Highlights from
IMS 20th meeting 2023

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Terapie di reindirizzamento delle cellule immuni effettrici:
Anticorpi bispecifici anti-GPRC5D e FcRH5 con approvazione FDA/EMA ed in fase di sviluppo (e combinazione con altri agenti)

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

Disclosures of Paola Tacchetti

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

Non-BCMA Targets BsAbs

GPRC5D

- GPRC5D is a member of the G protein-coupled receptor family with an unknown function
- **It is highly expressed on malignant PCs, as well as hard keratinized structures** (hair shaft, nail, and central region of the tongue)

GPRC5D

Talquetamab
Forimtamig

TALQUETAMAB
FDA: RRMM ≥4 prior tp, TCE
EMA: RRMM ≥3 prior tp, TCE

FcRH5

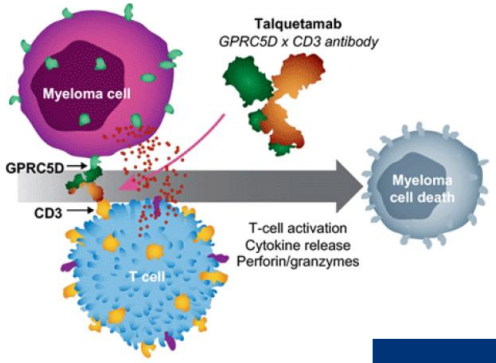
- FcRH5 is a surface protein in the Ig superfamily
- **It is expressed only in B cells, with increasing expression in mature B cells and plasma cells**
- FcRH5 is involved in proliferation and isotype expression

FcRH5

Cevostamab

Atamaniuk J, et al. Eur J Clin Invest 2012; Smith EL, et al. Sci Transl Med 2019; Li J et al. Cancer Cell 2017; Chari A, et al. N Engl J Med 2022; Carlo-Stella C et al. ASH 2022; Trudel S, et al. Blood 2021

Talquetamab, GPRC5D × CD3 T-Cell Redirecting BsAb: MonumenTAL-1



MonumenTAL-1 ph 1/2 st

Adults with measurable MM

Phase I: progression on or intolerance to all established therapies; ECOG PS 0–1

Phase II: ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 antibody; ECOG PS 0–2

Talquetamab 0.4 mg/kg SC QW* (n = 143)

Talquetamab 0.8 mg/kg SC Q2W* (n = 145)

Prior T-Cell Redirection Group: Talquetamab Either 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W (n = 51)

*Previous anti-BCMA therapy allowed; T-cell redirection therapy naive.

- Multicenter, open-label phase I/II trial
- **Primary endpoint (phase II):** ORR
- **Secondary endpoints (phase II):** DOR, ≥ VGPR rate, ≥ CR, sCR rate, TTR, PFS, OS, MRD, safety

RRMM patients after a median of 5 PL, 74% (@0.4mg/kg) / 69% (@0.8mg/kg) triple-class refractory

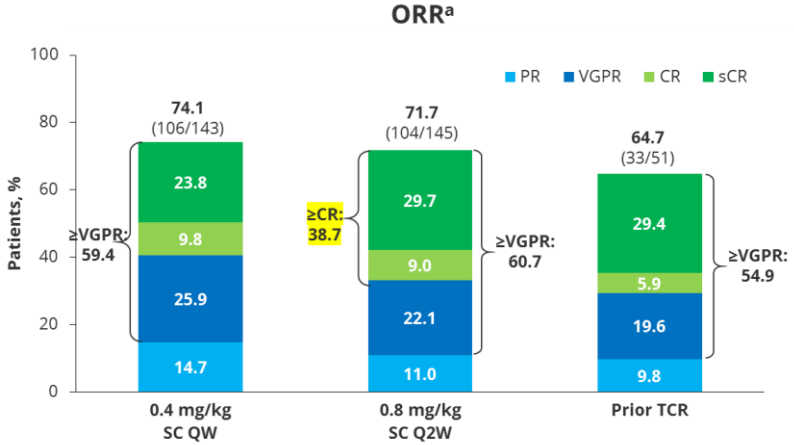
TALQUETAMAB
FDA: RRMM ≥4 prior tp, TCE
EMA: RRMM ≥3 prior tp, TCE

Characteristic	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=145)	Prior TCR (n=51)
Age (years), median (range)	67.0 (46–86)	67.0 (38–84)	61.0 (38–78)
Male, n (%)	78 (54.5)	83 (57.2)	31 (60.8)
Bone marrow plasma cells ≥60%,[a] n (%)	17 (12.3)	32 (22.7)	8 (17.0)
Extramedullary plasmacytomas ≥1,[b] n (%)	33 (23.1)	37 (25.5)	16 (31.4)
High-risk cytogenetics,[c] n (%)	41 (31.1)	37 (28.9)	18 (40.9)
ISS stage,[d] n (%)			
I	62 (43.4)	64 (44.4)	24 (47.1)
II	53 (37.1)	45 (31.3)	18 (35.3)
III	28 (19.6)	35 (24.3)	9 (17.6)
Prior lines of therapy, median (range)	5 (2–13)	5 (2–17)	6 (3–15)

Characteristic	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=145)	Prior TCR (n=51)
Exposure status, n (%)			
Triple-class[e]	143 (100)	145 (100)	51 (100)
Penta-drug[f]	105 (73.4)	101 (69.7)	40 (78.4)
BsAb	NA	NA	18 (35.3)[g]
CAR-T therapy	NA	NA	36 (70.6)[h]
BsAb + CAR-T therapy	NA	NA	3 (6.0)
Refractory status, n (%)			
Triple-class[e]	106 (74.1)	100 (69.0)	43 (84.3)
Penta-drug[f]	42 (29.4)	34 (23.4)	21 (41.2)
To last line of therapy	134 (93.7)	137 (94.5)	31 (60.8)

Chari A, et al. N Engl J Med 2022; Schinke CD et al. EHA 2023

MonumenTAL-1: Efficacy



MonumenTAL-1:[1]

- >71% ORR across QW and Q2W TCR naïve cohorts
- 65% ORR in the prior TCR cohort

ASH23 update:[2]

- **ORR of 73% and mDOR of >1 year in the post–CAR-T setting**
- **52% response in patients exposed to prior bispecific antibodies**

Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=145)	Prior TCR (n=51)
mFU, mo	18.8	12.7	14.8
12-mo DOR rate in patients with ≥CR, %	78.9	90.5	80.5
mPFS, mo (95% CI)	7.5 (5.7–9.4)	14.2 (9.6–NE)[b]	5.1 (3.4–12.3)
12-mo PFS rate, %	34.9	54.4	38.1
12-mo OS rate, %	76.4	77.4	62.9

Chari A, et al. N Engl J Med 2022; Schinke CD et al. EHA 2023; Jakuboviak A et al ASH 2023

MonumenTAL-1: Efficacy and Safety of Patient Subgroups From MonumenTAL-1

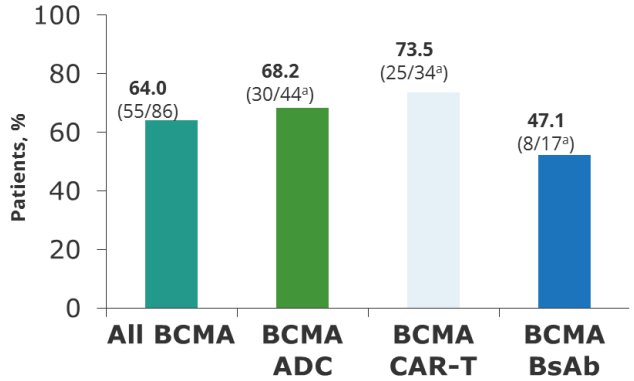
TABLE 2: ORR in high-risk subgroups

Outcome	0.4 mg/kg QW						
	Overall (N=143)	Age ≥75 years (n=21)	Renal impairment (n=40)	High-risk cytogenetics (n=41)	ISS stage III (n=28)	EMD (n=33)	Triple-class refractory (n=106)
mFU, mo	18.8	18.7	19.5	19.2	18.5	18.4	18.7
ORR, n (%)	106 (74.1)	15 (71.4)	26 (65.0)	29 (70.7)	18 (64.3)	16 (48.5)	77 (72.6)

Outcome	0.8 mg/kg Q2W						
	Overall (N=145)	Age ≥75 years (n=32)	Renal impairment (n=45)	High-risk cytogenetics (n=37)	ISS stage III (n=35)	EMD (n=37)	Triple-class refractory (n=100)
mFU, mo	12.7	11.9	13.0	12.5	13.3	12.1	12.8
ORR, n (%)	104 (71.7)	24 (75.0)	30 (66.7)	28 (75.7)	21 (60.0)	16 (43.2)	69 (69.0)

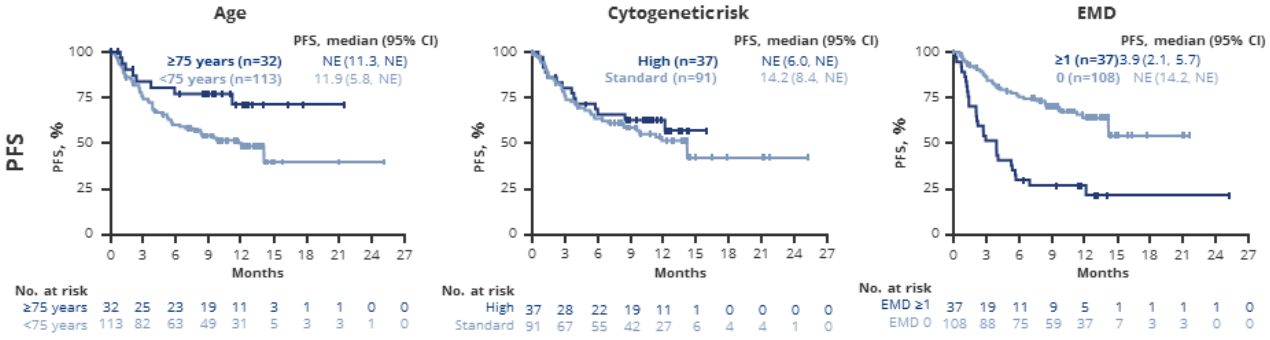
mFU, median follow-up.

FIGURE 3: ORR in prior BCMA subgroups



[a]Some patients received >1 prior BCMA therapy, leading to differences in total patient count.

FIGURE 2: Outcomes among select high-risk subgroups in Q2W cohort



Krishnan A, et al. IMS 2023. Poster P-023

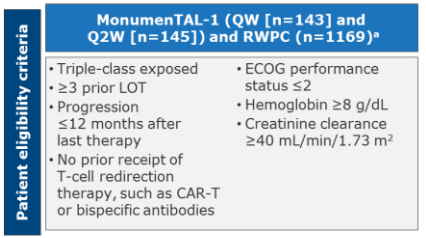
Talquetamab vs Real-World Physician's Choice of Therapy: Comparative Efficacy in Patients With TCE RRMM

Data sources

- Individual patient-level data from MonumenTAL-1 were included for pts who received sc talquetamab 0.4 mg/kg QW or 0.8 mg/kg Q2W by a data cut-off of January 2023
- An external control group was created from eligible pts in the Flatiron database who met MonumenTAL-1 eligibility criteria by a data cut-off of July 2022

Outcome/analysis	Talquetamab QW vs RWPC			Talquetamab Q2W vs RWPC		
	Median, mo	HR (95% CI)	*P* value	Median, mo	HR (95% CI)	*P* value
PFS						
Primary analysis	7.5 vs 4.0	0.55 (0.44–0.69)	<0.0001	14.2 vs 4.0	0.40 (0.31–0.53)	<0.0001
Fully adjusted model	7.5 vs 4.2	0.56 (0.45–0.71)	<0.0001	14.2 vs 4.0	0.41 (0.31–0.54)	<0.0001
TTNT						
Primary analysis	9.1 vs 5.1	0.59 (0.47–0.74)	<0.0001	13.3 vs 5.1	0.45 (0.35–0.59)	<0.0001
Fully adjusted model	9.1 vs 5.1	0.60 (0.48–0.77)	<0.0001	13.3 vs 5.0	0.46 (0.36–0.61)	<0.0001
OS						
Primary analysis	NR vs 16.5	0.56 (0.40–0.78)	0.0007	NR vs 15.9	0.48 (0.33–0.70)	0.0002
Fully adjusted model	NR vs 16.8	0.58 (0.41–0.83)	0.0029	NR vs 17.5	0.50 (0.34–0.75)	0.0008

FIGURE 1: Key patient eligibility criteria



aRWPC cohort included 629 patients who received 1169 treatment regimens across all eligible lines of therapy.
CAR, chimeric antigen receptor.

TABLE 1: Treatment regimens in the RWPC cohort[a]

Treatment regimen	Frequency, n (%)[b] (n=1169)
Pomalidomide, elotuzumab, dexamethasone	56 (4.8)
Pomalidomide, daratumumab, dexamethasone	46 (3.9)
Clinical study drug	43 (3.7)
Carfilzomib, dexamethasone	42 (3.6)
Carfilzomib, cyclophosphamide, dexamethasone	36 (3.1)
Carfilzomib, dexamethasone, pomalidomide	32 (2.7)
Belantamab mafodotin-blmf	23 (2.0)
Bortezomib, selinexor, dexamethasone	23 (2.0)
Elotuzumab, lenalidomide, dexamethasone	22 (1.9)
Daratumumab, dexamethasone	21 (1.8)
Selinexor, dexamethasone	21 (1.8)
Daratumumab, dexamethasone, lenalidomide	19 (1.6)
Pomalidomide, dexamethasone	19 (1.6)
Bortezomib, daratumumab, dexamethasone	18 (1.5)
Clinical study drug, dexamethasone	18 (1.5)
Daratumumab/hyaluronidase-fihj, dexamethasone, pomalidomide	16 (1.4)

[a]Only treatment combinations used in ≥16 patients are presented.
[b]Percentages are calculated with the number of treatment regimens received by the 629 patients in the RWPC cohort set as the denominator (n=1169).

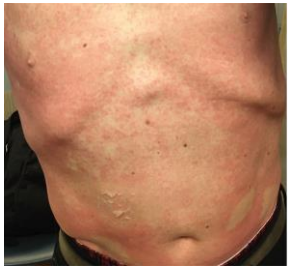
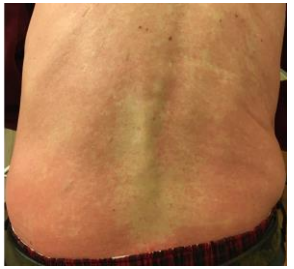
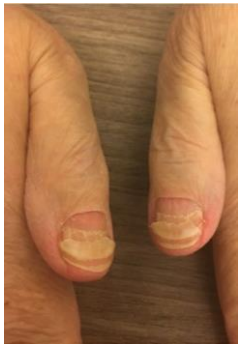
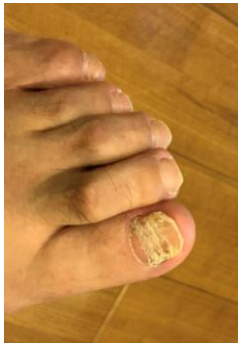
Ye JC, et al. IMS 2023. Poster P-328

MonumenTAL-1: Safety

- Most common AEs included CRS, infection, dysgeusia, and skin/nail toxicity
- 5 patients discontinued due to skin-related AEs and dysgeusia

Most Common AEs, N (%)	TCR-Naive, QW Dose n = 143		TCR-Naive, Q2W Dose n = 145		Prior TCR n = 51	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hematologic						
Anemia	66 (44.8)	45 (31.5)	66 (45.5)	40 (27.6)	25 (49.0)	14 (27.5)
Neutropenia	50 (53.0)	44 (30.8)	41 (28.3)	32 (22.1)	28 (54.9)	27 (52.9)
Thrombocytopenia	39 (27.3)	29 (20.3)	43 (29.7)	27 (18.6)	19 (37.3)	15 (29.4)
Nonhematologic						
CRS	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)	39 (76.5)	1 (2.0)
Infection	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)	37 (72.5)	14 (27.5)
On-target, off-tumor effects: Dysgeusia	103 (72.0)	-	103 (71.0)	-	39 (76.5)	-
On-target, off-tumor effects: Skin related	80 (55.9)	0	106 (73.1)	1 (0.7)	35 (68.6)	0
On-target, off-tumor effects: Nail related	78 (54.5)	0	78 (53.8)	0	32 (62.7)	0
On-target, off-tumor effects: Rash related	57 (39.9)	2 (1.4)	43 (29.7)	8 (5.5)	18 (35.3)	2 (3.9)
Weight decrease	59 (41.3)	3 (2.1)	60 (41.4)	8 (5.5)	15 (29.4)	0



Chari A, et al. N Engl J Med 2022; Schinke CD et al. EHA 2023; Purcell K, et al. IMS 2023. Oral NSO-07

Management Considerations for Dermatologic Toxicities Associated With Talquetamab

A **single-center experience of dermatologic AEs** in patients from MonumenTAL-1

Skin, rash, and nail AEs were generally not painful

Incidence of AEs in Mount Sinai patients, n (%)	Total (N=24)		0.4 mg/kg SC QW (n=8)		0.8 mg/kg SC Q2W (n=16)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin (dry skin and exfoliation)	21 (88)	1 (4)	6 (75)	0	15 (94)	1 (6)
Rash	11 (46)	8 (33)	3 (38)	1 (13)	8 (50)	7 (44)
Nail (thinning and peeling)	14 (58)	0	4 (50)	0	10 (63)	0

Dry skin	Heavy moisturizers	**Pruritus**	Loratadine 10 mg PO daily for 3–5 days post talquetamab dose and triamcinolone 0.1% cream BID
Hand and/or foot peeling	Ammonium lactate 12% lotion to soles and palms BID	**Injection site reaction**	
Nail thinning and peeling	Nail hardeners, topical vitamin E oil, and triamcinolone 0.025% ointment	**Body rash/drug rash**	Above plus consider methylprednisolone taper and betamethasone 0.05% cream BID

Consider dose **HOLD** for other grade 3 dermatologic AEs

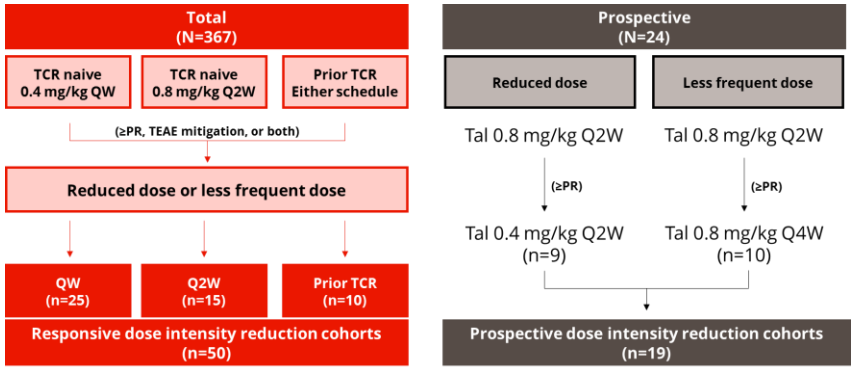
Most dermatologic non-nail Aes
(dry skin/exfoliation and rash AEs) resolved (63–86%)

Timing of AEs	Median time to onset	Median time to resolution
Skin (dry skin and exfoliation)	4.6 weeks	7.1 weeks
Rash	6.6 weeks	3.2 weeks
Nail (thinning and peeling)	15.0 weeks	16.4 weeks

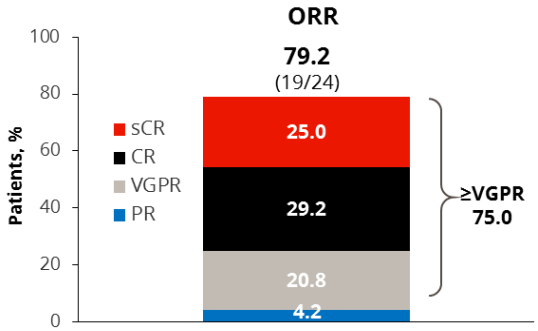
AEs	Patient education
Skin (dry skin and exfoliation) and rash	• Short, lukewarm showers, and moisturize afterward and throughout the day • Alert team of any rashes or redness around injection area immediately • Alert team of any secondary (fungal, bacterial) skin infections immediately
Nail	• Apply heavy moisturizer to cuticles and keep nails/cuticles short and clean • Alert team of any signs of a fungal infection (thickened or discolored nails)

Purcell K, et al. IMS 2023. Oral NSO-07

MonumentTAL-1: Efficacy and Safety of Less Frequent/Lower Intensity Dosing of Talquetamab



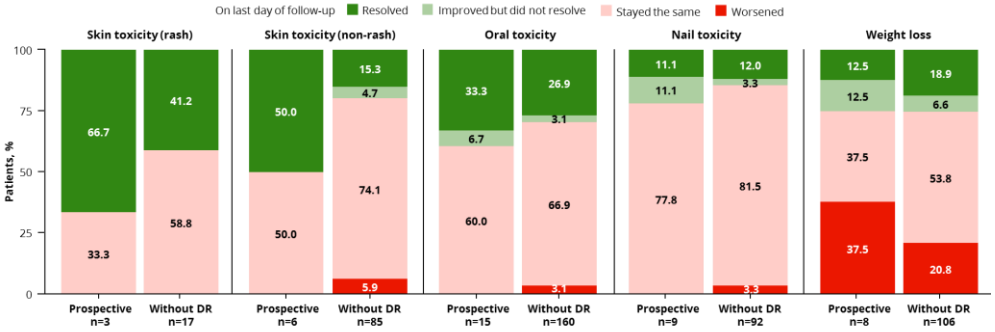
Patients with dose reductions had to be in response (n=19); dose reduction occurred at a median of 3.1 mo (range, 2.3–4.2) relative to treatment start



	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)

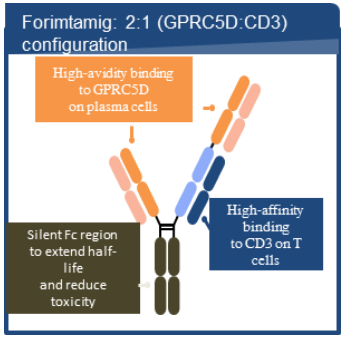
Prospective cohorts with change in AE status after switch vs matched cohort without dose reduction[a]



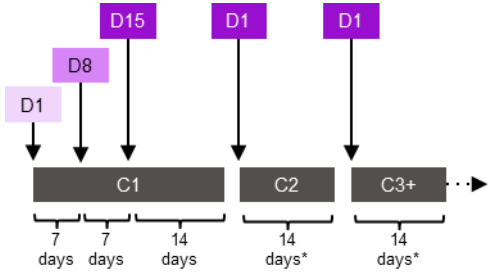
- Trend toward improved resolution of GPRC5D-related AEs, except weight loss

Chari A, et al. ASH 2023

Forimtamig: anti GPRC5DxCD3 Bispecific antibody



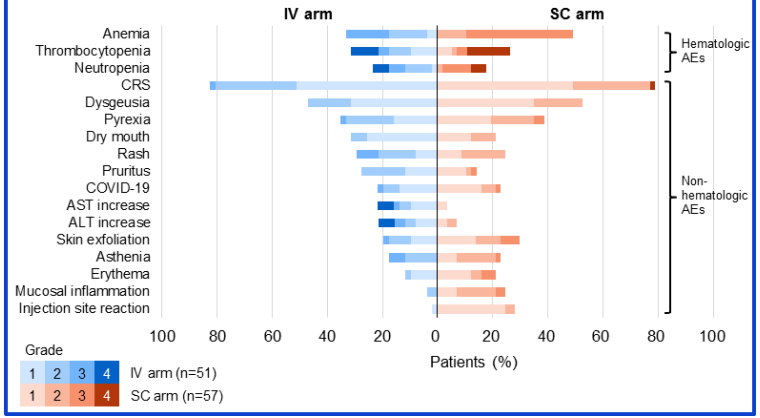
Phase 1/2 study



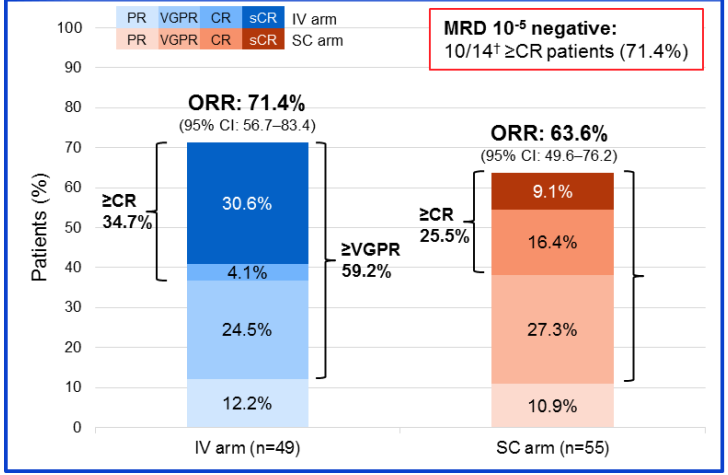
51 (iv) and 57 (sc) pts, 5 median prior LOT

- 70% TCR
- 20% prior anti-BCMA
- 30% EMD

Common (≥20%) hematologic and non-hematologic AEs by Grade



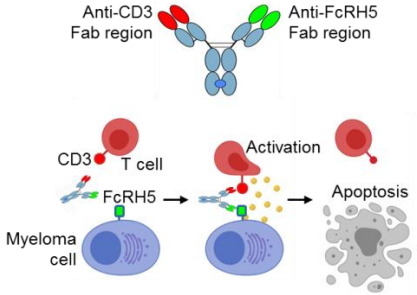
Response rate across all tested target doses (IV: 18–10,000µg; SC 30–7200µg) in efficacy-evaluable patients*



mDOR **10.8 mo (IV)** **12.5 mo (SC)**

Carlo-Stella C et al. ASH 2022

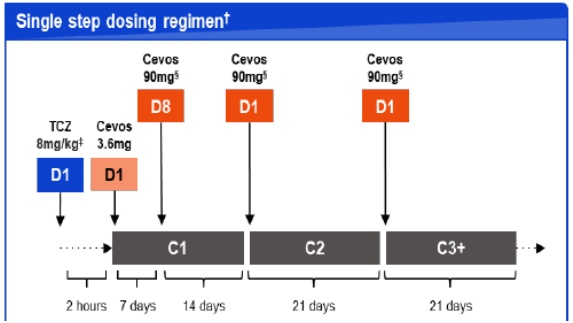
Cevostamab: anti FcRH5xCD3 Bispecific antibody

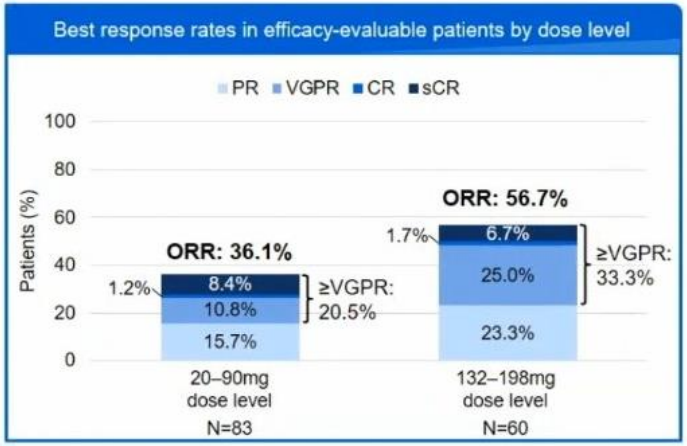


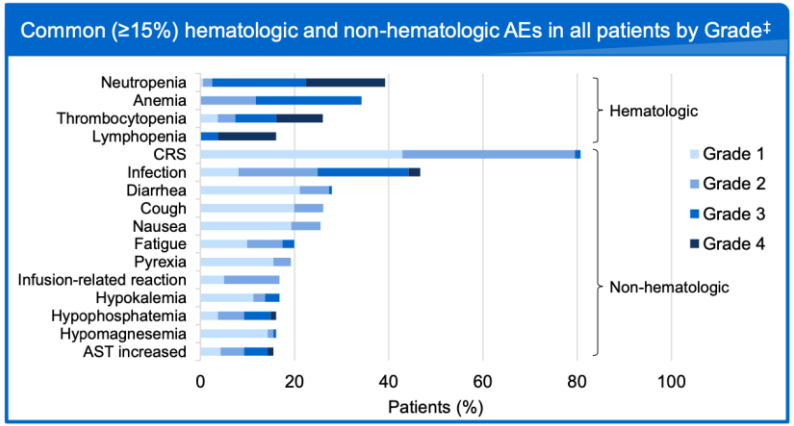
Phase 1 study

161 pts, 6 median prior LOT

- 84.5% TCR
- 33.5% prior anti-BCMA
- 21% EMD



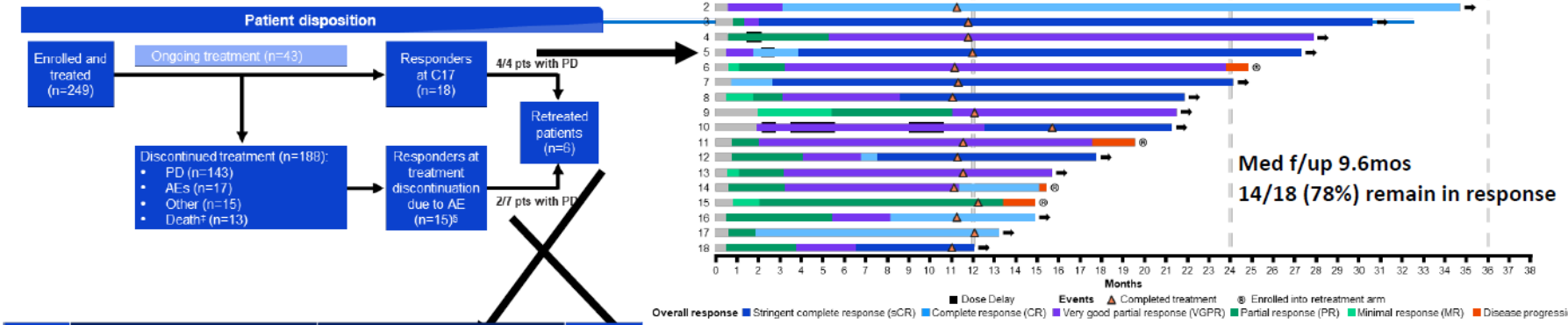




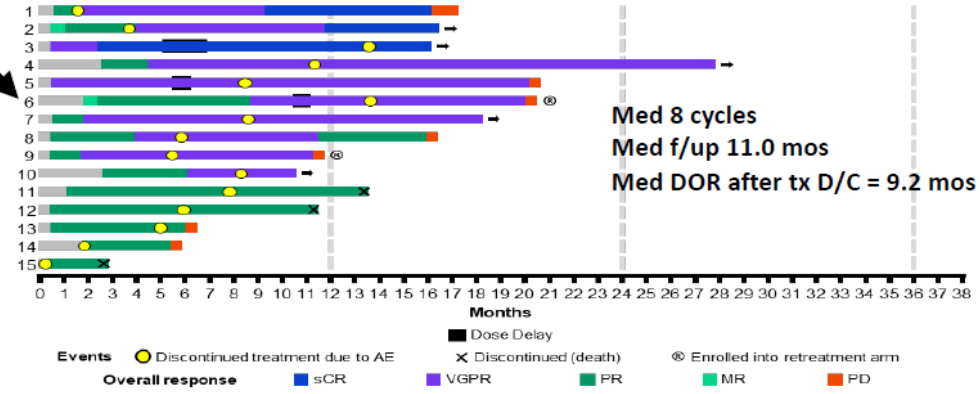
mDOR: 11.5 mo

Trudel S, et al. Blood 2021

Cevostamab: durable responses off therapy



	Initial treatment phase			Retreatment phase			Total time on study (months)
	Time on treatment (months)	Best response	Time from last initial treatment to retreatment (months)	Time on retreatment (months)	Best response	Data cut-off	
Patient 1	12.2	PR	2.5	5.1	MR	Ongoing	19.8
Patient 2	11.1	VGPR	14.0	4.4	SD	Ongoing	29.5
Patient 3	11.1	VGPR	10.1	0.7	SD	Ongoing	21.9
Patient 4	11.5	VGPR	8.5	8.3	PR	PD at 8.3 months	28.3
Patient 5	11.1	CR	4.8	1.0	SD	PD at 1.9 months	16.9
Patient 6	4.8	VGPR	7.1	1.5	PD	PD at 0.7 months	13.4



Leshokin et al, ASH 2022, #1924; Mateos et al, EHA 2023

Non-BCMA Bispecific Antibodies

	Anti-GPRC5d Talquetamab			Anti-GPRC5D Forimtamig		Anti-FCRH5 Cevostamab
Patients (n)	143 T-cell redirecting therapy naïve (ADC allowed)	145 T-cell redirecting therapy naïve (ADC allowed)	51 Prior anti-BCMA TT (CARs/BsAb) allowed	51 Prior anti-BCMA TT (CARs/BsAb) allowed	57 Prior anti-BCMA TT (CARs/BsAb) allowed	161
Dosing schedule	405 µg/Kg SC QW	800 µg/Kg SC Q2W	5-1600 µg/Kg SC	18-10000µg/Kg IV Q2-3W	1200-7200 µg/Kg IV Q2-3W	20-198 mg IV Q3W
Prior LoT	5	5	6	5	4	6
TCR/Penta-ref (%)	74/29	69/23	84/41	62/36	72/42	85/68
ORR/≥CR (%) ORR prior BCMA (%)	74.1/33.6	71.7/38.7	64.7/35.3 75% prior CAR-T 44.4% prior BsAbs	71/35 50	64/25 55	56.7/8.9
PFS DoR OS	7.5 79% at 12m (≥CR) 76% at 12m	14.2 90% at 12m (≥CR) 76% at 12m	5.1 63% at 12m (≥CR) 80% at 12m	NR	NR	NR 11.5 m NR
Toxicity	CRS overall is reported in 74-80% of patients and no more tan 3% G3-4 Infections overall are reported in 46-73% of patients and nearly 20% G3-4 Dysgeusia is reported in 70-75% of patients Skin/Nails toxicity reported in 56-70% of the patients					

Schinke et al- ASCO 2023; Chari et al. NEJM 2023; Carlo-Stella et al. ASH 2022; Trudel et a ASH2021; Harrison et al . IMS 2023

Talquetamab + Daratumumab: TriMM-2 Ph 1b study

Key eligibility criteria

- MM per IMWG
- ≥3 prior LOT[a] or double refractory to PI and IMiD
- Anti-CD38 mAb >90 days prior allowed
- Refractory to anti-CD38 mAb and prior BsAb or CAR-T allowed

Tal[b,c]
0.4 mg/kg SC QW or
0.8 mg/kg SC Q2W
+
Dara[d] 1800 mg SC
QW (cycles 1–2)
Q2W (cycles 3–6)
Q4W (cycles ≥7)[†]

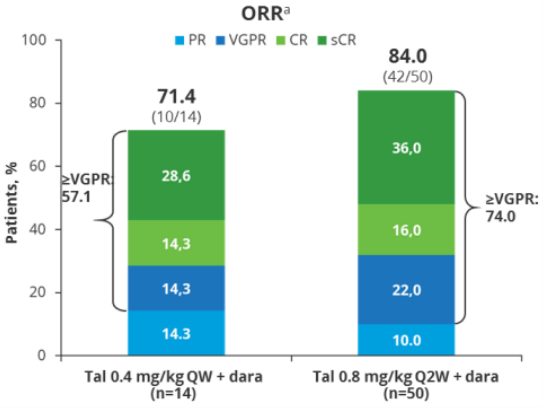
- *Dara given first if both administered on same day*
- *Option to transition to tal Q2W or Q4W*

Key objectives

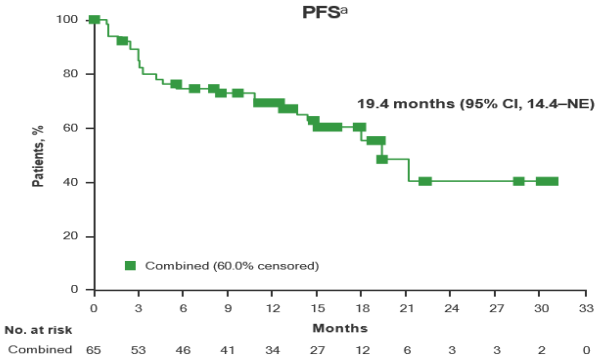
- Part 1: Identify RP2D(s)
- Part 2: Safety at RP2D(s)
- Antitumor activity

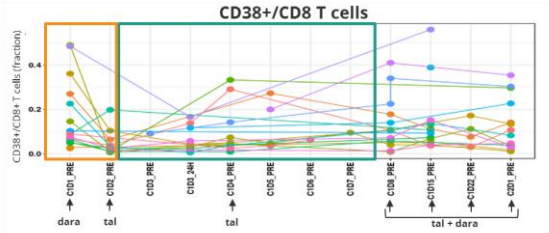
65 pts, 5 median prior LOT

- 57% (0.4) / 61% (0.8) TCR
- 57% (0.4) / 53% (0.8) prior anti-BCMA
- 79% (0.4) / 78% (0.8) anti-CD38 mAb refractory



Parameter	Tal 0.4 mg/kg QW + dara (n=14)	Tal 0.8 mg/kg Q2W + dara (n=51)
Median (range) follow-up, mo	16.8 (1.9–31.0)	15.0 (1.0–23.3)
Median (range) time to first response, mo	1.0 (0.9–2.4)	1.0 (0.9–8.3)
ORR in anti-CD38, n (%)		
Naive	3/3 (100.0)	5/5 (100.0)
Exposed	7/11 (63.6)	37/45 (82.2)
Refractory	7/11 (63.6)	32/40 (80.0)
ORR in T-cell redirection therapy[b] exposed, n (%)	4/6 (66.7)[c]	15/19 (78.9)
CAR-T	1/2 (50.0)	8/9 (88.9)
BsAb	4/5 (80.0)	7/10 (70.0)





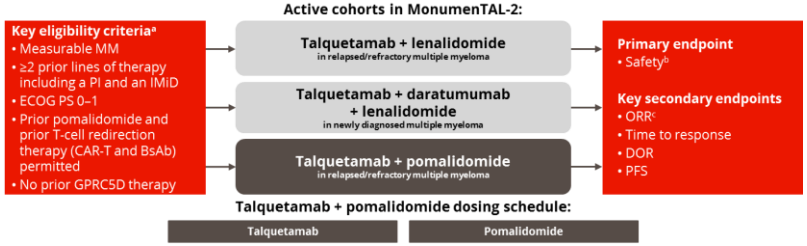
- The proportion of CD38+CD8+ T cells declined after initial dara dosing on C1D1 (orange box), consistent with previous data for dara
- Tal administration led to induction of CD38+ CD8+ T cells after the first step up dose of tec (green box)

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

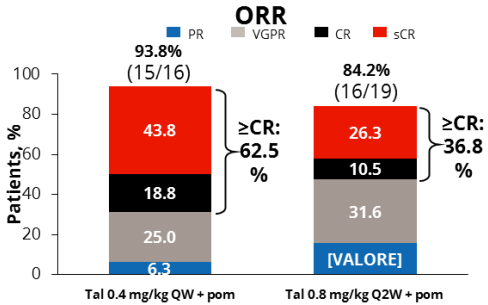
Dholaria B et al. ASCO 2023

Talquetamab + Pomalidomide: MonumenTAL-2 Ph 1b study



35 pts, 3 median prior LOT

- 31% (0.4) / 21% (0.8) TCR
- 25% (0.4) / 0% (0.8) prior anti-BCMA TCRed tp
- 31% (0.4) / 16% (0.8) poma exposed



ORRs were consistent across patient subgroups

- 100% (3/3) in CAR-T–exposed pts in the QW cohort (no patients had CAR-T exposure in Q2W)
- 100% (5/5 in QW, 3/3 in Q2W) in poma-exposed pts in both cohorts
- 50% (1/2 in QW) and 67% (2/3 in Q2W) in pts with EMD
- 80% (4/5 in QW) and 75% (3/4 in Q2W) in pts with HRCg

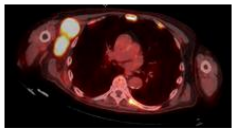
TEAE (≥20%), n (%)	All patients (N=35)	
	Any Grade	Grade 3/4
Hematologic TEAEs		
Neutropenia	22 (62.9)	19 (54.3)
Anemia	13 (37.1)	9 (25.7)
Thrombocytopenia	10 (28.6)	7 (20.0)

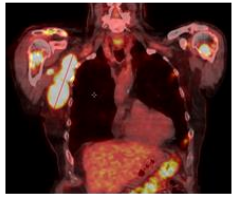
TEAE (≥5%), n (%)	All patients (N=35)	
	Any Grade	Grade 3/4
Infections	**28 (80.0)**	**8 (22.9)**
Pneumonia	8 (22.9)	5 (14.3)
Upper respiratory tract infection	8 (22.9)	1 (2.9)
COVID-19	6 (17.1)	1 (2.9)
Oral candidiasis	3 (8.6)	0
Urinary tract infection	3 (8.6)	1 (2.9)
Influenza	2 (5.7)	0
Respiratory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

TEAE (≥25%), n (%)	All patients (N=35)	
	Any Grade	Grade 3/4
Nonhematologic TEAEs		
Taste related[a]	30 (85.7)	N/A
Infections	28 (80.0)	8 (22.9)
CRS	26 (74.3)	1 (2.9)
Skin related[b]	26 (74.3)	2 (5.7)
Nail related[c]	24 (68.6)	0
Dry mouth	19 (54.3)	0
Fatigue	19 (54.3)	5 (14.3)
Pyrexia	13 (37.1)	1 (2.9)
Nausea	12 (34.3)	0
Diarrhea	10 (28.6)	0
Hypokalemia	10 (28.6)	2 (5.7)
Back pain	9 (25.7)	1 (2.9)
Headache	9 (25.7)	1 (2.9)

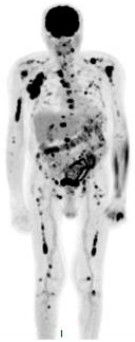
Matous J et al. ASH 2023

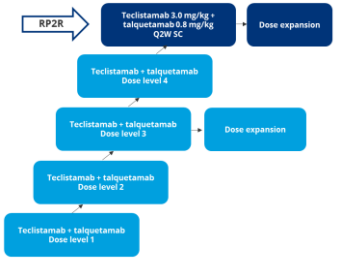
Teclistamab and Talquetamab: First Combination of Bispecific Antibodies to Target 2 Distinct Myeloma Antigens – RedirecTT-1 phase 1b study



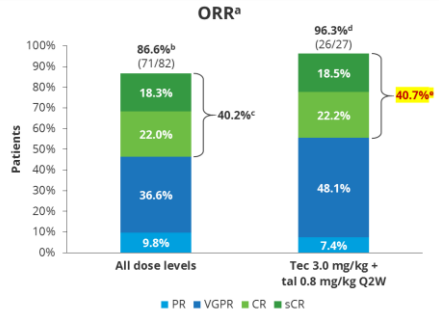


October 25, 2021

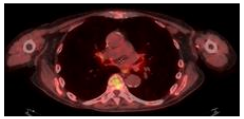


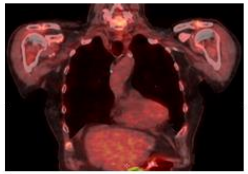


Age 65 (39-81)
Prior lines 4 (1-11); HR 33%; EMD 37%; TCR 78%

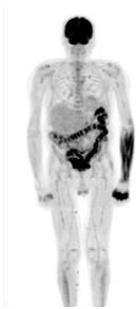


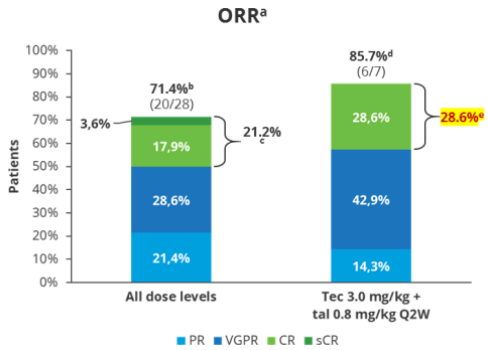
	All dose levels (N=93)	Tec 3.0 mg/kg + tal 0.8 mg/kg Q2W (n=34)
Median follow-up, months (range)	13.4 (0.3–25.6)	8.1 (0.7–15.0)
Median DOR,[f] months (95% CI)	NE (NE–NE)	NE (NE–NE)
Median time to first response,[f] months (range)	1.97 (0–7.7)	1.48 (0–4.0)
Median time to best response,[f] months (range)	3.98 (1.1–15.7)	3.22 (1.4–10.7)
Median PFS,[g] months (95% CI)	20.9 (13.0–NE)	NE (9.9–NE)
9-month PFS rate[g] (95% CI)	70.1 (58.0–79.4)	77.1 (50.8–90.5)





January 2022





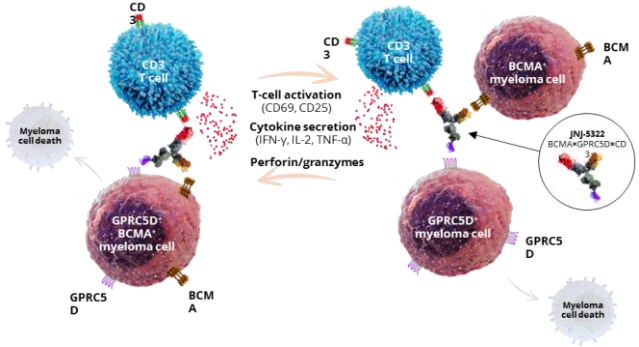
Extramedullary disease

	All dose levels (N=35)	Tec 3.0 mg/kg + tal 0.8 mg/kg Q2W (N=11)
Median DOR,[f] months (95% CI)	12.9 (4.17–NE)	NE (4.17–NE)
Median PFS,[g] months (95% CI)	6.1 (2.5–9.9)	9.9 (2.4–NE)

Cohen et al. ASCO 2023

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



- In vitro, JNJ-5322 induced potent and dose-dependent cytotoxicity with concomitant T-cell activation only in myeloma cell lines that expressed one or both target proteins (BCMA, GPRC5D)
- JNJ-5322 also induced CD138^{+} plasma cell depletion when tested using patient-derived myeloma bone marrow mononuclear cells in a co-culture assay
- In vivo, JNJ-5322 induced potent antitumor activity in models that expressed one or both target proteins

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

Pillarisetti K et al. ASH 2023

Combination strategies of Non-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
NCT05050097_MonumenTAL-2 (Phase 1b)	Talquetamab + carfilzomib; Talquetamab + carfilzomib + daratumumab; Talquetamab + lenalidomide; Talquetamab + lenalidomide + daratumumab; Talquetamab + pomalidomide
NCT05338775_TriMM-3 (Phase 1)	Teclistamab + PD-1 inhibitor; Talquetamab + PD-1 inhibitor
NCT06055075 (Phase 1)	Forimtamig + carfilzomib; Forimtamig + daratumumab
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

Ongoing phase 3 studies with Non-BCMA BsAbs as treatment of RRMM at early relapse or NDMM

Study	Regimen	Condition
MonumenTAL-3 NCT05455320	Tal-Dara vs Tal-Dara-Poma vs DaraPd	RRMM ≥ 1 prior LOT (including len and PI)
MajesTEC-7 NCT05552222	Tec-Dara-Len vs DaraRd Tal-Dara-Len vs DaraRd	NDMM ineligible or not intended for ASCT

nature medicine

Article

https://doi.org/10.1038/s41591-023-02491-5

Mechanisms of antigen escape from BCMA- or GPRC5D-targeted immunotherapies in multiple myeloma

- **Genomic events on the *TNFRSF17* locus were identified in 8 out of 16 patients (50%) who progressed after prior anti-BCMA/GPRC5D CAR-T and/or TCE therapies.**
- **BCMA extracellular domain mutations leading to functional loss of epitopes were demonstrated at the time of PD in 5 out of 14 patients treated with BCMA-targeting TCE.** These events were possibly driven by the longitudinal selective therapeutic pressure exerted by TCE in comparison to the transient immune selection post-CAR T.
- **Biallelic mutations of the *GPRC5D* locus after GPRC5D-targeting TCE** were found in 4 patients, suggesting that under the immune-therapeutic pressure GPRC5D can be more readily lost than *TNFRSF17* in MM cells.

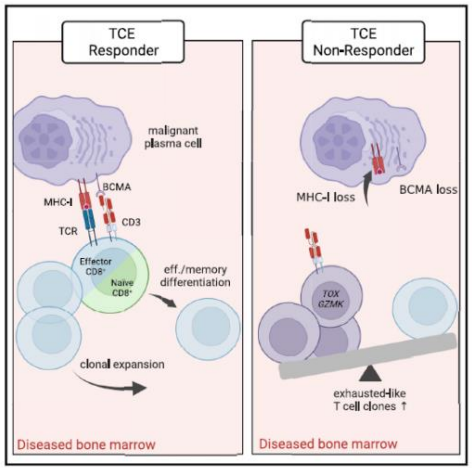
Lee H et al, Nature Medicine 2023

Cancer Cell

Article

The pre-existing T cell landscape determines the response to bispecific T cell engagers in multiple myeloma patients

- Single-cell TCR tracing identifies conserved T cell responses to TCEs in humans
- Clonal expansion of effector CD8+ T cells is an immunological driver of TCE therapy
- Naive T cells require additional MHC class I signal and differentiate upon TCE activation
- The abundance of exhausted CD8+ clones predicts response failure in multiple myeloma



Friedrich MJ al, Cancer Cell 2023

Thanks!

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