Anticorpi Bispecifici non-BCMA

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LE NUOVE FRONTIERE
DELL'IMMUNOTERAPIA
PER LA CURA DEL
MIELOMA
MULTIPLO
dalla teoria alla pratica

TORINO **3**-**4** MARZO **2023**

Disclosures of NAME SURNAME

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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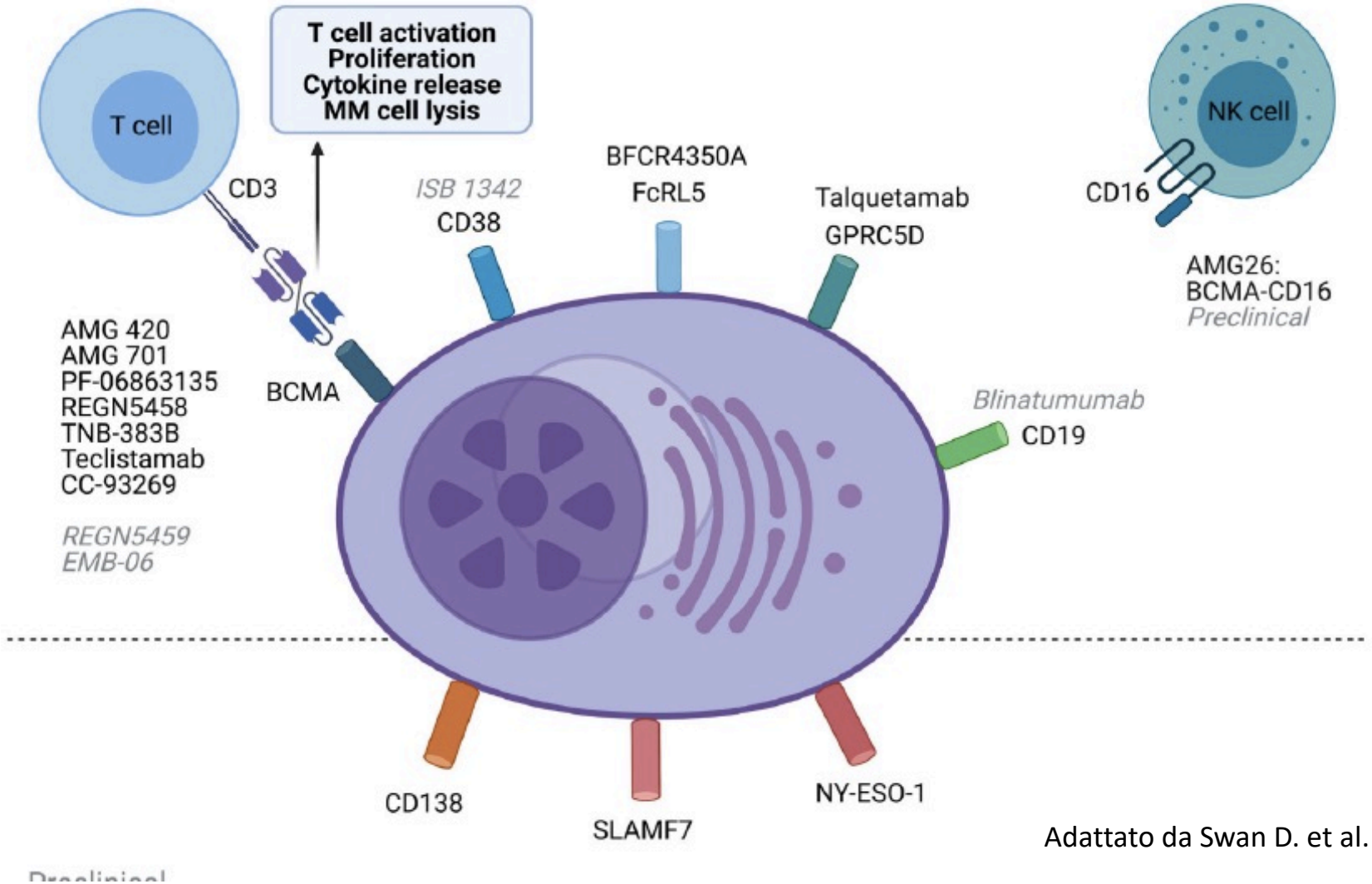
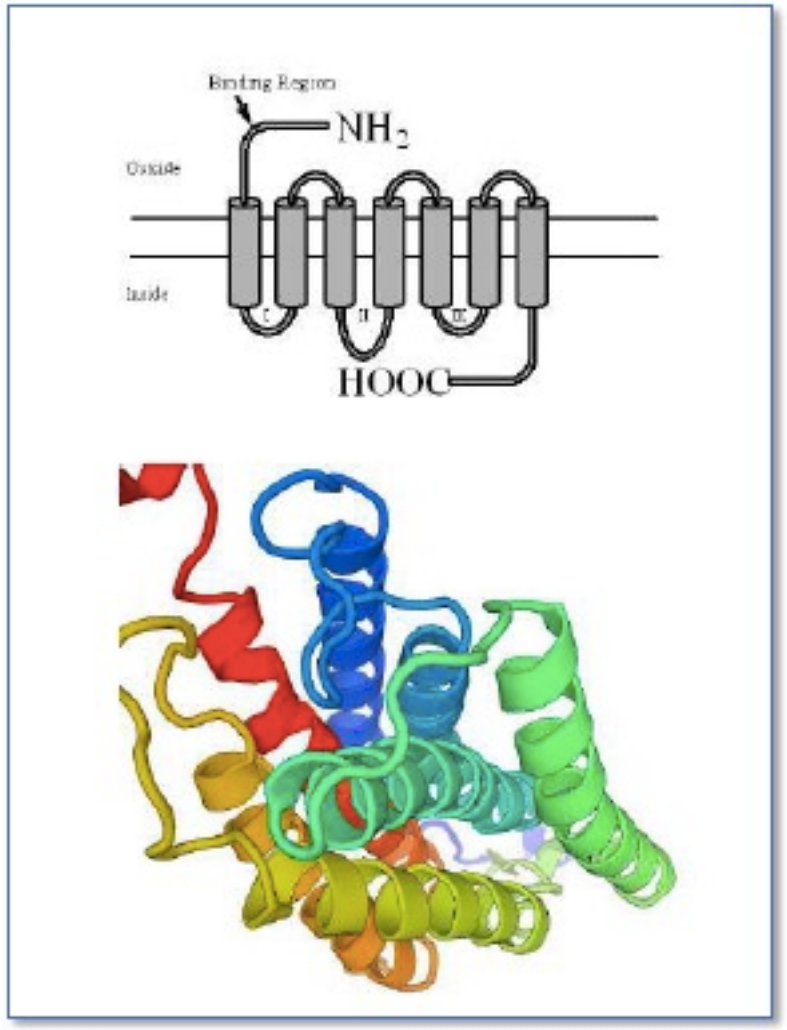


Adattato da Swan D. et al. BJH, 2022,196,488–506

Antigen	Structure	Expression	Role	Prognostic relevance
BCMA	Type III transmembrane glycoprotein of the tumour necrosis family receptor superfamily [30,31]	MM cells, plasma cells, mature B lymphocytes[30,32,33,34]	Long-term survival of plasma cells.[35] Ligand binding leads to upregulation of the anti-apoptotic proteins MCL-1 and BCL-2[36-38]	Soluble BCMA increases with disease progression.[39] High soluble levels correlate with poor outcomes.[40,41]
FcRH5 (CD305)	Membrane protein	MM cells, B cells and plasma cells[42,43]	Regulates BCR signalling and binds to IgG[42,43]	FcRH5 gene is located on chromosome 1q21, with overexpression in 1q gain[44-46]
GPRC5D	Transmembrane orphan receptor of the G protein-coupled receptor family[47,48]	MM cells, B cells and plasma cells[49]	Function is poorly characterised but a role in MM cell proliferation has been postulated	Enhanced expression observed in certain high-risk cytogenetic MM groups, e.g. Del13q and t(4;14)[47]
CD38	Type II glycoprotein of the ADP-ribosyl cyclase family	MM cells, B cells and plasma cells[50]	Regulation of calcium homeostasis, signalling and adhesion[51-53]	

GPRC5D



Recettore transmembrana

Ligando sconosciuto

Attività non nota

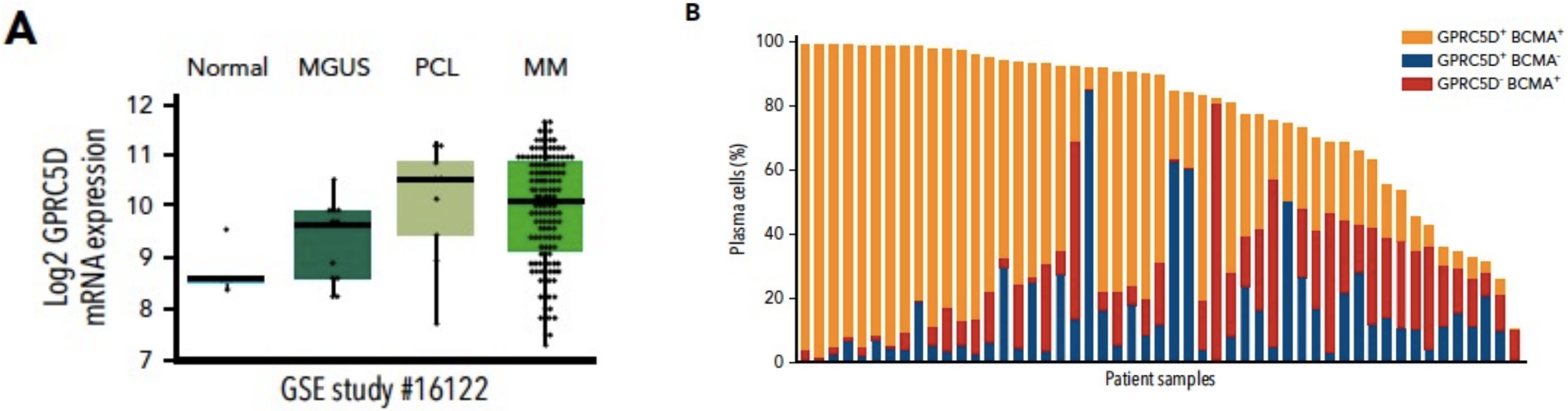
Espresso da plasmacellule e da plasmacellule di pazienti affetti da mieloma multiplo

Espresso da cute (follicoli piliferi) e tessuti cheratinizzati

A T-cell–redirecting bispecific G-protein–coupled receptor class 5 member D x CD3 antibody to treat multiple myeloma

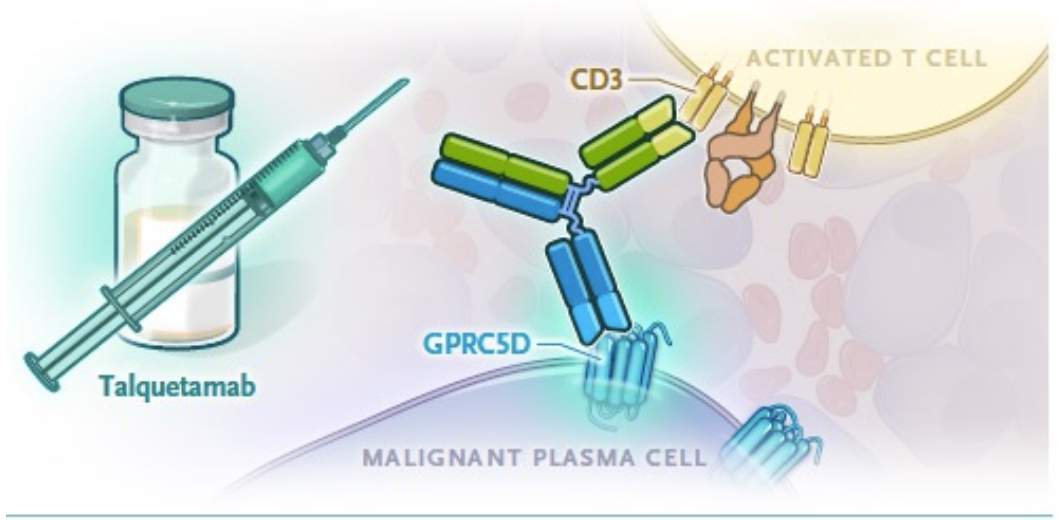
Kodandaram Pillarisetti,[1] Suzanne Edavettal,[2] Mark Mendonça,[1] Yingzhe Li,[1] Mark Tornetta,[3] Alexander Babich,[1] Nate Majewski,[3] Matt Husovsky,[2] Dara Reeves,[1] Eileen Walsh,[3] Diana Chin,[1] Leopoldo Luistro,[1] Jocelin Joseph,[1] Gerald Chu,[1] Kathryn Packman,[1] Shoba Shetty,[4] Yusri Elsayed,[1] Ricardo Attar,[1] and François Gaudet[1]

(*Blood*. 2020;135(15):1232-1243)



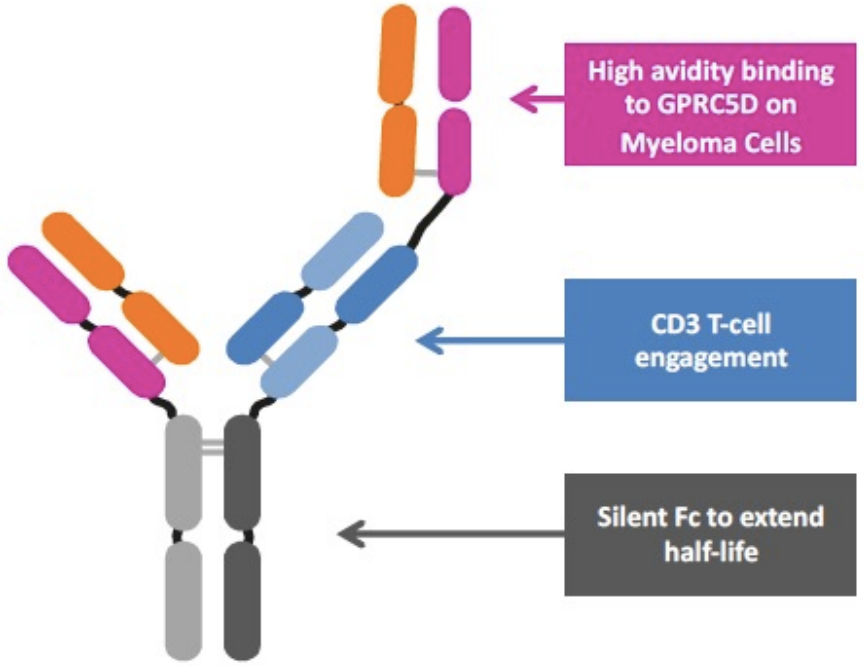
Targeting GPRC5D

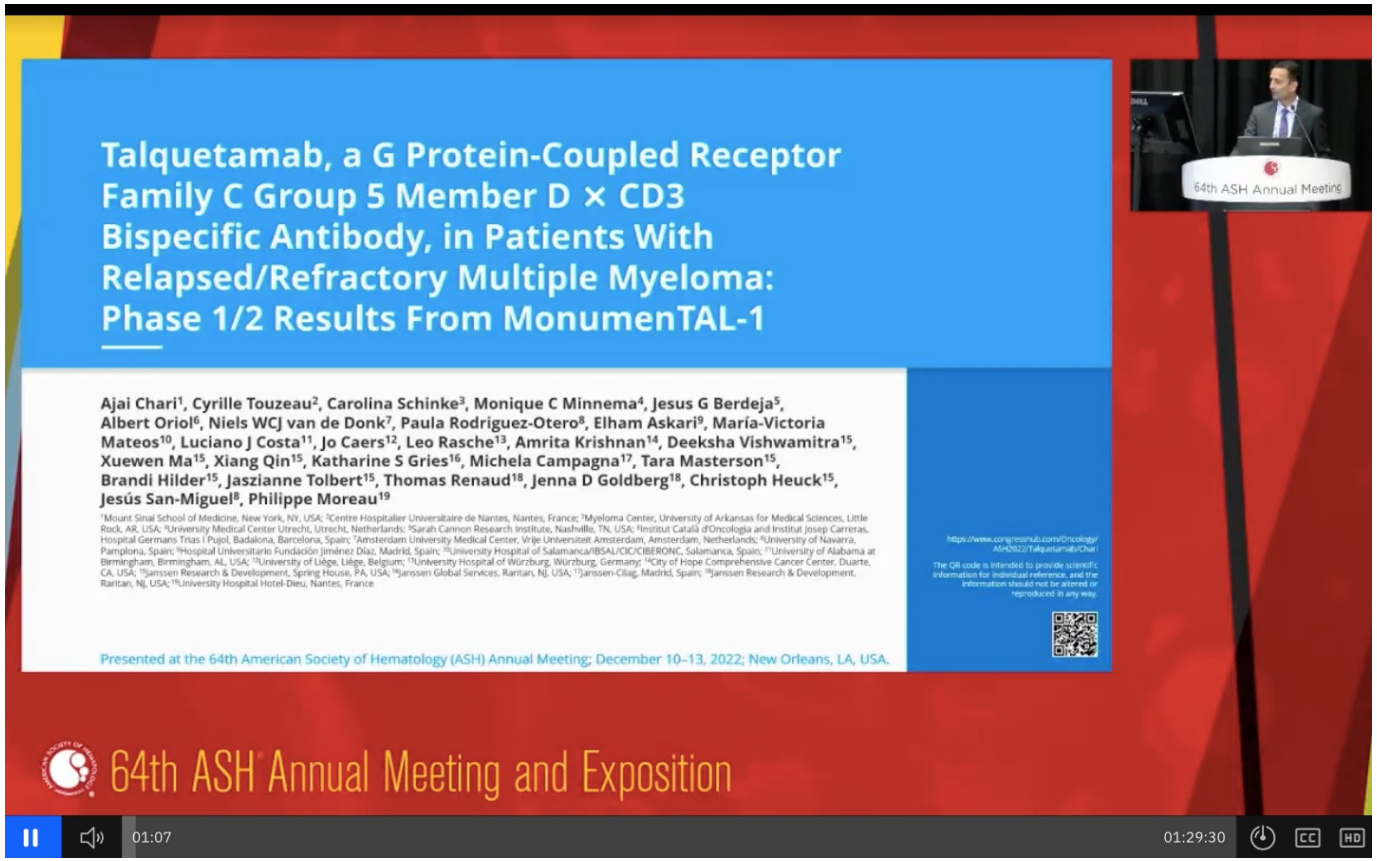
Talquetamab



Adapted N Engl J Med 2022; 387:2232-2244

Forimtamig





ORIGINAL ARTICLE

Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma

Ajai Chari, M.D., Monique C. Minnema, M.D., Jesus G. Berdeja, M.D., Albert Oriol, M.D., Ph.D., Niels W.C.J. van de Donk, M.D., Ph.D., Paula Rodríguez-Otero, M.D., Ph.D., Elham Askari, M.D., María-Victoria Mateos, M.D., Ph.D., Luciano J. Costa, M.D., Ph.D., Jo Caers, M.D., Ph.D., Raluca Verona, Ph.D., Suzette Girgis, Ph.D., Shiyi Yang, Ph.D., Rachel B. Goldsmith, Ph.D., Xiang Yao, Ph.D., Kodandaram Pillarisetti, M.Sc., Brandi W. Hilder, Ph.D., Jeffery Russell, M.D., Ph.D., Jenna D. Goldberg, M.D., and Amrita Krishnan, M.D.

N Engl J Med 2022; 387:2232-2244

MonumenTAL-1: Phase 1/2 Study Design
(NCT03399799/NCT04634552)

Key objectives

- Describe the efficacy and safety at the RP2Ds

Key eligibility criteria

- Adults with measurable MM
- Phase 1: Progression on or intolerance to all established therapies, ECOG PS 0–1
- Phase 2: ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 antibody, ECOG PS 0–2

RP2D 0.4 mg/kg QW SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

(Phase 1 [n=21] + **Phase 2 [n=122]**: N=143)

RP2D 0.8 mg/kg Q2W SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

(Phase 1 [n=36] + **Phase 2 [n=109]**: N=145)

Prior T-cell redirection (QW and Q2W)
Previously exposed to T-cell redirection therapies
Dosed with either 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC

(Phase 1 [n=17] + **Phase 2 [n=34]**: N=51)

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteasome inhibitor; Q2W, every other week; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous.

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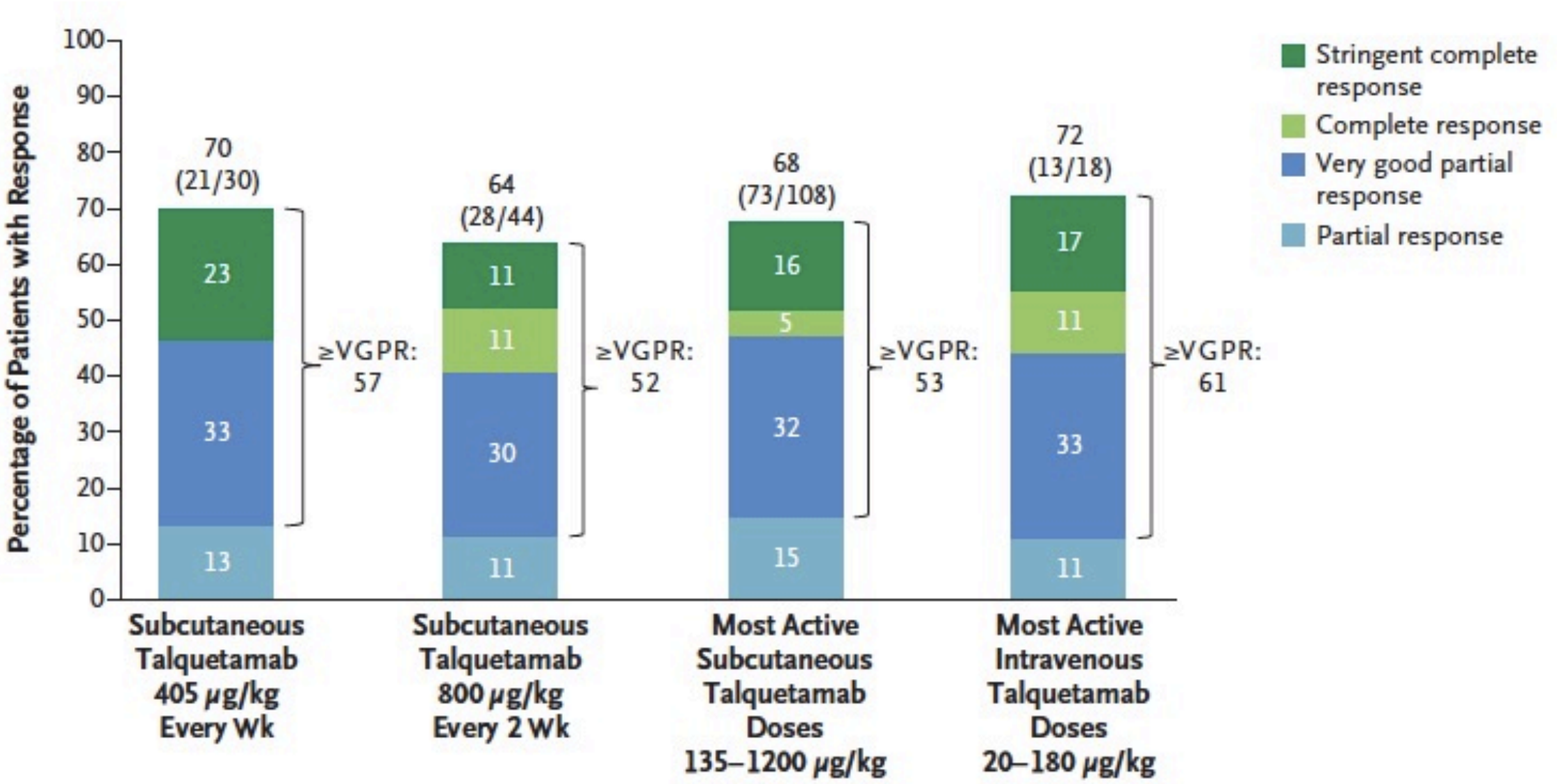
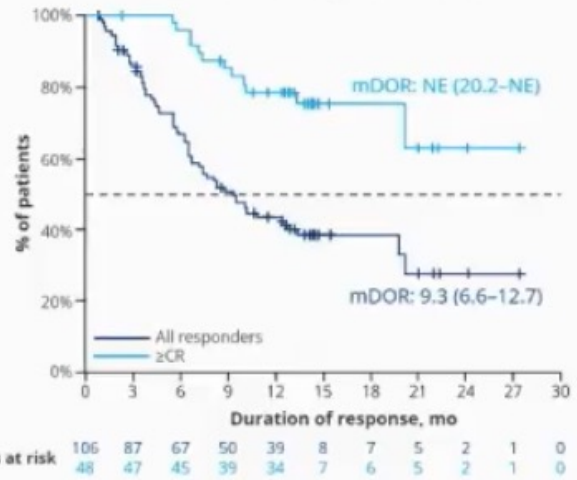

Percentage of Patients with Response
100
90
80
70
60
50
40
30
20
10
0
70
(21/30)
23
33
13
≥VGPR:
57
64
(28/44)
11
11
30
11
≥VGPR:
52
68
(73/108)
16
5
32
15
≥VGPR:
53
72
(13/18)
17
11
33
11
≥VGPR:
61
Stringent complete response
Complete response
Very good partial response
Partial response
Subcutaneous Talquetamab 405 µg/kg Every Wk
Subcutaneous Talquetamab 800 µg/kg Every 2 Wk
Most Active Subcutaneous Talquetamab Doses 135–1200 µg/kg
Most Active Intravenous Talquetamab Doses 20–180 µg/kg

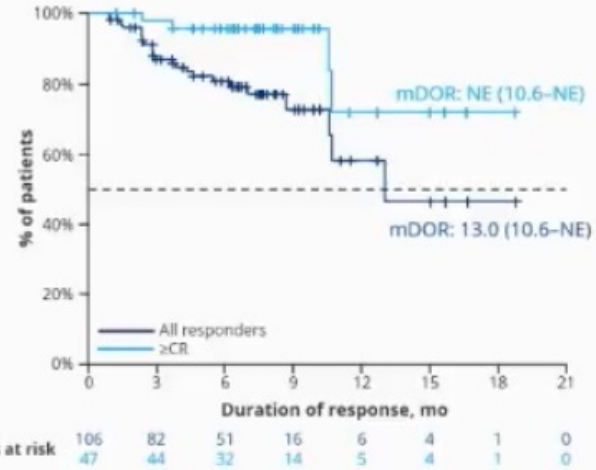
MonumenTAL-1: Duration of Response

- Treatment at both doses led to durable responses
  - Median DOR not reached for those patients who achieved ≥CR

DOR, 0.4 mg/kg SC QW
mFU: 14.9 months (range, 0.5[a]–29.0)



DOR, 0.8 mg/kg SC Q2W
mFU: 8.6 (range, 0.2[a]–22.5)



mPFS: 7.5 months (95% CI: 5.7–9.4; 33% censored)

11.9 months (95% CI: 8.4–NE; 61% censored)

Data cut-off date: September 12, 2022. [a]Denotes patients who died. ≥CR, complete response or better; DOR, duration of response; mDOR, median DOR; mFU, median follow-up; mPFS, median progression-free survival; NE, not estimable; Q2W, every other week; QW, weekly; SC, subcutaneous.

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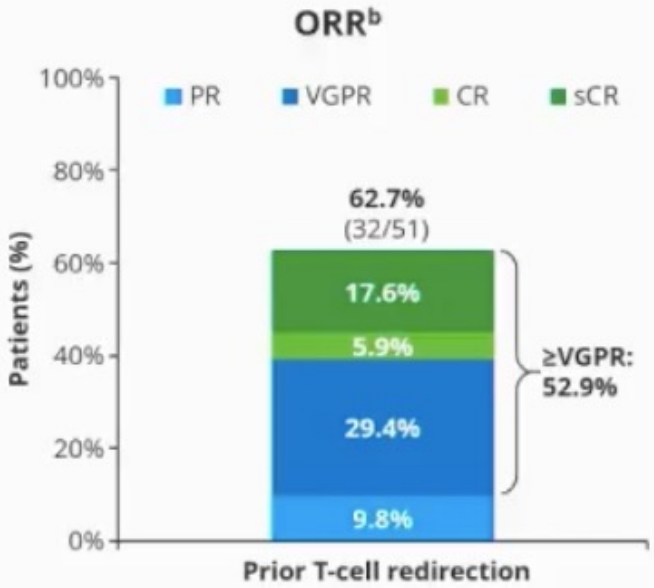
	Cohort 0.4	Cohort 0.8
Median Time to first response	1.2 ms (0.2-10.9)	1.3 (0.2 – 9-2)
Median Time to best response	2.2 ms (0.8 -12.7)	2.7 (0.3-12.5

Talquetamab ORR in Patients With Prior T-Cell Redirection

- **Patients enrolled in cohort of prior T-cell redirection therapy:**
  - **Were younger** and had a **higher prevalence of high-risk cytogenetics**
  - **Median of 6 prior lines of therapy** (range, 3–15)
  - 70.6% (n=36) received prior CAR-T cell therapy and 35.3% (n=18) prior bispecific antibody therapy; 3 patients received both
  - 7.8% (n=4) were refractory to belantamab
  - Most patients received QW (n=43) vs Q2W (n=8) talquetamab dosing
- **ORR was 62.7%**
  - **72.2% ORR** (26/36) in patients with **prior CAR-T therapy**
  - **44.4% ORR** (8/18) in patients with **prior bispecific antibody treatment**
- Median DOR was 12.7 months (range, 3.7–NE) at a median follow-up of 11.8 months (range, 1.0[a]–25.4)
  - Data are still immature, with 56.3% of patients censored
- Safety profile comparable in patients with and without prior T-cell redirection therapy

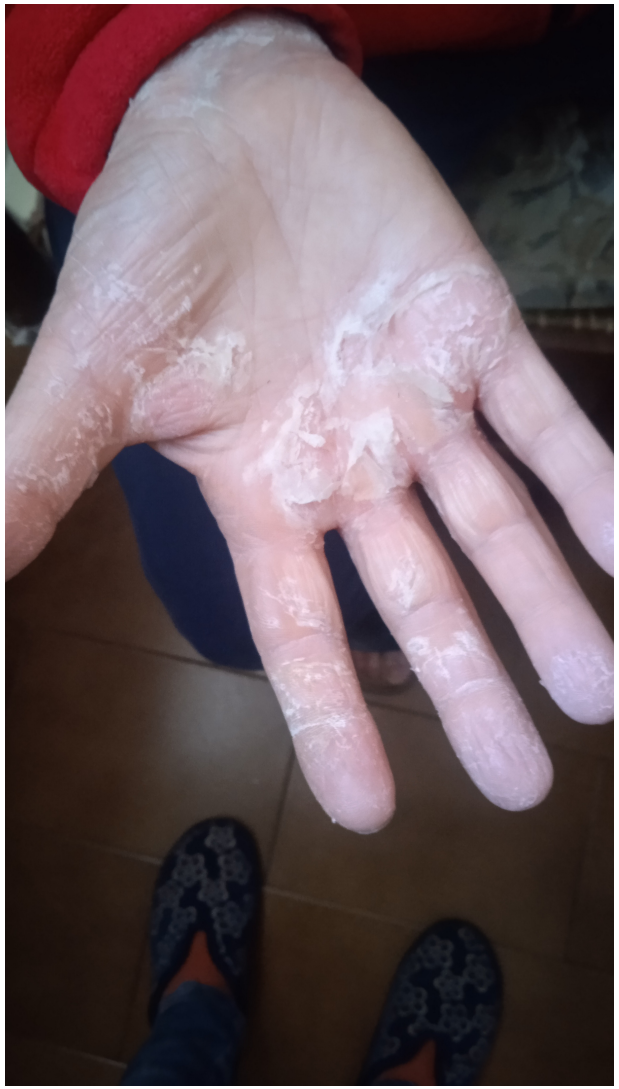


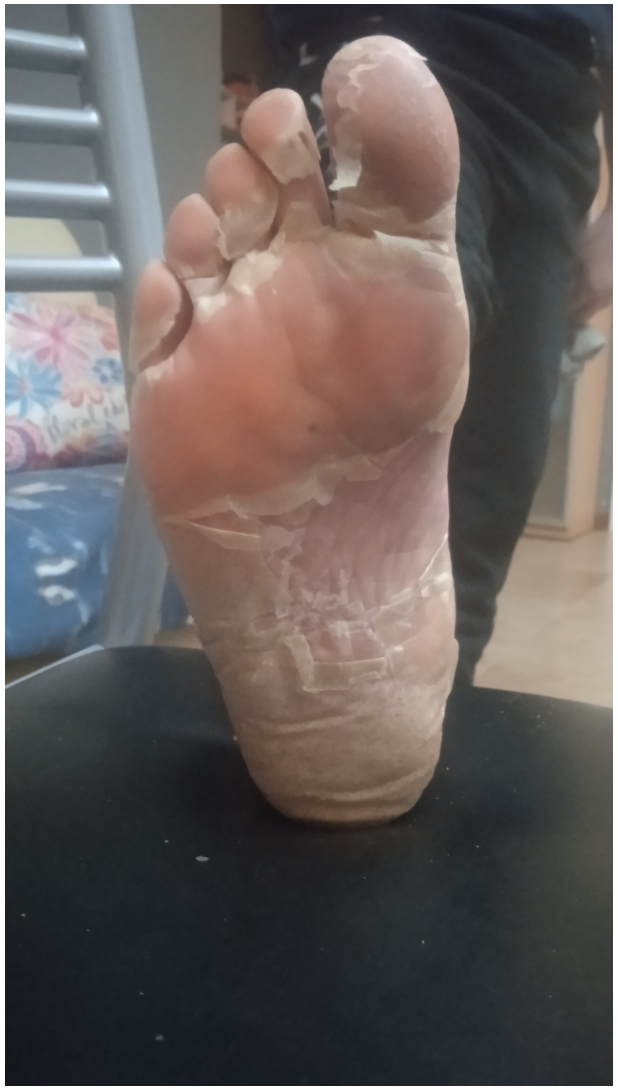
Data cut-off date: September 12, 2022 (efficacy), May 16, 2022 (safety).
[a]Denotes patient who died. [b]Independent review committee assessment of evaluable patients per 2011 IMWG response criteria; due to rounding, individual response rates may not sum to the ORR. CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; IMWG, International Myeloma Working Group; NE, not estimable; ORR, overall response rate; PR, partial response; QW, weekly; Q2W, every other week; sCR, stringent complete response; VGPR, very good partial response.

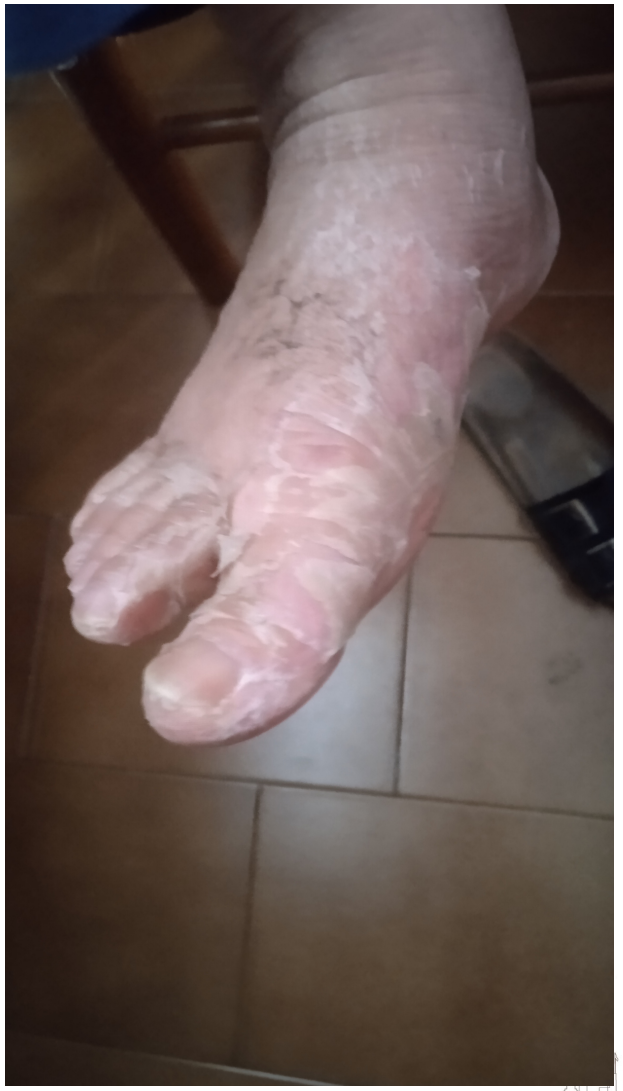
Table 2. Adverse Events.*

Event	Subcutaneous Talquetamab, 405 μg Weekly (N=30)		Subcutaneous Talquetamab, 800 μg Every 2 Wk (N=44)		Intravenous Talquetamab, All Doses (N=102)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)					
Any adverse event	30 (100)	26 (87)	44 (100)	38 (86)	102 (100)	92 (90)
Hematologic event						
Anemia	18 (60)	9 (30)	19 (43)	10 (23)	59 (58)	34 (33)
Neutropenia	20 (67)	18 (60)	16 (36)	14 (32)	48 (47)	27 (26)
Lymphopenia	12 (40)	12 (40)	17 (39)	17 (39)	53 (52)	48 (47)
Thrombocytopenia	11 (37)	7 (23)	10 (23)	5 (11)	36 (35)	13 (13)
Leukopenia	12 (40)	9 (30)	8 (18)	6 (14)	38 (37)	16 (16)
Nonhematologic event						
Cytokine release syndrome	23 (77)	1 (3)	35 (80)	0	50 (49)	5 (5)
Skin-related event†	20 (67)	0	31 (70)	1 (2)	24 (24)	0
Dysgeusia	19 (63)	NA	25 (57)	NA	38 (37)	NA
Fatigue	10 (33)	1 (3)	12 (27)	0	37 (36)	1 (1)
Nail-related event‡	17 (57)	0	12 (27)	1 (2)	20 (20)	0
Pyrexia	10 (33)	0	8 (18)	0	32 (31)	0
Headache	6 (20)	0	11 (25)	0	35 (34)	2 (2)
Rash-related event§	14 (47)	0	13 (30)	7 (16)	15 (15)	1 (1)

Skin toxicity







Forimtamig (RG6234), a GPRC5DxCD3 T-cell-engaging bispecific antibody, is highly active in patients with relapsed/refractory multiple myeloma: updated intravenous and first subcutaneous results from a Phase I dose-escalation study

Carmelo Carlo-Stella,[1] Rita Mazza,[1] Salomon Manier,[2] Thierry Facon,[2] Sung-Soo Yoon,[3,4] Youngil Koh,[4] Simon J Harrison,[5,6] Jeremy Er,[5,7] Antonio Pinto,[8] Francesco Volzone,[8] Giulia Perrone,[9] Paolo Corradini,[9] Titouan Cazaubiel,[10] Cyrille Hulin,[10] Cyrille Touzeau,[11] Philippe Moreau,[11] Enrique M Ocio,[12] Carmen Montes Gaisán,[12] Rakesh Popat,[13] Sarah Leong,[13] Fritz Offner,[14] Paula Rodríguez Otero,[15] Ana Alfonso-Pierola,[15] Ann-Marie E Bröske,[16] Iryna Dekhtiarenko,[17] Hans-Joachim Helms,[18] Sara Belli,[18] Eva Rossmann,[18] Tanja Fauti,[17] Jan Eckmann,[16] Tom Moore,[16] Meike Schneider,[18] Wolfgang Jacob,[16] Martin Weisser,[16] Martin Hutchings,[19] Caroline Hasselbalch Riley[19]

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Presented at the 64th ASH Annual Meeting | December 10–13, 2022

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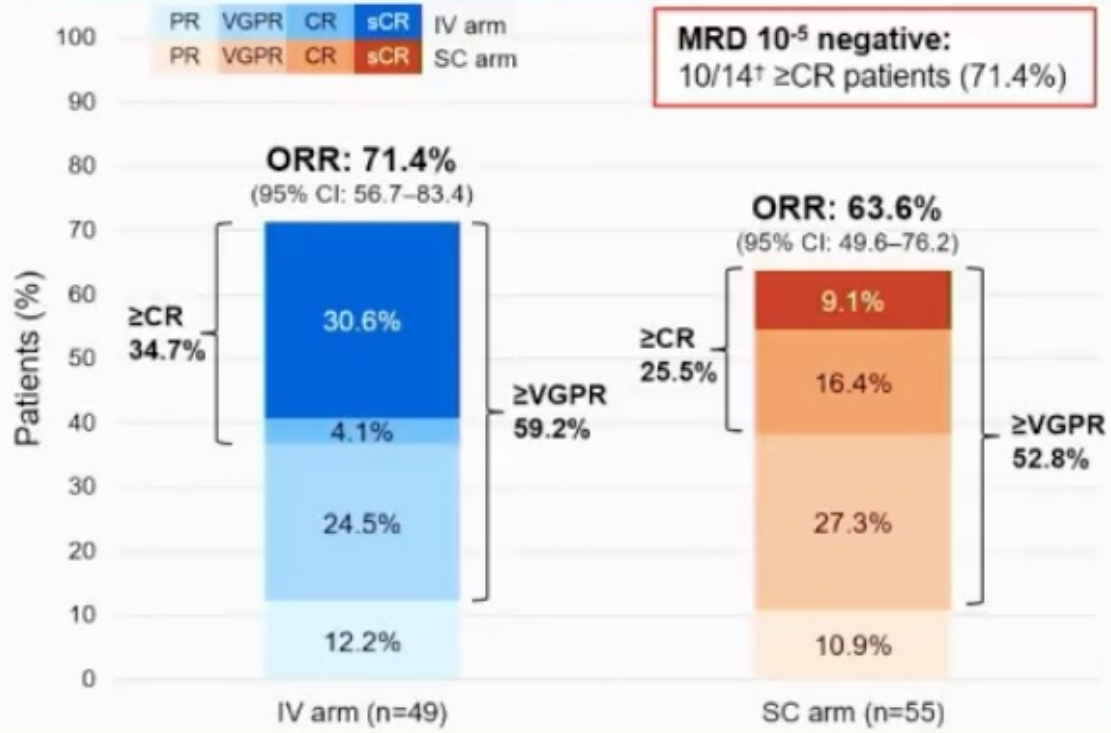
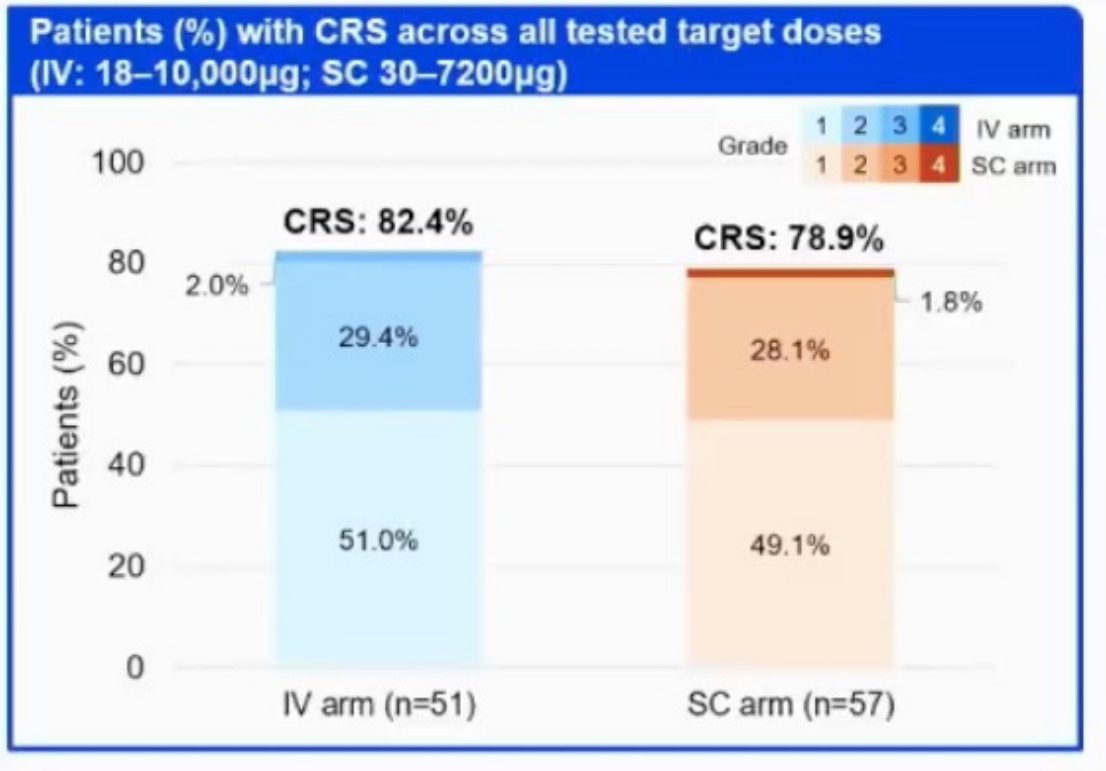
Forimtamig clinical efficacy

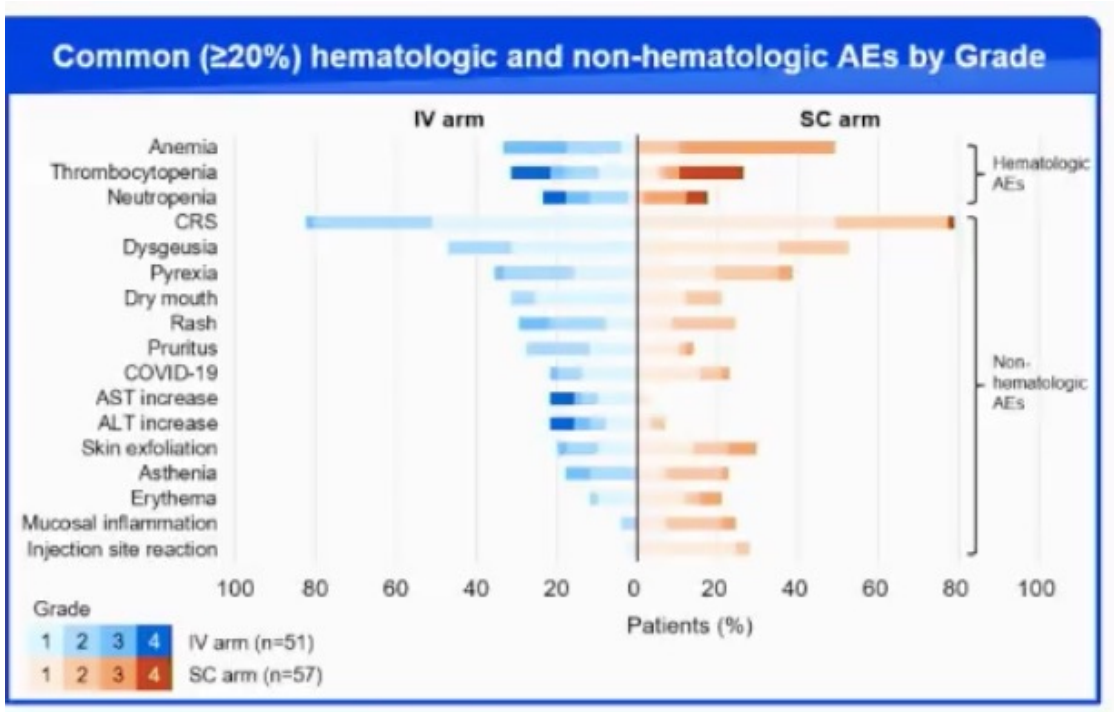
	IV arm (n=49)	SC arm (n=55)
Median follow-up, months (range)	11.6 (0.5–20.6)	8.0 (1.1–15.0)
Median time to first response, months (95% CI)	1.4 (1.2–1.8)	1.6 (1.2–2.1)
Median duration of response, months (range)	10.8 (0.0–17.6)	12.5 (1.2–12.5)
Patients with ongoing response at data cut-off, n/N (%)	23/35 (65.7)	25/35 (71.4)
Patients with prior anti-BCMA and response, n/N (%)	5/10 (50.0)	6/11 (54.5)

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



Data cut-off: October 21, 2022; *patients who received ≥1 target dose of forimtamig and had at least one baseline and one on-treatment tumor assessment or discontinued due to clinical progression; †of 14 evaluable patients with available BMA at the time of response across all IV and SC doses so far, 10 had MRD-negative CR at 10^{-5}. BMA, bone marrow aspirate; CI, confidence interval; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

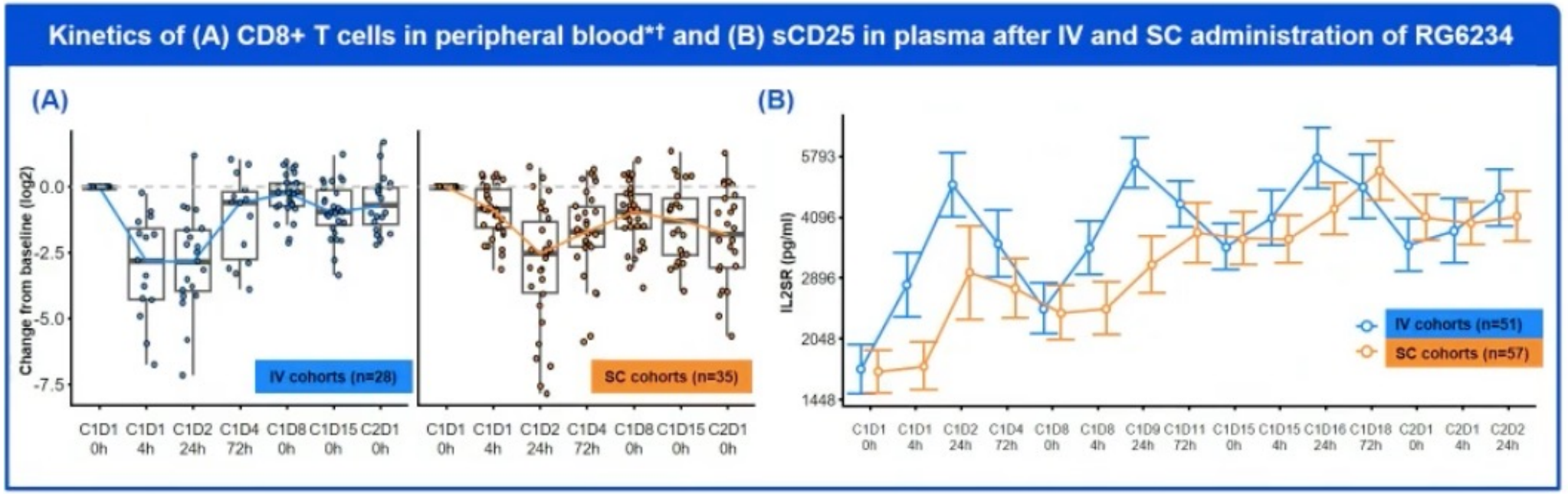

Patients (%) with CRS across all tested target doses
(IV: 18–10,000µg; SC 30–7200µg)
Grade
1 2 3 4 IV arm
1 2 3 4 SC arm
Patients (%)
100
80
60
40
20
0
CRS: 82.4%
2.0%
29.4%
51.0%
CRS: 78.9%
1.8%
28.1%
49.1%
IV arm (n=51)
SC arm (n=57)


Common (≥20%) hematologic and non-hematologic AEs by Grade
IV arm
SC arm
Anemia
Thrombocytopenia
Neutropenia
CRS
Dysgeusia
Pyrexia
Dry mouth
Rash
Pruritus
COVID-19
AST increase
ALT increase
Skin exfoliation
Asthenia
Erythema
Mucosal inflammation
Injection site reaction
Hematologic AEs
Non-hematologic AEs
100 80 60 40 20 0 20 40 60 80 100
Patients (%)
Grade
1 2 3 4 IV arm (n=51)
1 2 3 4 SC arm (n=57)

4554 Intravenous and Subcutaneous Administration of RG6234, a Novel GPRC5DxCD3 T-Cell Engaging Bispecific Antibody, Is Highly Active in Patients with Relapsed/Refractory Multiple Myeloma (RRMM): Biomarker Results from a Phase I Study

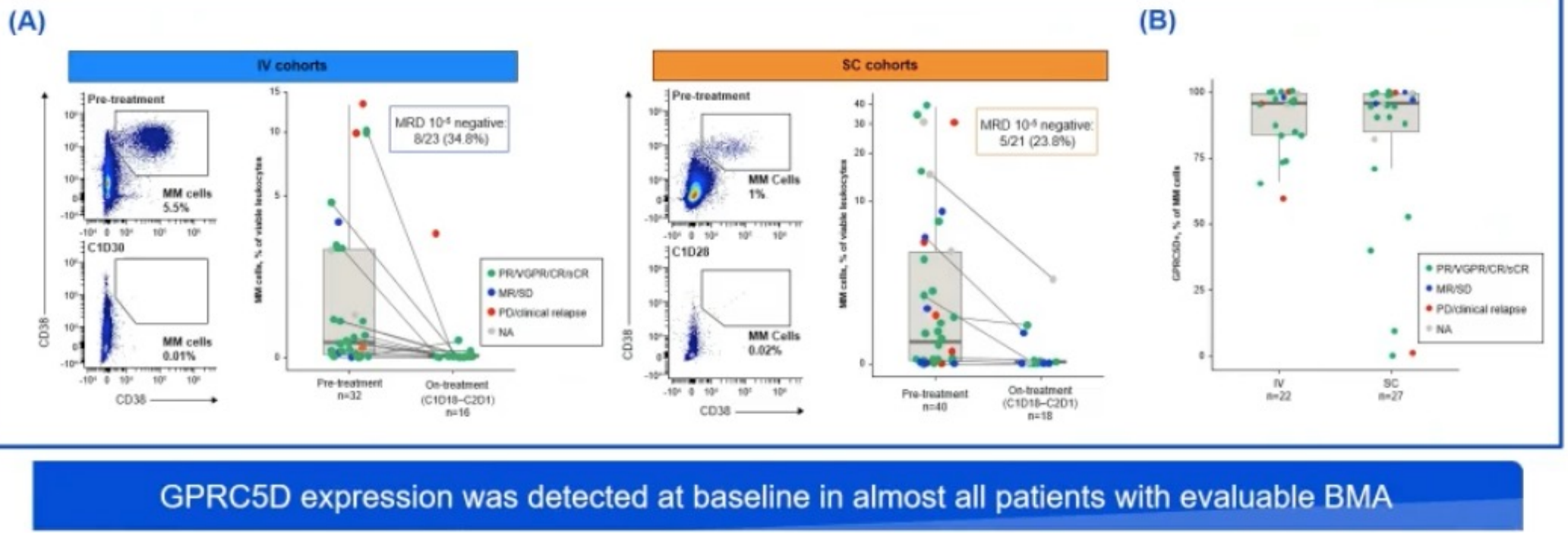
Dekhtiarenko I et al. ASH 2022

RG6234 leads to T-cell activation in peripheral blood independently of administration route



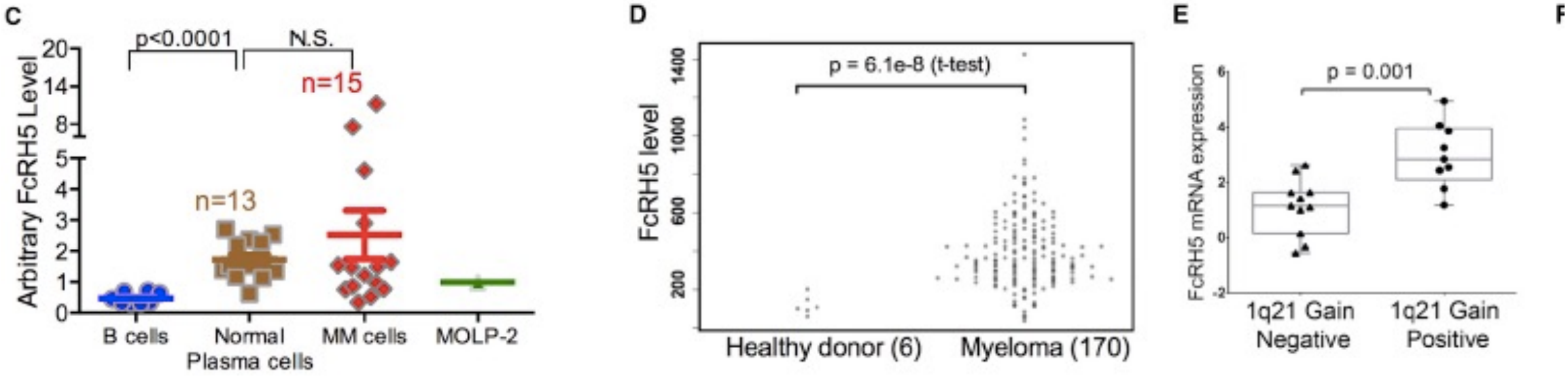
Rapid RG6234 efficacy was independent of target expression level

(A) Rapid depletion of MM cells upon treatment and (B) baseline GPRC5D expression on MM cells



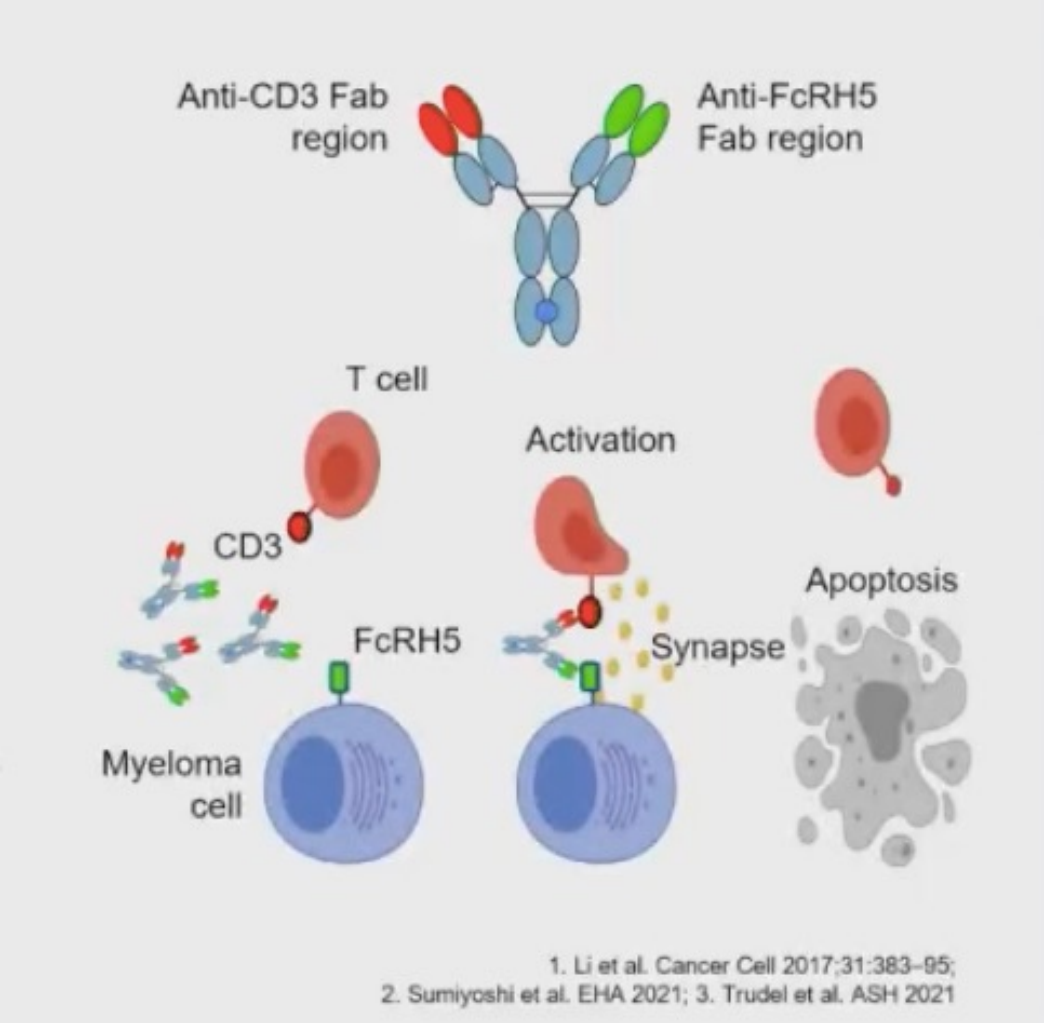
GPRC5D expression was detected at baseline in almost all patients with evaluable BMA

FcRH5 is a type I membrane protein expressed on B cells, PCs, and, most importantly, myeloma cells, with nearly 100% prevalence



Li J et al . Cancer Cell 31, 383–395, March 13, 2017

Cevostamab: FcRH5xCD3 bispecific antibody



1. Li et al. Cancer Cell 2017;31:383–95;
2. Sumiyoshi et al. EHA 2021; 3. Trudel et al. ASH 2021

157 Cevostamab Monotherapy Continues to Show Clinically Meaningful Activity and Manageable Safety in Patients with Heavily Pre-Treated Relapsed/Refractory Multiple Myeloma (RRMM): Updated Results from an Ongoing Phase I Study

ASH 2021. Trudel S et al.

A phase I trial (NCT03275103) is being conducted in high-risk patients with a median of six prior lines of therapy and exposure to several drug classes, including previously targeted BCMA therapy.

Data have been reported on 160 patients, of whom 85% had triple-class-refractory disease.

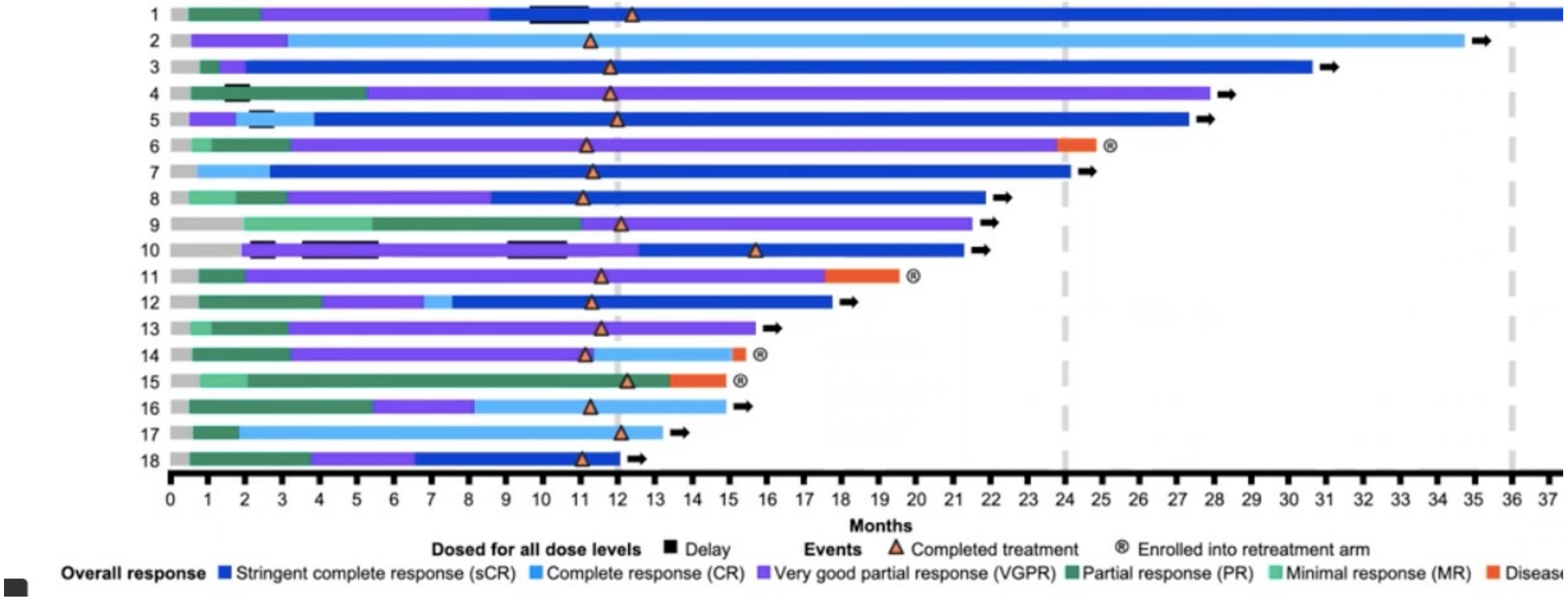
At a median 6-month follow up, the median time to response was 29 days.

Responses appeared to be dose dependent, **with an ORR of 54.4% at the higher dose level of 160 mg** compared with 36.7% at the 90 mg dose level. With target dose levels greater than 90 mg, patients with prior anti-BCMA therapy (n=8/22) had an ORR of 36.4%.

1924 Enduring Responses after 1-Year, Fixed-Duration Cevostamab Therapy in Patients with Relapsed/Refractory Multiple Myeloma: Early Experience from a Phase I Study

Lesokhin AM et al. ASH 2022

- As of August 22, 2022, median follow-up post treatment was 9.6 months (range:1.2–26.2). Target cevostamab doses ranged from 40–160mg
- At data cut-off, 14/18 (78%) patients treated for 17 cycles of therapy remain in response



Disease control observed in most patients during cevostamab retreatment

- Five of six patients retreated with cevostamab after PD (with doses ranging from 60–198mg) had disease control

	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

Pre-treatment with tocilizumab prior to the CD3 bispecific cevostamab in patients with relapsed/refractory multiple myeloma showed a marked reduction in cytokine release syndrome incidence

Suzanne Trudel,[1] Nizar Bahlis,[2] Andrew Spencer,[3] Rayan Kaedbey,[4] Paula Rodriguez,[5] Simon Harrison,[6] Chihunt Wong,[7] Grant Goodman,[7] Rin Nakamura,[7] Voleak Choeurng,[7] James Cooper,[7] Maria-Victoria Mateos[8]

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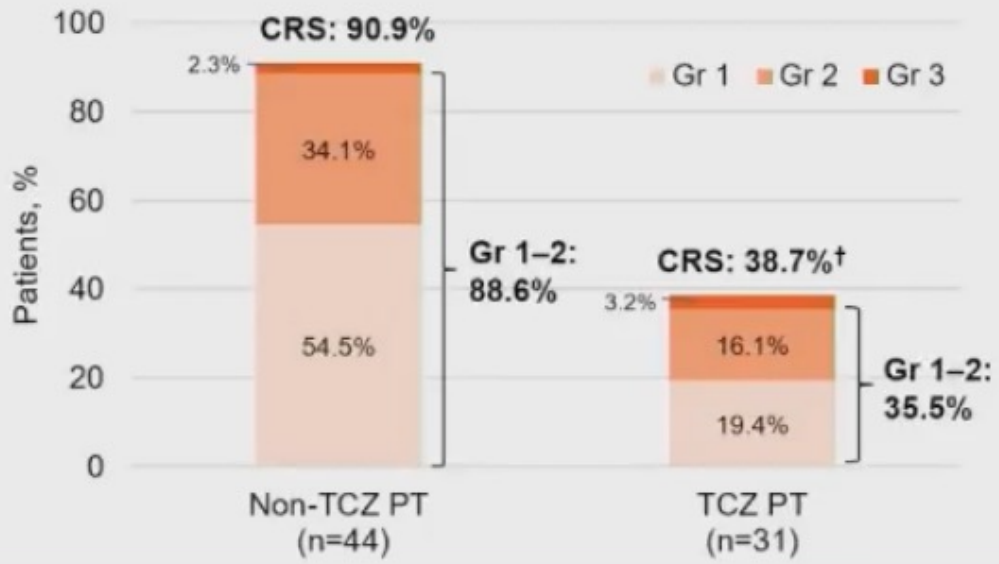
CRS rate and management

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



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

The overall rate of CRS was significantly lower in the TCZ PT group than in the non-TCZ PT group

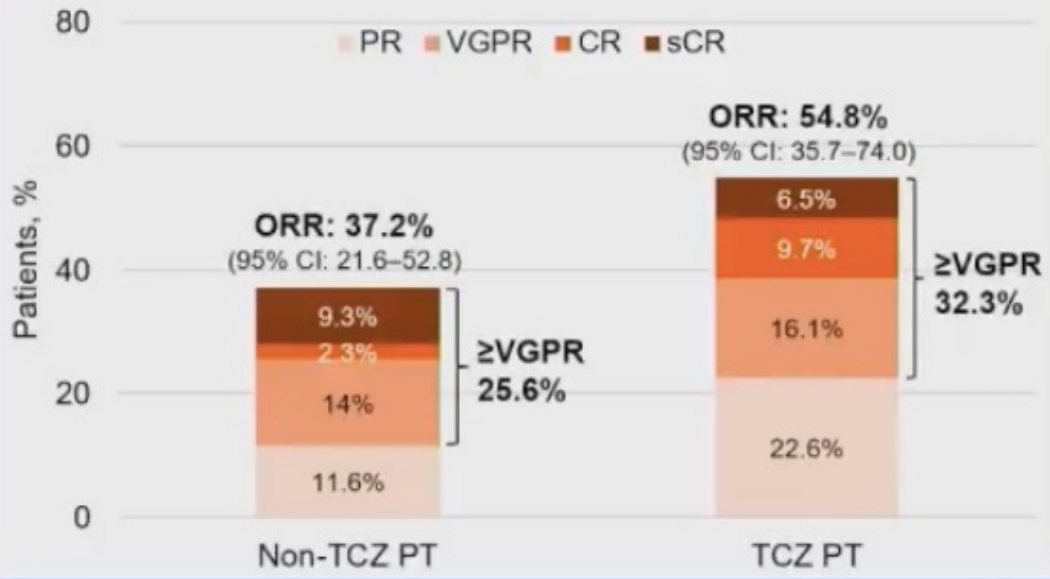
Data cut-off: August 22, 2022; *CRS reported using ASTCT 2019 criteria[1]; †p<0.001 for comparison vs overall CRS rate in non-TCZ PT arm using a proportions test

1. Lee et al. Biol Blood Marrow Transpl 2019;25:625–38

Response rate

	Non-TCZ PT (n=43)	TCZ PT (n=31)
Median follow-up, months (range)	12.8 (0.2–36.3)	8.5 (1.1–16.8)
Median time to first response, months (range)	1.2 (0.7–2.2)	0.8 (0.7–3.3)
Median time to best response, months (range)	2.2 (0.8–10.6)	2.2 (0.7–7.4)
Median duration of response, months (range)	10.9 (1–34*)	11.3 (1–12*)

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

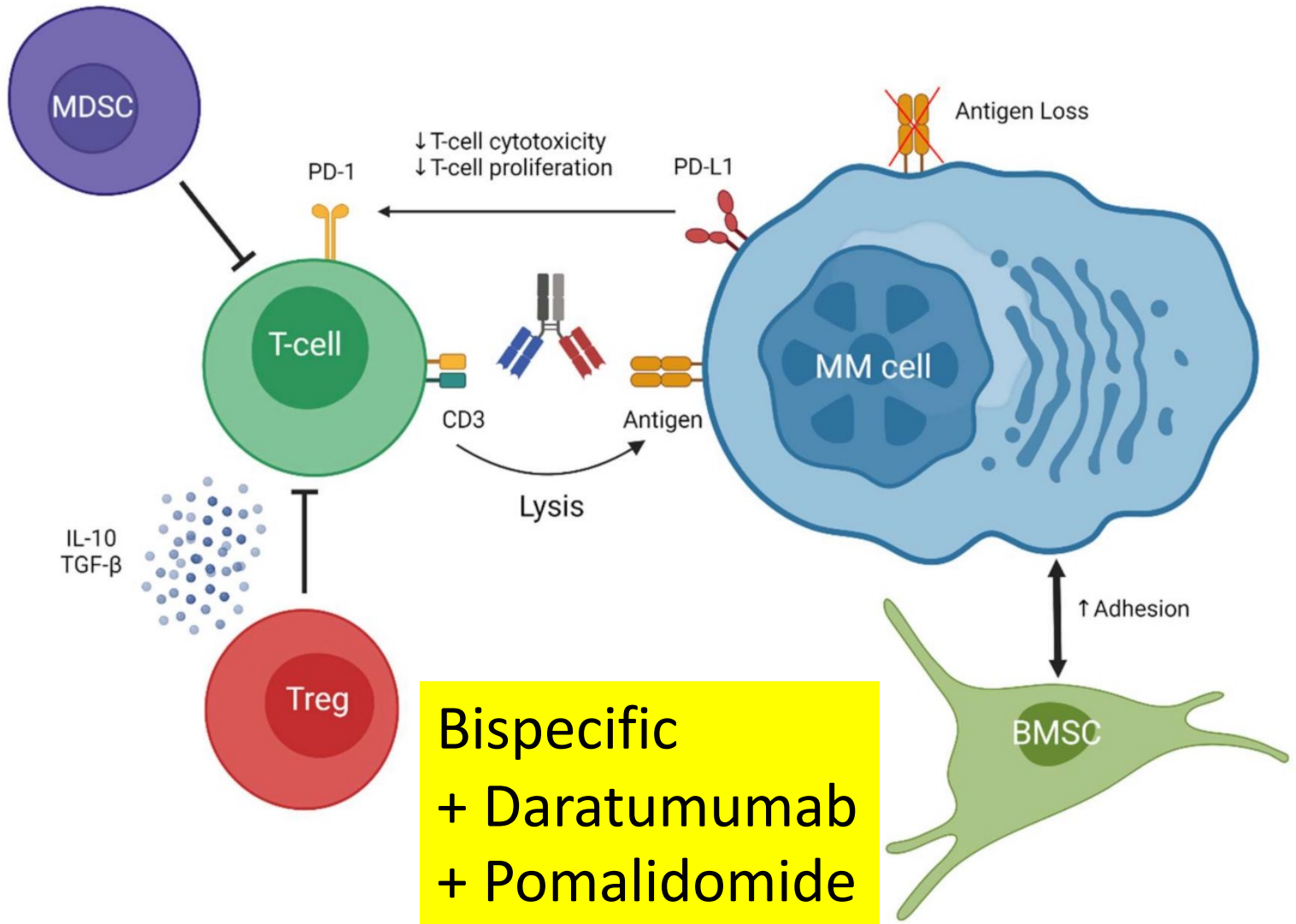


TCZ PT had no negative impact on response rate

Data cut-off: August 22, 2022; *censored observation
CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Rationale for a combination strategy

Bispecific[2]



Bispecific + Daratumumab

Bispecific + Daratumumab + Pomalidomide

Hosny M et al. *J. Clin. Med.* **2021**, *10*(19), 4593;

Open Questions

- ✓Fixed duration versus continuous therapy
- ✓Combination of drugs
- ✓Sequential treatment
- ✓Mitigation of CRS
- ✓Management of off-target Toxicity