Multiple Myeloma: BiTE therapy and New Immunotherapy on The Horizon

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Multiple Myeloma Translational Initiative

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Disclosures

- Consulting Fees: GSK, Amgen, Indapta Therapeutics, Sanofi, BMS, CareDx, Kite, Karyopharm
- Contracted Research: Celgene/BMS, Janssen, Bluebird Bio, Sutro Biopharma, Teneobio, Poseida, Nektar
- I will be discussing non-FDA approved indications during my presentation

Bispecific T cell engagers

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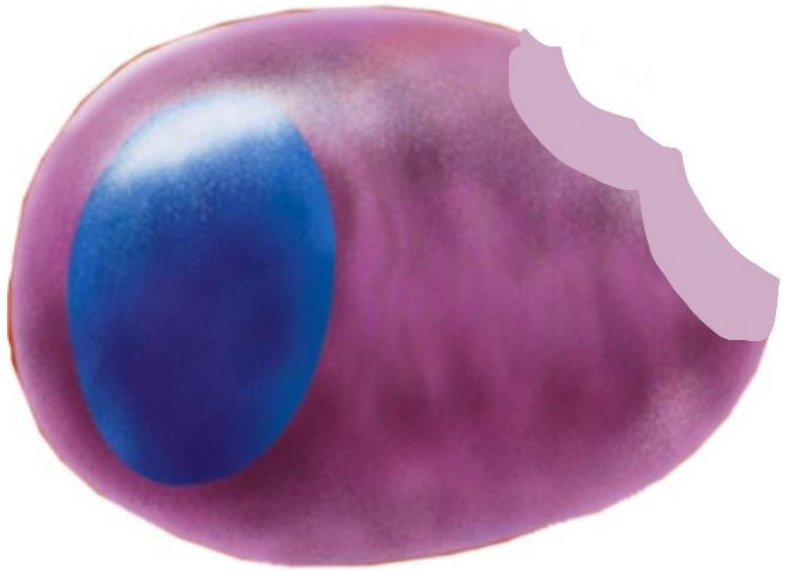
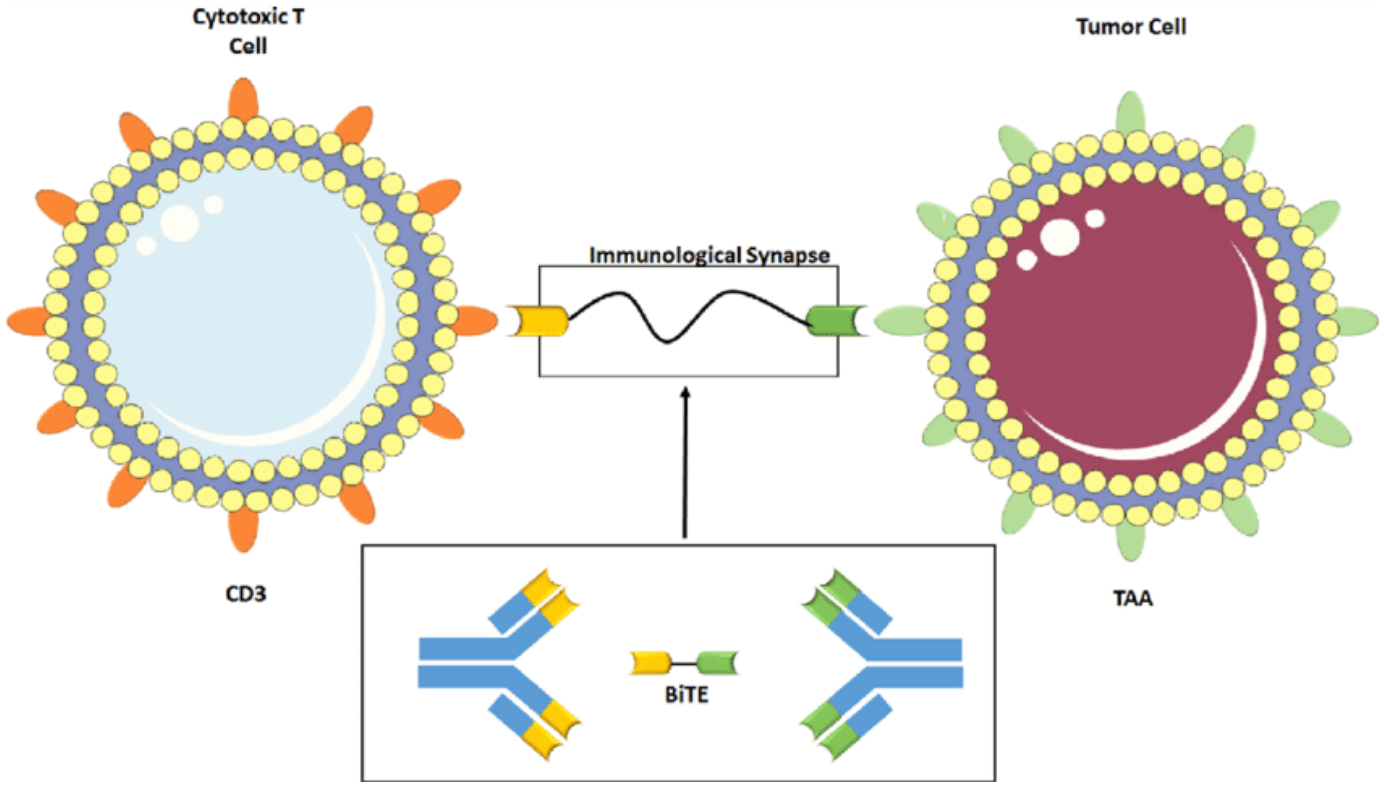
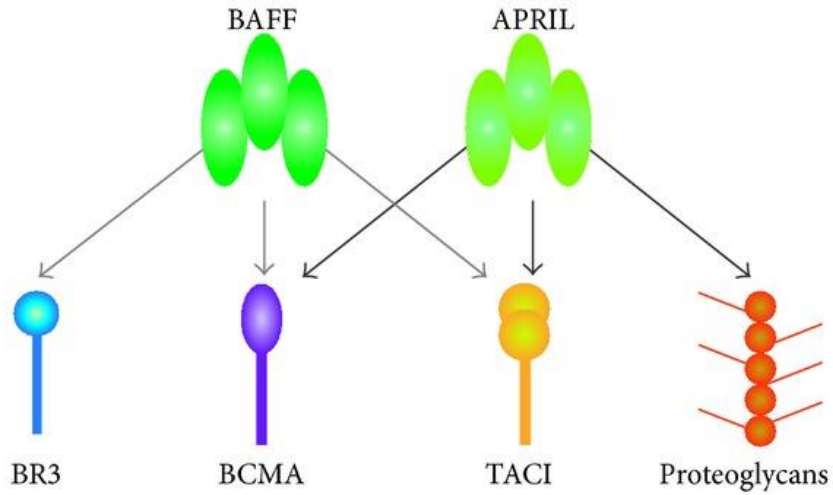


Bispecific T cell engagers



BCMA: B cell maturation antigen

- Member of TNFR (TNFRS17)
- Regulate B cell proliferation and survival, maturation to plasma cells
- Expression/ activation associated with myeloma cell growth/ survival
- Exclusively expressed on the surface of plasmablasts and differentiated PCs



Cho et al, *Frontiers in Immunol,* 2018
Tobon et al, *Autoimm Dis,* 2013

UCSF

Updated Results From MajesTEC-1: Phase 1/2 Study of Teclistamab, a B-Cell Maturation Antigen x CD3 Bispecific Antibody, in Relapsed/ Refractory Multiple Myeloma

Philippe Moreau[1*], Saad Z Usmani[2], Alfred Garfall[3], Niels WCJ van de Donk[4], Hareth Nahi[5], Jesús F San-Miguel[6], Albert Oriol[7], Ajay Nooka[8], Thomas Martin[9], Laura Rosinol[10], Ajai Chari[11], Lionel Karlin[12], Lotfi Benboubker[13], Maria-Victoria Mateos[14], Nizar Bahlis[15], Rakesh Popat[16], Britta Besemer[17], Joaquín Martínez-López[18], Surbhi Sidana[19], Lixia Pei[20], Danielle Trancucci[20], Raluca Verona[21], Suzette Girgis[21], Yunsi Olyslager[22], Mindy Jaffe[20], Clarissa Uhlar[21], Tara Stephenson[21], Rian Van Rampelbergh[22], Arnob Banerjee[21], Jenna D Goldberg[20], Rachel Kobos[20], Amrita Krishnan[23]

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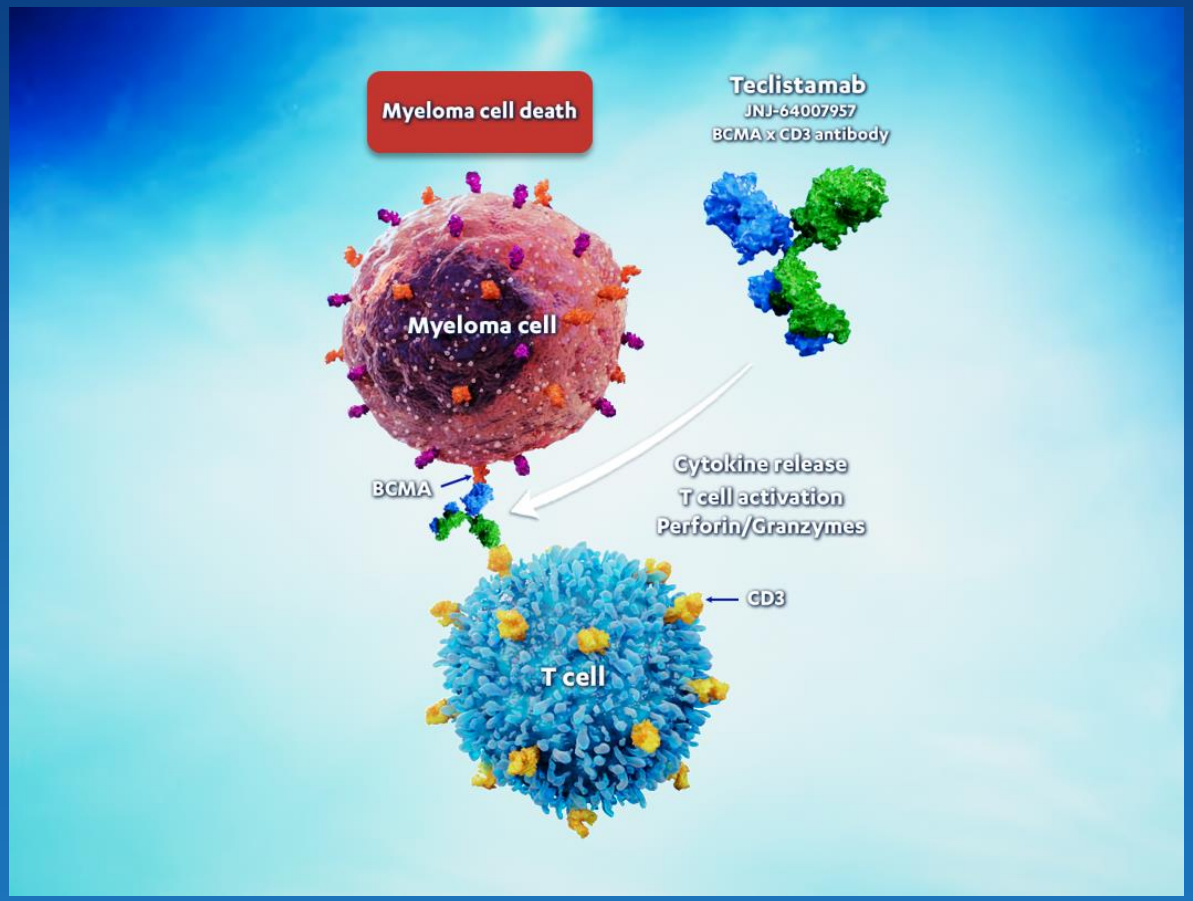
*Presenting author.

Teclistamab:
A Novel BCMA × CD3 T-Cell Redirecting Bispecific Antibody

- Despite newly approved therapies for triple-class exposed patients with RRMM, unmet medical need remains high[1-2]
- Teclistamab (JNJ-64007957) is an off-the-shelf, T-cell redirecting, bispecific antibody that binds to CD3 on T cells and BCMA on plasma cells to mediate T-cell activation and subsequent lysis of BCMA-expressing MM cells
- The phase 1 portion of the MajesTEC-1 study identified the RP2D for teclistamab monotherapy: 1.5 mg/kg subcutaneous (SC) QW with step-up doses of 0.06 and 0.3 mg/kg[3]
- Here we present pivotal phase 1/2 data from the 1.5 mg/kg dose of MajesTEC-1 (NCT03145181; NCT04557098)



BCMA, B-cell maturation antigen; IFN, interferon; IL, interleukin; MM, multiple myeloma; QW, once weekly; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; TNF, tumor necrosis factor

1. Mateos MV, et al. *J Clin Oncol* 2021; 39 (suppl): 8041. 2. Costa L et al. *J Clin Oncol* 2021; 39 (suppl): 8030. 3. Usmani SZ, et al. *Lancet* 2021; 398(10301): 665-74.

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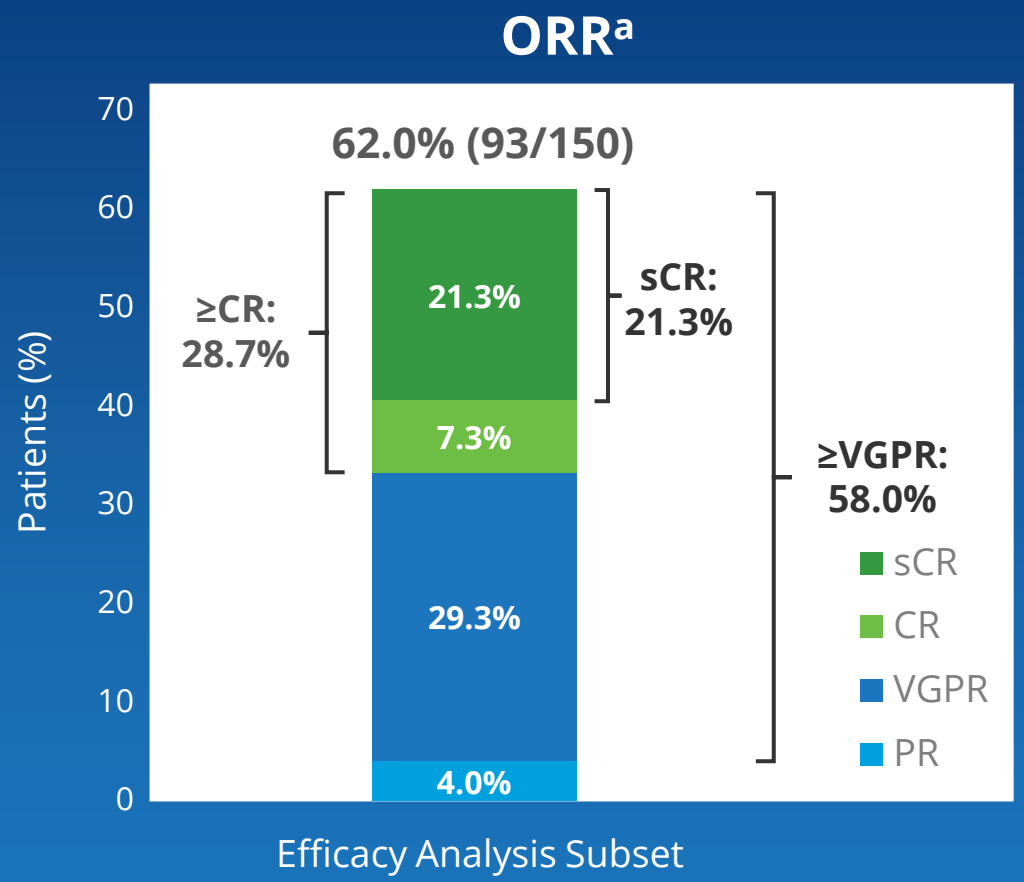
MajesTEC-1: Overall Response Rate for Teclistamab Monotherapy



- At a median follow-up of 7.8 months (range: 0.5+–18):
  - ORR of 62.0% (95% CI: 53.7–69.8) represents a substantial benefit for patients with triple-class exposed disease
- Median time to first response: 1.2 months (range: 0.2–5.5)
- MRD negativity rate[b]
  - 24.7% (37/150; 95% CI: 18.0–32.4) at a threshold of 10^{-5}
  - 16.7% (25/150; 95% CI: 11.1–23.6) at a threshold of 10^{-6}[,c]
- In patients who achieved ≥CR, the MRD-negativity rate was 41.9%

Dose: SC weekly
Med prior lines = 5
CRS 72%, neurotox= 13%

[a]PR or better, IRC assessed; ORR was assessed in efficacy analysis population, which includes all patients who received their first dose on or before March 18, 2021 (n=150); [b] Baseline clones were obtained for all patients All MRD assessments were done by next-generation sequencing; [c]Patients who were not negative at the 10^{-6} threshold were indeterminate.

CR, complete response; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

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A Phase 1 First-in-Human Study of TNB-383B, a BCMA × CD3 Bispecific T-Cell Redirecting Antibody, in Patients with Relapsed/Refractory Multiple Myeloma

Shaji Kumar, MD[1], Anita D'Souza, MD, MS[2-4], Nina Shah, MD[3,4], Cesar Rodriguez, MD[5], Peter M. Voorhees, MD[6], Orlando F. Bueno, MD, PhD[7], Ben Buelow, MD, PhD[8], Kevin J. Freise, PhD, MS[7], Susan Yue, MD[7], Rajvineeth Kumar Pothacamury, MD[7], Akshanth R. Polepally, PhD[7] and Ravi Vij, MD, MBA[9]

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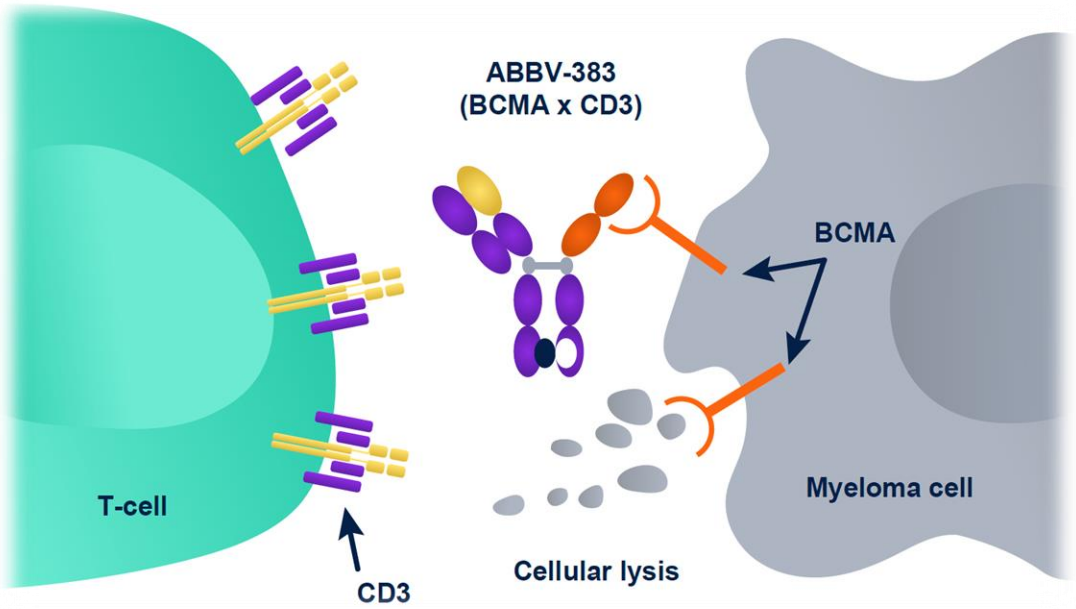
American Society of Hematology (ASH) – 63rd Annual Meeting and Exposition
December 11–14, 2021, Atlanta, Georgia

ABBV-383 in RRMM: Background

- ABBV-383, formerly known as TNB-383B, is a BCMA × CD3 T-cell–engaging bispecific monoclonal IgG4 antibody[1,2]
  - Specifically designed to evade systemic T-cell activation and minimize CRS
  - Recruits CD3+ cells to BCMA+ myeloma cells and induces tumor cell death in cell lines and mouse xenograft models
- Promising results have been demonstrated in an ongoing first-in-human phase 1 study (NCT03933735) in patients with RRMM[3]



Adapted from Shah N, et al. *Leukemia*. 2020;34:985-1005.

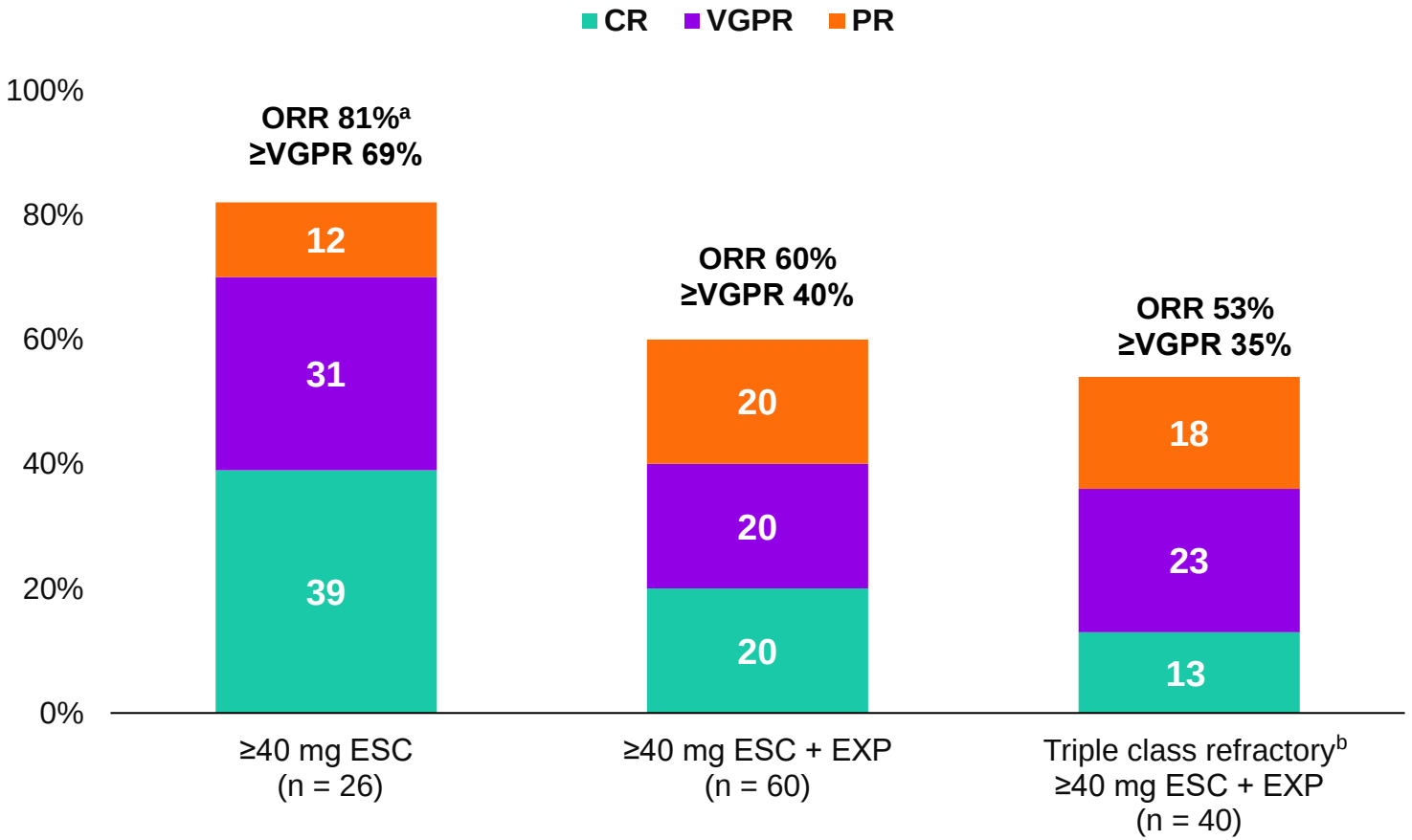
- Herein, updated safety and efficacy outcomes of this phase 1 study are reported

BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; IgG, immunoglobulin G; MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma.

1. Buelow B, et al. *J Clin Oncol*. 2018;36(15 suppl): abstract 8034. 2. Buelow B, et al. *Blood.* 2017;130(suppl 1): abstract 501. 3. Rodriguez C, et al. *Blood.* 2020;136(suppl 1):43-44.

Response Rates by IMWG Criteria

Dose: IV, q 3 week
Med prior lines = 5
CRS 54 -69%



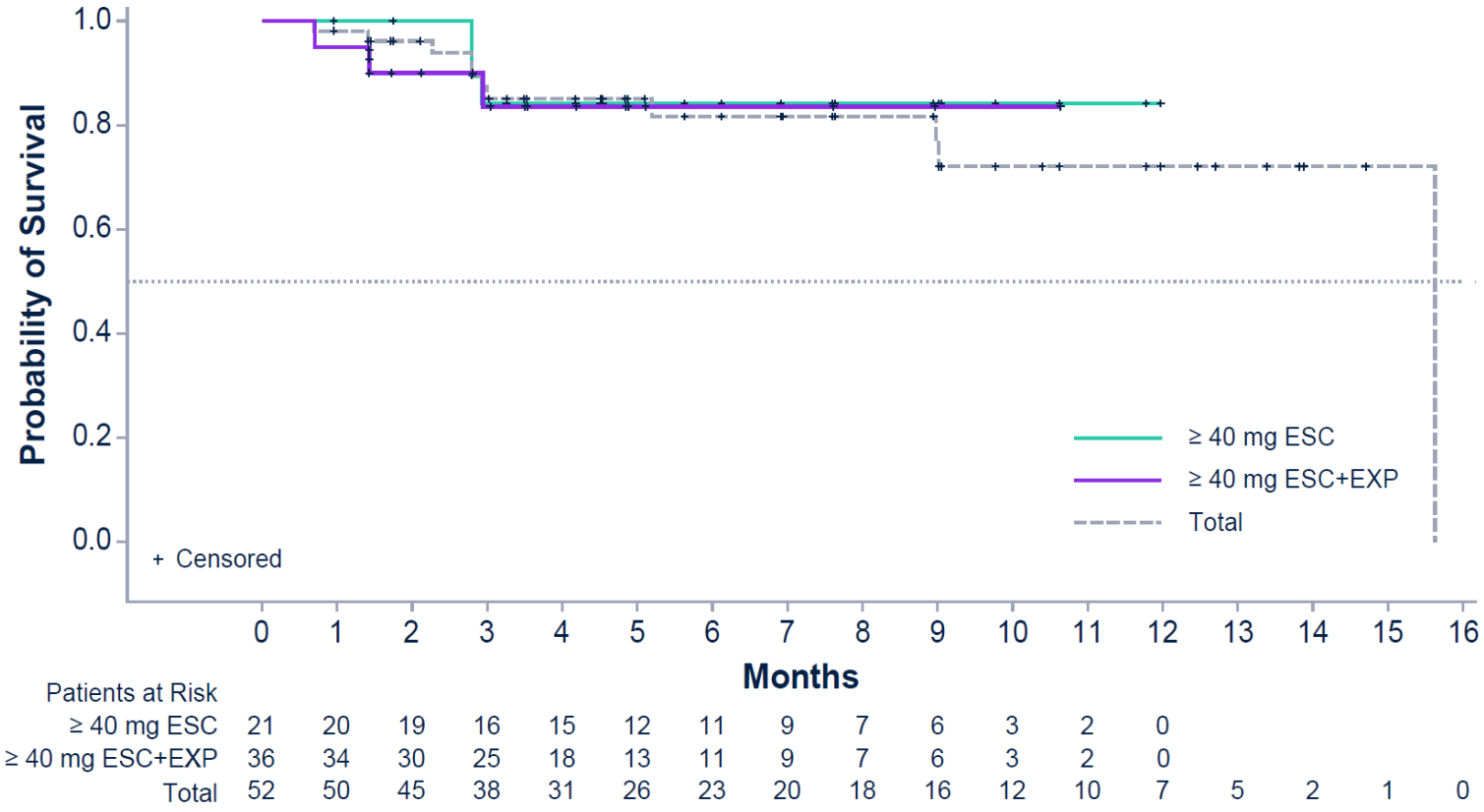
Duration of Follow-up, mo	≥40 mg ESC n = 26	≥40 mg ESC + EXP n = 60
Median	8.0	4.3
Range	0.8–12.8	0.6–12.8

Data cutoff date: Aug 9, 2021.
Modified efficacy-evaluable population includes patients who have received ≥1 dose of ABBV-383 and have ≥1 postdose disease assessment and/or discontinued treatment for any reason by data cutoff date.
[a]Total values due to rounding. [b]Refractory to an immunomodulatory drug, a proteasome inhibitor, and anti-CD38 antibody; programmatically derived confirmed or unconfirmed response (IMWG 2016).

CR, complete response; ESC, dose escalation; EXP, dose expansion; IMWG, International Myeloma Working Group; ORR, objective response rate; PR, partial response; VGPR, very good partial response; ≥VGPR, VGPR or better.

Duration of Response

Confirmed/Unconfirmed (IMWG); ≥40-mg Dose



Duration of Response	Total Patients ≥40 mg ESC + EXP N = 52
Median, mo (range)	NR
KM estimate (95% CI)	
6 mo	81.7 (66.2–90.6)
12 mo	72.1 (52.1–84.8)

Data cutoff date: Aug 9, 2021.

Total patients at risk are from ≥40-mg dose-escalation/dose-expansion cohorts. Median follow-up: ≥40-mg dose ESC, 8.0 months; ≥40-mg dose ESC and EXP, 4.3 months.
ESC, dose escalation; EXP, dose expansion; IMWG, International Myeloma Working Group; KM, Kaplan-Meier; NR, not reached.

Bispecifics

Drug	Target	Med prior lines	Dosing	ORR	CRS %	Neurotox %	Notes
Teclistamab (n=150)	**BCMA**	**6 (5@RP2D)**	**SC weekly for RP2D**	**62% @RP2D)**	**72%**	**13%**	**SC dosing, SC dosing, 9 month PFS 58.5% ***
Teneobio TNB-383B (n=60)	**BCMA**	**5**	**Q3 weeks**	**60-80% @ ≥ 40 mg dose, n=60**	**54-69%**	**2%**	**IV Q 3 week, allowed for CrCl 30***
REGN-5458 (n=24)	**BCMA**	**5**	**Q2 week after W 16**	**75% @ 200-800 mg doses, n=24**	**38%**	**4%**	*** IV**
AMG-701 (n=85, 6)	**BCMA**	**6**	**weekly**	**83% @highest does, n=6**	**64% (9% G3)**	**3.8%**	
Elrantamab (n=55)	**BCMA**	**6**	**SC weekly or Q2W (can do @ 6mo tx)**	**69% @ 1000 ug/kg QW dose**	**87% (↓ with priming & pre-meds)**	**20%**	**22% with prior BMCA tx→ 70% ORR***
Talquetamab n=30 @ 405ug QW, 25 @ 800 ug Q2W	GPRC5D	6, 5	RP2D = 405ug QW or 800 ug Q2w	70%, 67%	77%, 72%	5%, (7% @RP2D) *from previoius congress data	27% and 16% with prior BCMA tx in 405 and 800 respectively SC dosing Dysguesia, 75% skin/nail AE's DOR 52% at 405 dose at 10 m *
Cevostamab (n=161)	FcRH5	6	IV Q3 weeks (C2)	57% in higher doses, (n=60) 40% in prior BCMA pts (in Q/A, not slides)	81%	14%	mDOR 11.5 mo 34% with prior BCMA tx *

Updated Phase 1 Results From MonumenTAL-1: First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma

Amrita Krishnan[1*], Monique C. Minnema[2], Jesus G Berdeja[3], Albert Oriol[4], Niels WCJ van de Donk[5], Paula Rodríguez-Otero[6], Elham Askari[7], María-Victoria Mateos[8], Luciano J Costa[9], Raluca Verona[10], Joanne Ma[10], Suzette Girgis[10], Shiyi Yang[10], Brandi W Hilder[10], Jeffery Russell[10], Jenna D Goldberg[11], Ajai Chari[12]

[1]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [2]University Medical Center Utrecht, Utrecht, Netherlands; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]Hospital Germans Trias I Pujol, Spain; [5]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [6]University of Navarra, Pamplona, Spain, Navarra, Spain; [7]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [8]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; [9]University of Alabama at Birmingham, Birmingham, AL, USA; [10]Janssen Research & Development, Spring House, PA, USA; [11]Janssen Research & Development, Raritan, NJ, USA; [12]Mount Sinai School of Medicine, New York, NY, USA

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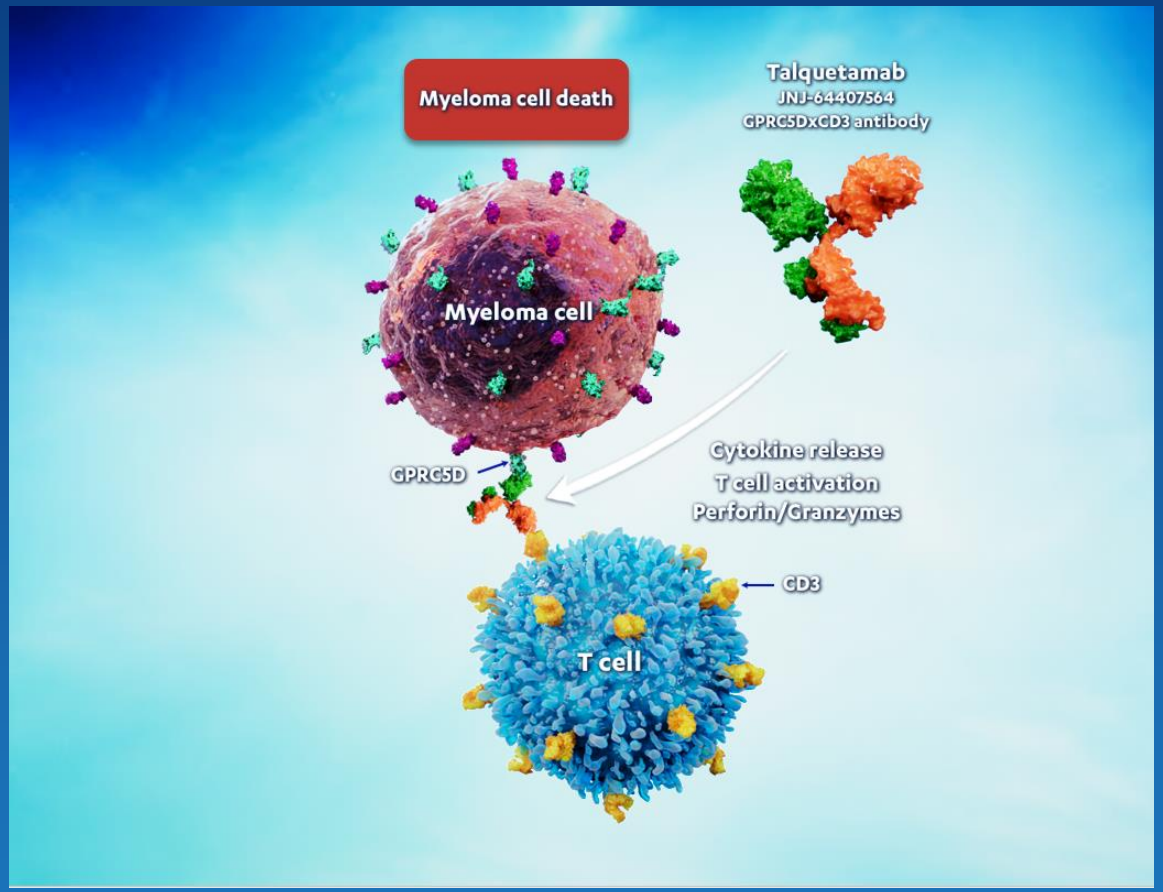
*Presenting author.

Additional information can be viewed by scanning the QR code or accessing this link: https://www.oncologysciencehub.com/ASH2021/Talquetamab/Krishnan

Talquetamab: A GPRC5D × CD3 Bispecific Antibody

- GPRC5D is highly expressed on MM plasma cells, making it a promising target for MM therapy[1-5]
- Talquetamab (JNJ-64407564) is a first-in-class antibody that binds to GPRC5D and CD3 receptors, mediating T cell recruitment, activation and subsequent lysis of GPRC5D+ MM cells[6]
- In the ongoing, phase 1, first-in-human study of talquetamab in patients with RRMM (MonumenTAL-1; NCT03399799), the first RP2D was identified as a weekly SC dose of 405 µg/kg[a,7–8]
- Here we present
  - Updated data from patients treated at the first RP2D[a]
  - Initial results from patients treated at a second RP2D of 800 µg/kg Q2W



[a]In phase 1, 405 µg/kg SC QW was the RP2D; 400 µg/kg SC QW was selected as final dosing concentration in phase 2 for operational convenience.
GPRC5D, G protein-coupled receptor family C group 5 member D; MM, multiple myeloma; RP2D, recommended phase 2 dose; Q2W, every other week; QW, weekly; RRMM, relapsed/refractory MM; SC, subcutaneous

1. Verkleij CPM, et al. *Blood Adv* 2021; 5:2196-215. 2. Smith EL, et al. *Sci Transl Med* 2019; 11:eaau7746. 3. Inoue S, et al. *J Invest Dermatol* 2004; 122:565-73. 4. Brauner-Osborne H, et al. *Biochim Biophys Acta* 2001; 1518:237-48. 5.Goldsmith, R et al. 18th International IMW Workshop 2021. Poster P095. 6. Pillarisetti K, et al. *Blood* 2020; 135:1232-43. 7. Chari A, et al. 62nd ASH Annual Meeting and Exposition 2020. Oral #290. 8. Berdeja J, et al. ASCO Annual Meeting 2021. Oral #8008.

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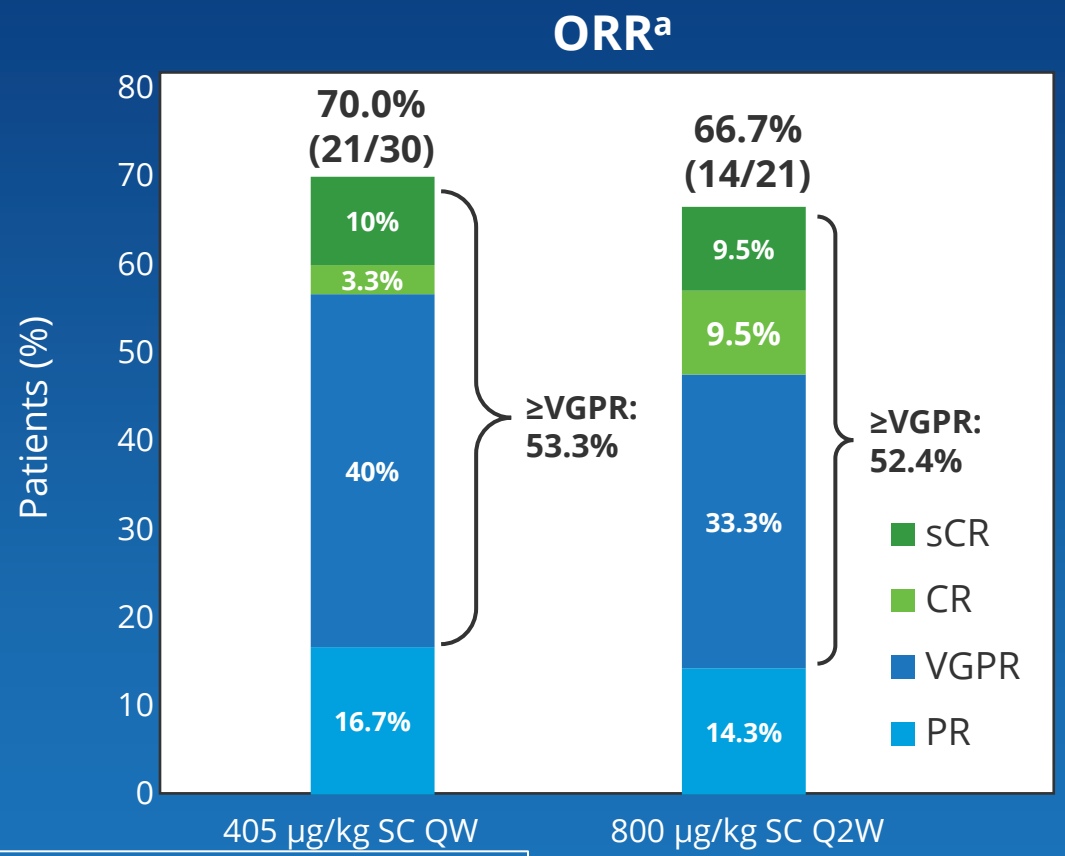
MonumenTAL-1: Overall Response Rate



Response	405 µg/kg SC QW[b] n=30	800 µg/kg SC Q2W[b] n=25
Median follow-up (months), median (range)	9.0 (0.9–17.1)	4.8 (0.4–11.1)
Response-evaluable patients,[c] n	30	21
ORR, n (%)	21 (70.0)	14 (66.7)
ORR in triple-class–refractory patients, n/N (%)	15/23 (65.2)	12/18 (66.7)
ORR in penta-drug–refractory patients, n/N (%)	5/6 (83.3)	5/6 (83.3)
Median time to first confirmed response (months), median (range)	0.9 (0.2–3.8)	1.2 (0.2–6.8)

- ORR appears to be comparable across both RP2Ds

Med prior lines = 5
CRS 77%, 72%

[a]Investigator assessment of evaluable patients per 2011 IMWG response criteria; includes unconfirmed responses; [b]With 2–3 step-up doses; [c]Patients who had ≥1 dose of talquetamab and ≥1 postbaseline disease evaluation.
CR, complete response; IMWG, International Myeloma Working Group; ORR, overall response rate; PR, partial response; Q2W, every other week; QW, weekly; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response

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Cevostamab monotherapy continues to show clinically meaningful activity and manageable safety in patients with heavily pre-treated relapsed/refractory multiple myeloma: updated results from an ongoing Phase I study

Suzanne Trudel,[1] Adam D Cohen,[2] Amrita Krishnan,[3] Rafael Fonseca,[4] Andrew Spencer,[5] Jesus G Berdeja,[6] Alexander Lesokhin,[7] Peter A Forsberg,[8] Jacob P Laubach,[9] Luciano J Costa,[10] Paula Rodriguez-Otero,[11] Rayan Kaedbey,[12] Joshua Richter,[13] Maria-Victoria Mateos,[14] Sheeba K Thomas,[15] Chihunt Wong,[16] Mengsong Li,[16] Voleak Choeurng,[16] Anjali Vaze,[16] Divya Samineni,[16] Teiko Sumiyoshi,[16] James Cooper,[16] Simon Harrison[17]

[1]Princess Margaret Cancer Centre and University of Toronto, Toronto, ON, Canada; [2]Abramson Cancer Center and University of Pennsylvania, Philadelphia, PA, USA; [3]City of Hope, Duarte, CA, USA; [4]Mayo Clinic in Arizona, Phoenix, AZ, USA; [5]Alfred Health-Monash University, Melbourne, VIC, Australia; [6]Sarah Cannon Research Institute, Nashville, TN, USA; [7]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [8]University of Colorado School of Medicine, Aurora, CO, USA; [9]Dana-Farber Cancer Institute, Boston, MA, USA; [10]O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL, USA; [11]Clínica Universidad de Navarra, Pamplona, Spain; [12]Jewish General Hospital, McGill University, Montreal, QC, Canada; [13]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [14]Instituto de Investigación Biomédica de Salamanca (IBSAL), Hospital Universitario de Salamanca, Salamanca, Spain; [15]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [16]Genentech, Inc., South San Francisco, CA, USA; [17]Peter MacCallum Cancer Centre, Sir Peter MacCallum Department of Oncology, Melbourne University, and The Royal Melbourne Hospital, Melbourne, VIC, Australia

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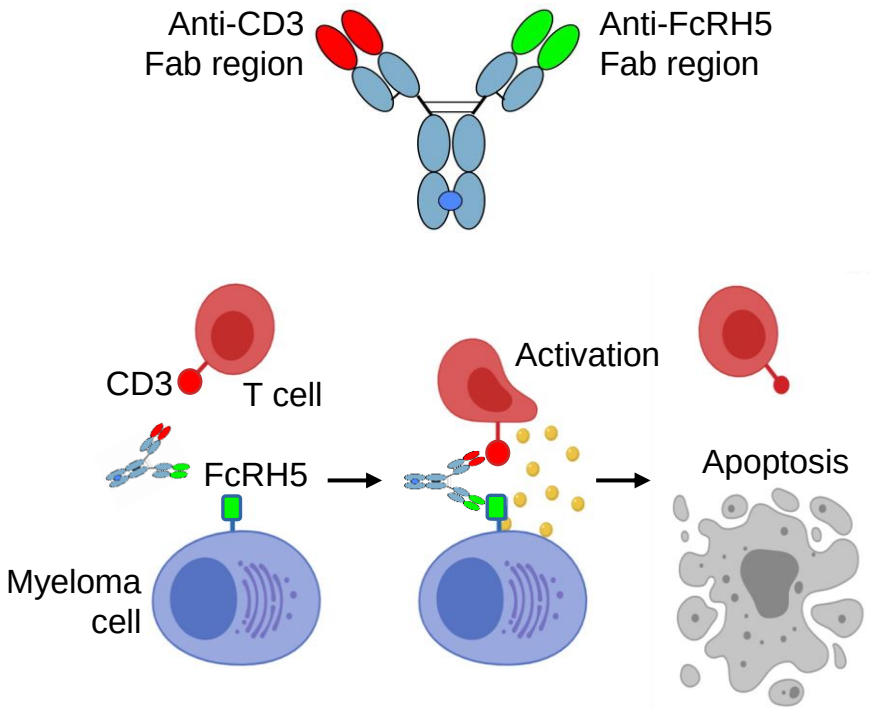
Cevostamab: FcRH5xCD3 bispecific antibody

- Fc receptor-homolog 5 (FcRH5)
  - expressed exclusively in B-cell lineage (myeloma cells > normal B cells)[1]
  - near ubiquitous expression on myeloma cells[1,2]
- Cevostamab bispecific antibody
  - targets membrane-proximal domain of FcRH5 on myeloma cells and epsilon domain of CD3 on T cells[1]
  - dual binding results in T-cell directed killing of myeloma cells[1]
- Previously reported Phase I dose-finding experience (NCT03275103)[3]
  - promising activity in patients with heavily pre-treated RRMM
  - manageable safety, with C1 single step-up dosing providing effective CRS mitigation



Aims: (1) share updated Phase I dosing-finding results, and
(2) evaluate the impact of C1 single step-up and C1 double step-up dosing on CRS

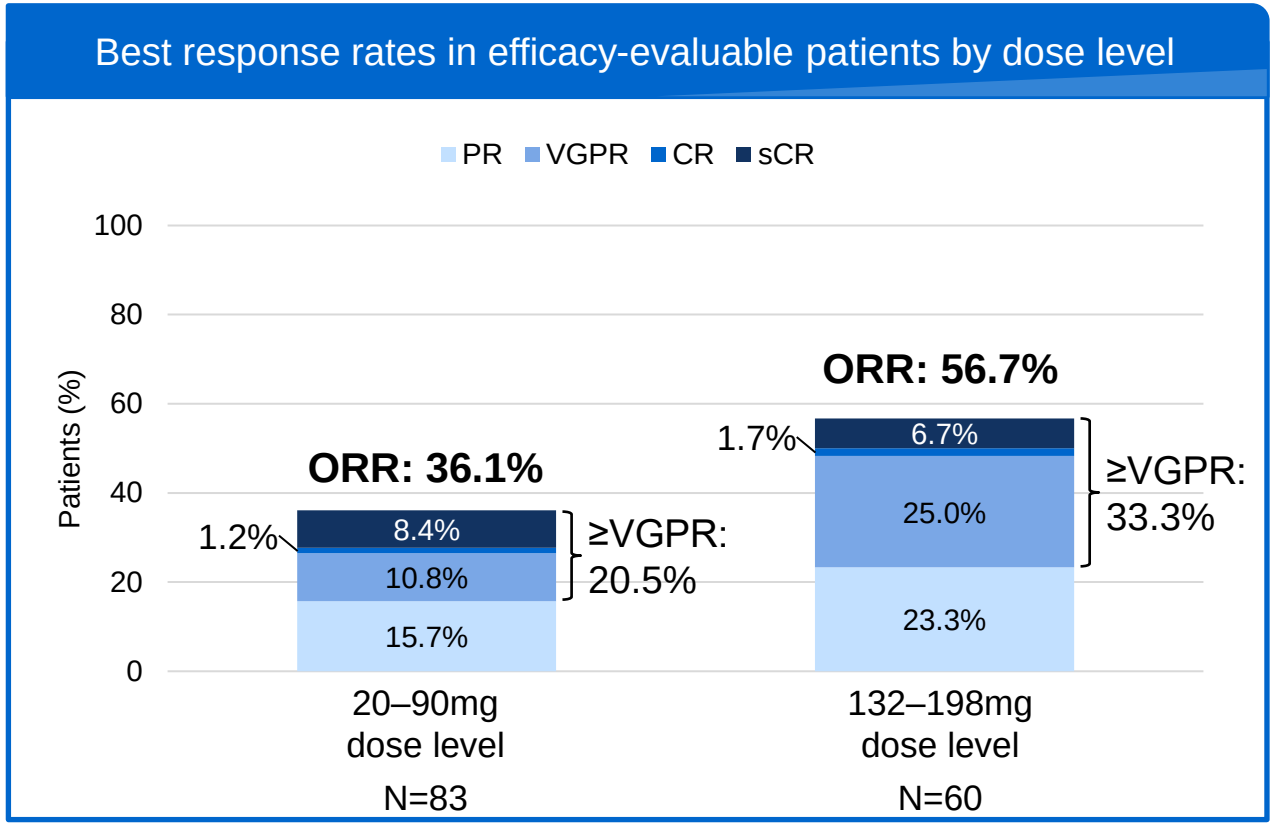
C, Cycle; CRS, cytokine release syndrome;
Fab, fragment antibody binding; RRMM, relapsed/refractory multiple myeloma

1. Li et al. Cancer Cell 2017;31:383–95
2. Sumiyoshi et al. EHA 2021; 3. Cohen et al. ASH 2020

Response

Dose: IV, q 3 week
Med prior lines = 6
CRS 81%; neurotox 14%

- Response observed at the 20mg target dose level and above (N=143 patients)
- ORR increases with target dose
  - ORR in C1 single step-up expansion (3.6/90mg): 29.0%
  - ORR in C1 double step-up expansion (0.3/3.6/160mg): 54.8%
- Response occurs early
  - median time to first response: 1.0 mo (range: 0.7–5.9)
- Response deepens over time
  - median time to best response: 2.1 mo (range: 0.7–11.4)
- MRD negativity by NGS ($<10^{-5}$) detected in 7/10 evaluable patients with ≥VGPR



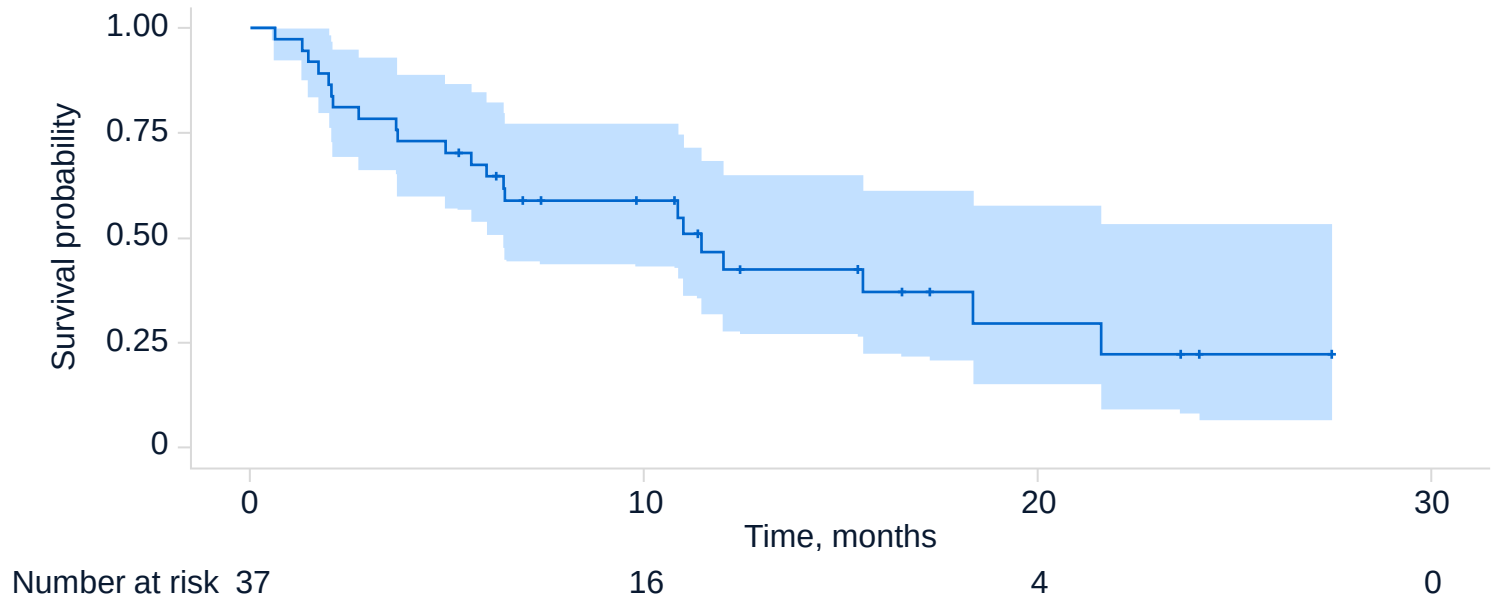
- Cevostamab was efficacious in patients with heavily pre-treated RRMM. ORR increased with target dose.

CR, complete response; MRD, minimal residual disease; NGS, next generation sequencing; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Duration of response

- Median follow-up in responders
  - C1 single step-up cohorts: 14.3 months (range: 2.7–31.8)
  - C1 double step-up cohorts: 6.5 months (range: 4.8–21.4)
- 6 patients in the C1 single step-up cohorts continued in response for ≥6 months after cessation of treatment

Median duration of response among responders in the C1 single step-up cohorts



Median duration of response: 11.5 months (95% CI: 6.0, 18.4)

- Responses were durable. Responses were maintained after cessation of treatment.

Bispecifics

Drug	Target	Med prior lines	Dosing	ORR	CRS %	Neurotox %	Notes
Teclistamab (n=150)	BCMA	6 (5@RP2D)	SC weekly for RP2D	62% @RP2D)	72%	13%	SC dosing, SC dosing, 9 month PFS 58.5% *
Teneobio TNB-383B (n=60)	BCMA	5	Q3 weeks	60-80% @ ≥ 40 mg dose, n=60	54-69%	2%	IV Q 3 week, allowed for CrCl 30*
REGN-5458 (n=24)	BCMA	5	Q2 week after W 16	75% @ 200-800 mg doses, n=24	38%	4%	* IV
AMG-701 (n=85, 6)	BCMA	6	weekly	83% @highest does, n=6	64% (9% G3)	3.8%	
Elrantamab (n=55)	BCMA	6	SC weekly or Q2W (can do @ 6mo tx)	69% @ 1000 ug/kg QW dose	87% (↓ with priming & pre-meds)	20%	22% with prior BMCA tx→ 70% ORR*
Talquetamab n=30 @ 405ug QW, 25 @ 800 ug Q2W	**GPRC5D**	**6, 5**	**RP2D = 405ug QW or 800 ug Q2w**	**70%, 67%**	**77%, 72%**	**5%, (7% @RP2D) *from previoius congress data**	**27% and 16% with prior BCMA tx in 405 and 800 respectively SC dosing Dysguesia, 75% skin/nail AE's DOR 52% at 405 dose at 10 m ***
Cevostamab (n=161)	**FcRH5**	**6**	**IV Q3 weeks (C2)**	**57% in higher doses, (n=60) 40% in prior BCMA pts (in Q/A, not slides)**	**81%**	**14%**	**mDOR 11.5 mo 34% with prior BCMA tx ***

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If this is so great… can we do better???

Phase 1b Results for Subcutaneous Talquetamab Plus Daratumumab in Patients With Relapsed/Refractory Multiple Myeloma

Ajai Chari[1*], Parameswaran Hari[2], Nizar Bahlis[3], Maria-Victoria Mateos[4], Niels WCJ van de Donk[5], Bhagirathbhai Dholaria[6], Alfred L Garfall[7], Hartmut Goldschmidt[8], K Martin Kortüm[9], Amrita Krishnan[10], Thomas Martin[11], Daniel Morillo[12], Albert Oriol[13], Donna Reece[14], Cesar Rodriguez[15], Paula Rodríguez-Otero[16], Jesús F San-Miguel[16], Saad Z Usmani[17], Raluca Verona[18], Shun Xin Wang Lin[18], Thomas J Prior[18], Mark Wade[18], Brendan Weiss[18], Jenna D Goldberg[19], Elham Askari[12]

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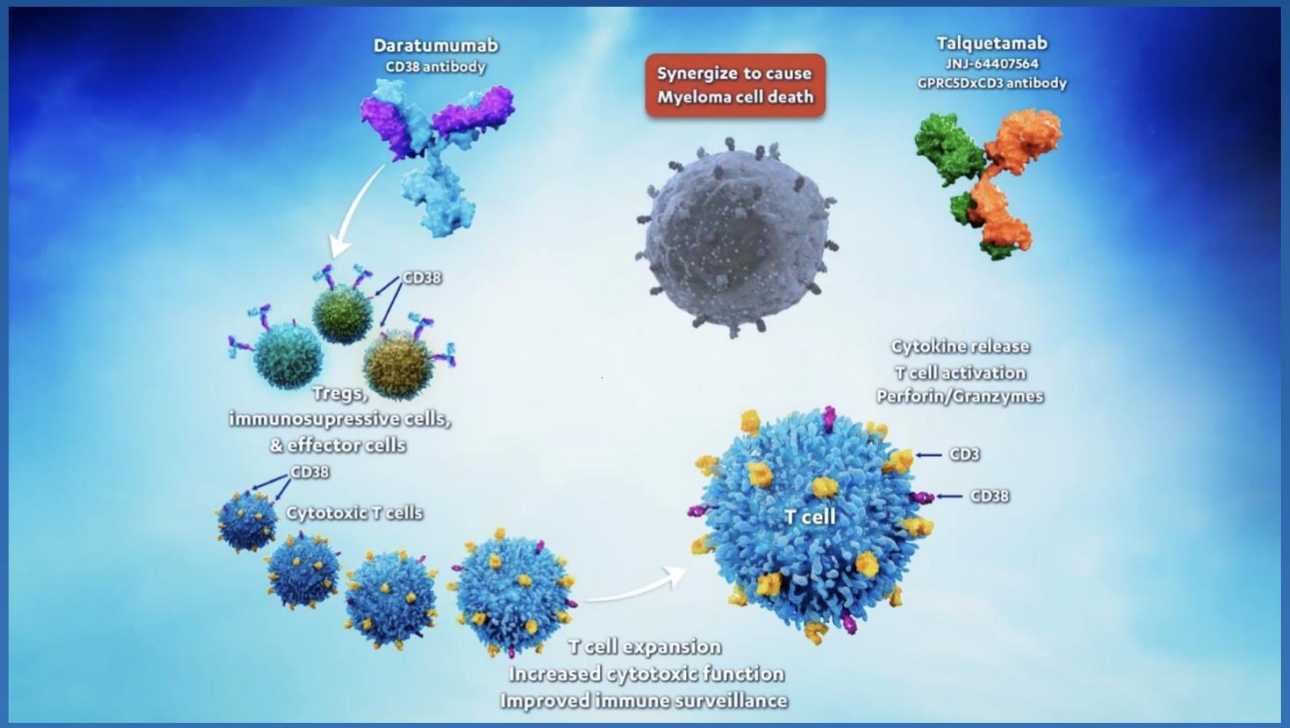
Talquetamab and Daratumumab: Rational Combination Partners

- Daratumumab (dara) is a human IgG1κ mAb targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action[1]
  - Dara monotherapy leads to T cell expansion and enhanced T cell cytotoxic potential[2]
  - Talquetamab (tal; JNJ-64407564) is a novel, first-in-class antibody that binds to GPRC5D and CD3 receptors, mediating T cell recruitment, activation, and subsequent lysis of GPRC5D+ MM cells[3]
- The combination of tal and dara has the potential to yield synergistic clinical efficacy
  - Preclinical studies showed the addition of dara enhanced tal-mediated lysis of MM cells[4]



TRIMM-2: Talquetamab and Daratumumab Study Design

Here we present data for RRMM patients who received tal in combination with dara in a phase 1b, open-label, multicenter, multicohort trial (TRIMM-2; NCT04108195); data cut-off September 7, 2021

Key Study Eligibility Criteria

- Adults with documented diagnosis of MM per IMWG criteria
- ≥3 prior lines of therapy[a] or double refractory to a PI and an IMiD
- Treatment with anti-CD38 therapy >90 days prior allowed, including patients who were refractory to anti-CD38 therapy

Key Study Objectives

- Part 1: Identify RP2D(s) for each treatment combination
- Part 2: Characterize safety of each treatment combination at the selected RP2D(s)
- Antitumor activity, PK/PD

Tal + Dara Dosing Cohorts (n=29)

Tal	Dara SC	Patients enrolled to date (n)
400 µg/kg SC Q2W	1800 mg SC Cycles 1-2: QW Cycles 3-6: Q2W Cycles 7+: monthly	5
400 µg/kg SC QW		9
800 µg/kg SC Q2W		15

- Step-up dosing was used for tal[b]
- Dara was administered according to the approved SC schedule[1]
- Premedications[c] were limited to the step-up doses and first full dose of tal
  - **No steroid requirement for tal after the first full dose**

[a]Including a PI and IMiD; [b]1-3 step-up doses given within 1 week before a full dose; [c]Glucocorticoid, antihistamine, and antipyretic.
Dara, daratumumab; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; PD, pharmacodynamic; PI, proteasome inhibitor; PK, pharmacokinetic; QW, weekly; Q2W, every 2 weeks; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; Tal, talquetamab

1. DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use [package insert].

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

TRIMM-2: Overall Response Rate

Med prior lines = 6
CRS 55%;
Skin/nail events: 65%

Response Categories	Evaluable patients[a], n (%)		
	Dara 1800 mg SC: Cycle 1-2: QW, Cycles 3-6: Q2W; Cycles 7+: monthly		
	Tal 400 µg/kg SC Q2W (n=5)	Tal 400 µg/kg SC QW (n=7)	Tal 800 µg/kg SC Q2W (n=9)
ORR[b]	**4 (80.0)**	**6 (85.7)**	**7 (77.8)**
sCR/CR	1 (20.0)	2 (28.6)	1 (11.1)
VGPR	2 (40.0)	3 (42.9)	5 (55.6)
PR	1 (20.0)	1 (14.3)	1 (11.1)
MR	0 (0)	0 (0)	0 (0)
SD	0 (0)	1 (14.3)	2 (22.2)
PD	1 (20.0)	0 (0)	0 (0)

- Median follow-up was 4.2 months
- Median time to first confirmed response: 1.0 month (range: 0.9–2.4)
- ORR across all dose levels was improved compared to RP2Ds for tal monotherapy

[a]Patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator. Includes unconfirmed responses;
[b]PR or better in response-evaluable patients; includes unconfirmed responses.
CR, complete response; Dara, daratumumab; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; QW, weekly; Q2W, every other week; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; Tal, talquetamab; VGPR, very good partial response

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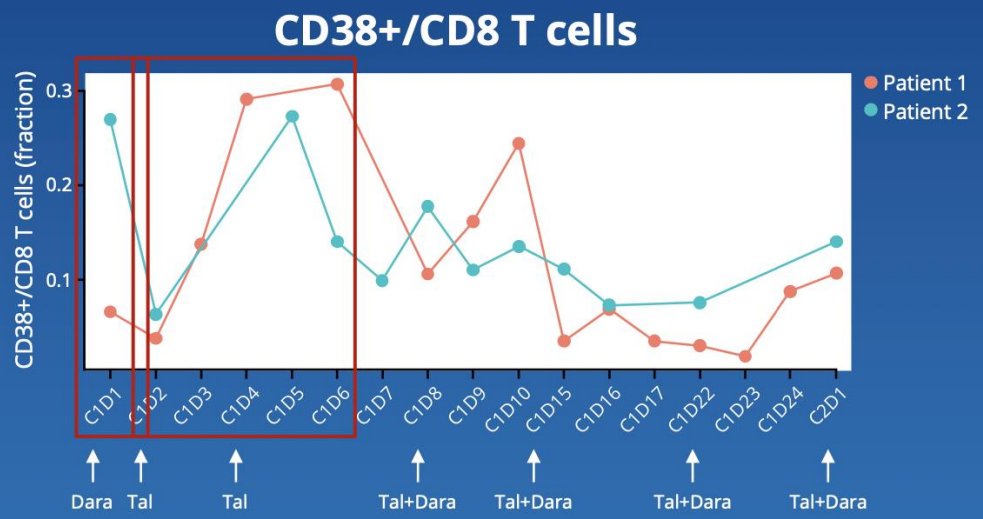
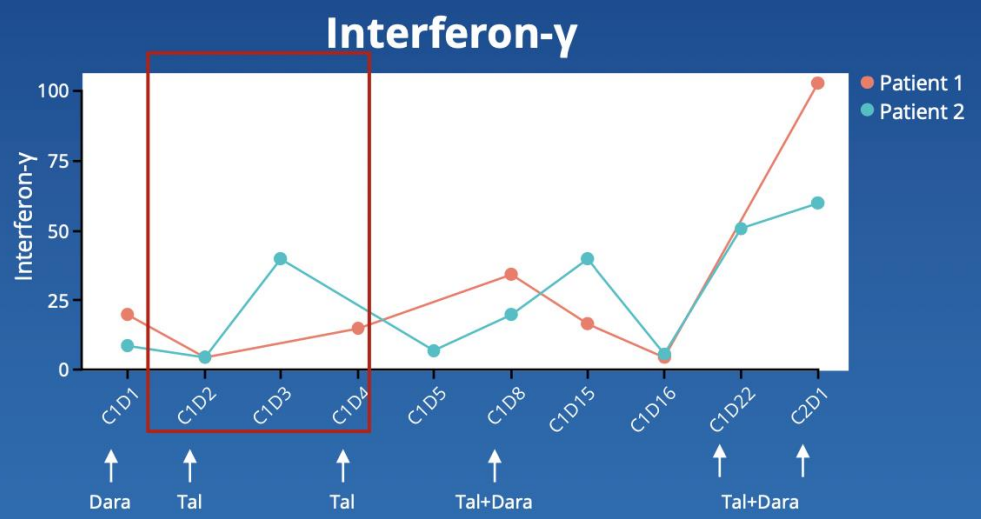
TRIMM-2: Tal + Dara Leads to Peripheral T-Cell Activation and Induction of CD38+/CD8+ T cells





- Peripheral T cell activation was observed with tal + dara, as evidenced by upregulation of CD38+/CD8+ T cells
  - The proportion of CD38+/CD8+ T cells declined after initial dara dosing on C1D1, consistent with previous data
  - **Notably, tal administration led to induction of CD38+ T cells after C1D2 despite concurrent dara treatment**
- Induction of pro-inflammatory cytokines was observed following tal dosing in presence of dara
- The pharmacokinetic profile of tal in the presence of dara was consistent with the profile observed in the phase 1 tal monotherapy (MonumenTAL-1)

Data cut-off Aug 6, 2021. C, cycle; D, day; Dara, daratumumab; Tal, talquetamab

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

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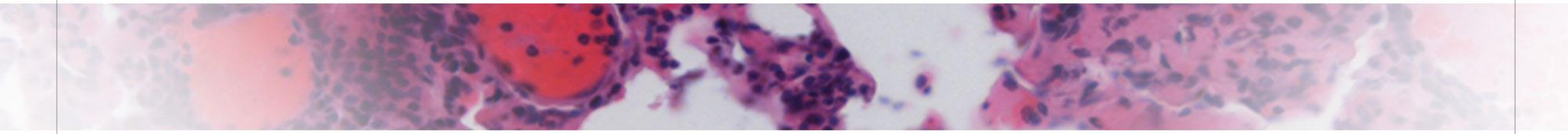

DREAMM-5 Study: Investigating the Synergetic Effects of Belantamab Mafodotin plus Inducible T-cell Co-Stimulator Agonist (aICOS) Combination Therapy in Patients with Relapsed/Refractory Multiple Myeloma

Natalie S. Callander, MD[1], Vincent Ribrag, MD[2], Paul G. Richardson, MD[3], Ajay K. Nooka, MD, MPH, FACP[4], Kevin Song, MD, FRCPC[5], Katarina Uttervall, MD, PhD[6], Monique C. Minnema, MD, PhD[7], Katja Weisel, MD[8], Hang Quach, MD[9], Chang-Ki Min, MD, PhD[10], Marc S. Ballas, MD, MPH[11], Xiaofang Li[11], Nirav Ratia[12], Morrys Kaisermann, MD, PhD[11], Beata Holkova, MD[11], Suzanne Trudel, MD[13]

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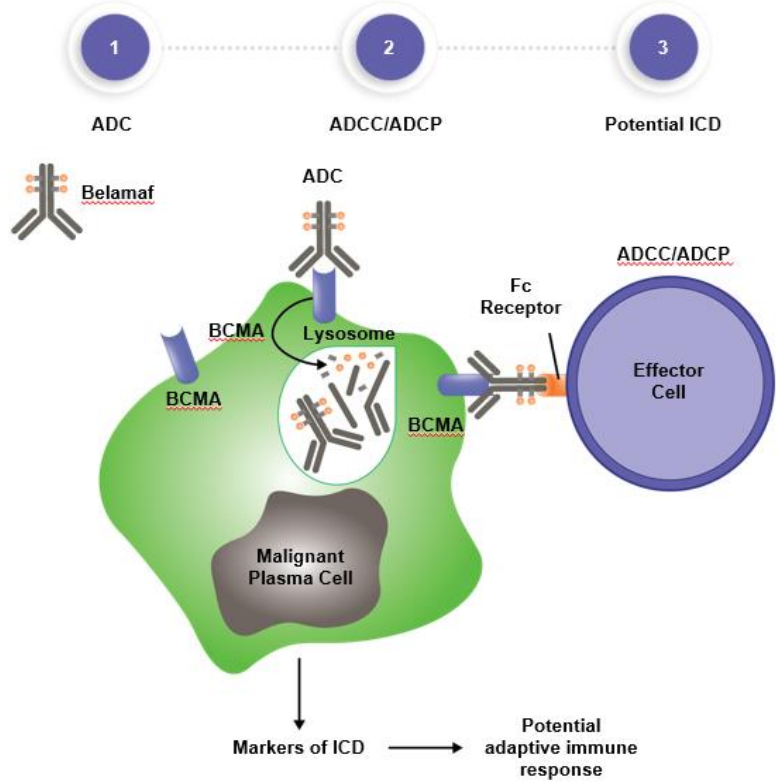
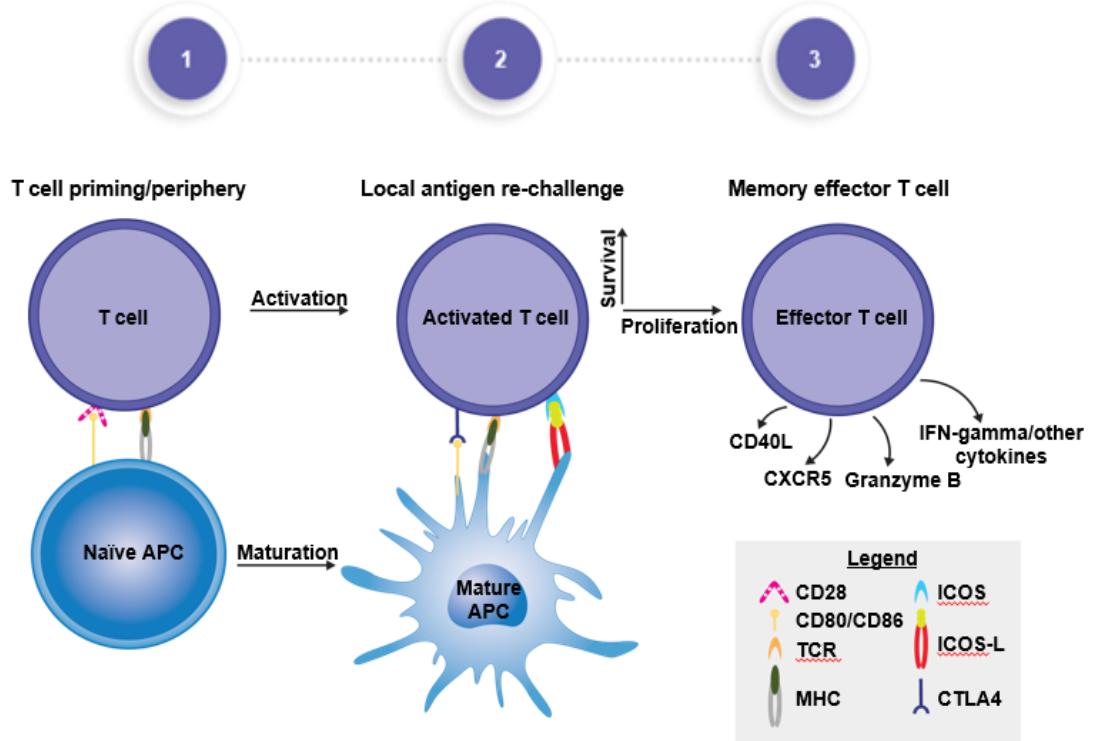
Complementary Mechanisms of Action

Combining belamaf and its ICD effects with immune response-enhancing agents such as feladilimab, an inducible co-stimulatory T-cell molecule (ICOS, CD278) agonist (aICOS), could offer enhanced antitumor activity due to complementary MoA targeting T-cells.

Belantamab mafodotin MoA[1]



aICOS MoA[1]



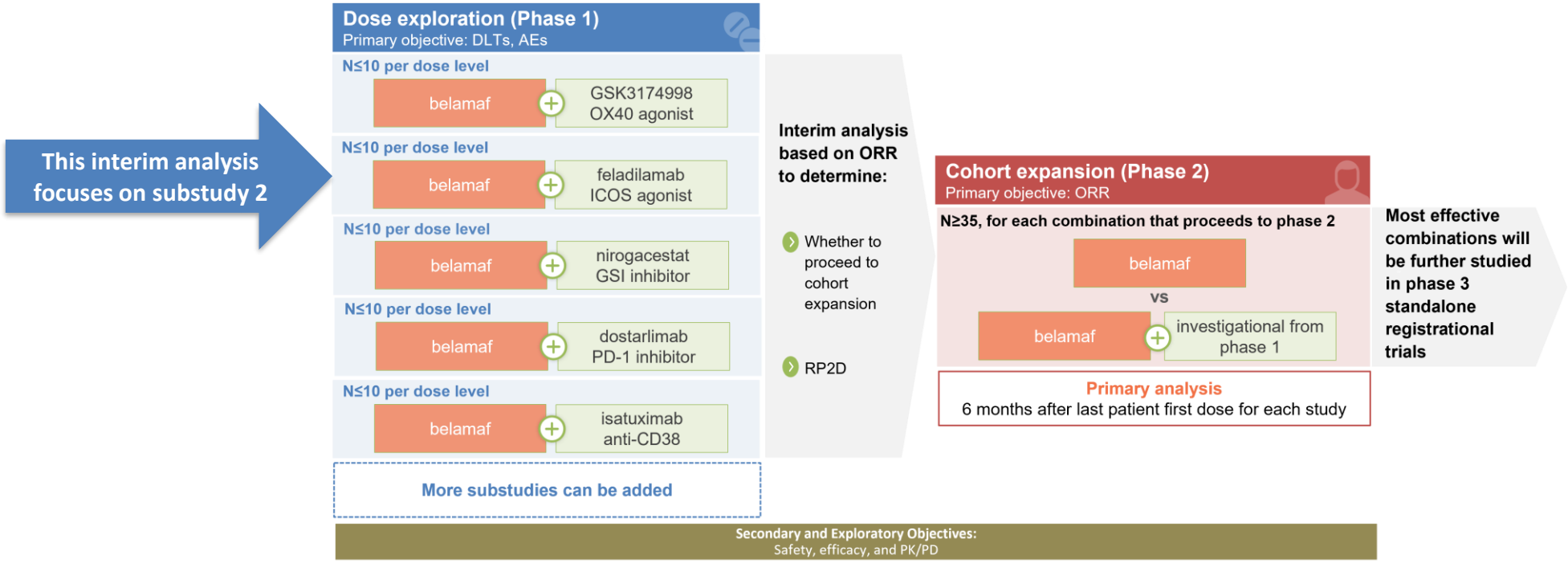
ADC, antibody-drug conjugate; ADCC/ADCP, antibody-dependent cellular cytotoxicity/phagocytosis; AE, adverse event; aICOS, inducible co-stimulatory T-cell molecule agonist; APC, antigen presenting cell; BCMA, B-cell maturation antigen; CDXX, cluster of differentiation XX; CTLA4, cytotoxic T-lymphocyte–associated antigen 4; CXCR5, C-X-C chemokine receptor type 5; Fc, fragment crystallizable; ICD, immune cell death; ICOS, inducible co-stimulatory T-cell molecule; ICOS-L, inducible co-stimulatory T-cell molecule ligand; IFN, interferon; MHC, major histocompatibility complex; MoA, mechanism of action; TCR, T cell receptor.

1. Nooka A, et al. *Future Oncol.* 2021;17:1987. Figures from Nooka et al. 2021; Belamaf MoA reproduced under Creative Commons Attribution license and aICOS MoA reproduced with permission Future Medicine Ltd.

DREAMM-5 Platform Trial Design

Phase 1/2 platform study that incorporates an efficient design into one master protocol evaluating multiple belamaf-containing combinations in separate substudies to identify efficacious combinations.[1]

Each substudy begins with a dose-exploration (DE) phase; substudies with successful DE phases will subsequently move into a cohort-expansion (CE) phase to compare the combination with a shared single-agent belamaf control arm.[1]



AE, adverse event; belamaf, belantamab mafodotin; CD38, cluster of differentiation 38; DLT, dose-limiting toxicities; ECOG; Eastern Cooperative Oncology Group; GSI, gamma secretase inhibitor; ICOS, inducible co-stimulatory T-cell molecule; ORR, overall response rate; PD, pharmacodynamics; PD-1, programmed cell death protein 1; PK, pharmacokinetics; RP2D, recommended phase 2 dose.

1. Nooka A, et al. *Future Oncol*. 2021;17:1987. Figure adapted from Nooka et al.

Median prior lines: 5

Preliminary Efficacy Outcomes

The preliminary overall response rate (ORR) for the total population was 52% (n=13; 95% CI: 31.3–72.2).

A very good partial response or better (≥VGPR) was achieved for 32% of patients (n=8), or 57% of responders (8/14).

Overview of Efficacy*, n (%)	Cohort A Belamaf 1.9 mg/kg + aICOS 8 mg N=9	Cohort B Belamaf 2.5 mg/kg + aICOS 8 mg N=10	Cohort C Belamaf 2.5 mg/kg + aICOS 24 mg N=6	Total Population N=25
Stringent complete response	0	1 (10)	0	1 (4)
Complete response	1 (11)	0	0	1 (4)
Very good partial response	2 (22)	1 (10)	3 (50)	6 (24)
Partial response	1 (11)	3 (30)	1 (17)	5 (20)
Minimal response	0	0	1 (17)	1 (4)
Stable disease	4 (44)	2 (20)	1 (17)	7 (28)
Progressive disease	1 (11)	1 (10)	0	2 (8)
Not evaluable	0	2 (20)	0	2 (8)
Overall response rate (%; 95% CI†) sCR+CR+VGPR+PR	**4 (44; 13.7–78.8)**	**5 (50; 18.7–81.3)**	**4 (67; 22.3–95.7)**	**13 (52; 31.3–72.2)**
Clinical benefit rate (%; 95% CI) sCR+CR+VGPR+PR+MR	4 (44; 13.7–78.8)	5 (50; 18.7–81.3)	5 (83; 35.9–99.6)	14 (56; 34.9–75.6)

aICOS, inducible T-cell costimulatory agonist; CI, confidence interval; CR, complete response; MR, minimal response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
*Investigator-assessed best confirmed response. †Confidence intervals are based on the exact method.

Preliminary Safety: AE of Special Interest

AESIs, n (%)	Cohort A Belamaf 1.9 mg/kg + aICOS 8 mg N=9	Cohort B Belamaf 2.5 mg/kg + aICOS 8 mg N=10	Cohort C Belamaf 2.5 mg/kg + aICOS 24 mg N=6	Total Population N=25
Any Event	5 (56)	8 (80)	5 (83)	18 (72)
Grade 3 or 4†	2 (22)	5 (50)	2 (33)	9 (36)
Corneal events*	3 (33)	7 (70)	5 (83)	15 (60)
Keratopathy	3 (33)	6 (60)	2 (33)	11 (44)
Grade 3 or 4†	1 (11)	2 (20)	2 (33)	5 (20)
Dry eye	1 (11)	3 (30)	4 (67)	8 (32)
Grade 3 or 4†	0	1 (10)	0	1 (4)
Photophobia	-	2 (20)	-	2 (8)
Grade 3 or 4†	-	0	-	0
Asthenopia	-	1 (10)	-	1 (4)
Grade 3 or 4†	-	0	-	0
Corneal opacity	-	1 (10)	-	1 (4)
Grade 3 or 4†	-	0	-	0
Xerophthalmia	-	1 (10)	1 (17)	2 (8)
Grade 3 or 4†	-	0	0	0
IRRs	4 (44)	3 (30)	1 (17)	8 (32)
Grade 3 or 4†	1 (11)	0	0	1 (4)
Thrombocytopenia	1 (11)	3 (30)	2 (33)	6 (24)
Grade 3 or 4†	1 (11)	2 (20)	0	3 (12)

AE, adverse event; AESIs, adverse events of special interest; aICOS, inducible T-cell co-stimulator agonist; belamaf, belantamab mafodotin; IRRs, infusion-related reactions; SAE, serious AE.
*Grading determined using the Common Term Criteria for Adverse Events v 5.0 and changes in best corrected visual acuity. †No patients experienced a Grade 5 AESI; If a subject has more than one AE in a given category, only the highest grade is counted in each row.

Conclusions

- Yesterday's immunotherapies
- Exciting therapies on the horizon
  - Off the shelf, combo off the shelf
  - Maybe steroid-free one day…?
- But no cures yet!
- The future is immunotherapy bright
  - I suspect 2nd line by 2023
  - No worries – always room for new CELMoDs, alkylating agents and Selinexor
  - Room for personalization
- Now have to consider: cost, quality of life, accessibility, referral patterns, logistics

THANK YOU!

@ninashah33

#myelennial

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