractory status no./total no. (%)		
triple-class	128/162 (77.6)	113/123 (92.6)
penta-drug	50/162 (30.3	74/123 (60.2)



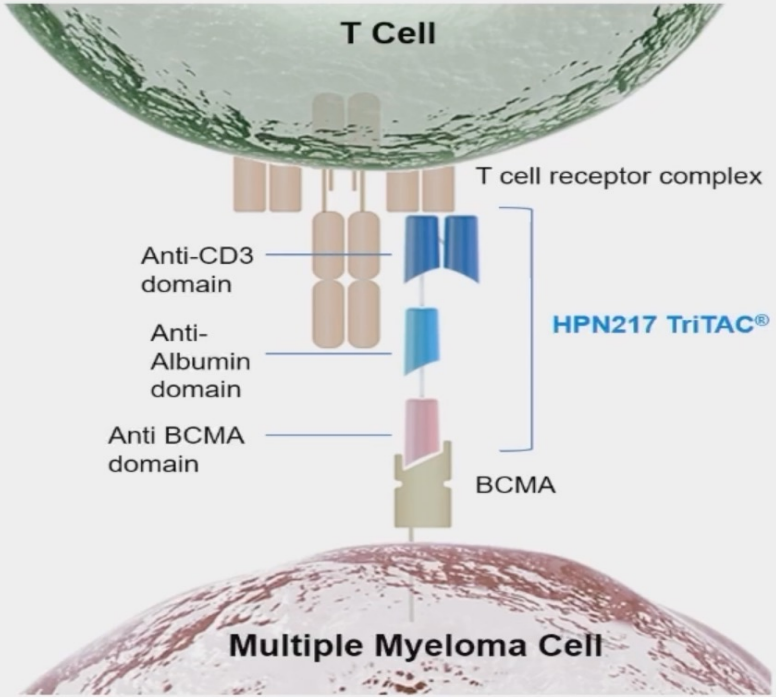


Adverse event	Any grade	Grade ≥ 3
Infections no. (%)	67/123 (54.5)	33/123 (26.8)
CRS no. (%)	72/123 (58.5)	2/123 (1.6)
ICANS no. (%)	9/123 (7.3)	1/123 (0.8)
Cytopenia any kind no. (%)	110/123 (89.4)	66/123 (53.6)
Neutropenia no. (%)	68/123 (55.3)	46/123 (38.0)
Anemia no. (%)	99/123 (80.5)	39/123 (31.7)
Thrombopenia no. (%)	78/123 (63.4)	32/132 (26.0)

Leukemia; https://doi.org/10.1038/s41375-024-02154-5

Background

- HPN217 is a BCMA-targeting T cell engager
- Redirects T cells to kill BCMA expressing multiple myeloma cells
- 3 binding domains
  - BCMA (for multiple myeloma cell binding)
  - CD3 (for T cell engagement)
  - Albumin (for half-life extension)
- Absence of Fc domain avoids Fc receptor binding
  - Minimizes T cell activation in the absence of Target cells
  - Designed to increase the therapeutic window
- Here we present the results from HPN 217-3001, the first in-human study



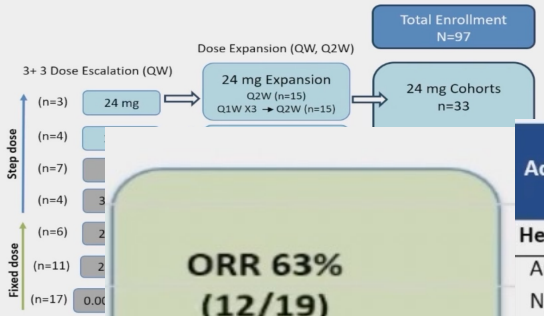
Madan S et al ASH 2023 abs 1012

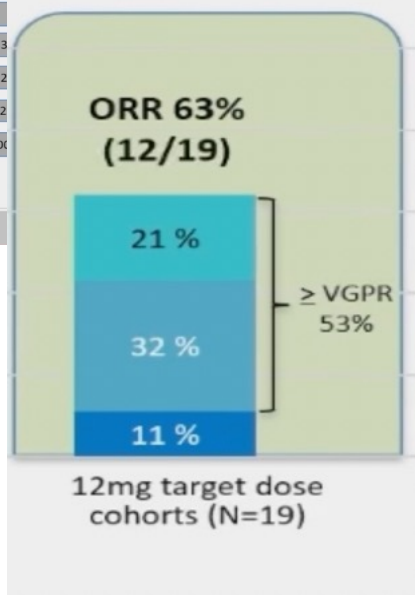
HPN217-3001 Trial Design

Primary Objectives
- Safety and tolerability
- Estimate MTD and/or identify RP2D

Key Secondary Objective
- Preliminary efficacy per IMWG

Key Eligibility Criteria
- Relapsed/refractory multiple myeloma
- ≥ 3 prior therapies including a PI, IMiD, an anti-CD38 antibody
- Prior treatment with BCMA targeted therapies allowed





Study Population

Baseline Characteristics	All Patients (N = 97)	12mg Target Dose (N=19)	24mg Target Dose (N=33)
Age (yr), Median (range)	69 (38-85)	69 (46-83)	68 (51-85)
Age ≥ 75 years, n (%)	23 (24)	7 (37)	7 (21)
Time Since Initial MM Diagnosis (yr), Median (range)	6.8 (0.6 - 20.2)	4.8 (0.6 - 12.1)	6.8 (1.0-19.4)
Baseline sBCMA (ng/mL),	249	204	236

	All Patients (N = 97)	12mg Target Dose (N=19)	24mg Target Dose (N=33)
Plasmacytoma at baseline, yes (%)	10 (10)	1 (5)	5 (15)
Prior Systemic Regimens, Median (range)	6 (2-19)	5 (2-9)	4 (2-14)
Prior Transplantation, n (%)	71 (73)	13 (68)	20 (61)
	97 (100)	19 (100)	33 (100)
	64 (66)	11 (58)	18 (55)
	20 (21)	4 (21)	5 (15)
(%)			
	76 (78)	14 (74)	23 (70)
	37 (38)	6 (32)	9 (27)
	14 (14)	1 (5)	3 (9)
	85 (88)	14 (74)	29 (88)

MiD, PI, and anti-CD38; [c]At least 2 PIs, at least 2 IMiDs, and at
o response to regimen or discontinued regimen due to
jkumar et al (Blood 2011)

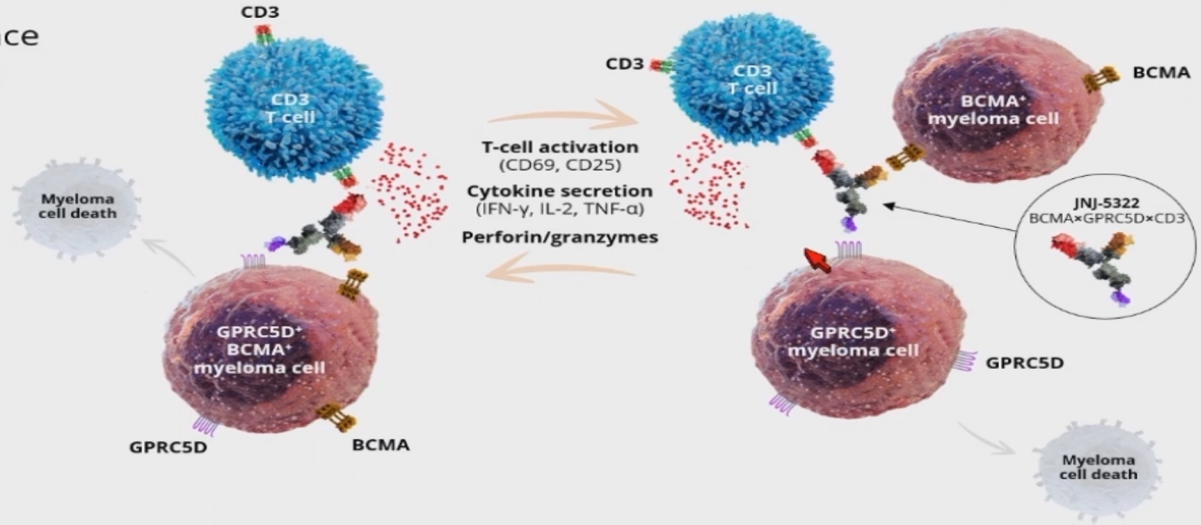
data are based on entries provided in open clinical database as of 10/17/23

Adverse Event[a]	12mg Target Dose (N=19)	
	All Grades	≥Gr 3
Hematologic n(%)		
Anaemia[b]	9 (47)	6 (32)
Neutropenia[b]	9 (47)	9 (47)
Thrombocytopenia[b]	6 (32)	4 (21)
Non-hematologic n(%)		
Fatigue	9 (47)	1 (5)
Cough	9 (47)	0
CRS [c]	3 (16)	0
Nausea	4 (21)	0
Arthralgia	3 (16)	0
Diarrhoea	5 (26)	0
Headache	4 (21)	0
Hypokalemia	7 (37)	2 (11)
Hypophosphatemia	6 (32)	0
Transaminases increased[b]	5 (26)	1 (5)
Back pain	3 (16)	0

Madan S et al ASH 2023 abs 1012

JNJ-79635322 Is a Potential First-in-Class Trispecific Antibody Targeting BCMA, GPRC5D, and CD3

- Dual antigen targeting may enhance tumor response by circumventing tumor heterogeneity and antigen loss and improving potency due to antigen binding avidity
- JNJ-79635322 (JNJ-5322) is an IgG1 trispecific antibody that binds to CD3 on T cells and BCMA and GPRC5D on MM cells



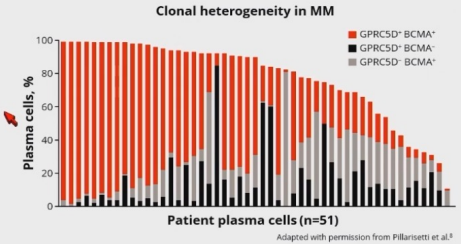
Pillarisetti K. ASH 2023 abs 456

BCMA, B-cell maturation antigen; GPRC5D, G protein–coupled receptor family C group 5 member D; IFN-γ, interferon-gamma; IgG, immunoglobulin G; IL, interleukin; MM, multiple myeloma; TNF, tumor necrosis factor.

Presented by K Pillarisetti at the 65th American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023; San Diego, CA, USA

Dual Targeting of BCMA and GPRC5D May Avoid Antigen Escape and Clonal Resistance

- Despite treatment advances, patients with triple-class exposed RRMM continue to have poor survival outcomes[1,2]
- BCMA- and GPRC5D-targeting BsAbs have improved outcomes for patients with triple-class exposed RRMM, with ORRs of 63% for teclistamab and >71% for talquetamab[3-6]
  - Teclistamab + talquetamab in the RedirecTT-1 trial has also shown robust efficacy in this patient population[7]
- However, due to antigen loss, antigen mutations, and the presence of target heterogeneity, disease can recur and new treatments are needed to overcome resistance and provide clinical benefit



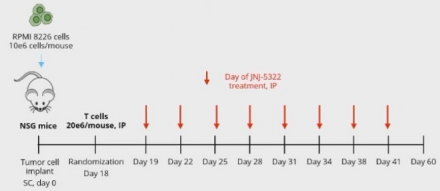
Adapted with permission from Pillarisetti et al.[8]

1. van de Donk NWCJ, et al. *Lancet* 2021;397:410-27. 2. van de Donk NWCJ, et al. *Curr Opin Oncol* 2023;35:601-11. 3. TECVAYLI (teclistamab-cqyv). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2022. 4. Moreau P, et al. *N Engl J Med* 2022;387:495-505. 5. TALVEY (talquetamab-tgvs). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2023. 6. Schinke C, et al. Presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual. 7. Cohen YC, et al. Presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual. 8. Pillarisetti K, et al. *Blood* 2020;135:1232-43.
BCMA, B-cell maturation antigen; BsAb, bispecific antibody; GPRC5D, G protein–coupled receptor family C group 5 member D; MM, multiple myeloma; ORR, overall response rate; RRMM, relapsed/refractory MM.

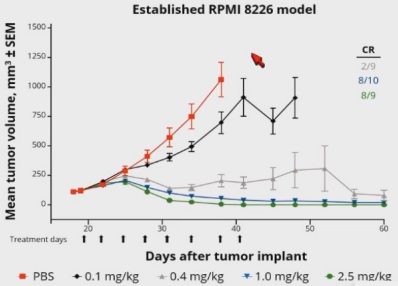
Presented by K Pillarisetti at the 65th American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023; San Diego, CA, USA

JNJ-5322 Induces Tumor Regression in Established Dual Target Mouse Model

- Efficacy at 0.4, 1.0, and 2.5 mg/kg with each group all $P<0.05$ vs PBS control



	Antigen	RPMI 8226 cells
Receptor density per cell	BCMA	2317
	GPRC5D	486



BCMA, B-cell maturation antigen; CR, complete response; GPRC5D, G protein–coupled receptor family C group 5 member D; IP, intraperitoneal; PBS, phosphate-buffered saline; SC, subcutaneous; SEM, standard error of the mean.

Presented by K Pillarisetti at the 65th American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023; San Diego, CA, USA

A phase 1 dose-escalating study of JNJ-5322 in patients with RRMM is ongoing (NCT05652335)

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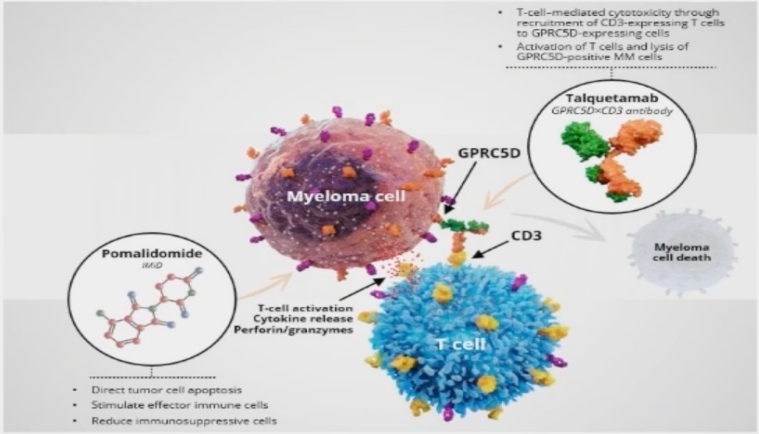
Talquetamab and Pomalidomide: First Combination of GPRC5D-Targeted Therapy and IMiDs

Talquetamab is the first GPRC5D×CD3 bispecific antibody approved for treatment of relapsed/refractory multiple myeloma (RRMM)[1-3]

- In the phase 1/2 MonumenTAL-1 study, talquetamab showed overall response rates of >71% with a clinically manageable safety profile in patients with heavily pretreated RRMM[4]

Pomalidomide, an established immunomodulatory drug, has direct on-tumor apoptotic activity and enhances immune activity[5,6]

- Combining pomalidomide with T-cell redirection therapy may lead to synergistic antimyeloma effects



We present initial efficacy and safety results of talquetamab + pomalidomide from the MonumenTAL-2 study

MonumenTAL-1 ClinicalTrials.gov identifier: NCT03399799/NCT04634552. MonumenTAL-2 ClinicalTrials.gov identifier: NCT05050097. GPRC5D, G protein–coupled receptor family C group 5 member D; IMiD, immunomodulatory drug; MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma. 1. Verkleij CPM, et al. *Blood Adv* 2021;5:2196-215. 2. TALVEY (talquetamab-tgvs). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2023. 3. European Medicines Agency. TALVEY (talquetamab). Accessed October 3, 2023. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/talvey. 4. Schinke C, et al. Presented at ASCO; June 2–6, 2023; Chicago, IL, USA & Virtual. Poster #8036. 5. Bazarbachi AH, et al. *Leukemia* 2019;33:2243-357. 6. Pomalyst. Prescribing information. Summit, NJ: Celgene Corporation; 2020.

J. Matous et al ASH 2023 abs 1014

MonumenTAL-2: Phase 1b Study Design

Active cohorts in MonumenTAL-2:

Key eligibility criteria[a]
- Measurable MM
- ≥2 prior lines of therapy including a PI and an IMiD
- ECOG PS 0–1
- Prior pomalidomide and prior T-cell redirection therapy (CAR-T and BsAb) permitted
- No prior GPRC5D therapy

→ **Talquetamab + lenalidomide**
in relapsed/refractory multiple myeloma

→ **Talquetamab + daratumumab + lenalidomide**
in newly diagnosed multiple myeloma

→ **Talquetamab + pomalidomide**
in relapsed/refractory multiple myeloma

Primary endpoint
- Safety[b]

Key secondary endpoints
- ORR[c]
- Time to response
- DOR
- PFS

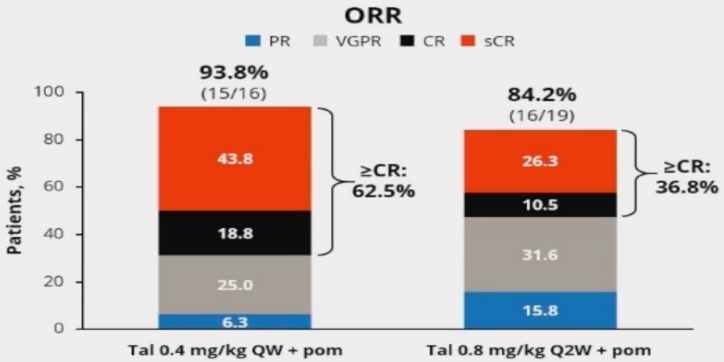
Talquetamab + pomalidomide dosing schedule:

Talquetamab	Pomalidomide
Following step-up dosing 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W	Starting at cycle 2 2 mg PO daily, with dose escalation to 4 mg PO daily permitted

[a]For talquetamab + pomalidomide cohort. [b]AEs assessed per CTCAE v5.0, except for CRS and ICANS, which were graded per ASTCT guidelines. [c]Assessed per IMWG 2016 criteria.
AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BsAb, bispecific antibody; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GPRC5D, G protein–coupled receptor family C group 5 member D; ICANS, immune effector cell–associated neurotoxicity syndrome; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; PO, by mouth; Q2W, every other week; QW, weekly, SC, subcutaneous.

J. Matous et al ASH 2023 abs 1014

MonumenTAL-2 (Tal+Pom): High ORR With Rapid and Deep Responses



	Tal 0.4 mg/kg QW + pom (n=16)	Tal 0.8 mg/kg Q2W + pom (n=19)
Median follow-up, months (range)	15.0 (1.2–19.0)	11.1 (1.2–14.8)
Median time to first response, months (range)	1.7 (0.9–3.3)	1.2 (0–4.8)

- ORRs were consistent across patient subgroups
  - 100% (3/3) in CAR-T–exposed patients in the QW cohort (no patients had CAR-T exposure in Q2W)
  - 100% (5/5 in QW, 3/3 in Q2W) in pomalidomide-exposed patients in both cohorts
  - 50% (1/2 in QW) and 67% (2/3 in Q2W) in patients with EMD
  - 80% (4/5 in QW) and 75% (3/4 in Q2W) in patients with high-risk cytogenetics

Data cut-off date: October 11, 2023.
CAR, chimeric antigen receptor; CR, complete response; EMD, extramedullary disease; ORR, overall response rate; pom, pomalidomide; PR, partial response; Q2W, every other week; QW, weekly; sCR, stringent complete response; tal, talquetamab; VGPR, very good partial response.

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MonumenTAL-2 (Tal+Pom): Most Infections Low Grade

TEAE (≥5%), n (%)	All patients (N=35)	
	Any Grade	Grade 3/4
Infections	**28 (80.0)**	**8 (22.9)**
Pneumonia	8 (22.9)	5 (14.3)
Upper respiratory tract infection	8 (22.9)	1 (2.9)
COVID-19	6 (17.1)	1 (2.9)
Oral candidiasis	3 (8.6)	0
Urinary tract infection	3 (8.6)	1 (2.9)
Influenza	2 (5.7)	0
Respiratory syncytial virus infection	2 (5.7)	1 (2.9)
Rhinovirus infection	2 (5.7)	0
Sinusitis	2 (5.7)	0

- First-onset infections generally occurred in the first few cycles of treatment
- 1 opportunistic infection of esophageal candidiasis occurred
- 77.1% of patients had ≥1 postbaseline IgG value <400 mg/dL or hypogammaglobulinemia TEAE
  - 34.3% of patients received IVIG

This first combination of talquetamab + pomalidomide showed promising efficacy and a manageable safety profile that further supports talquetamab as a versatile combination partner in RRMM

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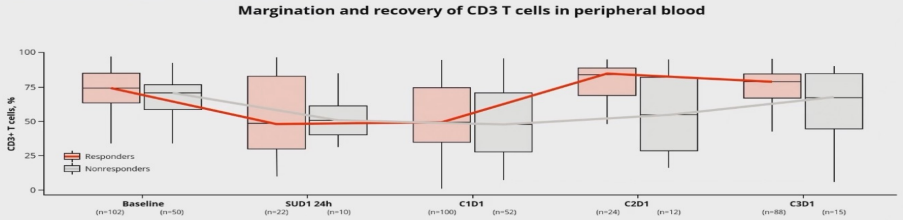
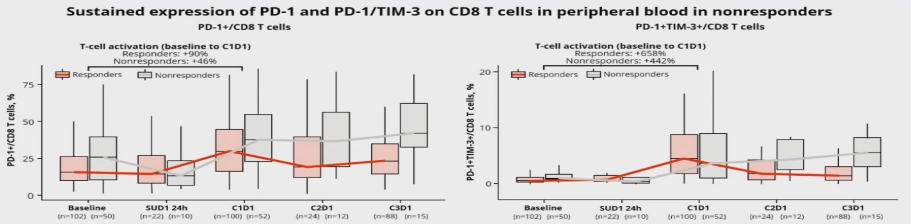
Clinical Response Was Associated With Greater T-Cell Recovery in Peripheral Blood



- In peripheral blood, patients who responded to teclistamab (compared with nonresponders) exhibited:

C, cycle; D, day; SUD1 24h, 24 hours after first step-up dose.

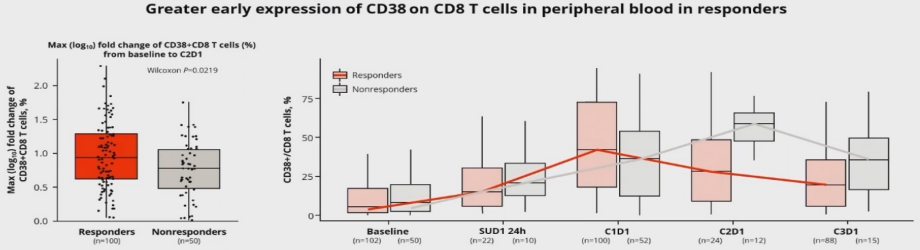
Lack of Response Was Associated With Sustained Expression of Checkpoints on CD8 T Cells Longitudinally in Early Cycles



- Increased expression of checkpoints, including PD-1 and TIM-3, on CD8 T cells was observed in the first treatment cycle in responders in peripheral blood, which was **transient**

C, cycle; D, day; SUD1 24h, 24 hours after first step-up dose.

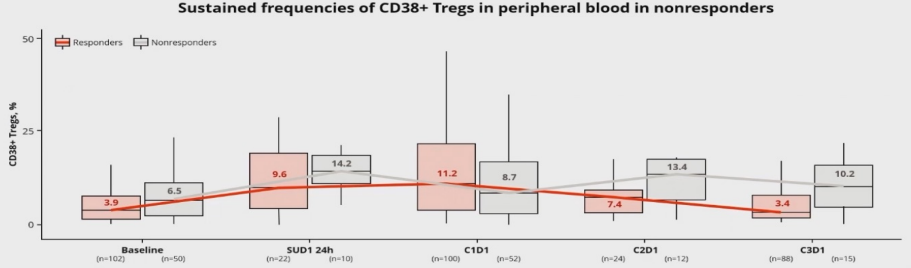
Response Was Associated With Greater T-Cell Activation in the First Treatment Cycle Compared With Nonresponders



- Patients responding to teclistamab exhibited greater T-cell activation early in the first treatment cycle, indicated by a greater maximum fold change in induction of CD38 on CD8 T cells in peripheral blood

C, cycle; D, day; SUD1 24h, 24 hours after first step-up dose.

Lack of Response Was Associated With Sustained Frequencies of CD38+ Tregs in the Periphery

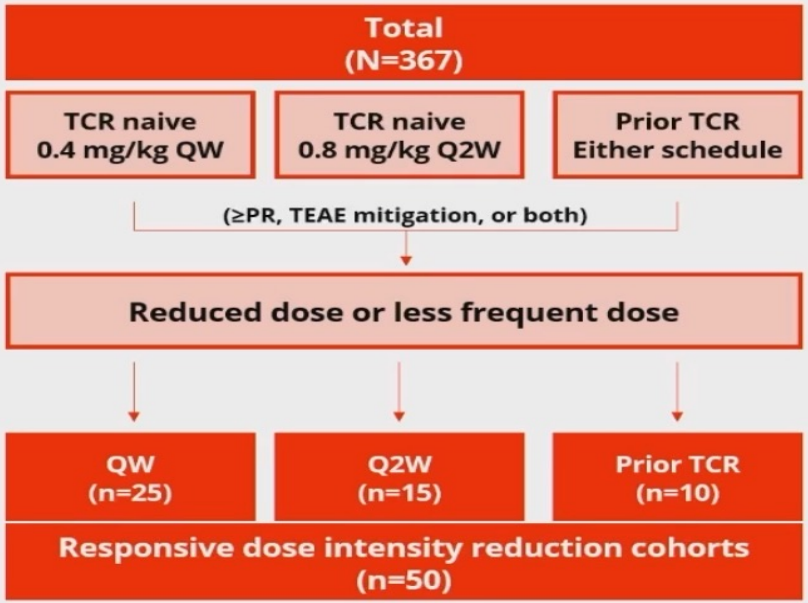


- Nonresponders also exhibited elevated and sustained levels of CD38+ Tregs, which are key suppressors of

cycle; D, day; SUD1 24h, 24 hours after first step-up dose; Treg, regulatory T cell.

Vishwamitra D. et al ASH 2023 abs 455

MonumenTAL-1: Responsive and Prospective Dose Intensity Reduction Cohorts



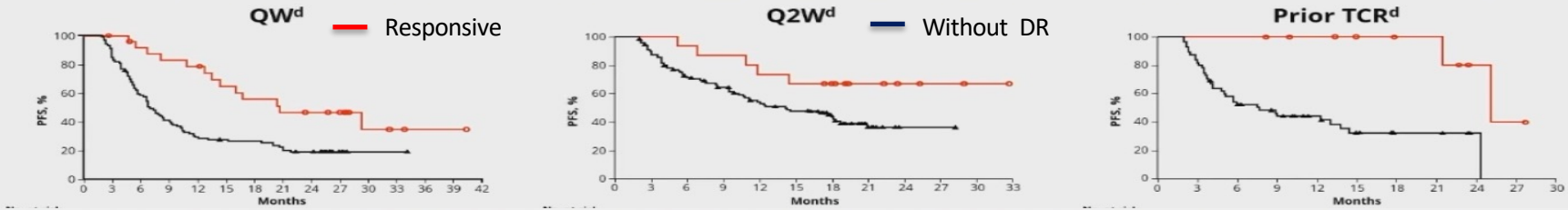
PR, partial response; Q2W, every other wee

A. Chari et al ASH 2023 abs 1010

MonumenTAL-1: Responsive Dose Intensity Reduction Cohorts – Disease Response Maintained Even With Dose Reduction

- Most patients with dose reductions were in response; dose reduction occurred at a median of 3.2 mo (QW; range, 1.8–27.0), 4.5 mo (Q2W; range, 1.2–28.9), and 4.7 mo (prior TCR; range, 2.3–9.7) relative to treatment start

	Responders with dose reductions		
	QW[a] (n=24)	Q2W[b] (n=13)	Prior TCR[c] (n=10)
Median follow-up, mo (range)	27.6 (2.7–41.2)	20.8 (12.3+–33.6)	21.3 (9.2–29.4)
Median DOR, mo (95% CI)	19.8 (12.7–NE)	NE (12.5–NE)	24.2 (20.4–NE)
12-mo DOR rate, % (95% CI)	78.3 (55.4–90.3)	84.6 (51.2–95.9)	100 (100–100)

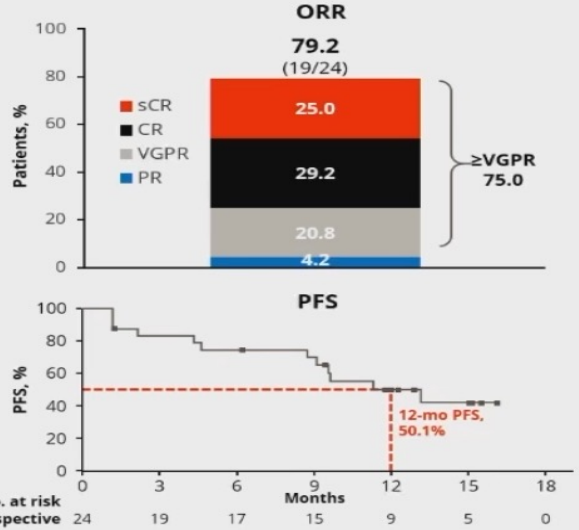


Here, we report safety and efficacy in patients with talquetamab dose reductions; these patients were treated at the RP2Ds and reduced dose once they achieved a response, to determine impact on GPRC5D-related AEs and maintenance of response

Chari et al ASH 2023 abs 1010

MonumenTAL-1: Prospective Dose Intensity Reduction Cohorts – Response Maintained After Switch

- Patients with dose reductions had to be in response (n=19); dose reduction occurred at a median of 3.1 mo (range, 2.3–4.2) relative to treatment start



	Prospective (n=19)
Median follow-up, mo (range)[a]	13.2 (4.0+–16.1)
Median PFS, mo (95% CI)[a]	13.2 (8.8–NE)
12-mo PFS rate, % (95% CI)[a]	50.1 (27.9–68.7)
Median DOR, mo (95% CI)	NE (8.3–NE)

- In the 0.8 mg/kg Q2W registrational cohort (n=145)[1,b]
  - ORR: 71.7%
  - Median PFS: 14.2 mo (95% CI, 9.6–NE)
    - 12-mo PFS rate: 54.4%
  - Median DOR: NE (95% CI, 13.0–NE)

Data cut-off date: October 2, 2023. [a]Based on all patients included in the cohorts (N=24). [b]Data cut-off date: January 17, 2023. CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every other week; sCR, stringent complete response; VGPR, very good partial response.

1. Touzeau C, et al. Presented at EHA; June

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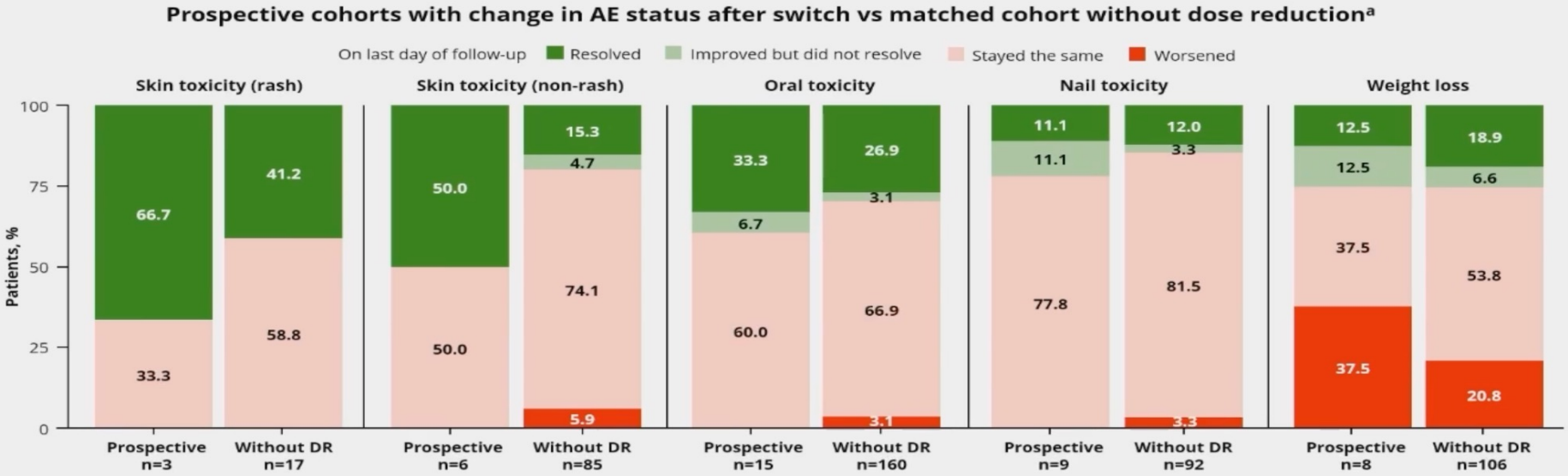
MonumenTAL-1: Prospective Dose Intensity Reduction Cohorts – Resolution of GPRC5D-Related AEs vs Matched Cohort



- Trend toward improved resolution of GPRC5D-related AEs, except weight loss

Data cut-off date: October 2, 2023. [a]Patients included had ≥PR before day 200 from the prospective dose intensity reduction cohorts (n=18) and from the MonumenTAL-1 cohort who did not dose reduce (n=206). Each category shows only patients who had a respective AE on day 100. Color signifies how that respective AE grade changed from day 100 to last day of follow-up (within 30 days of last treatment; capped at 500 days).
AE, adverse event; DR, dose reduction; GPRC5D, G protein–coupled receptor family C group 5 member D; PR, partial response.

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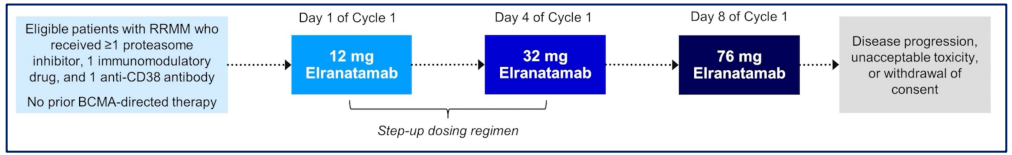
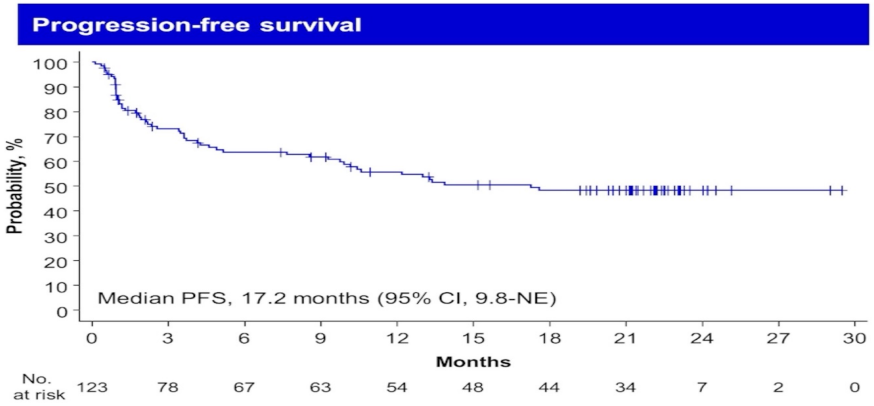
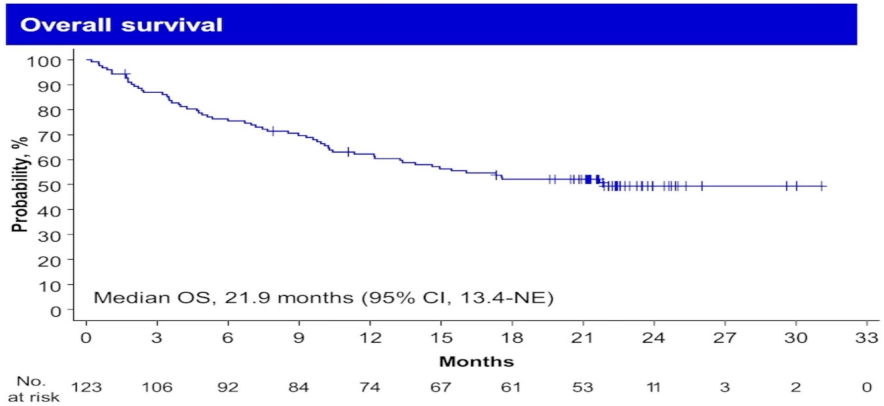
Long term efficacy and safety of Elranatamab in the Phase 2 MagnetisMM-3 trial in relapsed or refractory multiple myeloma

Efficacy: PFS and OS

- Median PFS was 17.2 months (95% CI, 9.8-NE)
- Median OS was 21.9 months (95% CI, 13.4-NE)
  - Data for OS was not yet mature as >50% of patients are still censored





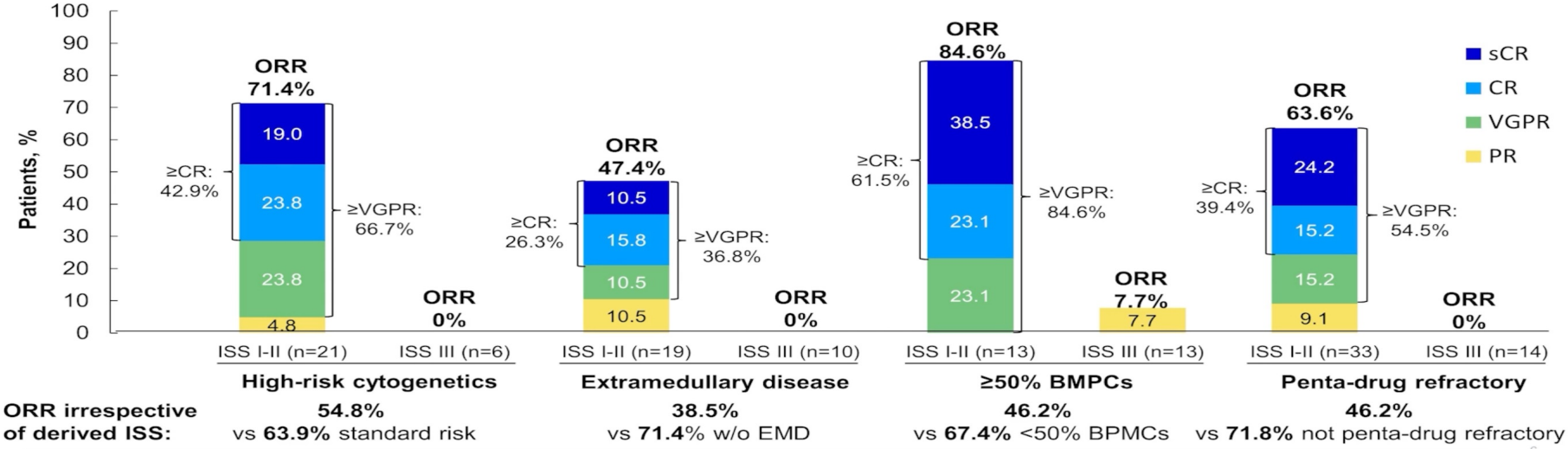


The median duration of follow-up was 17.6 months (range, 0.2-31.1)

Tomasson MH et al ASH 2023 abs 3385

Efficacy: Overall response rate

- ORR per BICR for the overall cohort was 61.0% (95% CI, 51.8-69.6); ≥CR was 37.4%
  - MRD negativity rate was 90.0% in sCR/CR patients who were MRD evaluable (n=30)
- ORRs were lower in patients with poor prognostic factors
  - A more advanced disease (ISS III vs ISS I-II) was a driver of poor response within the poor prognosis subgroups



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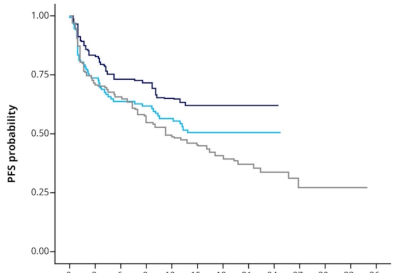
MAIC of efficacy of Teclistamab and Elranatamab in triple class exposed/ refractory MM

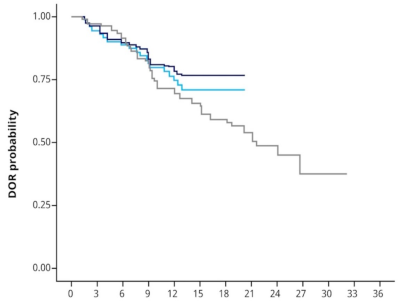
MAIC (base-case): PFS



	Elranatamab	Teclistamab
Median PFS	NE at 15 months	11.3 months
Unweighted HR (95% CI)		0.86 (0.61-1.21); *P*=0.37
Weighted HR, base-case (95% CI)		0.59 (0.39-0.89); *P*=0.01

Unweighted elranatamab
Weighted elranatamab
Teclistamab

MAIC (base-case): DOR[a]



	Elranatamab	Teclistamab
Median DOR	NE at 15 months	21.6 months
Unweighted HR (95% CI)		0.78 (0.45-1.36); *P*=0.38
Weighted HR, base-case (95% CI)		0.64 (0.33-1.23); *P*=0.18

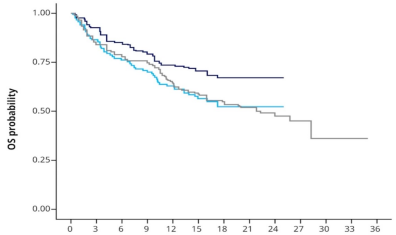
Unweighted elranatamab
Weighted elranatamab
Teclistamab

No. patients at risk

Unweighted elranatamab	72	67	62	54	41	14	3	0	0	0	0	0	0
Weighted elranatamab	67	64	59	53	40	13	1	0	0	0	0	0	0
Teclistamab	104	101	92	82	71	61	53	32	13	4	1	0	0

[a] While DOR is only captured among patients with a response, the MAIC weighs all patients (regardless of response)
DOR=duration of response; HR=hazard ratio; NE=not estimable

MAIC (base-case): OS



	Elranatamab	Teclistamab
Median OS	NE at 15 months	21.9 months
Unweighted HR (95% CI)		1.05 (0.74-1.50); *P*=0.78
Weighted HR, base-case (95% CI)		0.66 (0.42-1.03); *P*=0.07

Unweighted elranatamab
Weighted elranatamab
Teclistamab

No. patients at risk

Unweighted elranatamab	116	100	88	80	71	55	12	3	2	0	0	0	0
Weighted elranatamab	88	81	74	69	63	52	11	0	0	0	0	0	0
Teclistamab	165	136	124	119	102	93	81	76	29	11	4	1	0

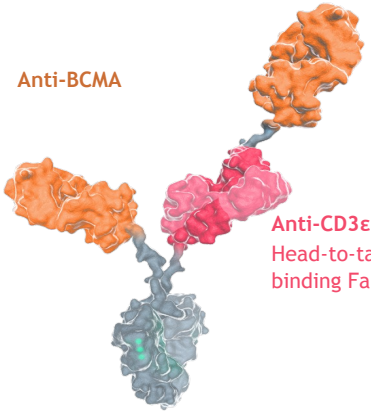
HR=hazard ratio; NE=not estimable; OS=overall survival

In the present MAIC, Elranatamab exhibited statistical significant improvement of ORR and PFS compared with Teclistamab

Mol I et al ASH 2023 abs 2015

IV and sc Alnuctamab: Phase 1 study

Alnuctamab: 2+1 BCMA x CD3 TCE[1-4]



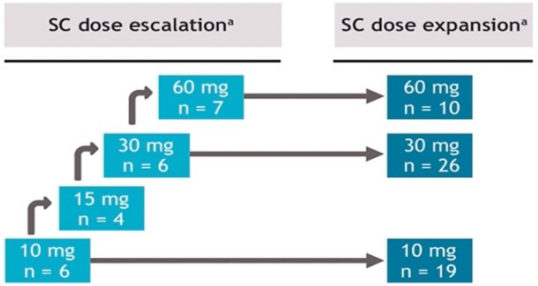
Anti-BCMA
Bivalent binding to BCMA in a 2+1 format for superior potency and tumor targeting

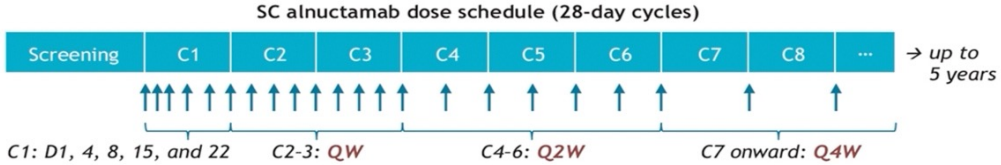
Anti-CD3ε
Head-to-tail geometry of BCMA- and CD3ε-binding Fab domains using a flexible linker

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

Key eligibility criteria

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

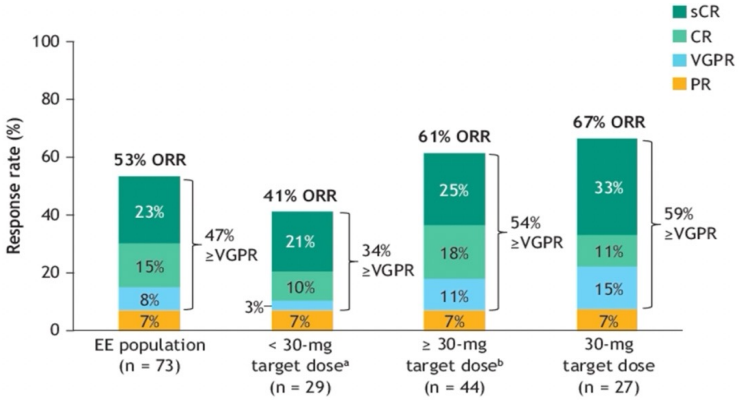




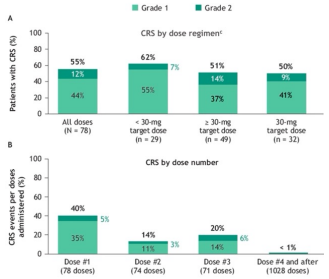
BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; Fab, antigen-binding fragment; FcγR, Fc gamma receptor, Ig, immunoglobulin; RRMM, relapsed/refractory multiple myeloma; TCE, T-cell engager.

1. Seckinger A, et al. *Cancer Cell* 2017;31:396-410; 2. van der Vuurst de Vries A-R, et al. *HemaSphere* 2020;4(S1). Abstract S198; 3. Costa LJ, et al. *Blood* 2019;134(suppl 1):143;
4. Klein C, et al. *Cancer Res* 2017;77(13_Supplement):3629.

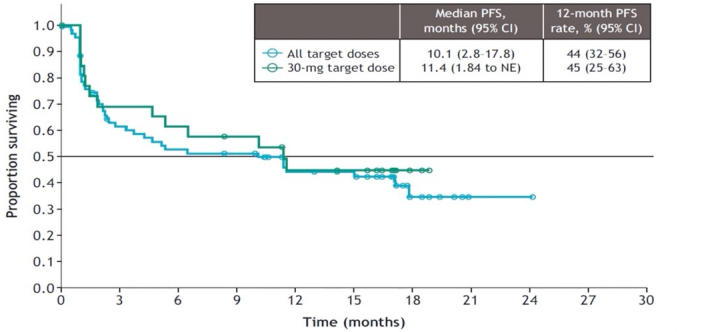
Efficacy and toxicity in patients treated with sc Alnuctamab

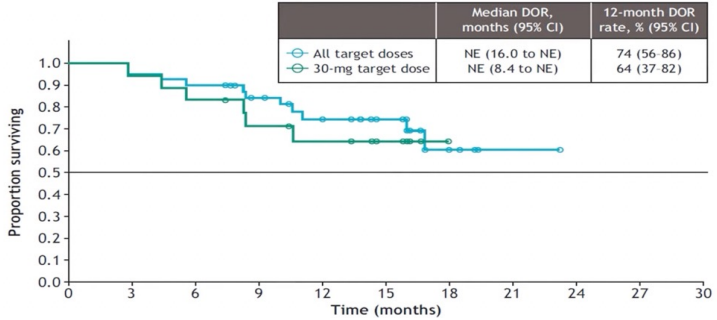


- Stable disease was reported as best response in 15 (21%) patients, and progressive disease was reported as best response in 15 (21%) patients



- Any-grade and grade 3/4 infections were reported in 59% and 17% of patients, respectively
- Prophylactic medications for select infections were required during the alnuctamab treatment period





Bar N et al ASH 2023 abs 2011

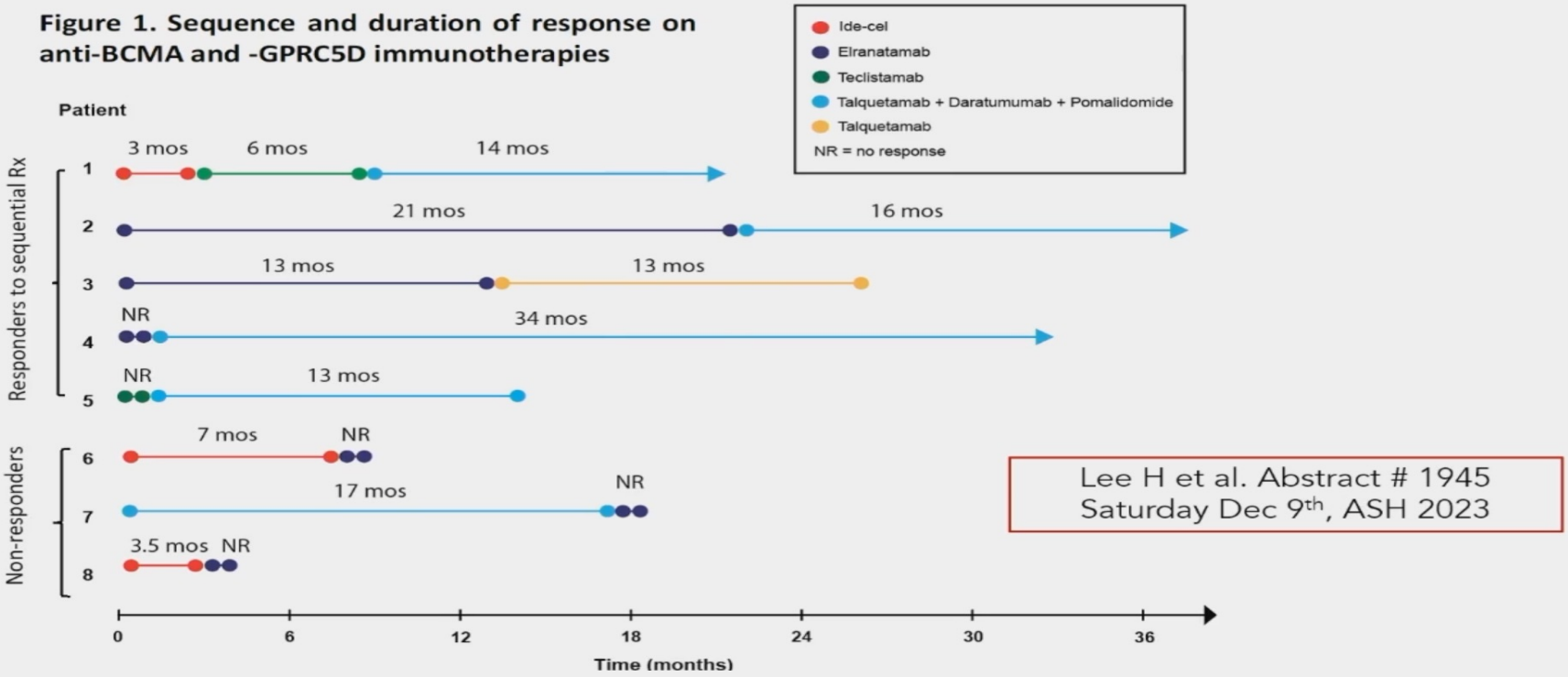
Sequencing and duration of therapy

- Can we treat sequentially with BsAb?
- How do we sequence CAR Ts and BsAbs?
- How long to treat? Continuous vs treatment free intervals?

NJ Balhis Educational Section ASH 2023

Can we treat sequentially with BsAb → BsAb?

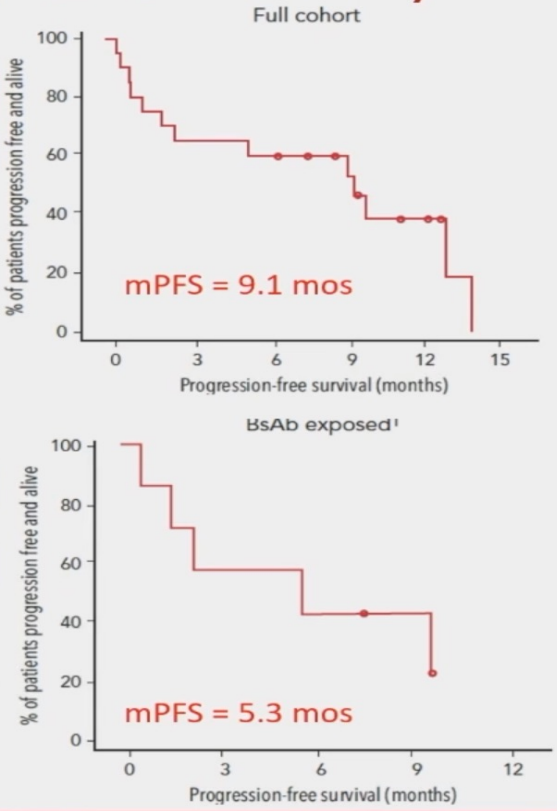
Figure 1. Sequence and duration of response on anti-BCMA and -GPRC5D immunotherapies



Lee H et al. Abstract # 1945
Saturday Dec 9th, ASH 2023

Sequencing CAR T post BCMA BsAb (BsAb→CART)

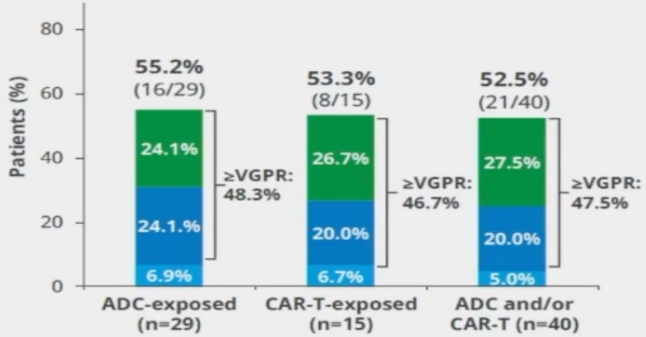
	Full cohort N = 20	ADC exposed* N = 13	Bispecific exposed* N = 7
Overall response rate,† % (95% CI)	60.0 (36.1-80.9)	61.5 (31.6-86.1)	57.1 (18.4-90.1)
Best response, rate, n (%)			
Stringent complete response	1 (5.0)	1 (7.7)	0
Complete response	5 (25.0)	4 (30.8)	1 (14.3)
Very good partial response	5 (25.0)	3 (23.1)	2 (28.6)
Partial response	1 (5.0)	0	1 (14.3)
Minimal response‡	1 (5.0)	0	1 (14.3)
Stable disease	3 (15.0)	2 (15.4)	1 (14.3)
Progressive disease	3 (15.0)	3 (23.1)	0
Not evaluable‡,§	1 (5.0)	0	1 (14.3)
≥VGPR	11 (55.0)	8 (61.5)	3 (42.9)
Median duration of response (95% CI), mo	11.5 (7.9-NE)	11.5 (7.9-NE)	8.2 (4.4-NE)
Median time to first response (range), mo	0.95 (0.9-6.0)	0.97 (0.9-5.1)	0.92 (0.9-6.0)
Median time to best response (range), mo	2.22 (0.9-9.9)	2.58 (0.9-9.9)	1.41 (0.9-7.0)
MRD negativity, n (%)			
No. of patients evaluable at 10^{-5}	10	7	3
Rate, n (%)	7 (70.0)	5 (71.4)	2 (66.7)

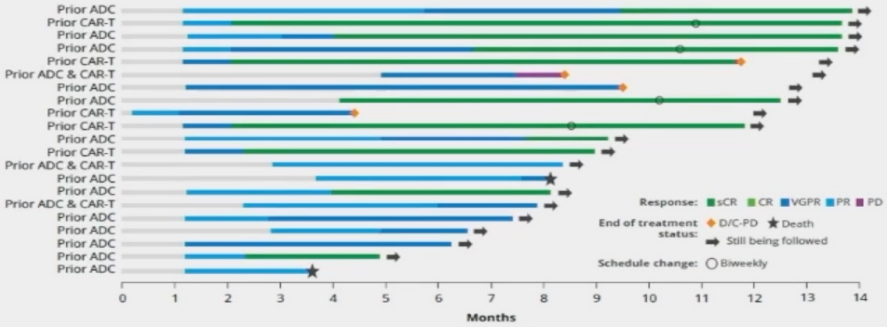


Cohen A et al Blood 2023;141:219-230

Sequencing BsAb post CAR T (CAR → BsAb)

- Teclistamab (MajesTEC-1, cohort C, previously exposed to BCMA-targeted agents): ORR 52.5% and mDOR not reached at median f/up 12 months



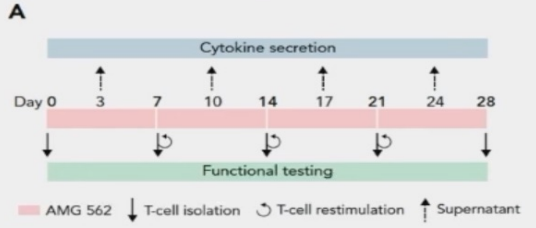


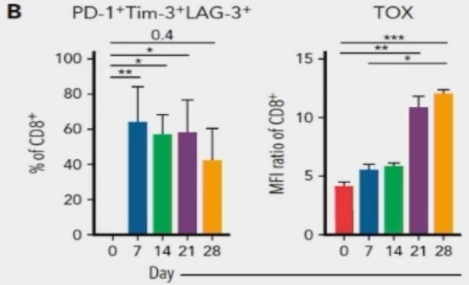
- Elranatamab (Magnestis-MM1 trial) : ORR 7/10 (70%) patients previously exposed to anti-BCMA ADC or CART treatments

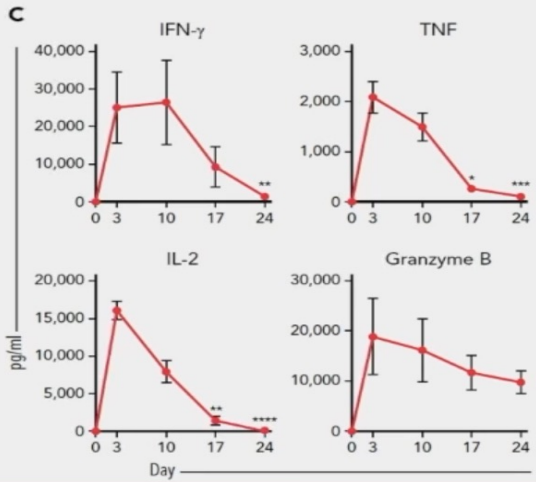
- Talquetamab with daratumumab (TRIMM-2 trial): ORR 18/25 (72%) response in patients with prior BCMA-targeted treatment (includes prior BCMA BsAb, CART and ADC)

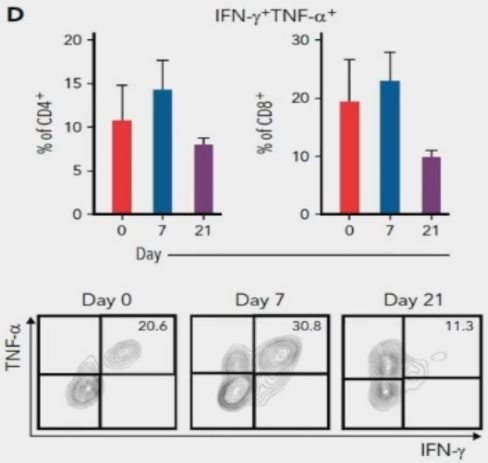
- Cevostamab : ORRs 33.3-50% (based on dose level) post anti-BCMA treatment.

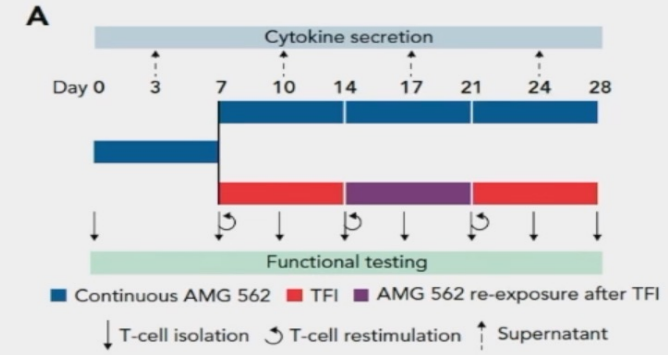
T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals

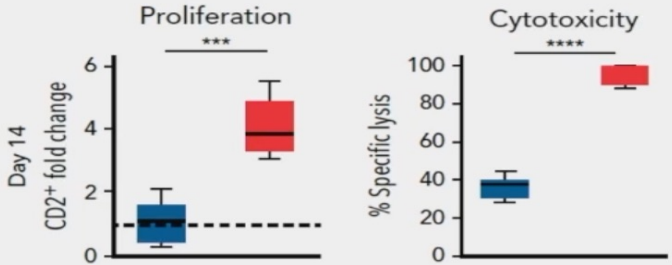






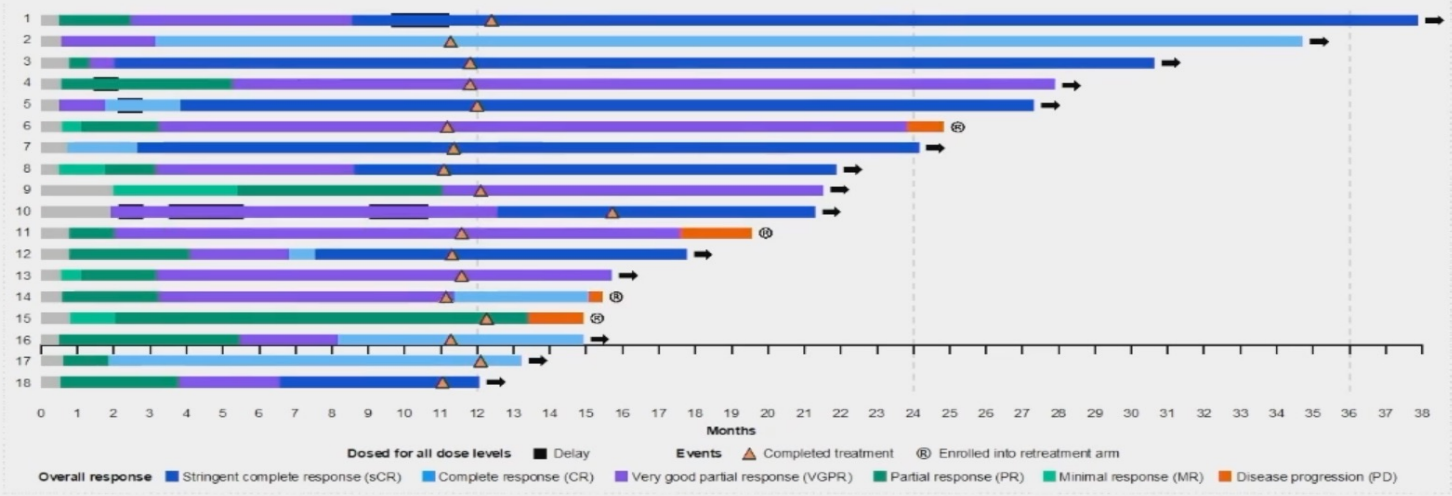






Philipp N et al Blood 2022;140:1104-1118

Fixed duration of therapy with Cevostamab

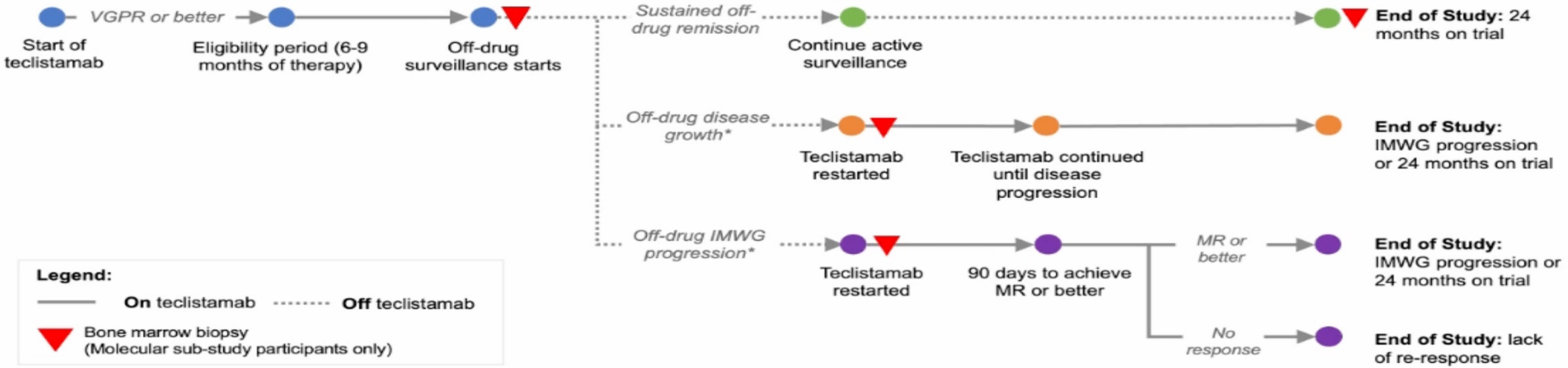


- 7 patients remained in response ≥12 months after completion
- No patients who achieved an sCR have relapsed
- 4/18 patients experienced PD with best response and time to progression as follows:
  VGPR 12.9, VGPR 6.3, CR 4.2, and PR 1.4 months

Lesokhin A et al Blood 2022 140 : 4415–4417

Penn Medicine

LimiTec: Phase 2 Study Design



Presented at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA.

Razzo B et al abs 3394

Pause

CONCLUSION

- Bispecific (BS) antibodies **targeting BCMA, GPRC5D, FcRH5** have demonstrated remarkable efficacy in relapsed Multiple Myeloma
- **New BS and combinations** therapy (BS with IMIDS or anti-CD38) represent a further step in Myeloma thetapy
- Strategies to **overcame toxicity and resistance** are under evaluation (continous vs fixed vs intermittent therapy)
- The **«sequencing issue»** of these newer treatment modalities is currently under investigation

Grazie per l'attenzione