The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Dr Abou-Alfa*

Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

CAR-T and Bispecific Therapy for Multiple Myeloma Faculty

Saad Zafar Usmani, MD, MBA
Chief of Myeloma Service
Memorial Sloan Kettering Cancer Center
New York, New York

RTP
RESEARCH
TO PRACTICE

CAR-T and Bispecific Therapy for Multiple Myeloma Agenda

Module 1: CAR T-Cell Therapy in the Management of Multiple Myeloma

Module 2: Antibody-Drug Conjugate Belantamab Mafodotin

Module 3: Integration of Bispecific Antibody Treatment Approaches

RTP
RESEARCH
TO PRACTICE

CAR-T and Bispecific Therapy for Multiple Myeloma Agenda

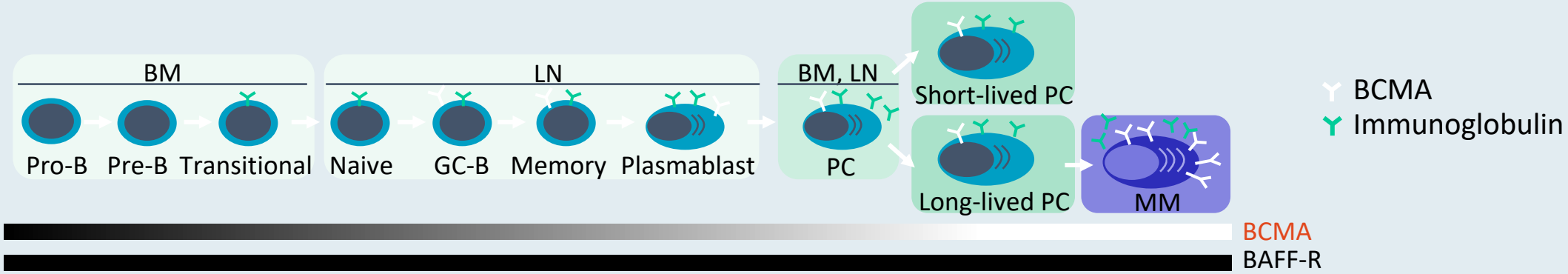
Module 1: CAR T-Cell Therapy in the Management of Multiple Myeloma

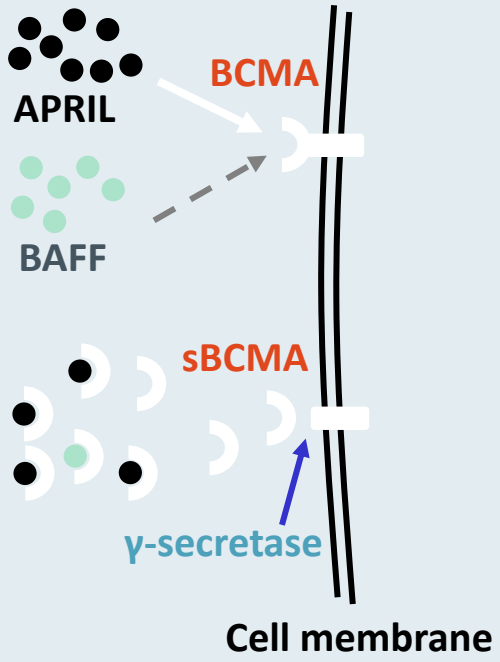
Module 2: Antibody-Drug Conjugate Belantamab Mafodotin

Module 3: Integration of Bispecific Antibody Treatment Approaches

RTP
RESEARCH
TO PRACTICE

BCMA as a Target in Myeloma Treatment





- **BCMA: antigen expressed specifically on PCs and myeloma cells**
- **Higher expression on myeloma cells than normal PCs**
- **Not expressed in other tissues**

- **Cell-surface receptor in TNF superfamily**
- **Receptor for APRIL and BAFF**
- **Key role in B-cell maturation and differentiation**
- **Promotes myeloma cell growth, chemotherapy resistance, immunosuppression in bone marrow microenvironment**

Cho S-F et al. *Front Immunol* 2018;9:1821. Moreaux J et al. *Blood* 2004;103(8):3148-57. Sanchez E at al. *Br J Haematol* 2012;158(6):727-38.

Content courtesy of Jesús G Berdeja, MD

FDA-Approved CAR T-Cell Therapies for Relapsed or Refractory Multiple Myeloma

February 28, 2022: Ciltacabtagene autoleucel approved for the treatment of relapsed or refractory multiple myeloma in adult patients after 4 or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, based on the CARTITUDE-1 study.

March 26, 2022: Idecabtagene vicleucel approved for the treatment of relapsed or refractory multiple myeloma in adult patients after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody. This is the first FDA-approved cell-based gene therapy for multiple myeloma, based on the KarMMa study.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ciltacabtagene-autoleucel-relapsed-or-refractory-multiple-myeloma
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-idecabtagene-vicleucel-multiple-myeloma

RTP RESEARCH TO PRACTICE

Select Clinical Trials of BCMA-Directed CAR T-Cell Therapy for Multiagent-Refractory Multiple Myeloma: Efficacy Summary

	KarMMa (N = 128)	CARTITUDE-1 (N = 97)	CRB-402 (N = 72)
Phase	II	Ib/II	I/II
Product	Idecabtagene vicleucel	Ciltacabtagene autoleucel	bb21217
Median prior lines of therapy	6	6	6
Overall response rate	73%	98%	69%
Complete response	33%	sCR: 83%	sCR/CR: 36%
MRD-negative	26%	92%	67%
Median PFS	8.6 months	Not reached	Not applicable
Median OS	24.8 months	Not reached	Not applicable

sCR = stringent complete response; MRD = minimal residual disease; PFS = progression-free survival; OS = overall survival

Anderson LD et al. ASCO 2021;Abstract 8016. Usmani SZ et al ASCO 2022;Abstract 8028. Martin T et al. *J Clin Oncol* 2022 June 4;[Online ahead of print]. Raje N et al. ASH 2021;Abstract 548. Mateos M-V et al. 2022 ASCO Educational Book.

Select Clinical Trials of BCMA-Directed CAR T-Cell Therapy for Multiagent-Refractory Multiple Myeloma: CRS and Neurotoxicity

	KarMMa (N = 128)	CARTITUDE-1 (N = 97)	CRB-402 (N = 72)
Product	Idecabtagene vicleucel	Ciltacabtagene autoleucel	bb21217
Median prior lines of therapy	6	6	6
CRS	Grade 3: 4%	Grade 3/4: 4%	Grade 3/4: 1%
Neurotoxicity	Grade 3: 3%	Grade 3/4: 11%	Grade 3/4: 4%

CRS = cytokine release syndrome

Anderson LD et al. ASCO 2021;Abstract 8016. Usmani SZ et al ASCO 2022;Abstract 8028. Martin T et al. *J Clin Oncol* 2022 June 4;[Online ahead of print]. Raje N et al. ASH 2021;Abstract 548. Mateos M-V et al. 2022 ASCO Educational Book.

Topline Results from KarMMa-3: Idecabtagene Vicleucel Significantly Improves PFS for Relapsed and Refractory Multiple Myeloma

Press Release: August 10, 2022

Positive topline results were announced from KarMMa-3, a Phase III, global, randomized, multicenter, open-label study evaluating idecabtagene vicleucel compared to standard combination regimens for adults with multiple myeloma that is relapsed and refractory after 2 to 4 prior lines of therapy and refractory to the last regimen.

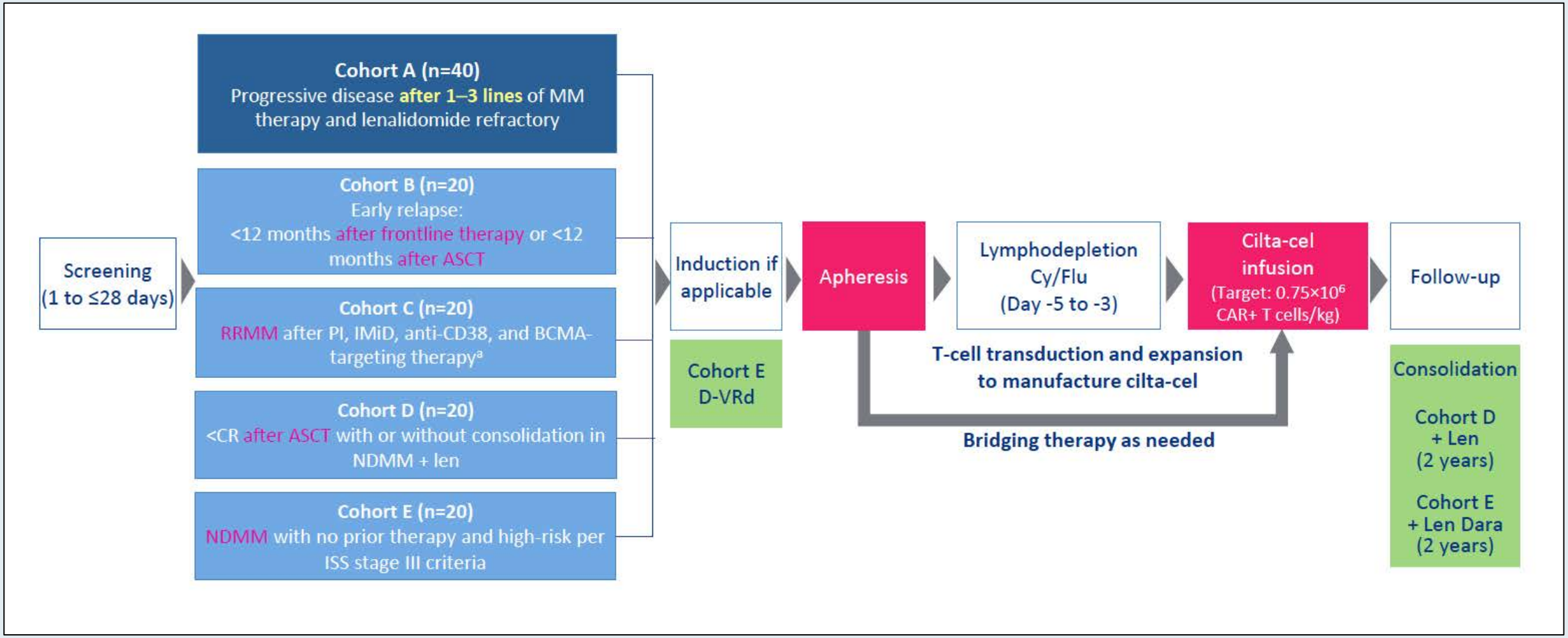
"KarMMa-3 is the first randomized clinical trial to evaluate a CAR T cell therapy in multiple myeloma. Results of a pre-specified interim analysis conducted through an independent review committee showed that KarMMa-3 met its primary endpoint of demonstrating a statistically significant improvement in progression-free survival. Treatment with idecabtagene vicleucel also showed an improvement in the key secondary endpoint of overall response rate compared to standard regimens. Follow-up for overall survival, a key secondary endpoint, remains ongoing.

Safety results in the trial were consistent with the well-established and predictable safety profile of idecabtagene vicleucel previously demonstrated in the pivotal KarMMa trial. No new safety signals were reported in this study."

https://news.bms.com/news/corporate-financial/2022/Bristol-Myers-Squibb-and-2seventy-bio-Announce-Topline-Results-from-KarMMa-3-Trial-Showing-Abecma-idecabtagene-vicleucel-Significantly-Improves-Progression-Free-Survival-Versus-Standard-Regimens-in-Relapsed-and-Refractory-Multiple-Myeloma/default.aspx

RTP RESEARCH TO PRACTICE

CARTITUDE-2 Multicohort Overall Trial Design



VRd = bortezomib/lenalidomide/dexamethasone; cilta-cel = ciltacabtagene autoleucel; len = lenalidomide; dara = daratumumab

Agha M et al. EHA 2021;Abstract S190.

ASCO 2022; Abstract 8020.

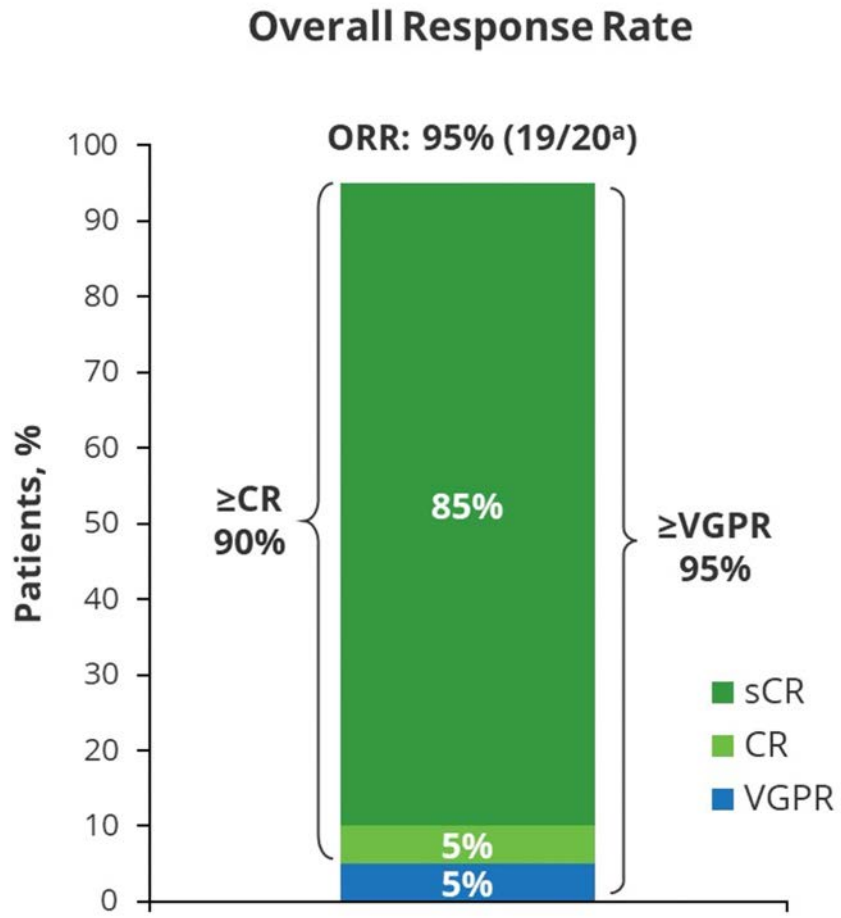
Biological Correlative Analyses and Updated Clinical Data of Ciltacabtagene Autoleucel, a BCMA-Directed CAR-T Cell Therapy, in Lenalidomide-Refractory Patients With Progressive Multiple Myeloma After 1–3 Prior Lines of Therapy: CARTITUDE-2, Cohort A

Hermann Einsele[1], Adam Cohen[2], Michel Delforge[3], Jens Hillengass[4], Hartmut Goldschmidt[5], Katja Weisel[6], Marc-Steffen Raab[7], Christoph Scheid[8], Jordan M Schecter[9], Kevin De Braganca[9], Helen Varsos[9], Tzu-Min Yeh[9], Pankaj Mistry[10], Tito Roccia[9], Christina Corsale[9], Muhammad Akram[11], Lida Pacaud[11], Tonia Nesheiwat[11], Mounzer Agha[12], Yael Cohen[13]

[1]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany; [2]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]University Hospitals (UZ) Leuven, Leuven, Belgium; [4]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [5]University Hospital Heidelberg and National Center of Tumor Diseases, Heidelberg, Germany; [6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]University Hospital Heidelberg and Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center, Heidelberg, Germany; [8]University of Cologne, Cologne, Germany; [9]Janssen Research & Development, Raritan, NJ, USA; [10]Janssen Research & Development, High Wycombe, UK; [11]Legend Biotech USA, Piscataway, NJ, USA; [12]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [13]Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL, USA & Virtual.

CARTITUDE-2 Cohort A: Ciltacabtagene Autoleucel for Lenalidomide-Refractory MM After 1 to 3 Prior Lines of Therapy



AEs ≥20%, n (%)	N=20	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	19 (95)	19 (95)
Thrombocytopenia	16 (80)	7 (35)
Anaemia	15 (75)	9 (45)
Lymphopenia	14 (70)	14 (70)
Leukopenia	11 (55)	11 (55)
CAR-T–related AEs		
CRS	19 (95)	2 (10)
Neurotoxicity	6 (30)	1 (5)
ICANS	3 (15)	0
Other	3 (15)[a]	1 (5)

CR = complete response; VGPR = very good partial response; sCR = stringent CR; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity

Einsele H et al. ASCO 2022;Abstract 8020.

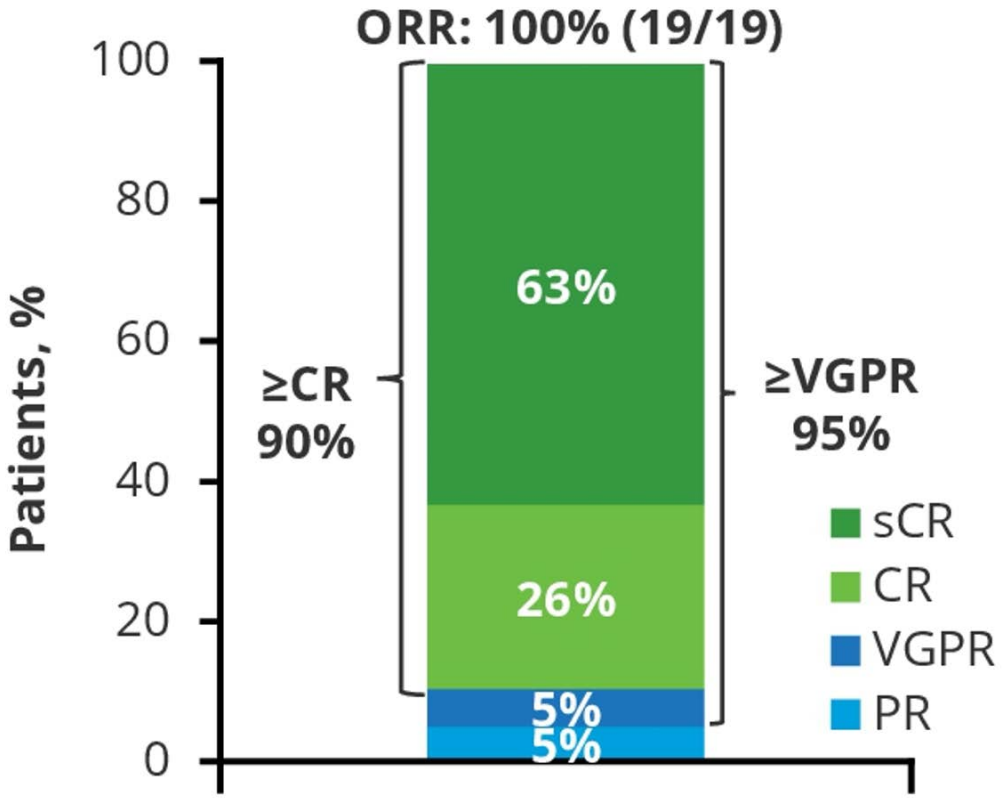
RTP RESEARCH TO PRACTICE

ASCO 2022 | Abstract 8029

Biological Correlative Analyses and Updated Clinical Data of Ciltacabtagene Autoleucel, a BCMA-Directed CAR-T Cell Therapy, in Patients with Multiple Myeloma and Early Relapse After Initial Therapy: CARTITUDE-2, Cohort B

Niels WCJ van de Donk[1] (n.vandedonk@amsterdamumc.nl), Mounzer Agha[2], Adam Cohen[3], Yael Cohen[4], Sébastien Anguille[5], Tessa Kerre[6], Wilfried Roeloffzen[7], Jordan M Schecter[8], Kevin De Braganca[8], Helen Varsos[8], Pankaj Mistry[9], Tito Roccia[8], Enrique Zudaire[10], Christina Corsale[8], Muhammad Akram[11], Dong Geng[11], Tonia Nesheiwat[11], Lida Pacaud[11], Pieter Sonneveld[12], Sonja Zweegman[1]

CARTITUDE-2 Cohort B: Ciltacabtagene Autoleucel for Patients with Multiple Myeloma and Early Relapse After Initial Therapy



AEs ≥20%, n (%)	N=19	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	18 (95)	17 (90)
Anemia	11 (58)	9 (47)
Thrombocytopenia	11 (58)	5 (26)
Lymphopenia	6 (32)	6 (32)
Leukopenia	5 (26)	5 (26)
CAR-T–related AEs		
CRS	16 (84)	1 (5)
Neurotoxicity	5 (26)	1 (5)
ICANS	1 (5)	0
Other	4 (21)	1 (5)
Parkinsonism	1 (5)	1 (5)

van de Donk NWCJ et al. ASCO 2022;Abstract 8029.

RTP RESEARCH TO PRACTICE

Key Ongoing Studies of BCMA-Directed CAR T-Cell Therapy with Ide-cel and Cilta-cel

Study	Phase	N	Setting	Treatments
CARTITUDE-4	III	419	Relapsed and lenalidomide-refractory	• Pomalidomide/bortezomib/dexamethasone or daralutamide/pomalidomide/dexamethasone • Cilta-cel
CARTITUDE-5	III	650	NDMM, with no ASCT planned	• VRd → cilta-cel • VRd → lenalidomide/dexamethasone
CARTITUDE-6	III	750	NDMM, ASCT eligible	• DVRd → cilta-cel • DVRd → ASCT
KarMMa-4	I	13	NDMM, high risk	• Ide-cel → lenalidomide maintenance
KarMMa-2	II	235	R/R MM, high risk NDMM	• Ide-cel • Ide-cel + lenalidomide

Ide-cel = idecabtagene vicleucel; cilta-cel = ciltacabtagene autoleucel; NDMM = newly diagnosed multiple myeloma; ASCT = autologous stem cell transplant; VRd = bortezomib/lenalidomide/dexamethasone; DVRd = daratumumab/VRd; R/R = relapsed/refractory

www.clinicaltrials.gov. Accessed August 2022.

CAR T-Cell-Associated Toxicities: Acute and Late Phase

Acute Phase (Days 0-30)

- Cytokine release syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Cytopenias
- B-cell aplasia and hypogammaglobulinemia
- Tumor lysis syndrome (rare and likely varies by disease burden)

Late Phase (Days 30+)

- Persistent cytopenias
- B-cell aplasia and hypogammaglobulinemia
- T-cell deficiency
- Residual effects of acute toxicity
- Delayed CRS and ICANS are rare but can occur
- Impairment to QoL – fatigue, memory issues not yet well described

Content courtesy of Jesús G Berdeja, MD

RTP RESEARCH TO PRACTICE

Cytokine Release Syndrome Associated with CAR T-Cell Therapy for Multiple Myeloma

- Potentially severe or life-threatening reactions, with the most common manifestations being pyrexia, hypotension, tachycardia, chills, hypoxia, fatigue and headache
- Grade 3 or higher events may include hypotension, hypoxia, hyperbilirubinemia, hypofibrinogenemia, acute respiratory distress syndrome, atrial fibrillation, hepatocellular injury, metabolic acidosis, pulmonary edema, multiple organ dysfunction syndrome and hemophagocytic lymphohistiocytosis/macrophage activation syndrome
- Occurs in approximately 85% to 95% of patients (Grade ≥3: 5%-9%)
- Time to onset: 1 to 7 days (range 1-23 days)
- Duration: 4 to 7 days (range 1-63 days)
- Manage with tocilizumab or tocilizumab and corticosteroids

www.carvyktihcp.com/safety; www.abecmahcp.com/safety/

ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome) Associated with CAR T-Cell Therapy for MM

- Potentially severe or life-threatening neurotoxicity, including encephalopathy, tremor, aphasia and delirium
- Occurs in about 25% of patients (Grade ≥3: 4%-5%)
- Time to onset: 2 to 8 days (range 1-42 days)
- Duration: 6 to 8 days (range 1-578 days)
- Resolved in 77% to 92% of patients
- Manage with supportive care and corticosteroids as needed

www.carvyktihcp.com/safety; www.abecmahcp.com/safety/

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

GPRC5D-Targeted CAR T Cells for Myeloma

Sham Mailankody, M.B., B.S., Sean M. Devlin, Ph.D., Jonathan Landa, D.O., Karthik Nath, M.B., B.S., Ph.D., Claudia Diamonte, B.S.N., R.N., O.C.N., Elizabeth J. Carstens, M.D., Douglas Russo, M.S., Romany Auclair, M.D., Lisa Fitzgerald, M.S.N., Briana Cadzin, B.S.N., R.N., Xiuyan Wang, Ph.D., Devanjan Sikder, Ph.D., Brigitte Senechal, Ph.D., Vladimir P. Bermudez, Ph.D., Terence J. Purdon, M.S., Kinga Hosszu, Ph.D., Devin P. McAvoy, B.S., Tasmin Farzana, M.P.H., Elena Mead, M.D., Jessica A. Wilcox, M.D., Bianca D. Santomasso, M.D., Ph.D., Gunjan L. Shah, M.D., Urvi A. Shah, M.D., Neha Korde, M.D., Alexander Lesokhin, M.D., Carlyn R. Tan, M.D., Malin Hultcrantz, M.D., Ph.D., Hani Hassoun, M.D., Mikhail Roshal, M.D., Filiz Sen, M.D., Ahmet Dogan, M.D., Ph.D., Ola Landgren, M.D., Ph.D., Sergio A. Giralt, M.D., Jae H. Park, M.D., Saad Z. Usmani, M.D., Isabelle Rivière, Ph.D., Renier J. Brentjens, M.D., Ph.D., and Eric L. Smith, M.D., Ph.D.

***N Engl J Med* 2022;387(13):1196-206.**

Phase I Trial of GPRC5D-Targeted CAR T-Cell Therapy (MCARH109) for Heavily Pretreated MM

Response	All Patients		Previous BCMA Therapies		No Previous BCMA Therapies	
	All Dose Levels (N=17)	25×10^6–150×10^6 CAR T Cells (N=12)	All Dose Levels (N=10)	25×10^6–150×10^6 CAR T Cells (N=6)	All Dose Levels (N=7)	25×10^6–150×10^6 CAR T Cells (N=6)
	number (percent)					
Partial response or better	12 (71)	7 (58)	7 (70)	3 (50)	5 (71)	4 (67)
Very good partial response or better	10 (59)	5 (42)	6 (60)	2 (33)	4 (57)	3 (50)
Complete response or better	6 (35)	3 (25)	4 (40)	2 (33)	2 (29)	1 (17)
Negativity for MRD in bone marrow*	8 (47)	6 (50)	3 (30)	2 (33)	5 (71)	4 (67)

* Negativity for minimal residual disease (MRD) in bone marrow was assessed by means of 10-color flow cytometry with a sensitivity of 1 in 10^5 at 4 weeks after CAR T-cell therapy, at the occurrence of a complete response, and as clinically indicated.

- The maximum tolerated dose was identified at 150 x 10^6 CAR T cells.
- At the 450 x 10^6 CAR T cell dose, 1 patient had Grade 4 cytokine release syndrome and ICANS, and 2 patients had a Grade 3 cerebellar disorder of unclear cause.
- No cerebellar disorder, ICANS of any grade, or cytokine release syndrome of Grade 3 or higher occurred in the 12 patients who received doses of 25 x 10^6 to 150 x 10^6 cells.

Mailankody S et al. *N Engl J Med* 2022;387(13):1196-206.

RTP RESEARCH TO PRACTICE

CAR-T and Bispecific Therapy for Multiple Myeloma Agenda

Module 1: CAR T-Cell Therapy in the Management of Multiple Myeloma

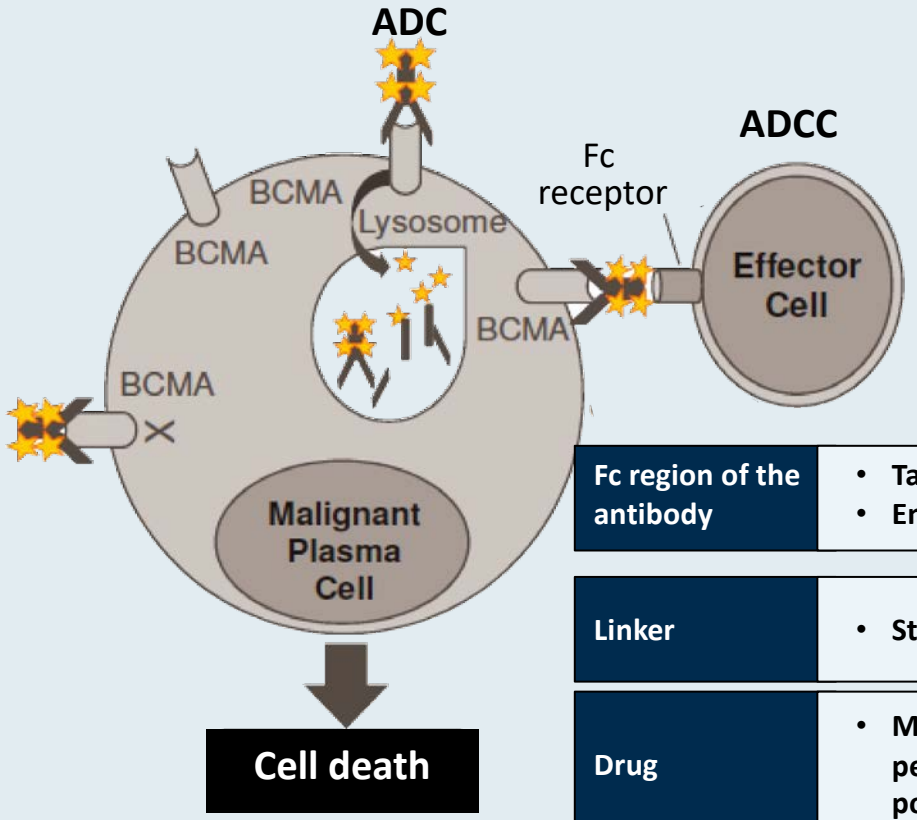
Module 2: Antibody-Drug Conjugate Belantamab Mafodotin

Module 3: Integration of Bispecific Antibody Treatment Approaches

RTP
RESEARCH
TO PRACTICE

Belantamab Mafodotin: Anti-BCMA Antibody-Drug Conjugate

- B-cell maturation factor (BCMA) expression is restricted to B cells at later stages of differentiation and is required for survival of plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- Belantamab mafodotin is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to microtubule disrupting agent MMAF via a stable, protease-resistant maleimidocaproyl linker



Fc region of the antibody	• **Target specific** • **Enhanced ADCC**
Linker	• **Stable in circulation**
Drug	• **MMAF (non cell permeable, highly potent auristatin)**

Mechanisms of action:
- ADC mechanism
- ADCC mechanism
- Immunogenic cell death
- BCMA receptor signaling inhibition

ADC = antibody-drug conjugate; ADCC = antibody-dependent cell-mediated cytotoxicity

Tai YT et al. *Blood* 2014;123(20):3128-38.

RTP RESEARCH TO PRACTICE

Longer Term Outcomes With Single-Agent Belantamab Mafodotin in Patients With Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study

Sagar Lonial, MD [1]; Hans C. Lee, MD[2]; Ashraf Badros, MD [3]; Suzanne Trudel, MD[4]; Ajay K. Nooka, MD [1]; Ajai Chari, MD [5]; Al-Ola Abdallah, MD[6]; Natalie Callander, MD[7]; Douglas Sborov, MD[8]; Attaya Suvannasankha, MD[9]; Katja Weisel, MD[10]; Peter M. Voorhees, MD[11]; Lynsey Womersley, MSc[12]; January Baron, MS[13]; Trisha Piontek, BSN[13]; Eric Lewis, MD[14]; Joanna Opalinska, MD[13]; Ira Gupta, MD[13]; and Adam D. Cohen, MD[15]

Cancer **2021;127(22):4198-212.**

RTP RESEARCH TO PRACTICE

DREAMM-2: Single-Agent Belantamab Mafodotin Efficacy Outcomes

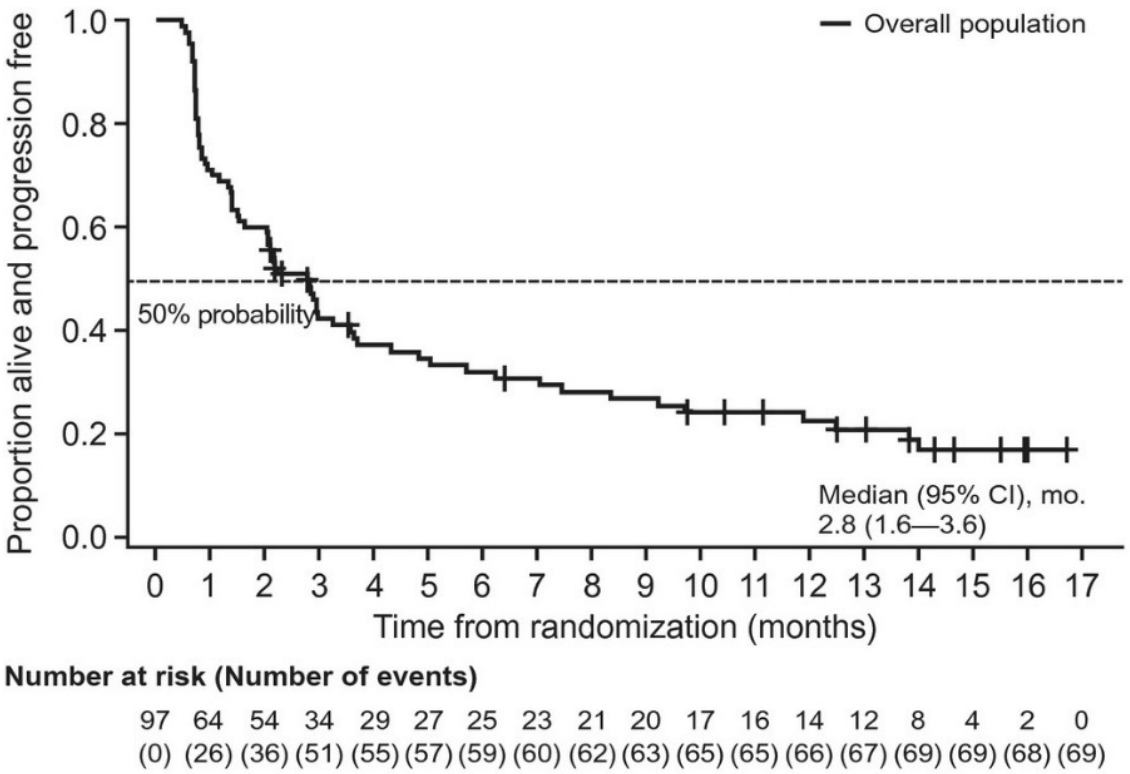
	Patients with 3-6 prior therapies (n = 47)	Patients with ≥7 prior therapies (n = 50)
ORR, % (97.5% CI)	32 (21.7-43.6)	30 (16.5-46.6)
Median DoR (95% CI estimates), months	11.0 (4.2-NR)	13.1 (4.0-NR)
Probability of DoR ≥6 months, % (95% CI estimates)	63 (31-83)	73 (44-89)
Median PFS (95% CI estimates), months	2.8 (1.6-3.6)	2.2 (1.2-3.6)
Probability of PFS at 6 months, % (95% CI estimates)	35 (20-50)	30 (17-43)

ORR = overall response rate; CI = confidence interval; DoR = duration of response; NR = not reached; PFS = progression-free survival

Lonial S et al. *Cancer* 2021;127(22):4198-212; ASH 2020;Abstract 1417.

DREAMM-2: Longitudinal Outcomes

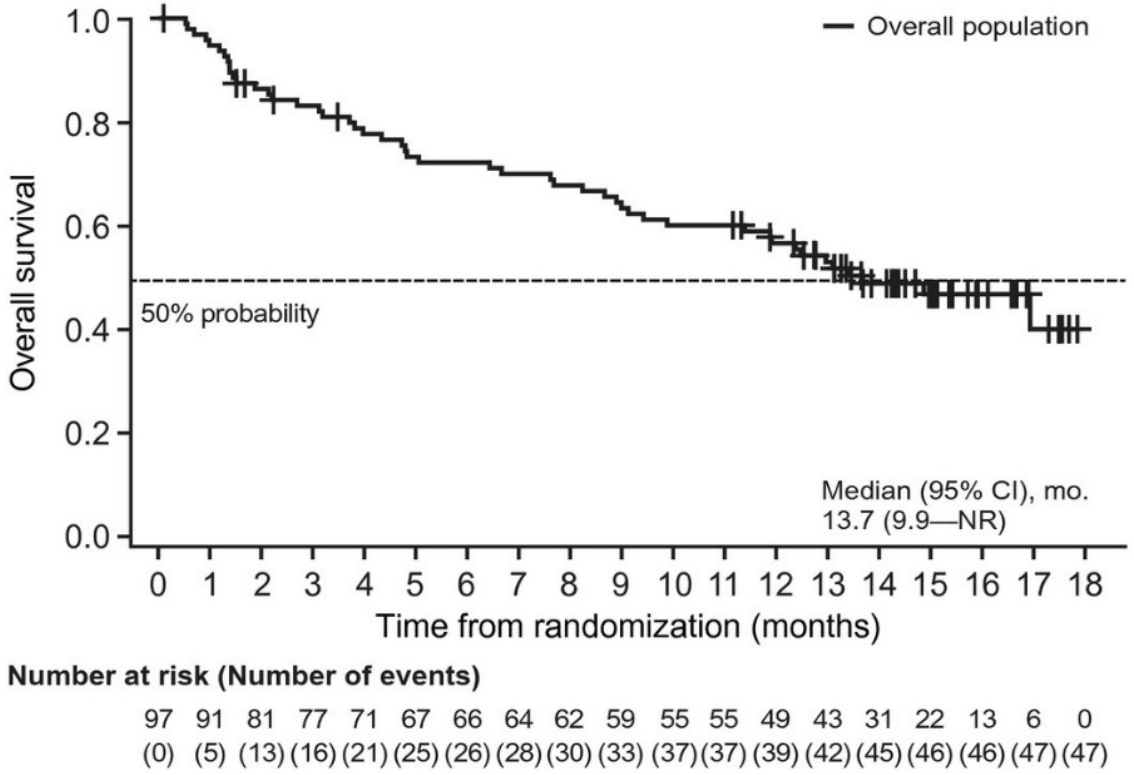
Progression-Free Survival



Number at risk (Number of events)

97	64	54	34	29	27	25	23	21	20	17	16	14	12	8	4	2	0
(0)	(26)	(36)	(51)	(55)	(57)	(59)	(60)	(62)	(63)	(65)	(65)	(66)	(67)	(69)	(69)	(68)	(69)

Overall Survival (OS)



Number at risk (Number of events)

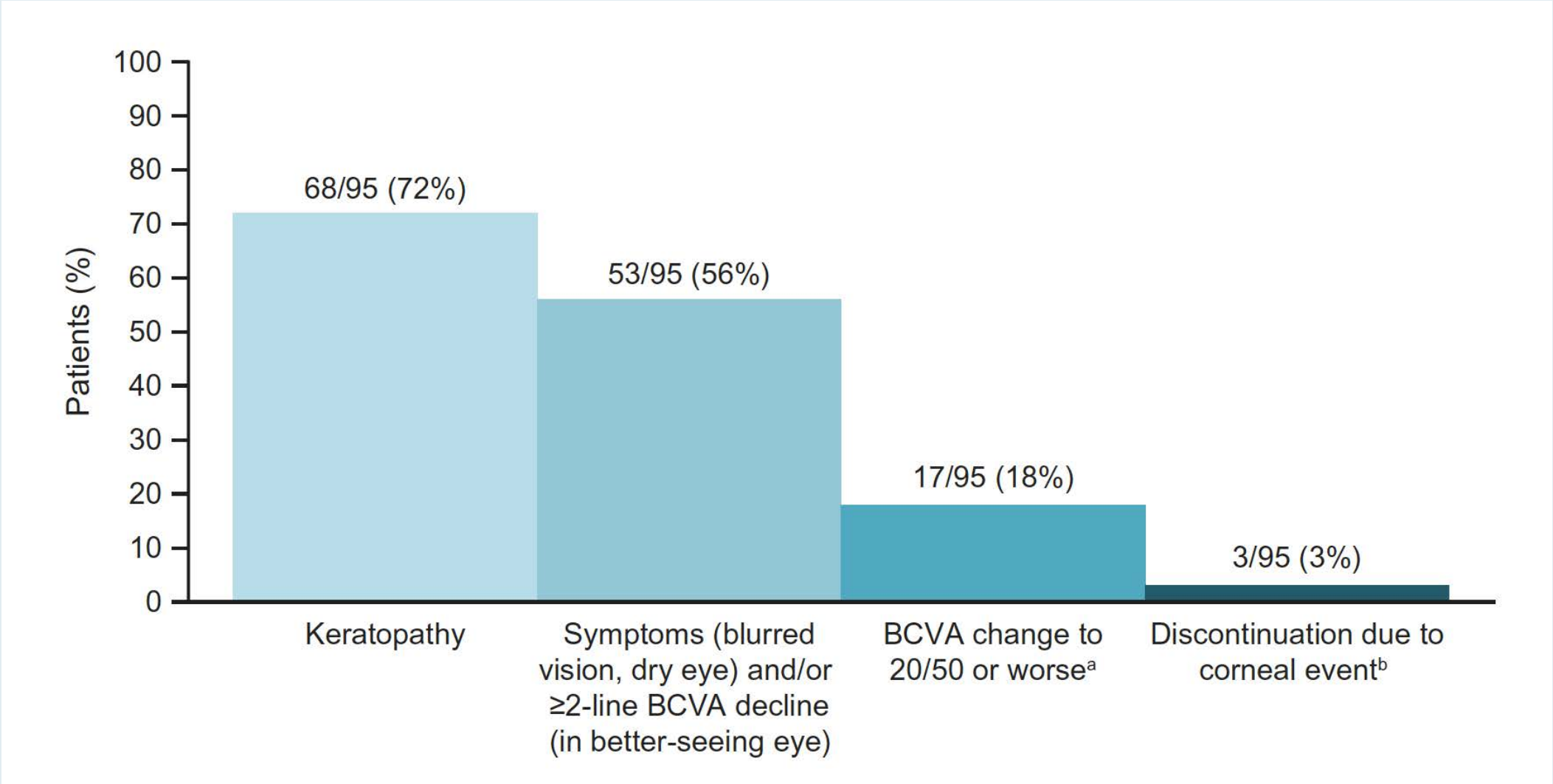
97	91	81	77	71	67	66	64	62	59	55	55	49	43	31	22	13	6	0
(0)	(5)	(13)	(16)	(21)	(25)	(26)	(28)	(30)	(33)	(37)	(37)	(39)	(42)	(45)	(46)	(46)	(47)	(47)

Expected median OS in triple-class refractory myeloma: 8.6 months

Lonial S et al. *Cancer* 2021;127(22):4198-212.

RTP RESEARCH TO PRACTICE

DREAMM-2: Frequency of Corneal and Vision-Related Events



BCVA = best corrected visual acuity

Lonial S et al. *Cancer* 2021;127(22):4198-212.

RTP RESEARCH TO PRACTICE

Summary of Select Clinical Trials of Belantamab Mafodotin (Belamaf) Combination Approaches for R/R Multiple Myeloma

Trial	Characteristics	ORR	Safety
DREAMM-6 (NCT03544281)	• Phase I/II • Arm A: Belamaf + len/dex (n = 45) • Arm B: Belamaf + bor/dex (n = 18)	• Arm A: Highest ORR of 75% with the 1.9 mg/kg q4wk dose • Arm B: 78%	Arm A Grade ≥3 AEs: • Thrombocytopenia – 3 (7%) • Keratopathy – 15 (33%) Arm B Grade ≥3 AEs: • Thrombocytopenia – 12 (67%) • Keratopathy – 11 (61%)
DREAMM-4 (NCT03848845)	▪ Phase I/II (N = 34) ▪ Belamaf + pembrolizumab ▪ Dose escalation: Belamaf 2.5 mg/kg and 3.4 mg/kg	• 47% at RP2D of 2.5 mg/kg	All grades: • Thrombocytopenia – 12 (35%) • Keratopathy – 26 (76%)
ALGONQUIN (NCT03715478)	▪ Phase I/II (N = 56) ▪ Belamaf + pom/dex	• ≥PR/VGPR 89%/72% across all dosing cohorts	Grade ≥3 TEAEs: • Thrombocytopenia – 19 (34%) • Keratopathy – 39 (70%)

ORR = overall response rate; len = lenalidomide; dex = dexamethasone; AEs = adverse events; RP2D = recommended Phase II dose; pom = pomalidomide; PR = partial response; VGPR = very good partial response; TEAEs = treatment-emergent AEs

Popat R et al. ASH 2020;Abstract 1419; Quach H et al. ASCO 2022;Abstract 8017; Lonial S et al. SOHO 2022;Abstract MM-459; Suvannasankha A et al. EHA 2022;Abstract P940; Trudel S et al. ASH 2021;Abstract 2736.

Ongoing Phase III Trials of Belantamab Mafodotin for R/R MM

Study	N	Setting	Treatment arms	Estimated primary completion
DREAMM-3 (NCT04162210)	380	≥2 prior lines of treatment, including ≥2 consecutive cycles of both lenalidomide and a proteasome inhibitor (separately or in combination)	• Belantamab mafodotin • Pomalidomide/low-dose dexamethasone	June 2022
DREAMM-8 (NCT04484623)	450	≥1 prior line of treatment, including a lenalidomide-containing regimen	• Belantamab mafodotin + pomalidomide/dexamethasone • Bortezomib + pomalidomide/dexamethasone	March 2023
DREAMM-7 (NCT04246047)	575	≥1 prior line of treatment	• Belantamab mafodotin + bortezomib/dexamethasone • Daratumumab + bortezomib/dexamethasone	April 2023

www.clinicaltrials.gov. Accessed August 2022.

Safety and Efficacy of Belantamab Mafodotin in Combination with Rd in Newly Diagnosed, Transplant Ineligible Multiple Myeloma Patients: A Phase 1/2 Study by the Hellenic Society of Hematology

Terpos E et al.

EHA 2022;Abstract S178.

BelaRd: Results Summary from a Phase I/II Study of Belantamab Mafodotin with Lenalidomide/Dexamethasone for Newly Diagnosed, Transplant-Ineligible MM

Clinical response, n	All patients	Cohort 1 Belamaf 2.5 mg/kg	Cohort 2 Belamaf 1.9 mg/kg	Cohort 3 Belamaf 1.4 mg/kg
Evaluable patients	28	9	9	10
Overall response rate	27 (96.4%)	9 (100.0%)	9 (100.0%)	9 (90%)
CR	4 (14.3%)	2 (22.2%)	2 (22.2%)	—
VGPR	10 (35.7%)	4 (44.4%)	2 (22.2%)	4 (40%)
Select Grade 3/4 AEs	**N = 36**	**n = 12**	**n = 12**	**n = 12**
Leukopenia	2 (5.6%)	2 (16.7%)	—	—
Neutropenia	2 (5.6%)	1 (8.3%)	—	1 (8.3%)
Keratopathy	—	—	—	—
Ocular symptoms	—	—	—	—
Visual acuity reduced	5 (13.9%)	3 (25%)	1 (8.3%)	—

CR = complete response; VGPR = very good partial response; AEs = adverse events

Terpos E et al. EHA 2022;Abstract S178.

DREAMM-9: Phase I Study of Belantamab Mafodotin plus Standard of Care in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma

Usmani SZ et al.

EHA 2022;Abstract P942.

DREAMM-9: Efficacy and Safety Summary with Belantamab Mafodotin and Standard Therapy (VRd) for Newly Diagnosed MM

Clinical response, n	Cohort 1 Belamaf 1.9 mg/kg q3 or 4wk, every cycle of VRd n = 12	Cohort 2 Belamaf 1.4 mg/kg q6 or 8wk, every other cycle of VRd n = 12	Cohort 3 Belamaf 1.9 mg/kg q6 or 8wk, every other cycle of VRd n = 12	Cohort 4 Belamaf 1.0 mg/kg q3 or 4wk, every cycle of VRd n = 15	Cohort 5 Belamaf 1.4 mg/kg q3 or 4wk, every cycle of VRd n = 13
ORR	12 (100%)	11 (92%)	12 (100%)	12 (80%)	12 (92%)
sCR	6 (50%)	1 (8%)	0	3 (20%)	2 (15%)
CR	3 (25%)	0	2 (17%)	2 (13%)	1 (8%)
VGPR	3 (25%)	9 (75%)	7 (58%)	5 (33%)	8 (62%)
Adverse events	**n = 12**	**n = 12**	**n = 12**	**n = 14**	**n = 13**
Grade 3/4 corneal exam findings	9 (75%)	4 (33%)	3 (25%)	7 (50%)	5 (39%)
Grade 3/4 visual acuity changes	10 (83%)	7 (58%)	4 (33%)	3 (21%)	6 (46%)

VRd = bortezomib/lenalidomide/dexamethasone; ORR = overall response rate; CR = complete response; sCR = stringent CR; VGPR = very good partial response

Usmani SZ et al. EHA 2022;Abstract P942.

Corneal Events: Mitigation Strategy

- Not corticosteroid eye drops — not beneficial for prophylaxis or treatment
- Lubricating eye drops ≥4 times per day throughout duration of the treatment period
- No contact lens use during treatment period
- Eye examination with BCVA assessment and slit lamp examination with fluorescein staining prior to each planned dose
- Dose delays and dose reductions per recommendations

Lonial S et al. *Blood Cancer J* 2021;11:103.

Belantamab Mafodotin Dose Modifications for Corneal Toxicity

	Exam findings per KVA scale	Recommended dose modifications
Grade 1	Corneal exam: Mild superficial keratopathy	Continue treatment at the current dose
	Change in BCVA: Decline from baseline of 1 line on the Snellen visual acuity chart	
Grade 2	Corneal exam: Moderate superficial keratopathy	Withhold treatment until improvement in both corneal examination findings and changes in BCVA to Grade 1 or better, and resume at same dose
	Change in BCVA: Decline from baseline of 2 or 3 lines (and Snellen visual acuity not worse than 20/200)	
Grade 3	Corneal exam: Severe superficial keratopathy	Withhold treatment until improvement in both corneal examination findings and changes in BCVA to Grade 1 or better, and resume at a reduced dose
	Change in BCVA: Decline from baseline by more than 3 lines (and Snellen visual acuity not worse than 20/200)	
Grade 4	Corneal exam: Corneal epithelial defect	Consider treatment discontinuation. Based on a benefit-risk ratio assessment, if continuing belantamab mafodotin is considered, treatment may be resumed at a reduced dose after the event has improved to Grade 1 or better
	Change in BCVA: Snellen visual acuity worse than 20/200	

Farooq AV et al. *Ophthalmol Ther* 2020;9(4):889-911; Lonial S et al. *Blood Cancer J* 2021;11:103.

CAR-T and Bispecific Therapy for Multiple Myeloma Agenda

Module 1: CAR T-Cell Therapy in the Management of Multiple Myeloma

Module 2: Antibody-Drug Conjugate Belantamab Mafodotin

Module 3: Integration of Bispecific Antibody Treatment Approaches

RTP
RESEARCH
TO PRACTICE

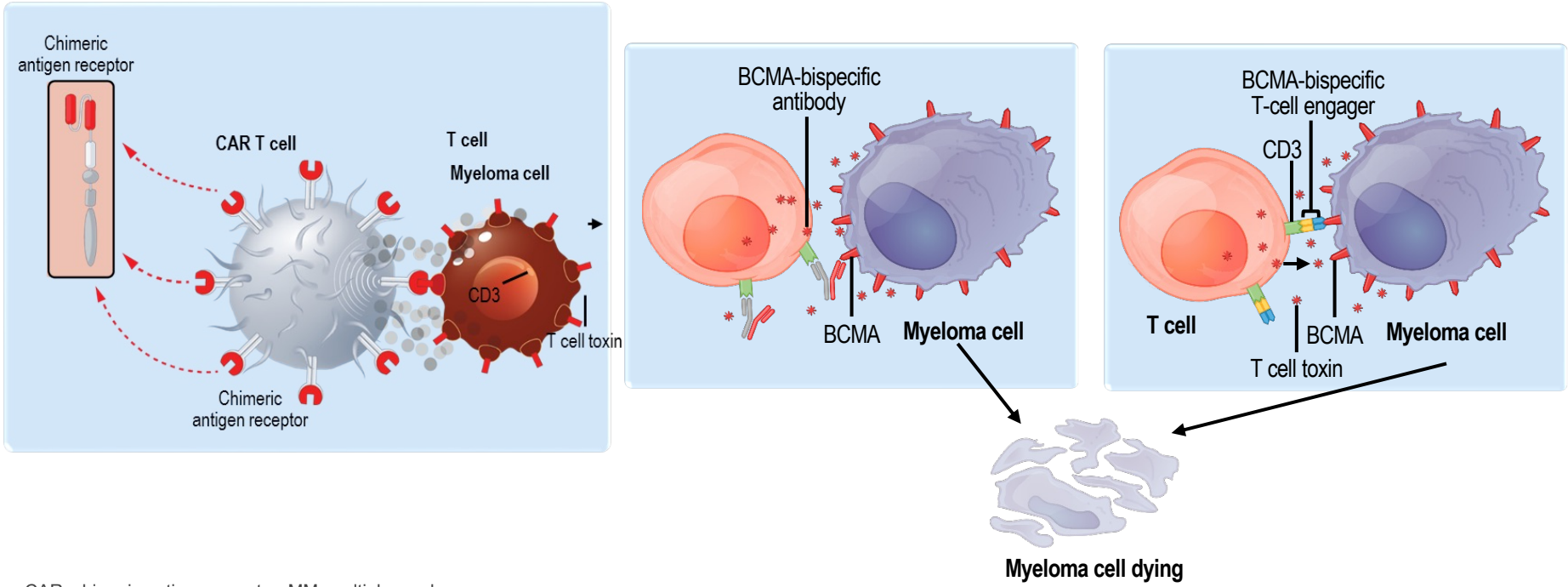
Memorial Sloan Kettering Cancer Center

Bispecific Antibodies and CAR T-Cell Therapies in MM.

Saad Z. Usmani, MD MBA FACP
Chief of Myeloma Service

Memorial Sloan Kettering Cancer Center

The Promise of T-cell redirection



CAR, chimeric antigen receptor; MM, multiple myeloma
CAR T-cell therapy is not yet FDA-approved for patients with MM.

Adapted from Cho S-F et al. *Front Immunol*. 2018;9:1821.

Memorial Sloan Kettering Cancer Center

BCMA Bispecific Antibodies (ASH 2021 Updates)

	Teclistamab[1]	Elranatamab[2]	TNB-383B[3]	REGN5458[4]
Schedule	Weekly SC	Weekly SC or Q2W SC	IV q3W	Weekly IV
Patients	165	55	118	73
Median prior lines	5	6	5	5
Triple Class and Penta Refractory	78% and 30%	91% and NA	61% and NA	89% and 38%
Prior BCMA	No	22%	No	No
CRS, All (Gr 3/4)	72% (0.6%)	87% (0%)	54% (3%)	38% (0%)
ICANS, All (Gr 3/4)	3% (0%)	NA	2% (NA)	4% (0%)
ORR at higher doses	62%	69% 70% in prior BCMA	60%	75%
CR at higher doses	29%	Not reported	20%	16%

1. Moreau et al. Abstract #896; 2.Sebag et al. Abstract#895; 3. Kumar et al. Abstract #900; 4. Zonder et al. Abstract #160 (ASH 2021)

Teclistamab-Daratumumab Combination

	Teclistamab + Daratumumab
Schedule	Weekly & Q2W SC
Patients	37
Median prior lines	5
Prior BCMA	**19%**
CD38 refractory	**60%**
Triple Class and Penta Refractory	54% and 19%
CRS, All (Gr 3/4)	65% (0%)
ICANS, All (Gr 3/4)	3% (0%)
ORR at higher doses	**82%**
CR at higher doses	**27%**

Rodriguez-Otero et al. ASH 2021 Annual Meeting.

MajesTEC Trials

- Majest-TEC-2: A Multi-arm Phase 1b Study of Teclistamab With Other Anticancer Therapies in Participants With Multiple Myeloma

- Majest-TEC-3: Phase III Study of Teclistamab in Combination With Daratumumab Subcutaneously (SC) (Tec-Dara) Versus Daratumumab SC, Pomalidomide, and Dexamethasone (DPd) or Daratumumab SC, Bortezomib, and Dexamethasone (DVd) in Participants With Relapsed or Refractory Multiple Myeloma

- MajesTEC-4: Phase III Study of Teclistamab in Combination With Lenalidomide Versus Lenalidomide Alone in Participants With Newly Diagnosed Multiple Myeloma as Maintenance Therapy Following Autologous Stem Cell Transplantation

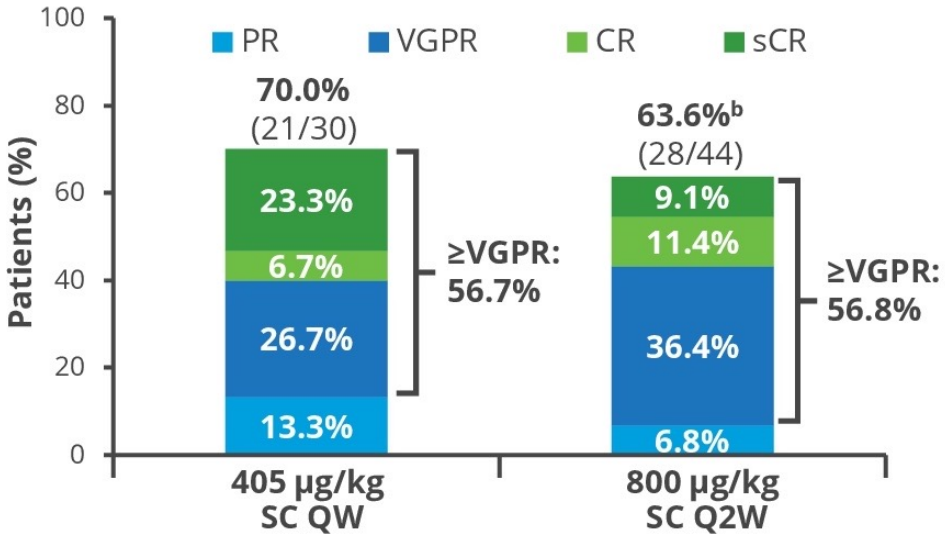
- MajesTEC-7: Phase III Study to Compare Teclistamab in Combination With Daratumumab and Lenalidomide (Tec-DR) in Participants With Newly Diagnosed Multiple Myeloma

Memorial Sloan Kettering Cancer Center

Talquetamab: A GPRC5D × CD3 bispecific antibody

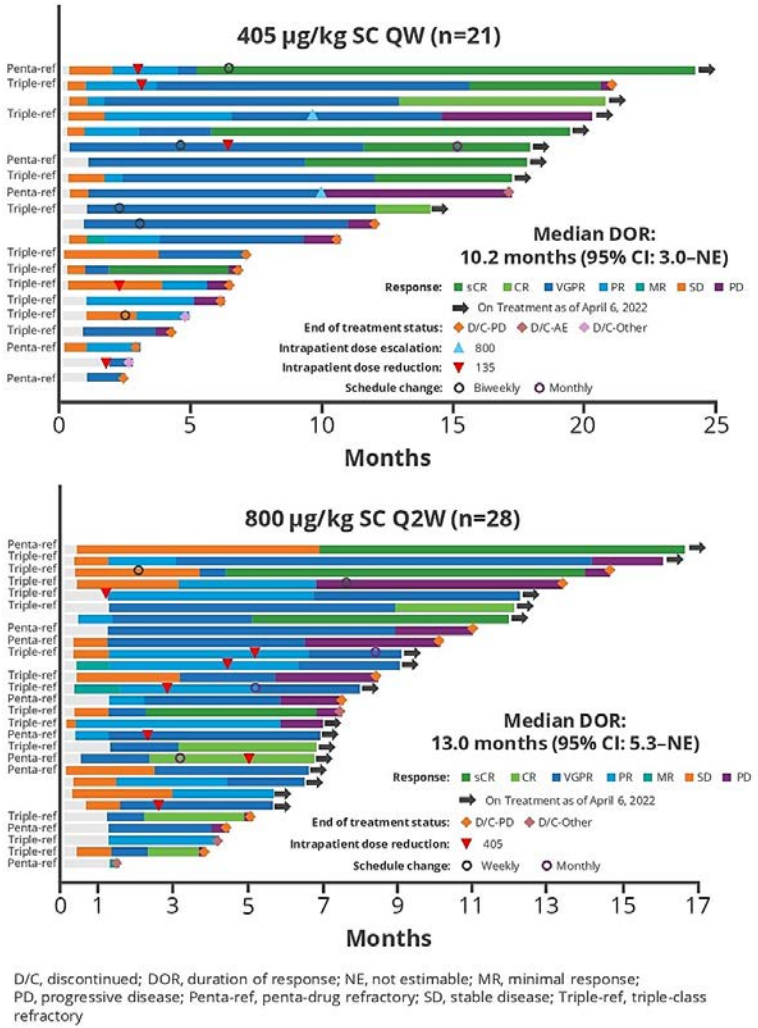
- Median age, years: 405 μg/Kg 61.5 (46-80); 800 μg/Kg 64 (47-84)
- Median PL: 6; 5
- High-risk cytogenetics: 3 (11.1%); 9 (22.5%)
- Triple-class refractory: 23 (76.7%); 34 (77.3%)
- CRS: all grade 23 (76.7%), grade 3 1 (3.3%); 35 (79.5%), grade 3 0

Overall response rate[a]



[a]Investigator assessment of evaluable patients per 2011 IMWG response criteria; includes unconfirmed responses. [b]Due to rounding, individual response rates do not sum to the ORR. CR, complete response; IMWG, International Myeloma Working Group; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Duration of response



D/C, discontinued; DOR, duration of response; NE, not estimable; MR, minimal response; PD, progressive disease; Penta-ref, penta-drug refractory; SD, stable disease; Triple-ref, triple-class refractory

Minnema M et al. EHA 2022;abstract S182 (oral presentation)

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

Memorial Sloan Kettering Cancer Center

TRIMM-2: Talquetamab and daratumumab

Tal	Dara SC	Patients enrolled to date (n)
800 µg/kg SC Q2W	1800 mg SC Cycles 1–2: QW Cycles 3–6: Q2W Cycles 7+: monthly	44
400 µg/kg SC QW		14

Analysis cutoff date: 06 April 2022

[a]Including a PI and an IMiD. [b]1–3 step-up doses given within 1 week before a full dose. [c]Glucocorticoid, antihistamine, and antipyretic.

- Median age, years: 400 µg/Kg 68 (50-77); 800 µg/Kg 62 (44-81)
- Median PL: 6; 5
- High-risk cytogenetics: 1 (10.0%); 5 (19.2%)
- Triple-class refractory: 8 (57.1%); 28 (63.6%)
- Anti-CD38 mAb refractory: 11 (78.6%); 33 (75.0%)

Parameter	Evaluable patients[a]	
	Tal 400 µg/kg QW + dara (n=14)	Tal 800 µg/kg Q2W + dara (n=37)
Follow-up, median (range)	**6.7 months** (1.9–19.6)	**4.2 months** (0.2–12.3)
ORR[b], n (%)	**10 (71.4)**	**31 (83.8)**
CR/sCR	4 (28.6)	11 (29.7)
VGPR	4 (28.6)	13 (35.1)
PR	2 (14.3)	7 (18.9)
SD	4 (28.6)	4 (10.8)
PD	0	2 (5.4)
Time to first confirmed response, median (range)	**1.0 month** (0.9–2.4)	**1.0 month** (0.9–6.5)

[a]Response-evaluable patients had received ≥1 study treatment and had ≥1 postbaseline response evaluation by the investigator. [b]PR or better in response-evaluable patients; includes unconfirmed responses.

- Median follow-up 5.1 months
- CRS all grades: 10 (71.4%); 34 (77.3%); Grade 3/4 0; 0
- ICANS: 2 patients, both grade 1 and resolved within 1 day
- Dysgeusia, all grades: 10 (71.4%), grade 3/4 NA; 26 (59.1%), grade 3/4 NA. Dry mouth, all grades: 10 (71.4%), grade 3/4 0; 18 (40.9%), grade 3/4 0
- 31 patients (53.4%) had infections (grade ≥3: 17.2%)
- Skin- and/or nail-related AEs: 81.0 % (47/58) patients

CR, complete response; CRS, cytokine release syndrome; dara, daratumumab; ICANS, immune effector cell-associated neurotoxicity syndrome; mAb, monoclonal antibody; ORR, overall response rate; PL, prior lines of treatment; PR, partial response; QW/Q2W, weekly/every 2 weeks; SC, subcutaneous; sCR, stringent CR; SD, stable disease; Tal, talquetamab; VGPR, very good partial response

van de Donk N et al. EHA 2022;abstract S183 (oral presentation)

Memorial Sloan Kettering Cancer Center

BCMA CARTs: Summary

	CARTITUDE-1[1] Cilta-cel Phase 1/2	CRB-401[2] Ide-cel Phase 1	KarMMa[3] Ide-cel Phase 2	LUMMICAR-2[4] Zivo-Cel Phase 1b	PRIME[5] P-BCMA-101 Phase 1/2	GC012F[6] Dual CAR-T BCMA+CD19
Patients	97	62	128	20	55	19
Median prior regimens	6	6	6	5	8	5
Triple refractory, %	87.6%	69.4%	84.0%	85%	60%	95%
CAR-T dose	0.71×10^6 (range 0.5–0.95×10^6)	50, 150, 450 and 800 x 10^6	150, 300, 450 x10^6	1.5-1.8/2.5-3.0 x10^8	0.75-15 x10^6	1.0-3.0 x10^5
ORR	97.9%	75.8%	50%/69%/82.0%	94.0%	67%[b]	94.7%
CR/sCR	80.4%	38.7%	25%/29%/39%	28%	NR	84.2%
PFS	66%@ 18m	8.8m	12m @450mil			
CRS, all grades	94.8%	75.8%	50%/76%/96%	77%/83%[a]	17%	95%
CRS, grade 3/4	4%	6.5%	0/7%/6%	0%	0%	11%
Neurotoxicity, all grades	20.6%	35.5%	0/17%/20%	15%/17%[a]	3.8%	0%
Neurotoxicity, grade 3/4	10.3%	1.6%	0/1%/6%	8%/0[a]	3.8%	0%

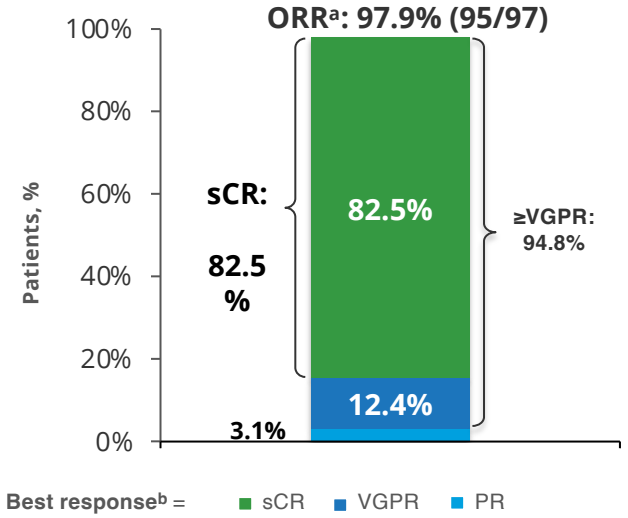
[a]1.5-1.8/2.5-3.0 x10^8 dose, [b]0.75x10^6 dose

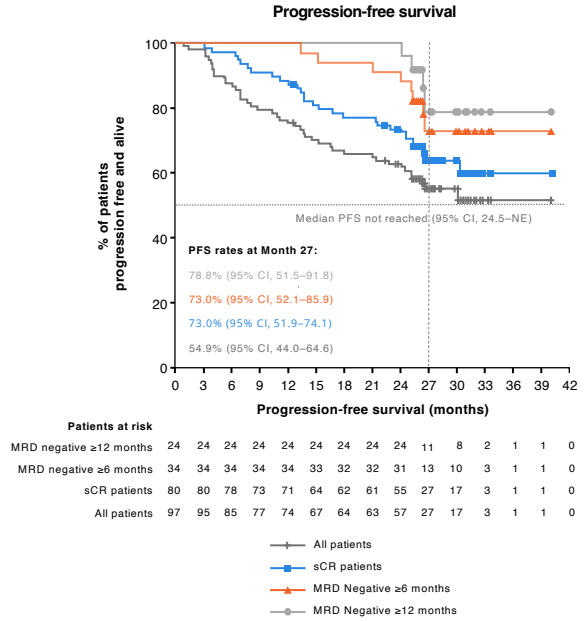
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; CRS, cytokine release syndrome; NR, not reported

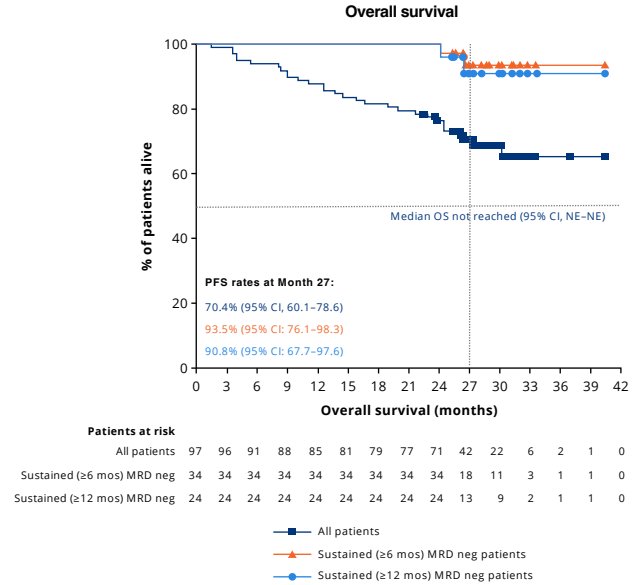
1. Usmani et al., ASCO 2021: Abstract 8005; 2. Lin et al., ASH 2020: Abstract 131;
3. Anderson et al., ASCO 2021: Abstract 130; 4. Kumar et al., ASH 2020: Abstract 133;
5. Costello et al., ASH 2020: Abstract 134; 6. Jiang et al., ASCO 2021: Abstract 8014

Memorial Sloan Kettering Cancer Center

CARTITUDE-1: Efficacy







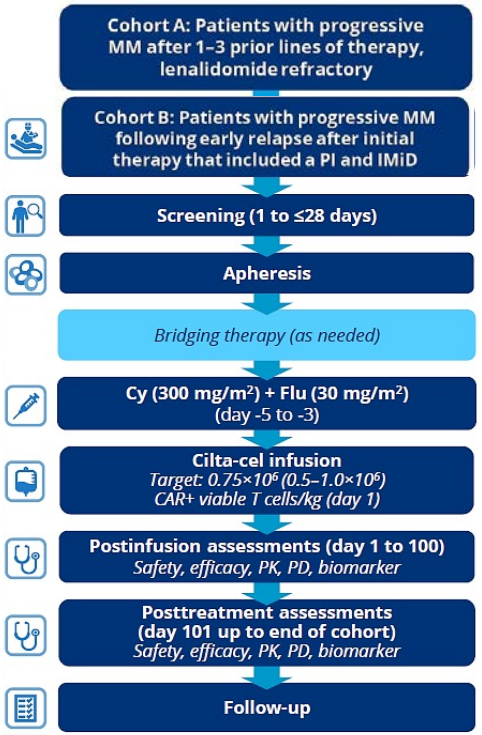
- Median PFS and OS were not reached
- Patients who achieved sCR had improved PFS compared with the overall population
- Of 61 patients evaluable for MRD, 91.8% were MRD-negative at (10^{-5})
- Patients with sustained MRD negativity (10^{-5}) for ≥6 and ≥12 months had improved PFS and OS compared with the overall population

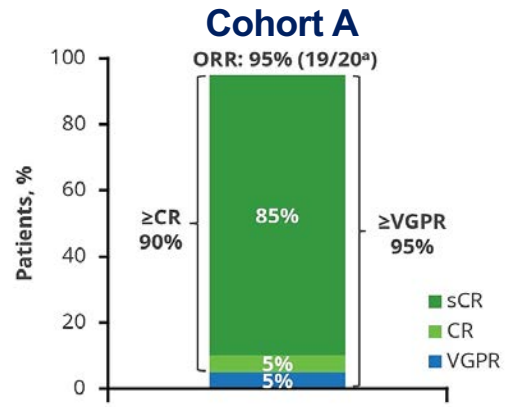
[a]ORR assessed by independent review committee. [b]No patient had CR or stable disease. CAR, chimeric antigen receptor; DOR, duration of response; ISS, International Staging System; MRD, minimal residual disease;
NE, not estimable; ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; sCR, stringent CR; VGPR, very good partial response

Usmani SZ et al, ASCO 2022.

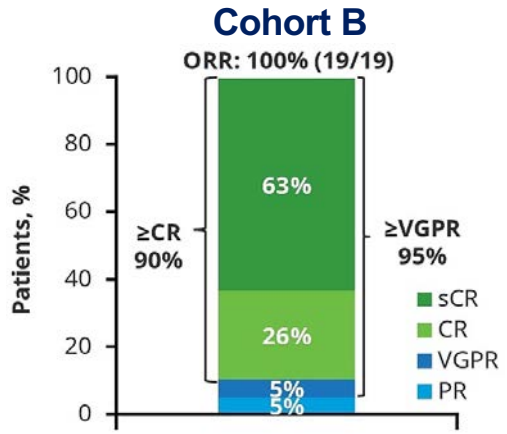
Memorial Sloan Kettering Cancer Center

Using CAR T-cell therapy at earlier lines of therapy: CARTITUDE-2





[a]One patient demonstrated a minimal response.
sCR, stringent CR



CR, complete response; CRS, cytokine release syndrome; Cy, cytarabine; Flu, fludarabine; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; sCR, stringent CR; VGPR, very good partial response

AEs ≥20%, n (%)	N=20	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	19 (95)	19 (95)
Thrombocytopenia	16 (80)	7 (35)
Anemia	15 (75)	9 (45)
Lymphopenia	14 (70)	14 (70)
Leukopenia	11 (55)	11 (55)
CAR-T–related AEs		
CRS	19 (95)	2 (10)
Neurotoxicity	6 (30)	1 (5)
ICANS	3 (15)	0
Other	3 (15)[a]	1 (5)

[a]One patient had peripheral sensorimotor neuropathy, one had anosmia and dysgeusia, and one had facial paralysis.

AEs ≥20%, n (%)	N=19	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	18 (95)	17 (90)
Anemia	11 (58)	9 (47)
Thrombocytopenia	11 (58)	5 (26)
Lymphopenia	6 (32)	6 (32)
Leukopenia	5 (26)	5 (26)
CAR-T–related AEs		
CRS	16 (84)	1 (5)
Neurotoxicity	5 (26)	1 (5)
ICANS	1 (5)	0
Other	4 (21)	1 (5)
Parkinsonism	1 (5)	1 (5)

Hillengass J et al. EHA 2022;abstract P959 (poster presentation)
Agha M et al. EHA 2022;abstract S185 (oral presentation)

Ongoing CAR T Trials

KarMMa-2

Phase 2 study NCT03601078
Ide-cel in early relapse + high-risk or late relapsed MM

KarMMa-3

Phase 3 study NCT03651128
Ide-cel vs standard regimens in RRMM after 2 – 4 prior lines

KarMMa-4

Phase 1 study NCT04196491
Ide-cel in high-risk NDMM

KarMMa-7

Phase 1/2 study NCT04855136

Ide-cel in combination with various agents in RRMM

CARTITUDE-4

Phase 3 study NCT04181827
Cilta-cel vs DPd or PVd in RRMM after 1 – 3 prior lines

CARTITUDE-5

Phase 3 study NCT04923893

VRd + Cilta-cel vs VRd + Rd maintenance in transplant-ineligible NDMM

CARTITUDE-6

Phase 3 study NCT04923893

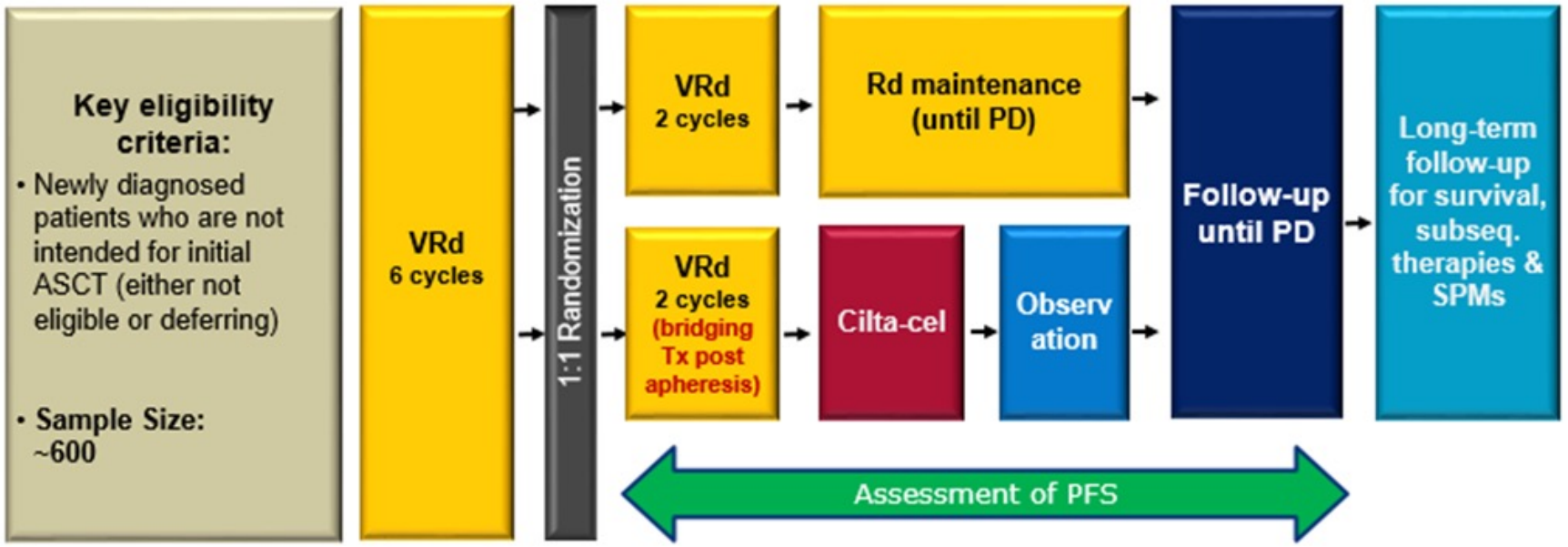
DVRd + Cilta-cel vs DVRd + AutoSCT in transplant-eligible NDMM

Phase 1 development

Many agents in early development with various constructs.

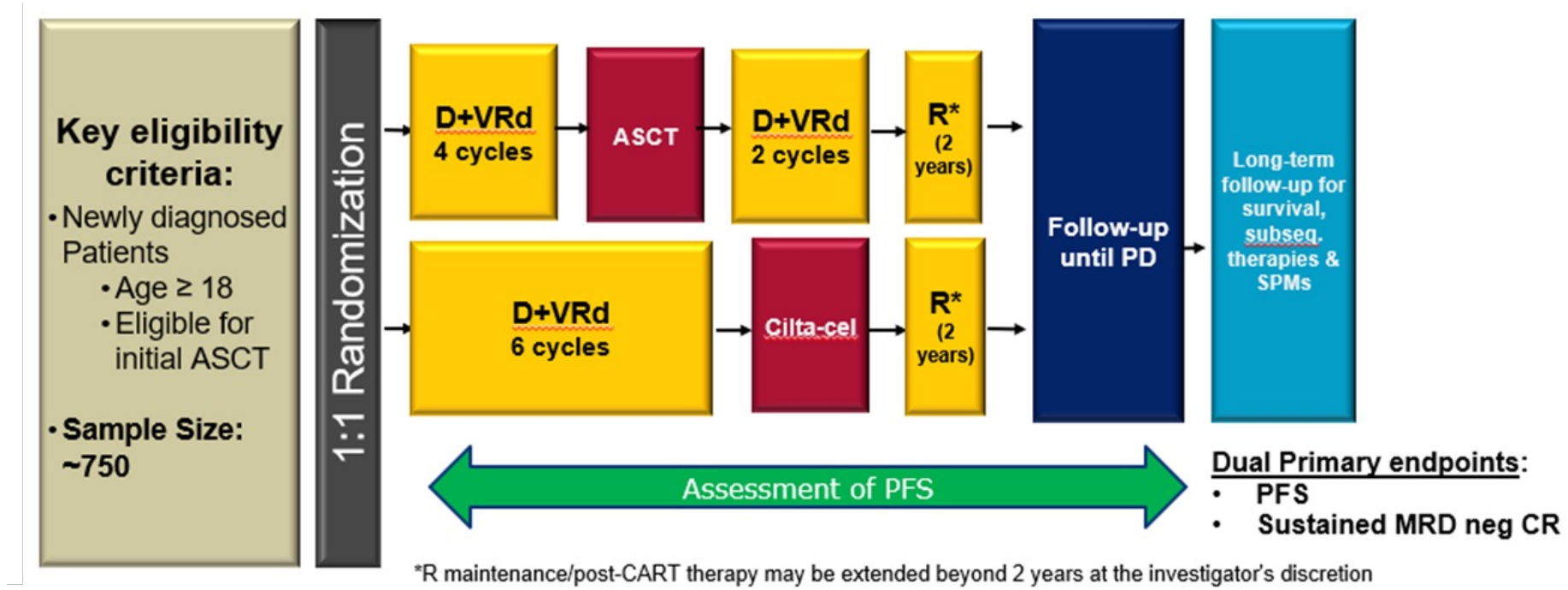
Memorial Sloan Kettering Cancer Center

CARTITUDE-5: Randomized, phase 3 in NDMM, not intended for transplant



Memorial Sloan Kettering Cancer Center

CARTITUDE-6: Randomized, phase 3 in NDMM, transplant eligible



Memorial Sloan Kettering Cancer Center

MSKCC Myeloma Service

Saad Z. Usmani (Chief)
High-Risk Disease
Biology/Trials
Bispecific Antibodies
CAR T Cells
Checkpoint Inhibitors
Developmental Therapeutics

Sham Mailankody
MM
Immunotherapy
CAR T Cells

Malin Hultcrantz
MM Precursor Disease
Antibody drug conjugates
Genetics/MRD

Urvi Shah
Early Relapse
MM Precursor Disease
Nutrition & Modifiable Risk Factors

Kylee Maclachlan
MM Precursor Disease
NDMM Trials
Genomics, Immune Profiling

Alex Lesokhin
MM Immunotherapy
Bispecific Antibodies
Checkpoint Inhibitors
Neoantigens
Microbiota

Hani Hassoun
MM Supportive Care
Alliance Liaison
NDMM/RRMM Trials
Elderly and Frail

Neha Korde
NDMM Clinical Trials
MRD Directed therapy
Supportive Care

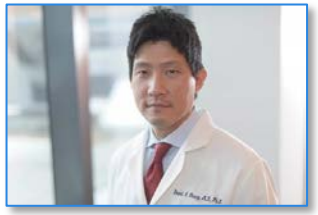
Carlyn Tan
MM Precursor Disease
Supportive Care
Bone Health

Memorial Sloan Kettering Cancer Center

MSKCC Myeloma TCT Program

Sergio Giralt
Allo/Auto HCT for MM
New Regimens
CAR T Cells

David Chung
T Cell exhaustion
Auto HCT + Vaccines
MM Immunotherapies



Gunjan Shah
HCT Toxicities
Precision Drug Dosing
CAR T Cells
Salvage Auto and Allo HCT

Saad Z. Usmani
High-Risk Disease Biology/Trials
CAR T Cells
Auto HCT for MM

Michael Scordo
HCT Toxicities
Precision Drug Dosing
CAR T Cells

Heather Landau
Amyloidosis
HCT Toxicities
Homebound HCT
Precision Drug Dosing
Novel Regimens for Salvage Auto

Oscar Lahoud
Auto HCT and CAR T Cells
Post HCT Therapies

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

ASCO 2022;Abstract 8007.

Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Results From MajesTEC-1

Ajay K Nooka (anooka@emory.edu)[1], Philippe Moreau[2], Saad Z Usmani[3], Alfred L Garfall[4], Niels WCJ van de Donk[5], Jesús San-Miguel[6], Albert Oriol[7], Ajai Chari[8], Lionel Karlin[9], Maria-Victoria Mateos[10], Rakesh Popat[11], Joaquín Martínez-López[12], Surbhi Sidana[13], Danielle Trancucci[14], Raluca Verona[15], Suzette Girgis[15], Clarissa Uhlar[15], Tara Stephenson[15], Arnob Banerjee[15], Amrita Krishnan[16]

[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]University Hospital Hôtel-Dieu, Nantes, France; [3]Memorial Sloan Kettering Cancer Cent NY, USA; [4]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Amsterdam University Medical Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [6]University of Navarra, Pamplona, Spain; [7]Hospital Germans Trias I Pu Spain; [8]Mount Sinai School of Medicine, New York, NY, USA; [9]Centre Hospitalier Lyon Sud, France; [10]University Hospital of Salamanca/IBSAL/CIC, Salar [11]University College London Hospitals, NHS Foundation Trust, London, UK; [12]Hematología Hospital 12 de Octubre, Madrid, Spain; [13]Stanford Universit Medicine, Stanford, CA, USA; [14]Janssen Research & Development, Raritan, NJ, USA; [15]Janssen Research & Development, Spring House, PA, USA; [16]City Comprehensive Cancer Center, Duarte, CA, USA

Presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL

N Engl J Med 2022 June 5;[Online ahead of print].

The NEW ENGLAND JOURNAL of MEDICINE

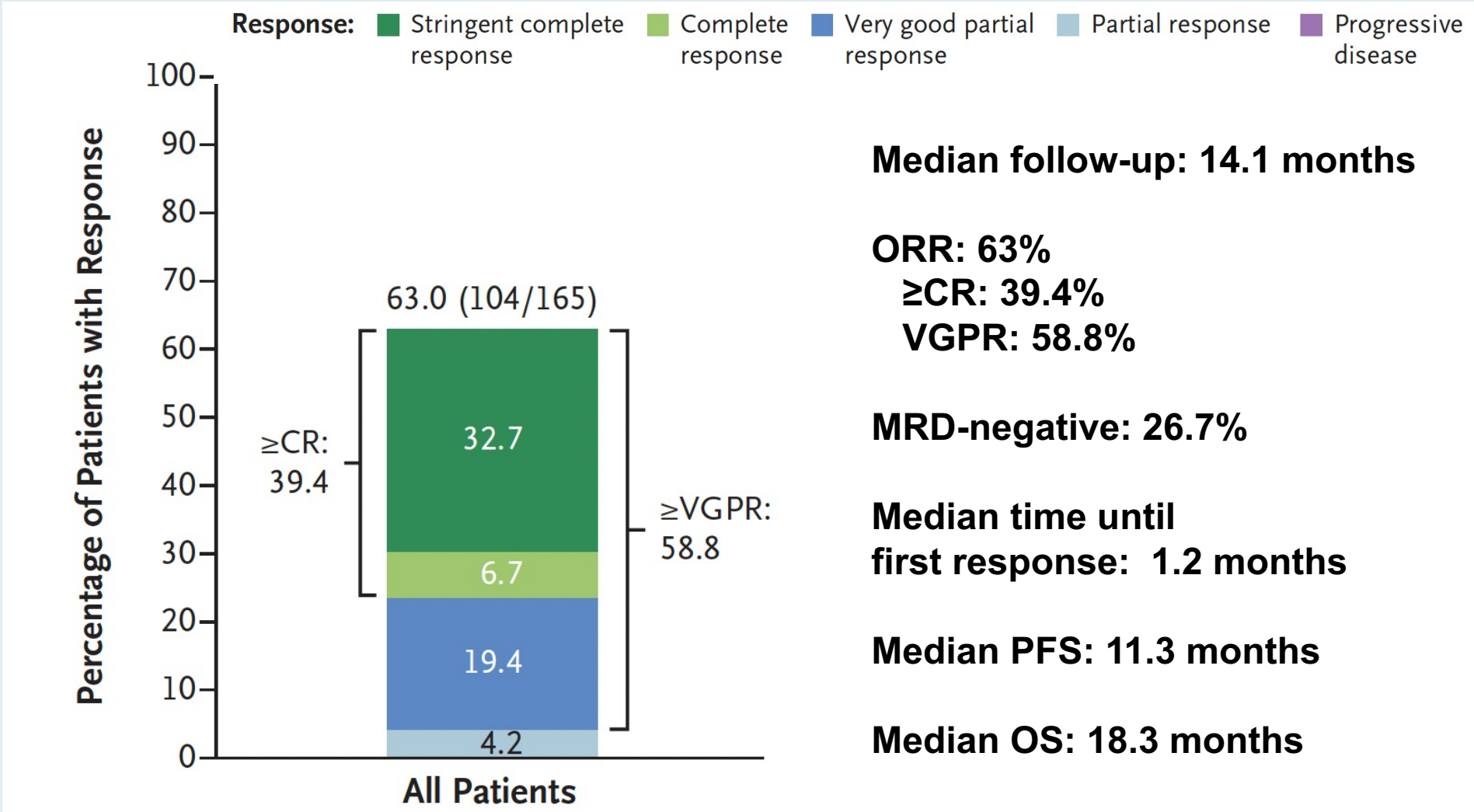
ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

P. Moreau, A.L. Garfall, N.W.C.J. van de Donk, H. Nahi, J.F. San-Miguel, A. Oriol, A.K. Nooka, T. Martin, L. Rosinol, A. Chari, L. Karlin, L. Benboubker, M.-V. Mateos, N. Bahlis, R. Popat, B. Besemer, J. Martínez-López, S. Sidana, M. Delforge, L. Pei, D. Trancucci, R. Verona, S. Girgis, S.X.W. Lin, Y. Olyslager, M. Jaffe, C. Uhlar, T. Stephenson, R. Van Rampelbergh, A. Banerjee, J.D. Goldberg, R. Kobos, A. Krishnan, and S.Z. Usmani

RTP RESEARCH TO PRACTICE

MajesTEC-1: Response and Survival



Median follow-up: 14.1 months

ORR: 63%
≥CR: 39.4%
VGPR: 58.8%

MRD-negative: 26.7%

Median time until first response: 1.2 months

Median PFS: 11.3 months

Median OS: 18.3 months

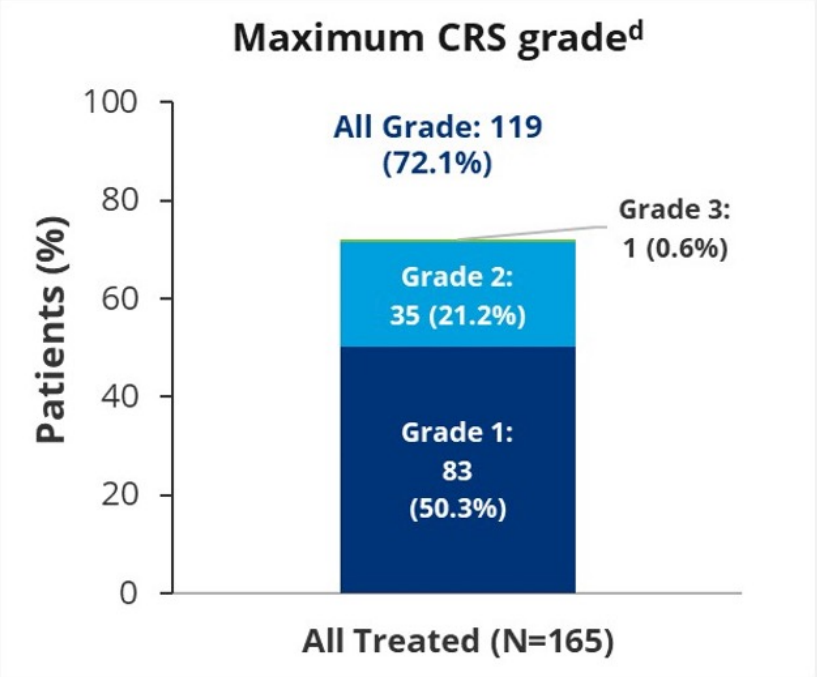
ORR = overall response rate; MRD = minimal residual disease

Moreau P et al. *N Engl J Med* 2022 June 5;[Online ahead of print].

RTP RESEARCH TO PRACTICE

MajesTEC-1: Cytokine Release Syndrome

Parameter	N=165
Patients with CRS, n (%)	119 (72.1)
Patients with ≥2 CRS events	55 (33.3)
Time to onset[a] (days), median (range)	2 (1–6)
Duration (days), median (range)	2 (1–9)
Received supportive measures[a] for CRS, n (%)	110 (66.7)
Tocilizumab[b]	60 (36.4)
Low-flow oxygen by nasal cannula[c]	21 (12.7)
Corticosteroids	14 (8.5)
Single vasopressor	1 (0.6)



- Most CRS events were confined to step-up and first full treatment doses
- All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that occurred in the context of concurrent pneumonia (resolved in 2 days)
- All CRS events fully resolved without treatment discontinuation or dose reduction

Nooka AK et al. ASCO 2022;Abstract 8007.

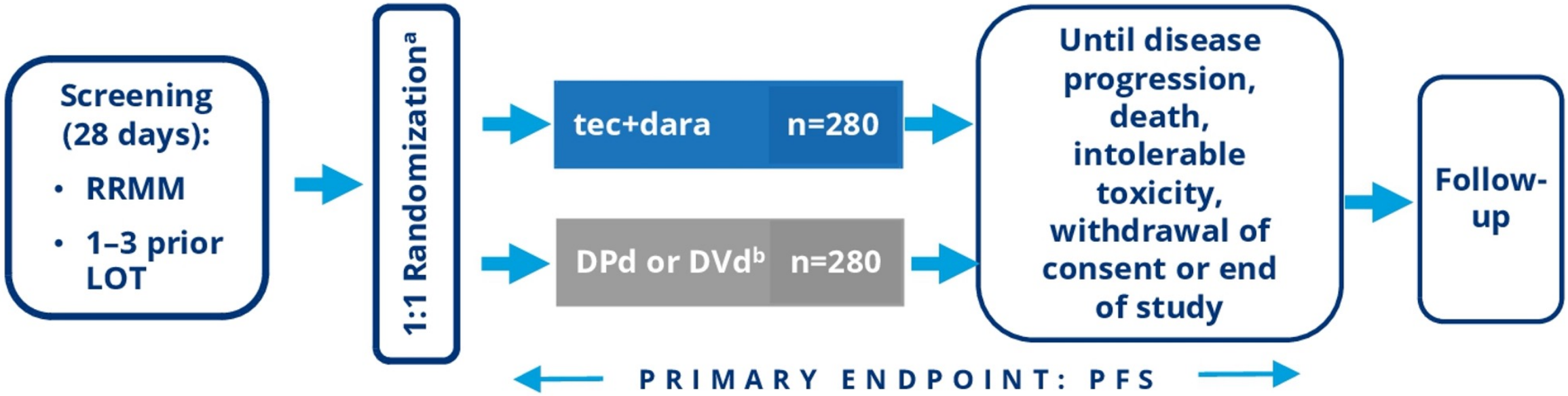
MajesTEC-1: Neurotoxic Events

Parameter	N=165
Neurotoxic event[a], n (%)	**24 (14.5)**
Headache	**14 (8.5)**
ICANS[b]	**5 (3.0)**
Dysgeusia	**2 (1.2)**
Lethargy	**2 (1.2)**
Tremor	**2 (1.2)**
Grade ≥3 events, n (%)	**1 (0.6)**
Time to onset, median (range) days	**3.0 (1–13)**
Duration, median (range) days	**7.0 (1–291)**
Received supportive measures for neurotoxic events[c], n (%)	**14 (8.5)**
Tocilizumab	**3 (1.8)**
Dexamethasone	**3 (1.8)**
Levetiracetam	**2 (1.2)**
Gabapentin	**1 (0.6)**

- The overall incidence of neurotoxic events was low
- All neurotoxic events were grade 1/2, except for 1 grade 4 seizure (in the context of bacterial meningitis during cycle 7)
- 5 patients (3.0%) had a total of 9 ICANS events
  - 7 events were concurrent with CRS
  - All ICANS events were grade 1/2 and fully resolved
- There were no treatment discontinuations or dose reductions due to neurotoxic events, including ICANS

Nooka AK et al. ASCO 2022;Abstract 8007.

MajesTEC-3 Ongoing Phase III Study Design



Key Eligibility Criteria

- Received 1-3 prior lines of therapy, including PI and lenalidomide
  - Patients with only 1 prior line of therapy must be lenalidomide refractory
- No prior BCMA-directed therapy and/or not refractory to anti-CD38 mAb

RRMM = relapsed/refractory multiple myeloma; PI = proteasome inhibitor; tec = teclistamab; dara = daratumumab; DPd = dara/pomalidomide/dexamethasone; DVd = bortezomib/dexamethasone; mAb = monoclonal antibody

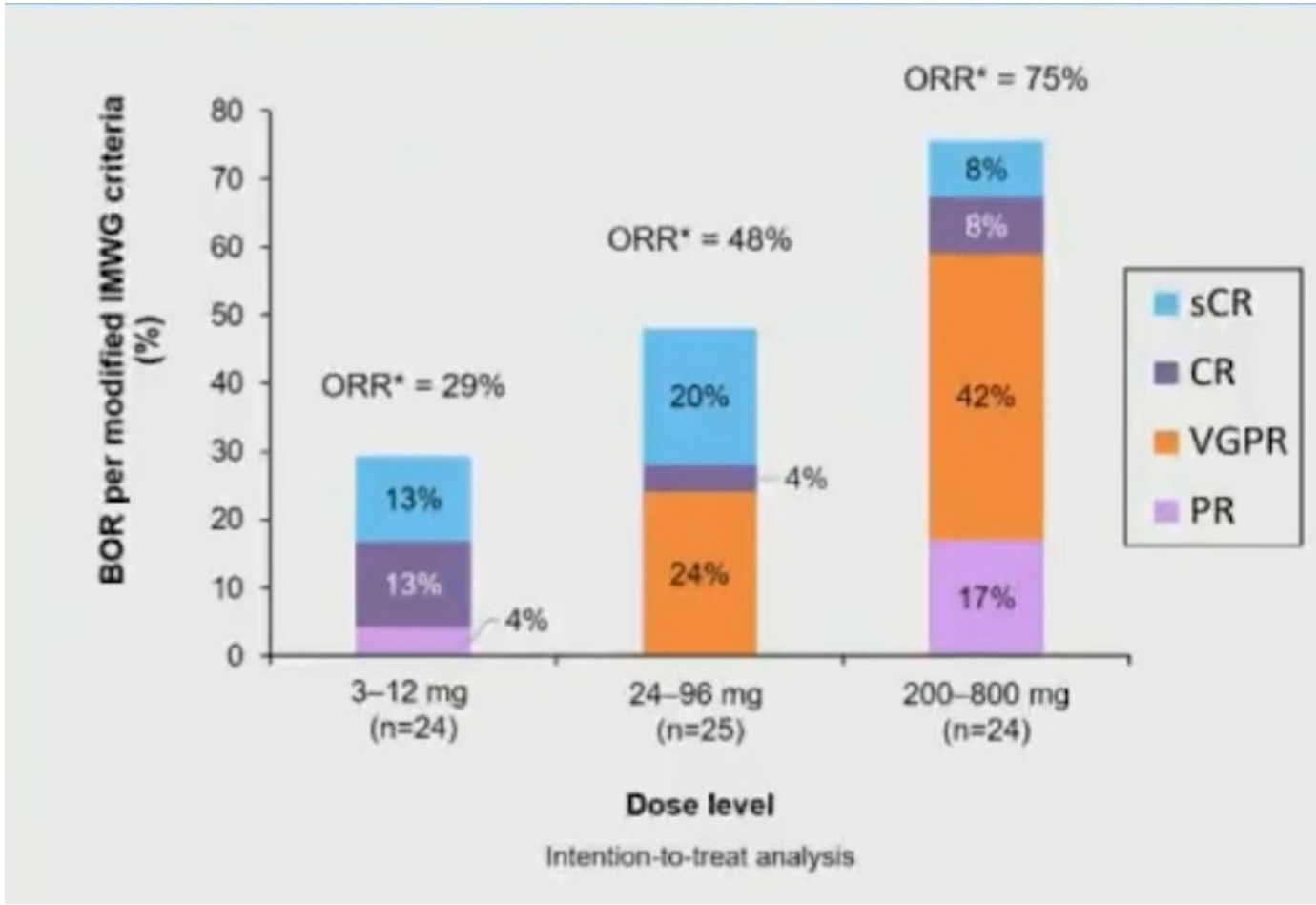
Mateos MV et al. ASCO 2022;Abstract TPS8072.

LINKER-MM1 — Early, Deep, and Durable Responses, and Low Rates of Cytokine Release Syndrome with REGN5458, a BCMA x CD3 Bispecific Antibody, in a Phase 1/2 Study in Patients with Relapsed/Refractory Multiple Myeloma

Zonder JA et al.

International Myeloma Society Meeting 2022;Abstract OAB-056.

LINKER-MM1: Phase I Efficacy with REGN5458

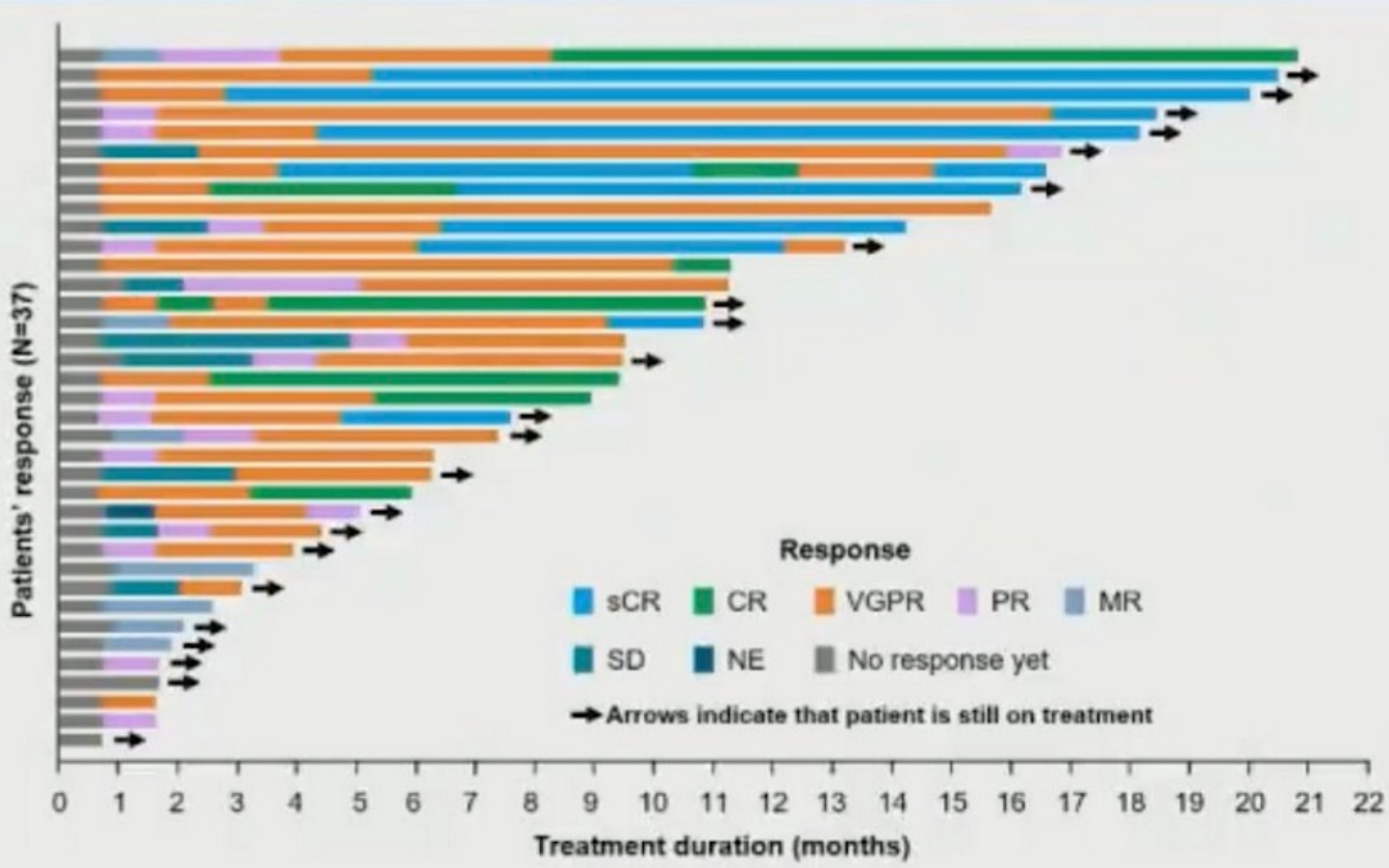


- Responses have been observed across all dose levels, with a trend for higher response rates at higher doses
  - 51% ORR among all enrolled patients*
- 75% ORR and 58% ≥VGPR with REGN5458 200–800 mg
- Among all responders, 86% achieved ≥VGPR, 43% ≥CR
- Among CR/sCR with available MRD data:
  - 4/10 MRD negative at 10^{-5}

ORR = overall response rate

Zonder JA et al. International Myeloma Society Meeting 2022;Abstract OAB-056.

LINKER-MM1: Duration of Response with REGN5458



- Responses occurred early, were durable, and deepened with time
  - Median time to response is <1 month
  - 70% of responses occurred within the first 2 months
- Estimated*,† median DOR was not reached
  - Probability† of responders being in response at 8 months was 90.2% (95% CI: 72.6, 96.7)
- The longest responses are ongoing for 19+ months at the latest data cut-off

Zonder JA et al. International Myeloma Society Meeting 2022;Abstract OAB-056.

RTP RESEARCH TO PRACTICE

LINKER-MM1: Safety with REGN5458

	Total (N=73)		
	Any grade	Grade 3	Grade 4
All treatment-emergent adverse events (TEAEs) n (%)			
Any	73 (100)	31 (42)	24 (33)
Hematologic TEAEs, *in ≥20% of patients (any grade)* **n (%)**			
Anemia	23 (32)	17 (23)	0
Lymphopenia	17 (23)	7 (10)	7 (10)
Neutropenia	17 (23)	5 (7)	11 (15)
Thrombocytopenia	15 (21)	6 (8)	4 (5)
Non-hematologic TEAEs, *in ≥20% of patients (any grade)* **n (%)**			
Fatigue	33 (45)	2 (3)	0
CRS	28 (38)	0	0
Pyrexia	26 (36)	3 (4)	0
Nausea	24 (33)	0	0
Dyspnea	19 (26)	0	0
Diarrhea	18 (25)	2 (3)	0
Back pain	18 (25)	4 (5)	0
Vomiting	18 (25)	0	0
Pneumonia	17 (23)	8 (11)	0
Chills	16 (22)	1 (1)	0
Cough	16 (22)	0	0
Headache	15 (21)	2 (3)	0

Dose-limiting toxicity (DLT)

- DLTs were reported in 2 patients
  - DL4 (24 mg) and DL6 (96 mg)
- Maximum-tolerated dose not reached

Potential ICANS events

- No Grade 3 ICANS events reported
- Grade 2 events occurred in 3 patients (4%)

Deaths

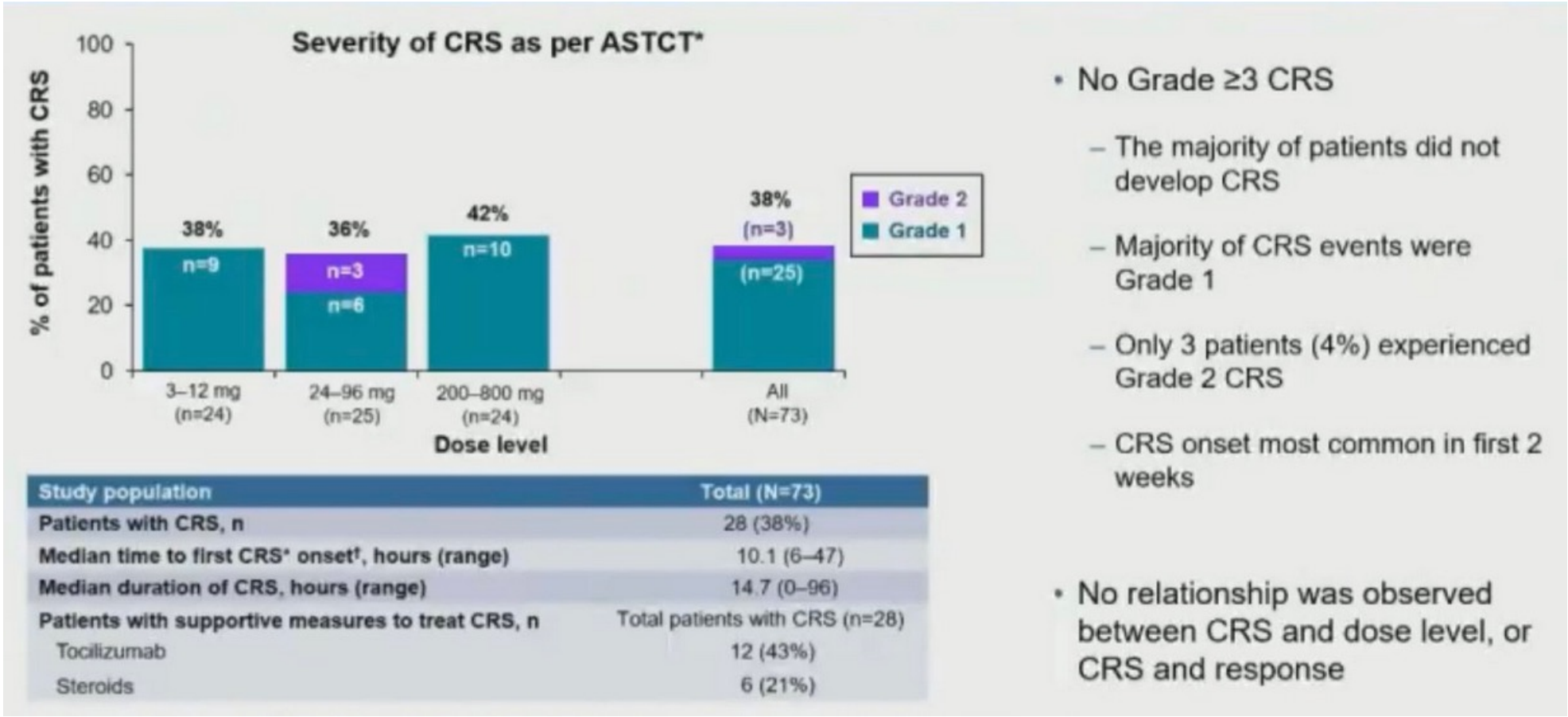
- 5 (7%) Grade 5 AEs were reported [sepsis (n=3); COVID (n=1); pneumonia (n=1)]
- All Grade 5 events were not related to study treatment

Pharmacokinetics

- REGN5458 serum concentration increased with dose, approximately dose proportionally

Zonder JA et al. International Myeloma Society Meeting 2022;Abstract OAB-056.

LINKER-MM1: Cytokine Release Syndrome with REGN5458



Study population	Total (N=73)
Patients with CRS, n	28 (38%)
Median time to first CRS* onset†, hours (range)	10.1 (6–47)
Median duration of CRS, hours (range)	14.7 (0–96)
Patients with supportive measures to treat CRS, n	Total patients with CRS (n=28)
Tocilizumab	12 (43%)
Steroids	6 (21%)

- No Grade ≥3 CRS
  - The majority of patients did not develop CRS
  - Majority of CRS events were Grade 1
  - Only 3 patients (4%) experienced Grade 2 CRS
  - CRS onset most common in first 2 weeks
- No relationship was observed between CRS and dose level, or CRS and response

ASTCT = American Society for Transplantation and Cellular Therapy

Zonder JA et al. International Myeloma Society Meeting 2022;Abstract OAB-056.

RTP RESEARCH TO PRACTICE

Other BCMA x CD3 Bispecific Antibodies: Summary

Therapy	Characteristics	N	Population	Safety	Response
AMG 701[2]	▪ BiTE® modified ▪ IV ▪ Weekly	82	▪ Median of 6 PL ▪ 62% triple refractory	▪ CRS 55%, G3-4: 9% ▪ No ICANS ▪ 20% cytopenias	83% ORR at the top dose level and 50% VGPR
TNB-383B[4]	▪ Triple chain anti-BCMA bispecific ▪ IV fixed doses ▪ Every 3 weeks	58	▪ Median of 6 PL ▪ 64% triple refractory ▪ 34% penta refractory	▪ CRS 45% and no G3-4 ▪ No ICANS ▪ Cytopenias 21% and infections 14%	80% (13% CR) at the dose levels 40-60 mg
Elranatamab (PF-3135[5])	▪ Bispecific ▪ SC and weekly ▪ RP2D: 1,000 µg/kg	30	▪ Median of 8 PL ▪ 87% triple refractory ▪ 23% prior BCMA-based therapy	▪ CRS 73% and no G3-4 ▪ ICANS 20% ▪ ISR 50%	83% ORR at RP2D

PL = prior lines of therapy; SC = subcutaneous; ISR = injection site reaction

1. Usmani SZ et al. *Lancet* 2021. 2. Harrison SJ et al. ASH 2020;Abstract 181. 3. Madduri D et al. ASH 2020;Abstract 291. 4. Rodriguez C et al. ASH 2020;Abstract 293.5. Bahlis NJ et al. ASCO 2021;Abstract 8006.

Content courtesy of Noopur Raje, MD

FDA Grants Breakthrough Therapy Designation to Talquetamab for Relapsed/Refractory Multiple Myeloma

Press Release: June 29, 2022

"Talquetamab was granted breakthrough therapy designation by the FDA for the treatment of patients with relapsed/refractory multiple myeloma who were treated with a minimum of 4 previous lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody.

The designation is supported by findings from the phase 1/2 MonumenTAL-1 trial (NCT03399799; NCT04634552), which assessed the agent in patients with relapsed/refractory disease. Data from the study, which were presented at the 2022 American Society of Clinical Oncology Annual Meeting, indicated that patients who were treated with 405 µg/kg of talquetamab (n = 30) experienced an overall response rate (ORR) of 70.0%, including a very good partial response (VGPR) rate or better of 56.7%. Additionally, the ORR among patients treated at the 800 µg/kg dose was 63.6%, including a VGPR or better of 56.8%. Moreover, the stringent complete response (CR) rates were 23.3% and 9.1%, CR rates were 6.7% and 11.4%, the VGPR rates were 26.7% and 36.4%, and PR rates were 13.3% and 6.8% in each respective arm.

Talquetamab is an off-the-shelf T-cell–redirecting bispecific antibody that targets GPRC5D on myeloma cells and CD3 on T cells."

https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-designation-to-talquentamab-for-relapsed-refractory-multiple-myeloma

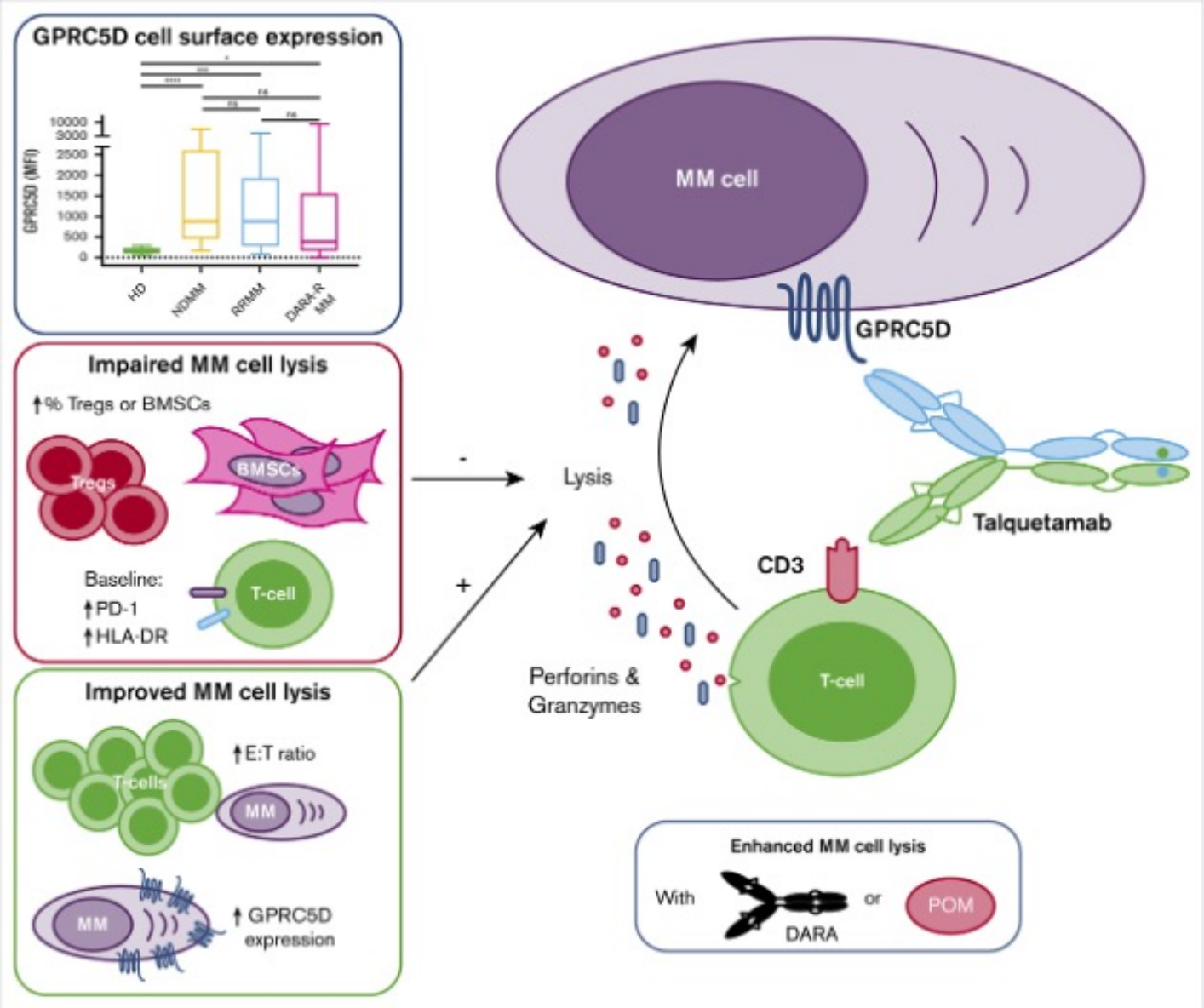
RTP RESEARCH TO PRACTICE

Biologic Rationale for Targeting GPRC5D in MM

GPRC5D expression levels are significantly higher on MM cells compared to normal plasma cells or other immune cells

Increased proportion of T cells expressing PD-1 or HLA-DR, and elevated regulatory T-cell (Treg) counts were associated with suboptimal killing

High levels of GPRC5D and high effector-target ratios were associated with improved talquetamab-mediated lysis of MM cells



Talquetamab kills GPRC5D+ MM cell lines in the presence of T cells from both healthy donors or heavily pretreated MM patients

Tumor cell lysis was accompanied by T-cell activation and degranulation as well as production of pro-inflammatory cytokines

Combination therapy with daratumumab or pomalidomide enhanced talquetamab-mediated lysis of primary MM cells in an additive fashion

Verkleij CPM et al. *Blood Adv* 2021; 5(8):2196–2215.

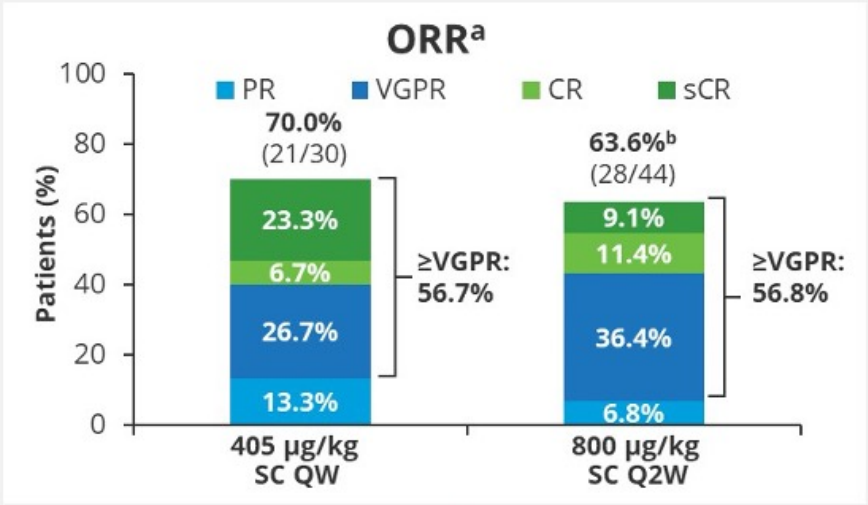
Efficacy and Safety of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients With Relapsed/ Refractory Multiple Myeloma: Updated Results From MonumenTAL-1

Monique C Minnema[1], Amrita Krishnan[2], Jesus G. Berdeja[3], Albert Oriol[4], Niels WCJ van de Donk[5], Paula Rodríguez-Otero[6], Daniel Morillo[7], María-Victoria Mateos[8], Luciano J. Costa[9], Jo Caers[10], Deeksha Vishwamitra[11], Joanne Ma[11], Shiyi Yang[11], Brandi W Hilder[11], Jaszianne Tolbert[11], Jenna D Goldberg[12], Ajai Chari[13]

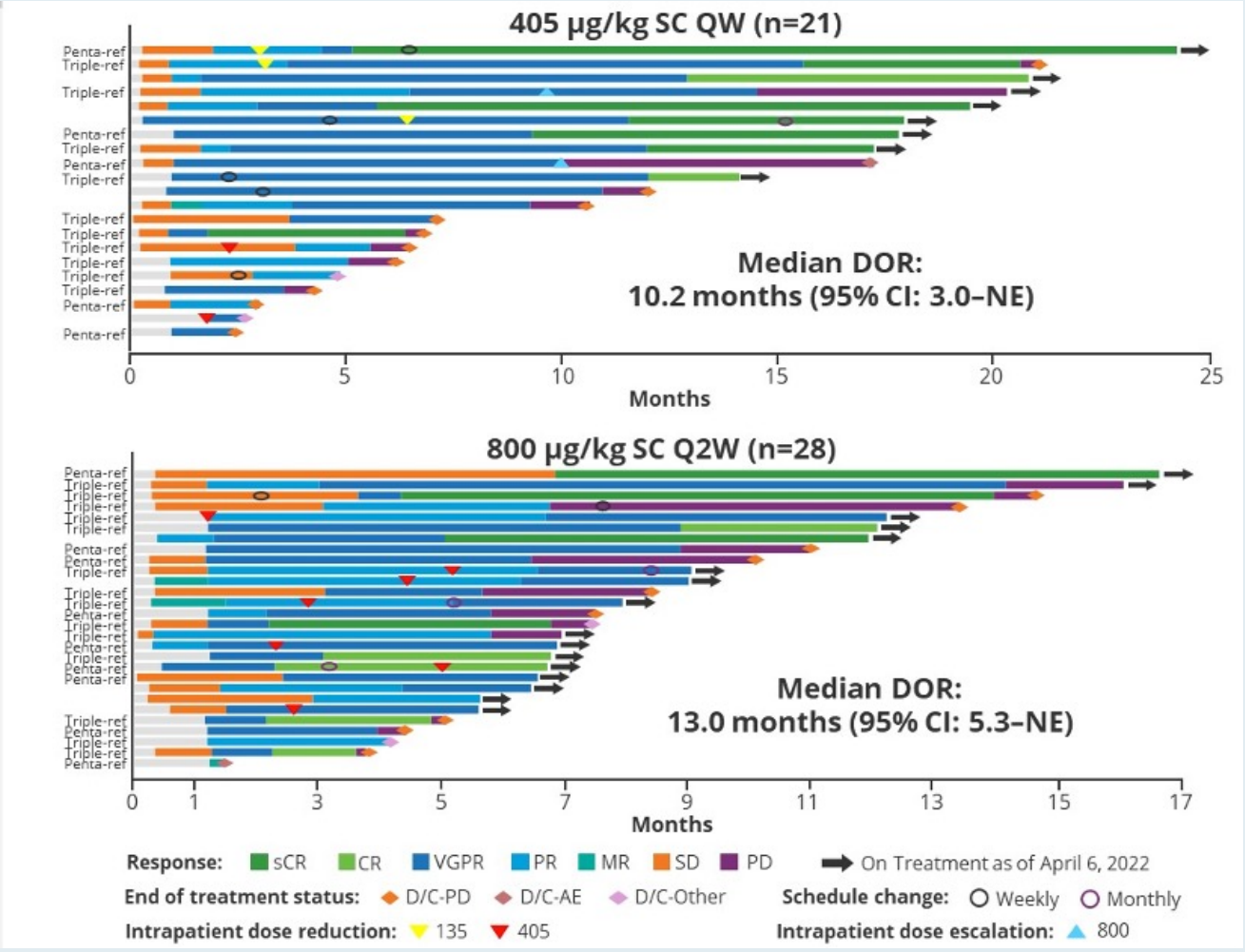
ASCO 2022;Abstract 8015.

RTP RESEARCH TO PRACTICE

MonumenTAL-1 Phase I Study: Duration of Response with Talquetamab for R/R MM



Response	405 µg/kg SC QW[c] n=30	800 µg/kg SC Q2W[c] n=44
Median follow-up (months), median (range)	13.2 (1.1–24.0)	7.7 (0.7–16.0)
ORR[a], n (%)	21 (70.0)	28 (63.6)
Triple-class–refractory patients, n/N (%)	15/23 (65.2)	23/34 (67.6)
Penta-drug–refractory patients, n/N (%)	5/6 (83.3)	9/12 (75.0)
Median time to first confirmed response (months), median (range)	0.9 (0.2–3.8)	1.2 (0.3–6.8)



Minnema MC et al. ASCO 2022;Abstract 8015.

MonumenTAL-1: Adverse Events with Talquetamab

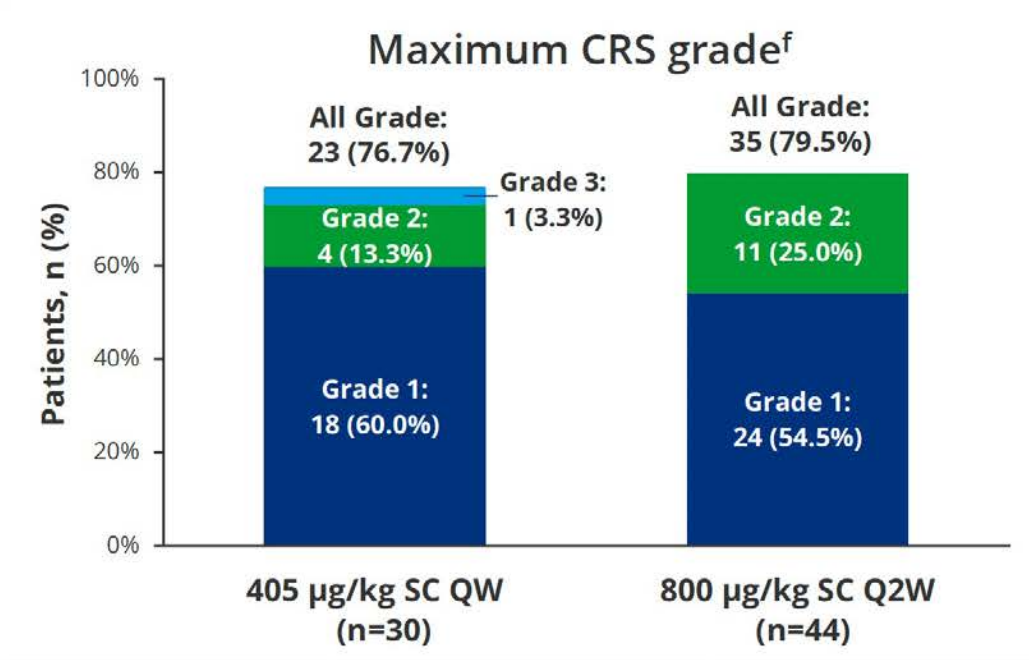
AEs (≥20% of total SC population), n (%)	405 µg/kg SC QW[a] n=30		800 µg/kg SC Q2W[a] n=44	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic				
Neutropenia	20 (66.7)	18 (60.0)	18 (40.9)	15 (34.1)
Anemia	17 (56.7)	9 (30.0)	21 (47.7)	12 (27.3)
Lymphopenia	12 (40.0)	12 (40.0)	18 (40.9)	18 (40.9)
Leukopenia	12 (40.0)	9 (30.0)	10 (22.7)	8 (18.2)
Thrombocytopenia	11 (36.7)	7 (23.3)	10 (22.7)	5 (11.4)
Nonhematologic				
CRS	23 (76.7)	1 (3.3)	35 (79.5)	0
Skin-related AEs[b]	20 (66.7)	0	32 (72.7)	1 (2.3)
Dysgeusia	19 (63.3)	N/A	25 (56.8)	N/A
Nail-related AEs[c]	18 (60.0)	0	15 (34.1)	0
Rash-related AEs[d]	14 (46.7)	1 (3.3)	13 (29.5)	7 (15.9)
Dysphagia	12 (40.0)	0	12 (27.3)	0
Pyrexia	11 (36.7)	0	10 (22.7)	0
Fatigue	10 (33.3)	1 (3.3)	12 (27.3)	0
Dry mouth	9 (30.0)	0	25 (56.8)	0
Weight decreased	9 (30.0)	0	19 (43.2)	1 (2.3)
Nausea	9 (30.0)	0	9 (20.5)	0
Diarrhea	9 (30.0)	0	8 (18.2)	0
ALT increased	6 (20.0)	1 (3.3)	14 (31.8)	3 (6.8)
Decreased appetite	7 (23.3)	1 (3.3)	11 (25.0)	1 (2.3)
Headache	7 (23.3)	0	11 (25.0)	0
AST increased	3 (10.0)	0	14 (31.8)	3 (6.8)

- Overall, the most common adverse events (AEs) were CRS, skin-related events, and dysgeusia
- Cytopenias were mostly confined to step-up and cycle 1–2 doses and generally resolved within 1 week
- Infections occurred in 46.7% of patients at 405 µg/kg QW and 38.6% at 800 µg/kg Q2W (grade 3/4: 6.7%/9.1%)
- CRS events were mostly grade 1/2 and were largely confined to the step-up doses and first full dose
- Dysgeusia was managed with supportive care, and at times with dose adjustments
- No patients died due to drug-related AEs

Minnema MC et al. ASCO 2022;Abstract 8015.

MonumenTAL-1: Cytokine Release Syndrome

Parameter	405 µg/kg SC QW[a] n=30	800 µg/kg SC Q2W[a] n=44
Patients with CRS, n (%)	23 (76.7)	35 (79.5)
Time to onset (days),[b] median (range)	2 (1–22)	2 (1–5)
Duration (days), median (range)	2 (1–3)	2 (1–5)
Patients who received supportive measures,[c] n (%)	23 (76.7)	35 (79.5)
Tocilizumab[d]	19 (63.3)	24 (54.5)
Steroids	1 (3.3)	3 (6.8)
Oxygen	1 (3.3)[e]	2 (4.5)
Single vasopressor	1 (3.3)[e]	0

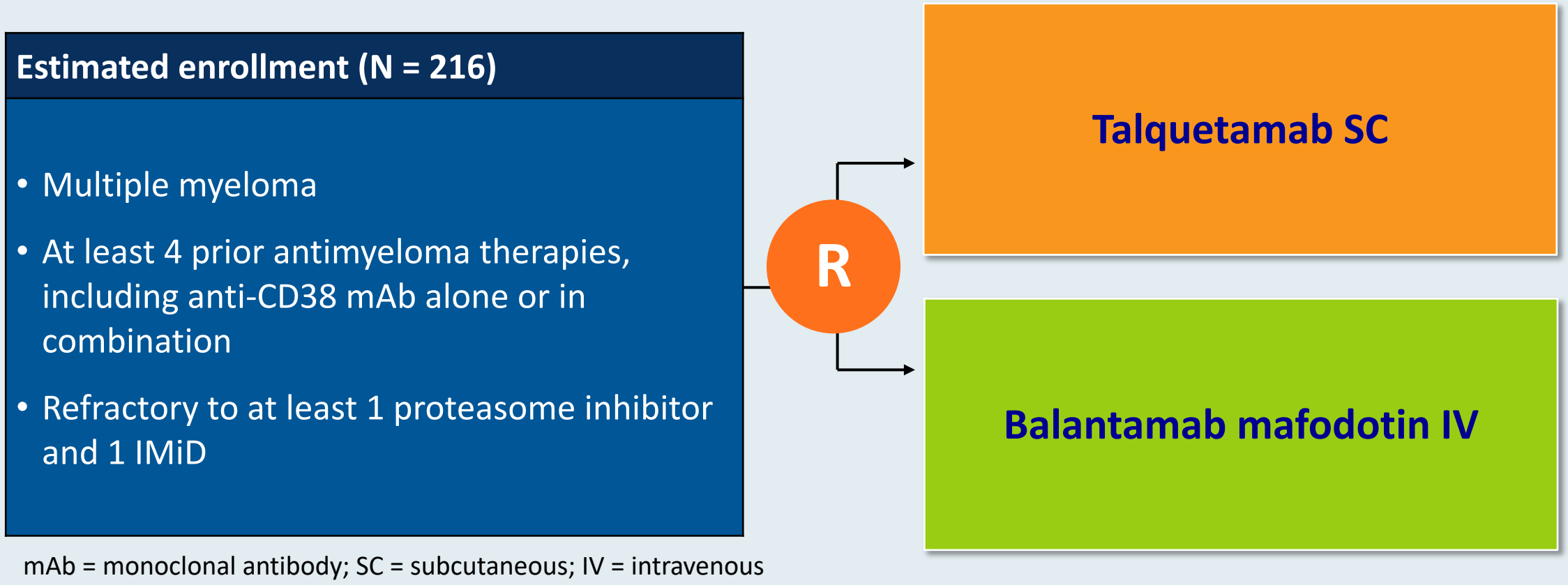


- All CRS events were grade 1/2, except for one grade 3 event
- CRS was largely confined to the step-up doses and first full dose

Minnema MC et al. ASCO 2022;Abstract 8015.

RTP RESEARCH TO PRACTICE

MonumenTAL-5 Phase III Study Design



mAb = monoclonal antibody; SC = subcutaneous; IV = intravenous

Primary endpoint: Overall response rate, progression-free survival

www.clinicaltrials.gov. NCT05461209. Accessed August 2022.

EHA 2022;Abstract S183.

Novel Combination Immunotherapy for the Treatment of Relapsed/Refractory Multiple Myeloma: Updated Phase 1b Results for Talquetamab (a GPRC5D x CD3 Bispecific Antibody) in Combination With Daratumumab

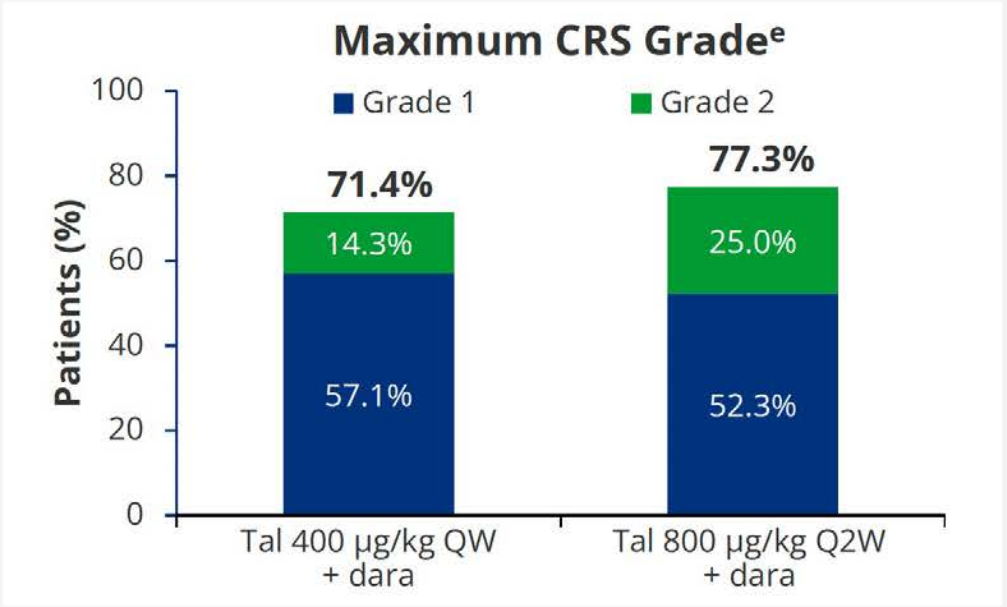
Niels WCJ van de Donk[1], Nizar Bahlis[2], Maria-Victoria Mateos[3], Katja Weisel[4], Bhagirathbhai Dholaria[5], Alfred L Garfall[6], Hartmut Goldschmidt[7], Thomas G Martin[8], Daniel Morillo[9], Donna Reece[10], David Hurd[11], Paula Rodríguez-Otero[12], Manisha Bhutani[13], Anita D'Souza[14], Albert Oriol[15], Elham Askari[9], Jesús F San-Miguel[12], K Martin Kortüm[16], Deeksha Vishwamitra[17], Shun Xin Wang Lin[17], Thomas J Prior[17], Lien Vandenberk[18], Marie-Anne Damiette Smit[19], Jenna D Goldberg[20], Ralph Wäsch[21], Ajai Chari[22]

[1]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [2]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, Canada; [3]University Hospital of Salamanca/IBSAL/CIC, Salamanca, Spain; [4]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]Vanderbilt University Medical Center, Nashville, TN, USA; [6]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [7]University Hospital Heidelberg and National Center of Tumor Diseases, Heidelberg, Germany; [8]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [9]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [10]Princess Margaret Cancer Centre, Toronto, ON, Canada; [11]Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC, USA; [12]University of Navarra, Pamplona, Spain; [13]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [14]Medical College of Wisconsin, Milwaukee, WI, USA; [15]Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [16]University Hospital of Würzburg, Würzburg, Germany, Würzburg, Germany; [17]Janssen Research & Development, Spring House, PA, USA; [18]Janssen Research & Development, Antwerp, Belgium; [19]Janssen Research & Development, Los Angeles, CA, USA; [20]Janssen Research & Development, Raritan, NJ, USA; [21]Freiburg University Medical Center, Freiburg, Germany; [22]Mount Sinai School of Medicine, New York, NY, USA

Presented at the European Hematology Association (EHA) 2022 Hybrid Congress; June 9–12, 2022; Vienna, Austria.

TRIMM-2: Cytokine Release Syndrome

Parameter	Tal 400 µg/kg QW + dara (n=14)	Tal 800 µg/kg Q2W + dara (n=44)
Patients with CRS, n (%)	10 (71.4)	34 (77.3)
Time to onset (days)[a], median (range)	3 (2–4)	2 (1–4)
Duration (days), median (range)	2 (1–10)	2 (1–28)
Received supportive measures[b], n (%)	9 (64.3)	30 (68.2)
Tocilizumab[c]	6 (42.9)	14 (31.8)
Corticosteroids	0	2 (4.5)
Oxygen	0	3 (6.8)
Vasopressor	0	0
Other[d]	7 (50.0)	30 (68.2)



- No grade 3/4 CRS events were observed
- CRS events were mostly confined to step-up doses and the first full treatment dose
- No discontinuations due to CRS
- Two patients had ICANS; both ICANS events were grade 1 and resolved within 1 day

van de Donk NWCJ et al. EHA 2022;Abstract S183.

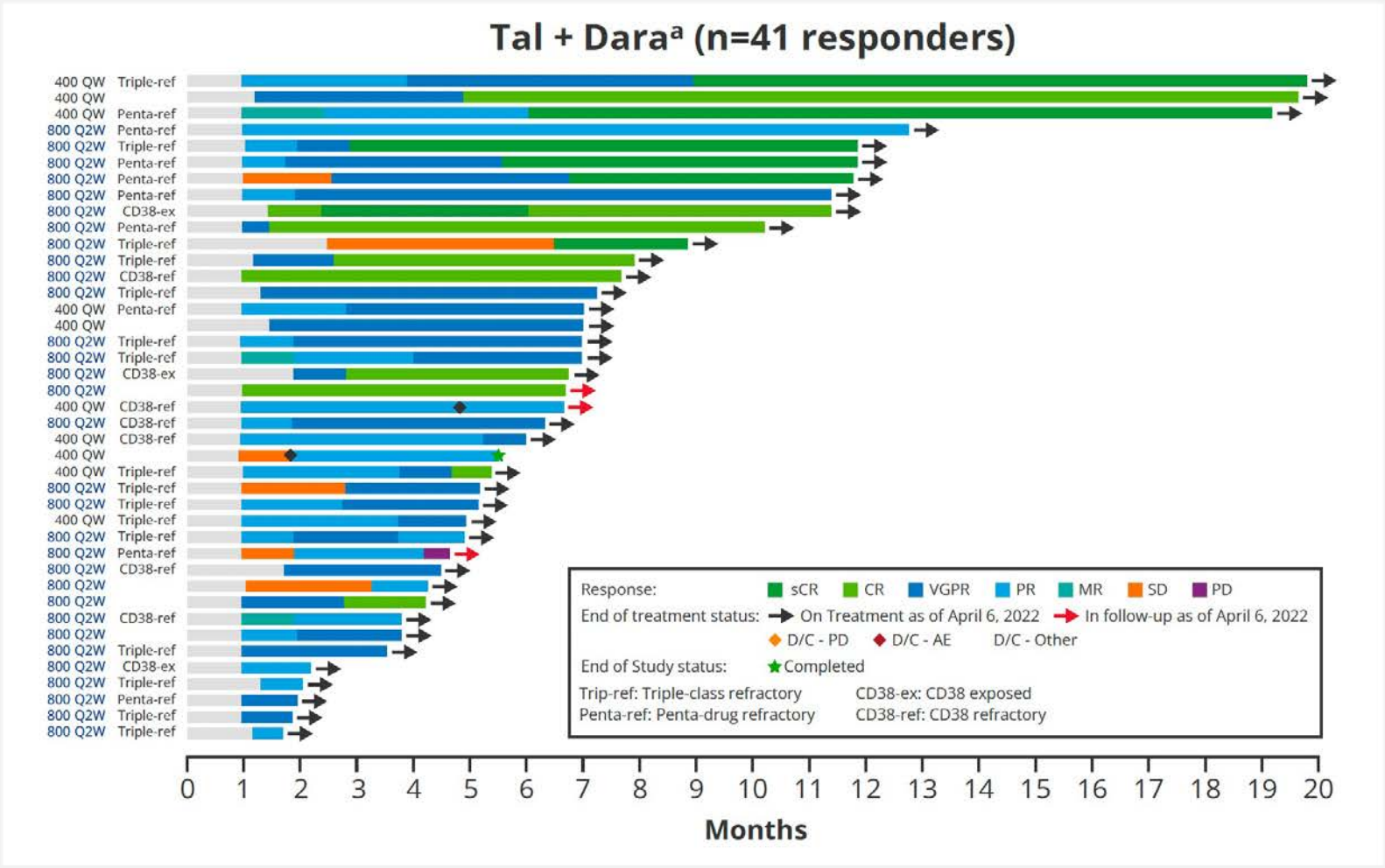
TRIMM-2: Overall Response Rate

Parameter	Evaluable patients[a]	
	Tal 400 µg/kg QW + dara (n=14)	Tal 800 µg/kg Q2W + dara (n=37)
Follow-up, median (range)	**6.7 months** (1.9–19.6)	**4.2 months** (0.2–12.3)
ORR[b], n (%)	**10 (71.4)**	**31 (83.8)**
CR/sCR	4 (28.6)	11 (29.7)
VGPR	4 (28.6)	13 (35.1)
PR	2 (14.3)	7 (18.9)
SD	4 (28.6)	4 (10.8)
PD	0	2 (5.4)
Time to first confirmed response, median (range)	**1.0 month** (0.9–2.4)	**1.0 month** (0.9–6.5)

- With overall median follow-up of 5.1 months, the ORR was **80.4%** (41/51) among all response-evaluable patients
  - VGPR or better: 62.7% (32/51)
  - CR or better: 29.4% (15/51)
- ORR in patients with prior anti-CD38 exposure: 77.3% (34/44)

van de Donk N WCJ et al. EHA 2022;Abstract S183.

TRIMM-2: Duration of Response



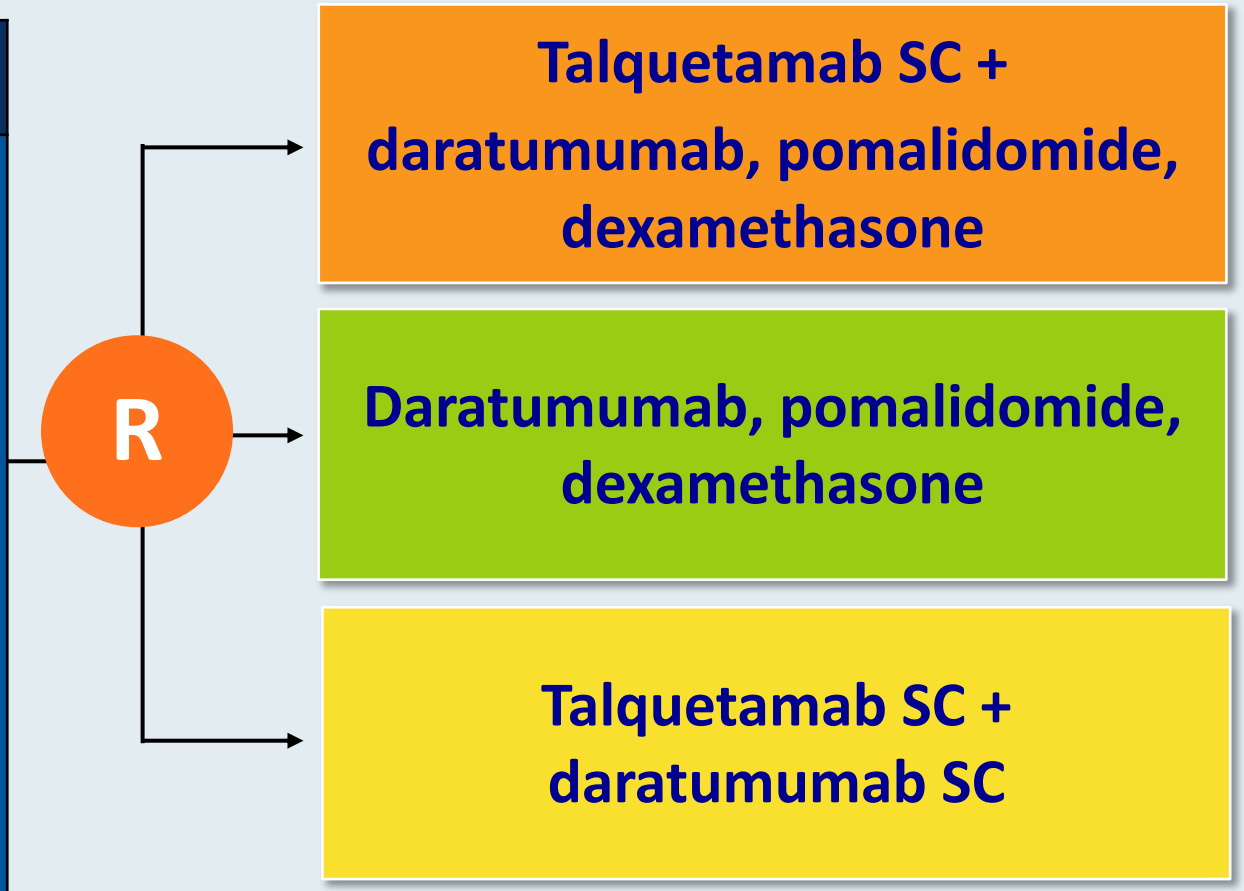
- Responses were observed in heavily pretreated patients, the majority of whom were anti-CD38 refractory
- Responses were durable and deepened over time
- Median duration of response was not reached
- With a median follow-up in responders of 6.5 months (range: 1.6–19.6), 90.2% of responders (37/41) remained on treatment

van de Donk N WCJ et al. EHA 2022;Abstract S183.

MonumenTAL-3 Phase III Study Design

Estimated enrollment (N = 810)

- Multiple myeloma
- Relapsed or refractory disease
- At least 1 prior line of antimyeloma therapy, including a proteasome inhibitor and lenalidomide
- Patients who received only 1 line of therapy must be considered lenalidomide refractory
- Patients who received ≥2 lines of therapy must be considered lenalidomide exposed



Primary endpoint: Progression-free survival

www.clinicaltrials.gov. NCT05455320. Accessed August 2022.

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

ASH 2021;Abstract 157.

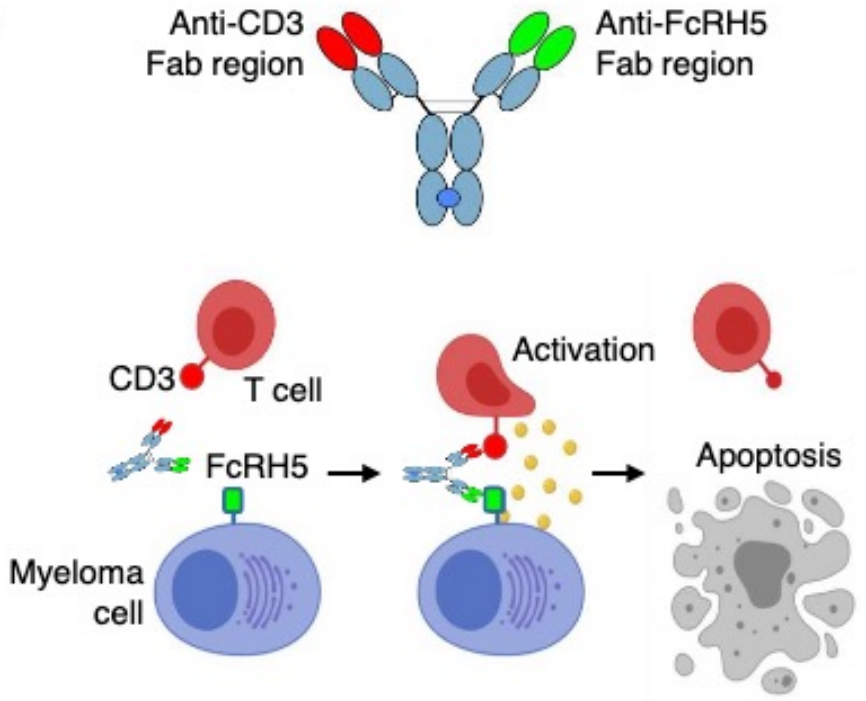
Suzanne Trudel,[1] Adam D Cohen,[2] Amrita Krishnan,[3] Rafael Fonseca,[4] Andrew Spencer,[5] Jesus G Berdeja,[6] Alexander Lesokhin,[7] Peter A Forsberg,[8] Jacob P Laubach,[9] Luciano J Costa,[10] Paula Rodriguez-Otero,[11] Rayan Kaedbey,[12] Joshua Richter,[13] Maria-Victoria Mateos,[14] Sheeba K 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

Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition

Cevostamab Mechanism of Action

- 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



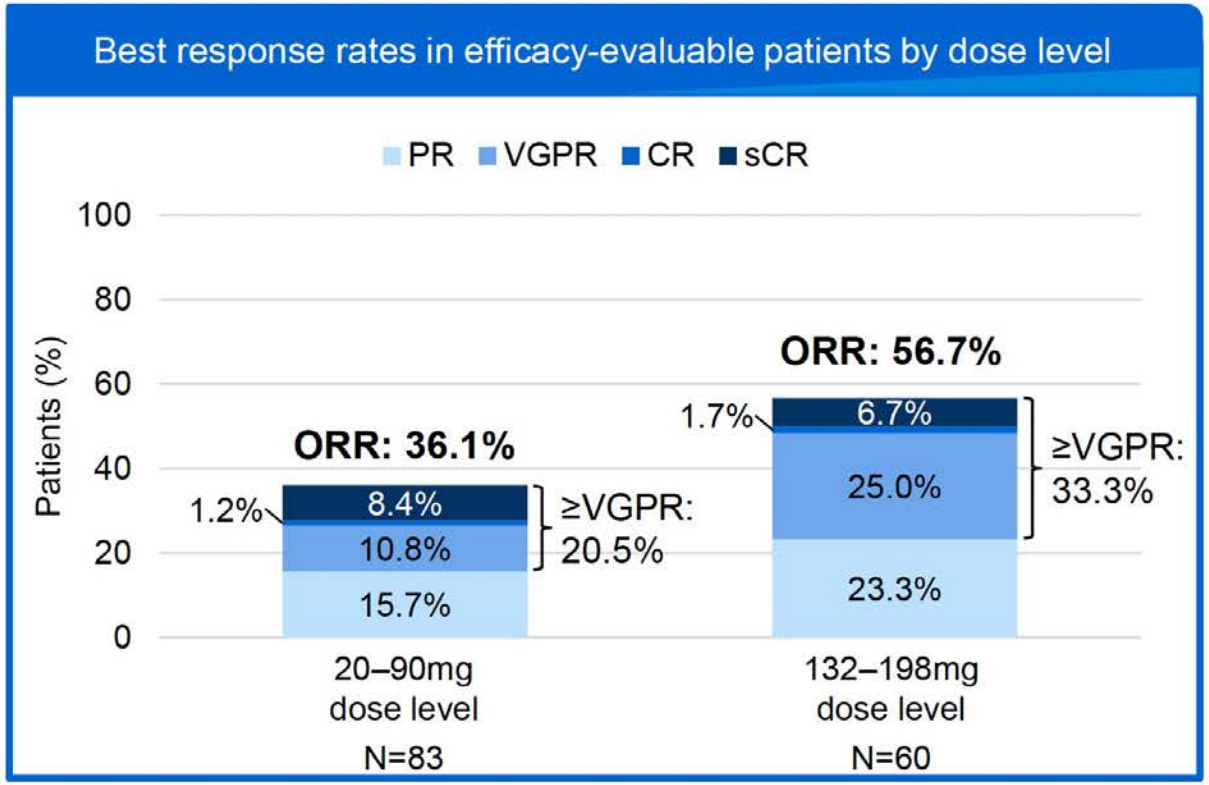
C, Cycle; CRS, cytokine release syndrome;
Fab, fragment antibody binding; RRMM, relapsed/refractory multiple myeloma

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

Trudel S et al. ASH 2021;Abstract 157.

Response to Cevostamab in Patients with Heavily Pretreated R/R MM

- 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.

Trudel S et al. ASH 2021;Abstract 157.

Cytokine Release Syndrome with Cevostamab

	N=161
N (%) of patients with CRS*	130 (80.7)
Grade 1	69 (42.9)
Grade 2	59 (36.6)
Grade 3	2 (1.2)
N (%) of patients with ICANS associated with CRS	23 (14.3)
Grade 1	13 (8.1)
Grade 2	9 (5.6)
Grade 3	1 (0.6)
Most common ICANS symptoms associated with CRS	
Confusional state	4 (2.5)
Aphasia	2 (1.2)
N (%) of patients with CRS leading to treatment discontinuation	1 (0.8)
N (%) of patients with CRS receiving CRS management with:	
Tocilizumab only	60 (37.3)
Steroids only	35 (21.7)
Tocilizumab and steroids	26 (20.0)

- CRS primarily observed in C1
- CRS onset within 24 hours of administration in 70% of patients
- CRS resolution within 48 hours of onset in 85% of patients
- All but one patient with ICANS associated with CRS had resolution of their ICANS symptoms
  - the patient whose symptoms did not resolve discontinued due to disease progression soon afterwards

- C1 step-up dosing provided effective CRS mitigation. CRS was generally confined to C1 and was mostly low Grade.

*assessed using ASTCT 2019 criteria[1]; ICANS, immune effector cell-associated neurotoxicity syndrome

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

Trudel S et al. ASH 2021;Abstract 157.

Thank you for joining us!

CME, MOC and NCPD credit information will be emailed to each participant within 5 business days.

RTP
RESEARCH
TO PRACTICE