Great Debates & Updates

Hematologic Malignancies

2023

April 13-15 | New York

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August 17-19 | Boston

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Great Debates & Updates Hematologic Malignancies

R/R Multiple Myeloma: Novel and Cellular Therapies in 2023

Monique Hartley-Brown, MD, MMSc

Disclosures

Consultancy honorarium:

AbbVie, Bristol Myers Squibb/Celgene, GSK, Janssen, Karyopharm, Sanofi, Pfizer

Speakers honorarium: Multiple Myeloma Research Foundation.

Learning Objectives

1. Evaluate the current treatment landscape and clinical trial data for sequencing novel and emerging therapies for R/R MM

2. Integrate clinical practice guidelines, multidisciplinary care approaches, and health equity strategies into practice

3. Discuss prevention and management of AEs seen with novel and emerging therapies for R/R MM

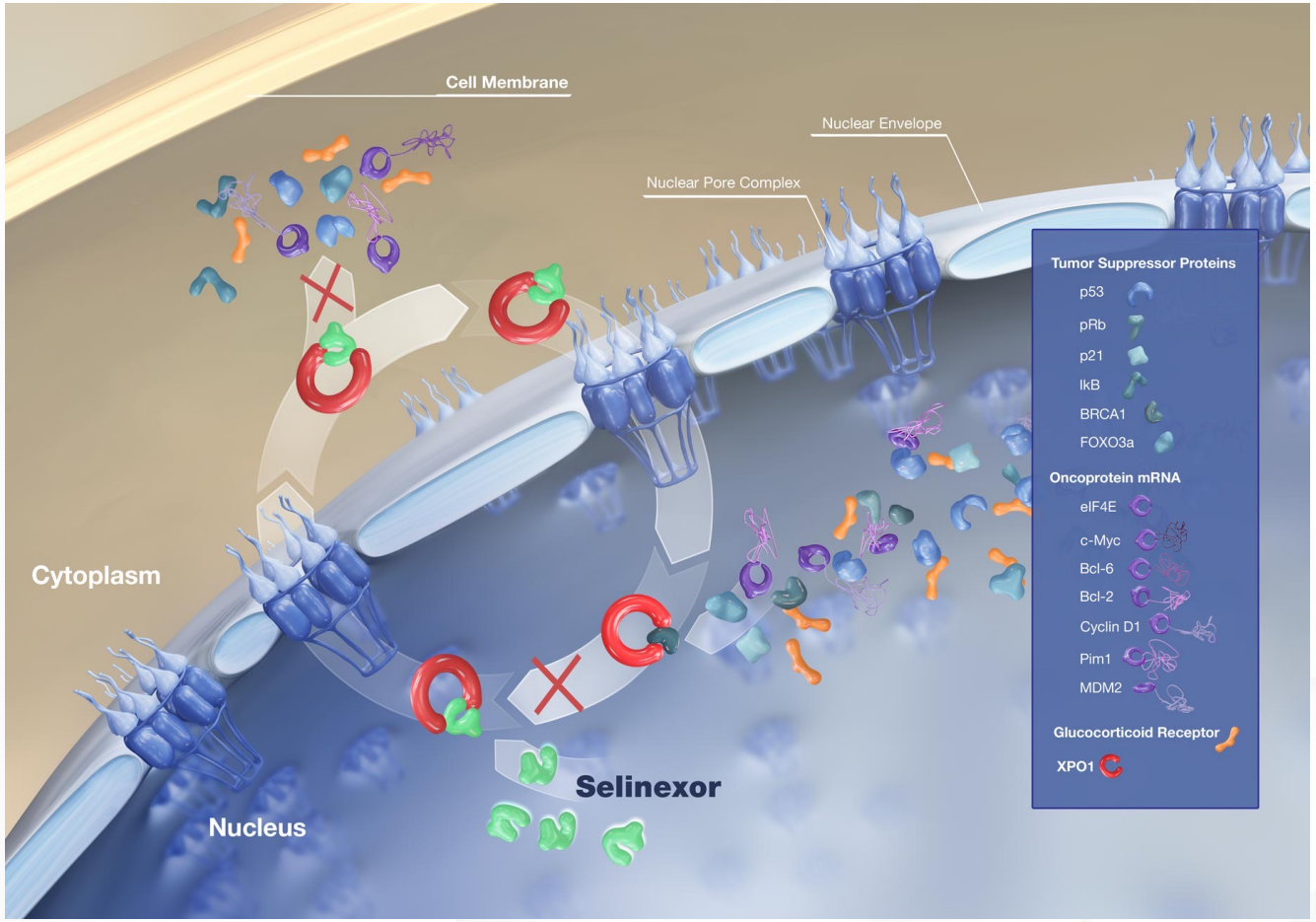
First Relapse

- PI refractory
- IMiD refractory
- Anti-CD38 MoAb exposed /refractory ***
- Triple (PI, IMiD & anti-CD38 MoAb) exposed
  - KPd, EloPd, Kcyd, VCd,
  - KRd, EloRd, Ird, PCd

Early Relapse

- Triple class exposed
- Triple class refractory

Selinexor is an oral selective XPO1 inhibitor that reactivates multiple TSPs and inhibits oncoprotein translation



1. Gupta A, et al. *J Thorac Oncol*. 2017;12(9):1446-1450. 2. Sun Q, et al. *Signal Transduct Target Ther*. 2016;1:16010. 3. Gandhi UH, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(5):335-345.
4. Gravina GL, et al. *J Hematol Oncol*. 2014;7:85. 5. Chari A, et al. *N Engl J Med*. 2019;381(8):727-738. 6. Gavriatopoulou M, et al. *N Engl J Med*. 2019;381(8):727-738.

BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients with Multiple Myeloma Who Had Received 1-3 Prior Therapies

Randomization 1:1

SVd Weekly
35-days cycles

Selinexor (oral)	100 mg	Days 1, 8, 15, 22, 29
Bortezomib (SC)	1.3 mg/m^2	Days 1, 8, 15, 22
Dexamethasone (oral)	20 mg	Days 1,2,8,9,15,16,22,23,29,30

Vd BIW
21-days cycles
Cycles 1-8

Bortezomib (SC)	1.3 mg/m^2	Days 1, 4, 8, 11
Dexamethasone (oral)	20 mg	Days 1,2,4,5,8,9,11,12

If IRC confirmed PD: crossover to SVd or Sd permitted

Vd Weekly*
35-Days cycles
Cycles ≥9

PD or Unacceptable Toxicity

Primary endpoint: PFS

Key Secondary Endpoints:
- ORR
- ≥VGPR
- Grade ≥2 PN

Secondary endpoints:
- OS
- DoR
- TTNT
- Safety

Efficacy Assessed by IRC

Planned 40% lower bortezomib and 25% lower dexamethasone dose at 24 weeks (8 cycles) in SVd arm vs. Vd arm

Stratification :
Prior proteasome inhibitor (PI) therapies (Yes vs No)
Number of prior anti-MM regimens (1 vs >1)
R-ISS stage at study entry (Stage III vs Stage I/II)

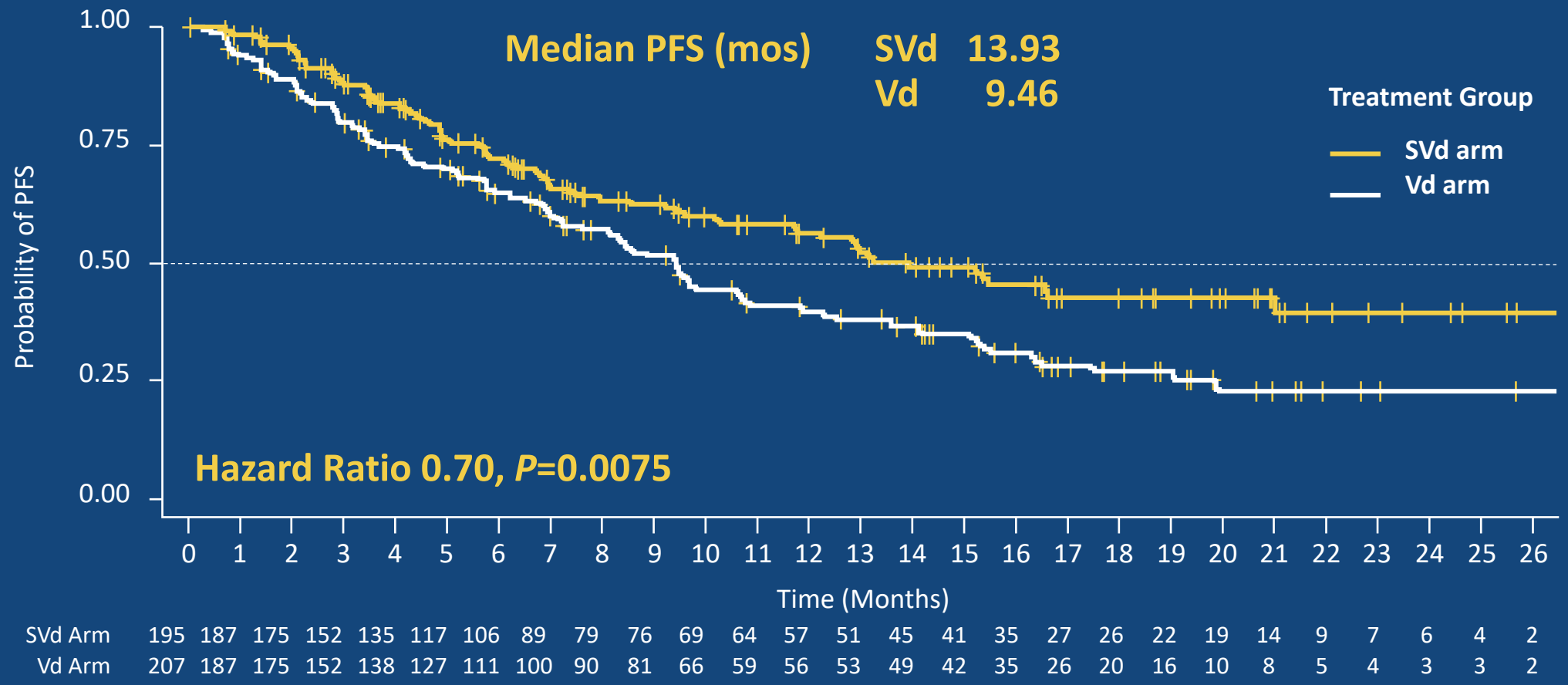
5HT-3 prophylactic recommended in SVd arm

Therapy, IRC = Independent Review Committee, IMWG = International Myeloma Working Group. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments. * Vd weekly dosing and schedule for cycles≥ 9 as per SVd arm description

Dimopoulos MA, et al. *J Clin Oncol*. 2020;38(15_suppl):8501.

BOSTON Trial: PFS Significantly Longer with SVd compared to Vd

Early and Sustained PFS benefit (assessed by IRC)

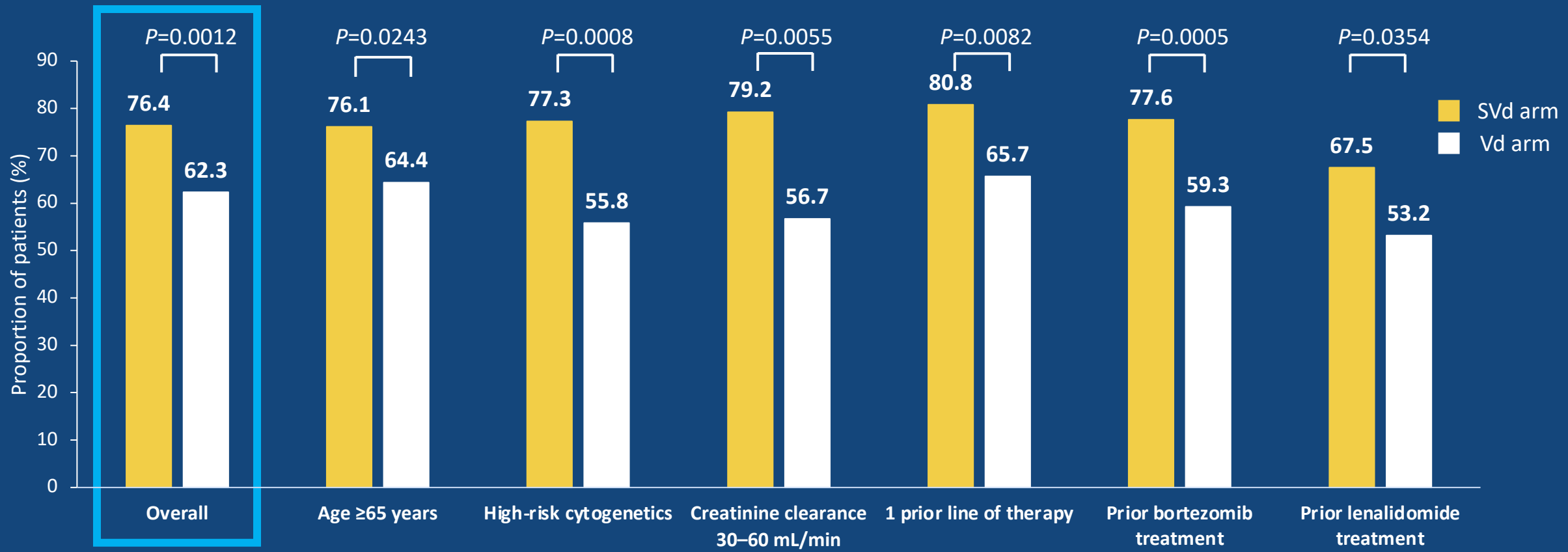


Intention-to-treat (ITT) population N=402, Data cut-off February 18, 2020
*HR=Hazard Ratio 95% CI=0.53–0.93 one-sided *P* value

Median follow-up 13.2 and 16.5 months in SVd and Vd arms respectively

Dimopoulos MA, et al. *J Clin Oncol*. 2020;38(15_suppl):8501.

SVd Was Associated with a Significantly Higher ORR Overall and Across Subgroups



One-sided P values for the Cochran-Mantel-Haenszel Test based on unstratified model. Data cut-off February 18, 2020.
ORR = Overall Response, based on Independent Review Committee's (IRC) response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet Oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments.

Dimopoulos MA, et al. *J Clin Oncol*. 2020;38(15_suppl):8501.

Later Relapse

Selinexor-based combinations

BCMA-targeted

- Cellular therapy
- Bispecific Antibodies

- Clinical Trials
  - BCMA
  - GPRC5D*
  - FcHR5
  - SLAMF7

STOMP: Phase I/II study

SKD

- 32 patients
- median LOT 4
- ORR 78.1%
- sCR 6.3% ; CR 9.4% ; VGPR 28.1%; PR 34.4%
- median PFS 15.0 months (95% CI, 12.0-not evaluable [NE]) w/ median follow-up 8.0 months
- median DOR 22.7 months (95% CI, 11.8-NE) w/ median follow-up 5.6 months.
- median OS NR w/ median follow-up 15.1 months.

SPD

- 52 patients
- median LOT 3
- 84.6% prior stem cell transplant
- ORR 65%
- median PFS 12.3 months
- OS 19.3 months
- RP2D 60 mg of selinexor weekly for 3 / 4 weeks; 4 mg of pomalidomide, and 40 mg of dexamethasone weekly.

SDd

- 3 or more LOT
- RP2D Selinexor 100 mg, Dara 16 mg/kg ; dexamethasone 40 mg weekly.
- Daratumumab-naive (n = 19), ORR 74% (5 VGPRs, 9 PRs, and 2 SD)
- 2 patients Dara-refractory (1 PD; 1 SD)

Chari A, Vogl DT, Gavriatopoulou M, et al. *N Engl J Med*. 2019;381(8):727-738. Chen CI, Bahlis NJ, Gasparetto C, et al. *Blood*. 2020;136(suppl 1):18-19. Gasparetto C, Schiller GJ, Tuchman SA, et al. *Br J Cancer*. 2022;126(5):718-725. Gasparetto CJ, Lentzsch S, Schiller GJ, et al. *Blood*. 2018;132(suppl 1):599.

Selinexor ADEs

Select TEAEs, %		STORM: Selinexor/Dex (n = 123)[1]		BOSTON: Selinexor-Vd (n = 195)[2,3]	
		All	Grade 3/4	All	Grade 3/4
Hematologic	Thrombocytopenia	73	59	60.0	39.5
	Anemia	67	44	36.4	15.9
	Neutropenia	40	21	14.9	8.7
	▪ Febrile neutropenia	--	2	--	0.5
	Leukopenia	33	14	NR	NR
	Lymphopenia	16	11	NR	NR
Gastrointestinal	Nausea	72	10	50.3	7.7
	Anorexia/decreased appetite	56	5	35.4	3.6
	Diarrhea	46	7	32.3	6.2
	Vomiting	38	3	20.5	4.1
Constitutional	Fatigue	73	25	42.1	13.3
	Weight loss	50	1	26.2	2.1

Supportive CARE

- IV fluids
- Salt tablets

Antiemetics (3 prophylaxis)

- Ondansetron
- Olanzapine + _____

Growth factors

- G-CSF
- Romiplostim

Appetite stimulants

Energy stimulants

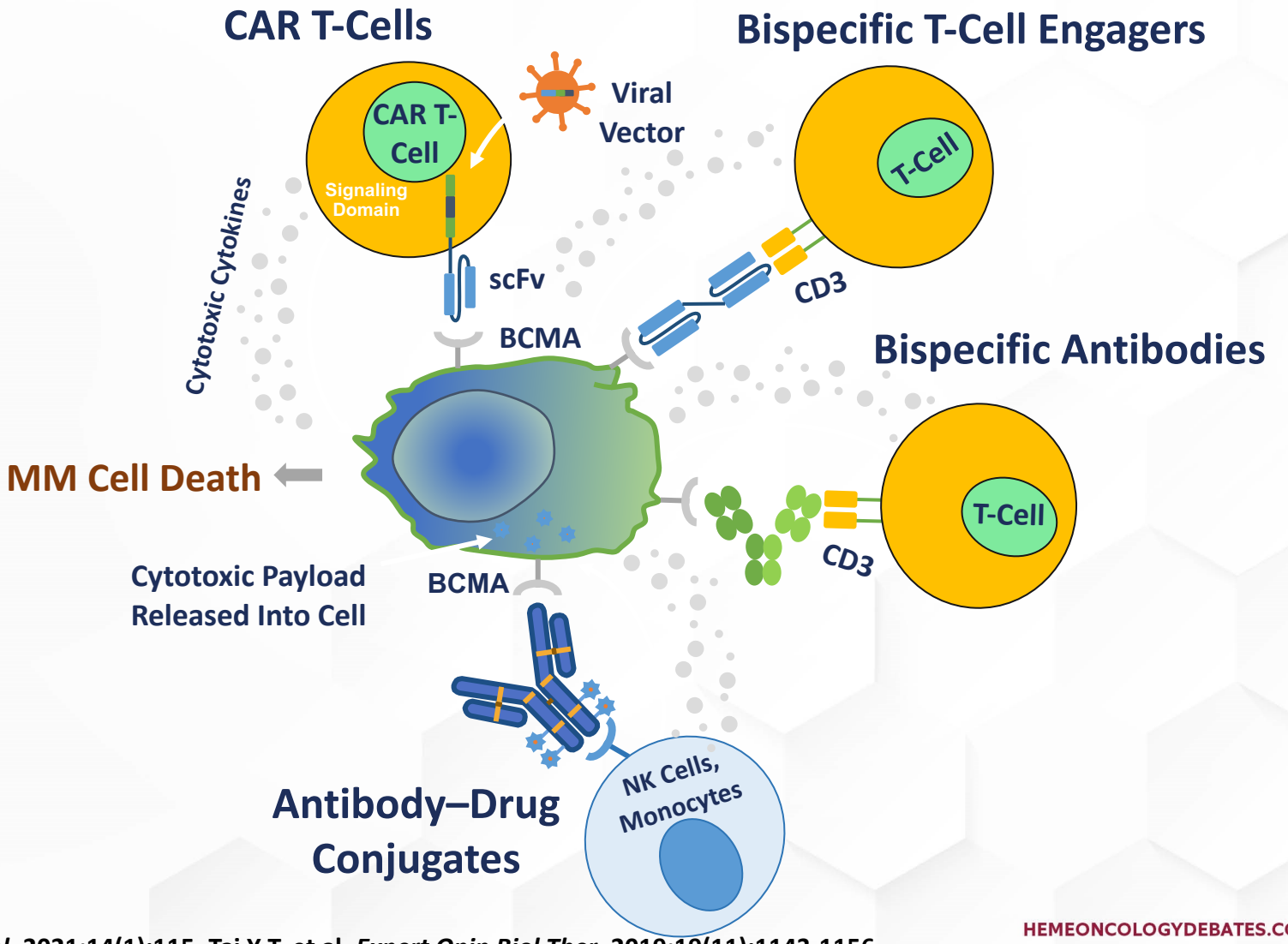
Chari. NEJM. 2019;381:727. 2. Dimopoulos. ASCO 2020. Abstr 8501. 3. Grosicki. Lancet. 2020;396:1563.

BCMA-Targeted Therapies

Antibody–drug conjugate
- Belantamab mafodotin-blmf

BCMA-directed CAR T-cell therapy
- Idecabtagene vicleucel
- Ciltacabtagene autoleucel

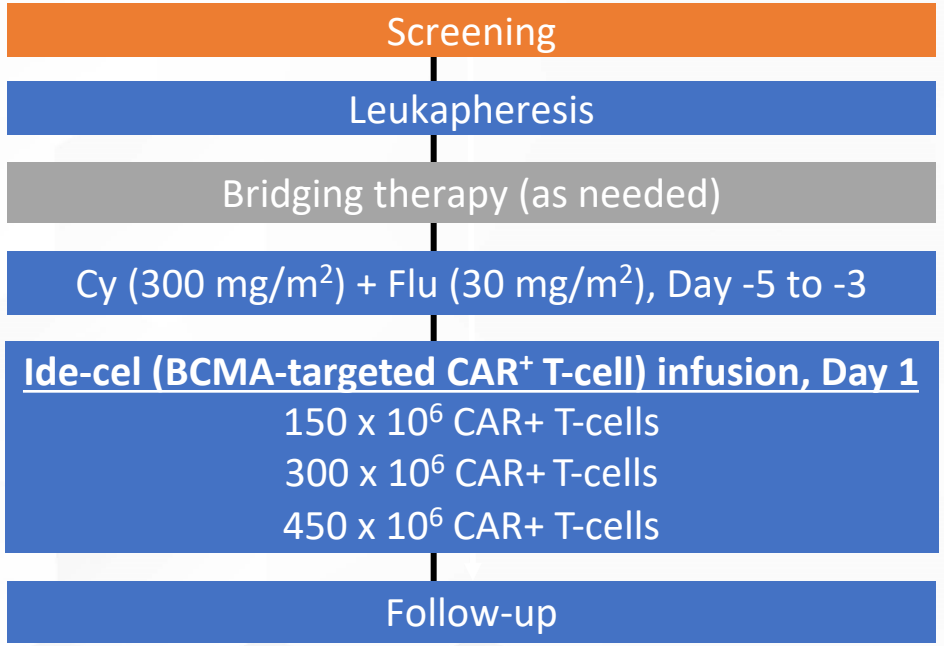
Bispecific antibodies
- Teclistamab
- Talquetamab



Cho S-F, et al. *Front Immunol*. 2018;9:1821. Su CT, et al. *J Hematol Oncol*. 2021;14(1):115. Tai Y-T, et al. *Expert Opin Biol Ther*. 2019;19(11):1143-1156.

KarMMa-1: Phase II Study

Key Eligibility Criteria
3 or more prior lines of antimyeloma therapy; refractory to PI and IMiD and anti-CD38 antibody; prior anti-BCMA therapy excluded

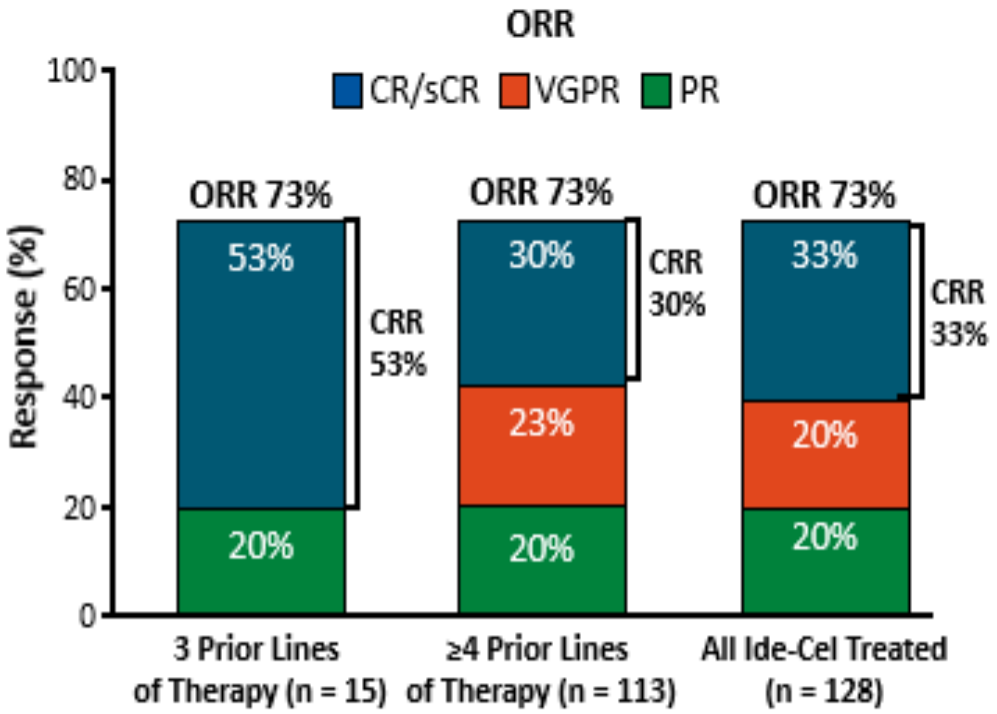


Patient Characteristics	(N = 128)
Median age, yr (range)	61 (33-78)
ISS stage (I/II/III), %	11/70/16
High-risk cytogenetics, %	35
High tumor burden (≥50% BMPCs), %	51
Tumor BCMA expression (≥50% BCMA+), %	85
Extramedullary disease, %	39
Median prior tx, n (range)	6 (3-16)
Received 1 or >1 prior ASCT, %	94/34
Received bridging tx for MM, %	88
Refractory to anti-CD38 mAb/triple refractory to PI, IMiD, and anti-CD38 mAb, %	94/84

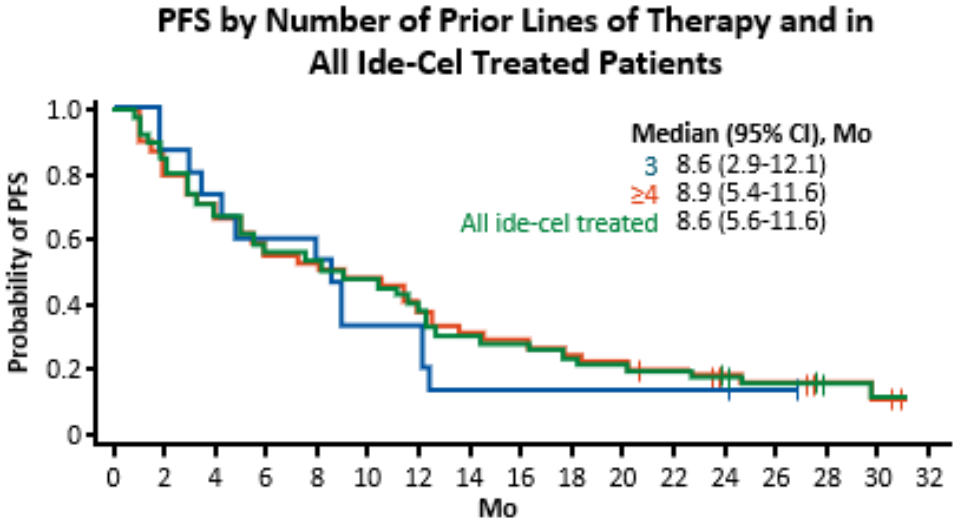
- **Primary endpoint**: ORR
- **Secondary endpoints**: CRR (key), safety, DoR, PFS, OS, PK, MRD, QoL, HEOR

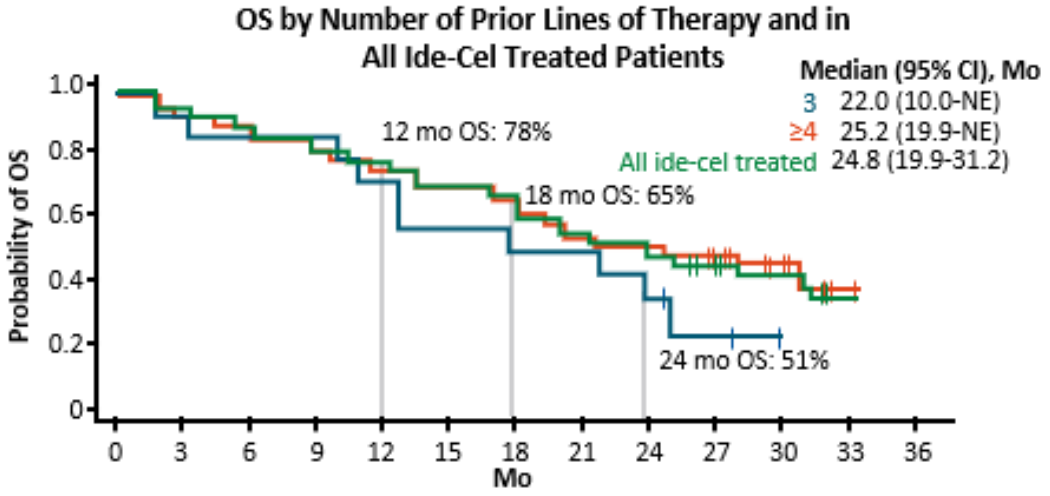
Munshi NC, et al. *N Engl J Med*. 2021;384(8):705-716.

KarMMa-1: Results



- ORR: 73%
- Median DoR: 10.9 mo





Anderson LD, et al. *J Clin Oncol*. 2021;39(15_suppl):8016.

KarMMa-1: Ide-cel CRS and Neurotoxicity

Cytokine-Release Syndrome	All Patients (N = 128)
Patients with CRS, n (%)	
▪ Any grade	107 (84)
▪ Grade ≥3	7 (5)
Median time of onset, days (range)	1 (1-12)
Median duration, days (range)	5 (1-63)
Supportive measures, n (%)	
▪ Tocilizumab	67 (52)
▪ Corticosteroids	19 (15)
▪ Anakinra	2 (2)
▪ Siltuximab	1 (1)

Neurologic Toxicity Events*	All Patients (N = 128)
Patients with neurotoxicity, n (%)	
▪ Any grade	23 (18)
▪ Grade ≥3	4 (3)
Median time of onset, days (range)	2 (1-10)
Median duration, days (range)	3 (1-26)
Supportive measures, n (%)	
▪ Corticosteroids	10 (8)
▪ Tocilizumab	3 (2)
▪ Anakinra	2 (2)

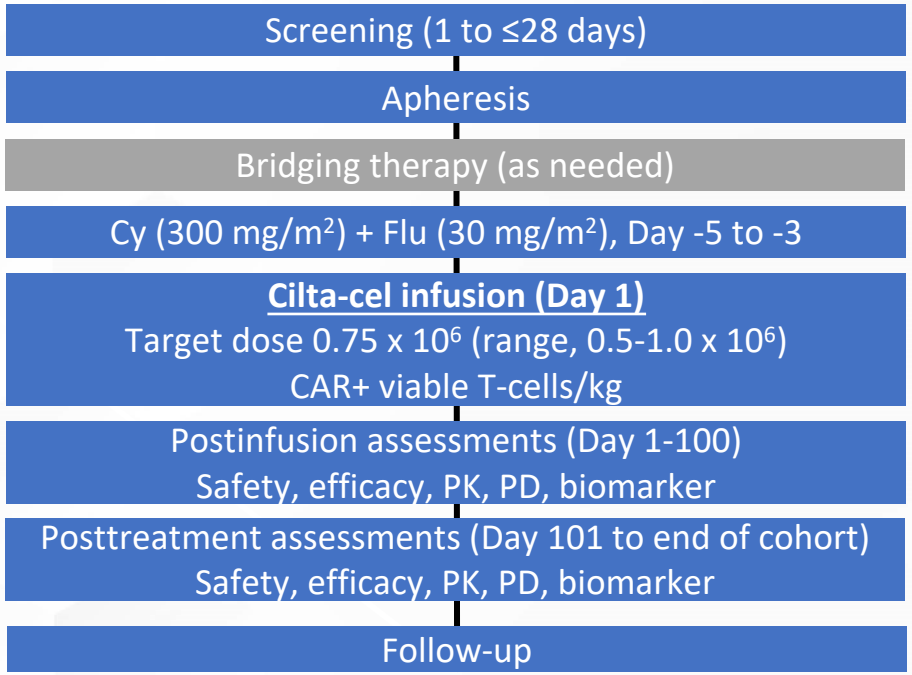
*Investigator-identified neurologic toxicity events classified under a single term.

Munshi NC, et al. *N Engl J Med*. 2021;384(8):705-716.

CARTITUDE-1: Phase Ib/II Study

Key Eligibility Criteria

Progressive MM per IMWG criteria; ECOG PS ≤1; **3 or more** prior lines or double refractory; Prior PI, IMiD, and anti-CD38 mAb

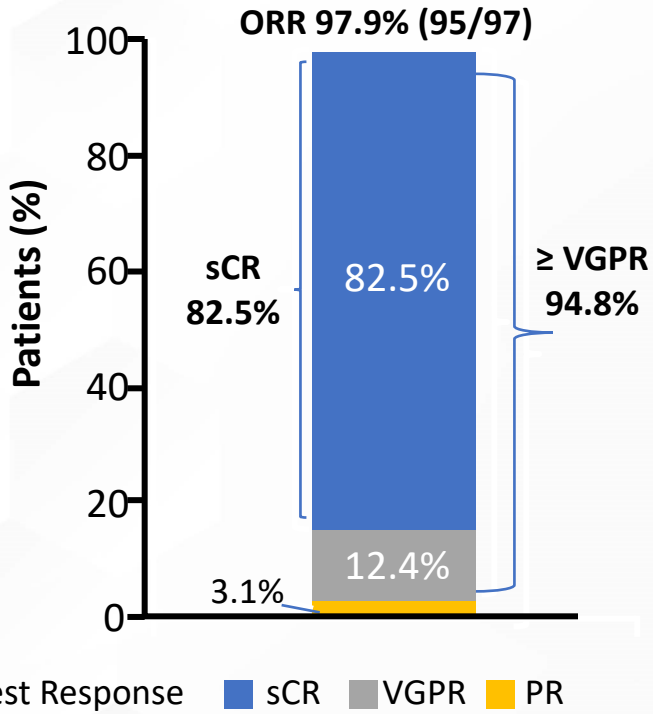


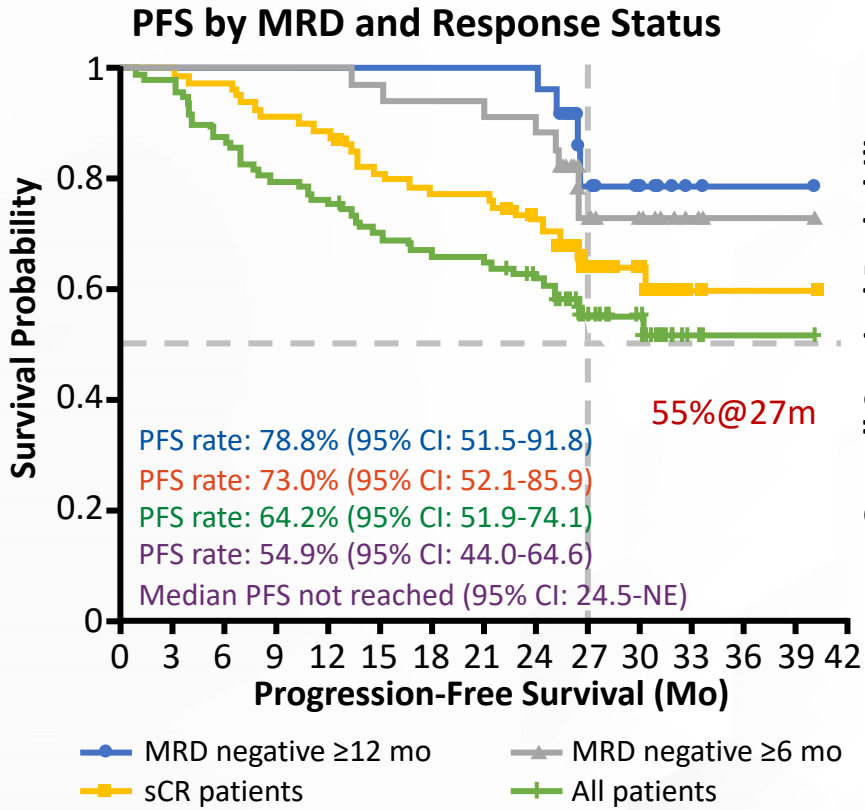
Patient Characteristics	Phase Ib (n = 29)	Phase II (n = 68)	Total (N = 97)
Median age, yr (range)	60 (57-67)	62 (55-70)	61 (56-68)
Extramedullary plasmacytomas, n (%)	4 (14)	9 (13)	13 (13)
BM plasma cells ≥60%, n (%)	7 (24)	14 (21)	21 (22)
High-risk cytogenetics, n (%)	7 (24)	16 (24)	23 (24)
del(17p)	4 (14)	15 (22)	19 (20)
t(14;16)	2 (7)	0	2 (2)
t(4;14)	1 (3)	2 (3)	3 (3)
Tumor BCMA expression ≥50%, n/N (%)	18/20 (90)	39/42 (93)	57/62 (92)
Median prior therapies, n (range)	5 (4-8)	6 (4-8)	6 (4-8)
Prior ASCT, n (%)	26 (90)	61 (90)	87 (90)
Triple-class refractory, n (%)	25 (86)	60 (88)	85 (88)
Penta-refractory, n (%)	9 (31)	32 (47)	41 (42)
Refractory to last line of therapy, n (%)	28 (97)	68 (100)	96 (99)
Median yr since diagnosis (range)	5.1 (3.5-7.8)	6.7 (4.6-8.5)	5.9 (4.4-8.4)

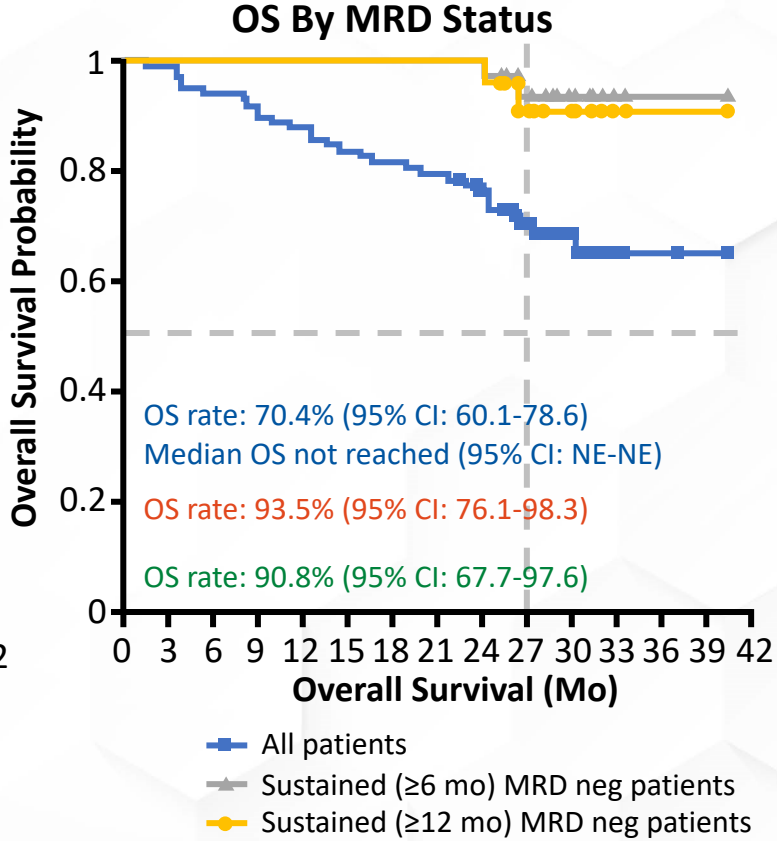
- **Primary endpoints:** safety and confirm RP2D (phase Ib); efficacy (phase II)
- Median administered dose: 0.71 x 10^6 (range: 0.51-0.95 x 10^6)/kg CAR+ viable T-cells/kg

Martin TM, et al. *J Clin Oncol*. 2023;41(6):1265-1274. Usmani SZ, et al. J Clin Oncol. 2022;40(16_suppl):8028. Lin Y, et al. Presented at: EHA;2022. Abstract P961.

CARTITUDE-1: Results







- **Median DoR: NE (95% CI: 23.3 mo-NE)**
- **Of 61 patients evaluable, 91.8% were MRD neg (10^{-5})**
- **DoR, PFS, and/or OS were shorter in subgroups with HR cytogenetics, ISS III, and high burden**

Usmani SZ, et al. Presented at: ASCO;2022. Abstract 8028. Lin Y, et al. Presented at: EHA;2022. Abstract P961. Usmani SZ, et al. Presented at: SOHO;2022. Abstract MM-181.

CARTITUDE-1: CRS and Neurotoxicity

Cytokine Release Syndrome	All Patients (N = 97)
Patients with CRS, n (%)	92 (94.8)
Median time of onset, days (range)	7 (1-12)
Median duration, days (range)	4 (1-97)
Supportive measures, n (%)	88 (90.7)
▪ Tocilizumab	67 (69.1)
▪ Corticosteroids	21 (21.6)
▪ Anakinra	18 (18.6)
▪ Vasopressor	4 (4.1)
▪ Intubation/mechanical ventilation	1 (1.0)
▪ Other*	2 (2.0)

*Includes cyclophosphamide (n = 1) and etanercept (n = 1).

- Among 92 patients with CRS, 94.6% were grade 1/2
- CRS resolved in 91 (98.9%) patients ≤14 days of onset

Neurotoxicity (NT)	All Patients (N = 97)
Patients with CAR T-cell NT, n (%)	
▪ Any grade	20 (20.6)
▪ Grade ≥3	10 (10.3)
Patients with ICANS, n (%)	
▪ Any grade	16 (16.5)
▪ Grade ≥3	2 (2.1)
Patients with other NTs, n (%)	
▪ Any grade	12 (12.4)
▪ Grade ≥3	9 (9.3)

- No new safety signals with longer follow-up
  - Common hematologic AEs included neutropenia, anemia, thrombocytopenia, leukopenia, lymphopenia
  - Common nonhematologic AEs included fatigue, cough, hypocalcemia, hypophosphatemia, diarrhea, decreased appetite, nausea, hypoalbuminemia, and AST/ALT increases

CRS = cytokine release syndrome.

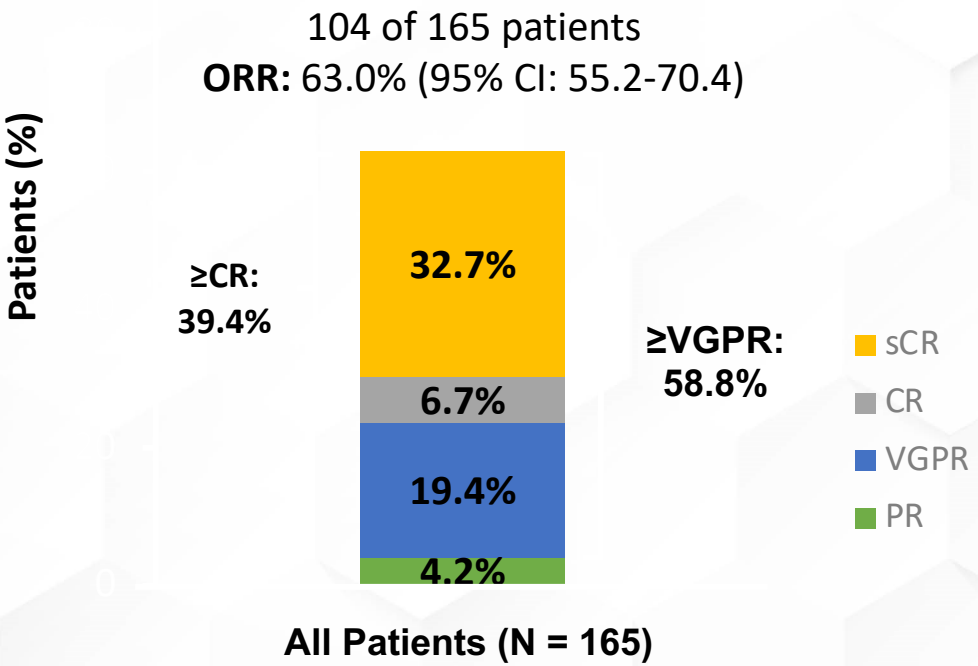
Berdeja JC, et al. *Lancet.* 2021;398(10297):314-324.

MajesTEC-1: Phase I/II Study

- RRMM after ≥3 lines of Tx, triple exposure (IMiD, PI, and anti-CD38 mAb)
  - 77.6% triple-class refractory
  - 26% HRC
  - 17% EMD
- **Teclistamab**: 1.5 mg/kg SQ weekly, after step-up doses

Event	All Patients (N = 165)
MRD negativity at 10^{-5}, n (%; 95% CI)	44 (26.7; 20.1-34.1)
Median DoR, mo (95% CI)	18.4 (14.9-NE)
Median PFS, mo (95% CI)	11.3 (8.8-17.1)
Median OS, mo (95% CI)	18.3 (15.1-NE)

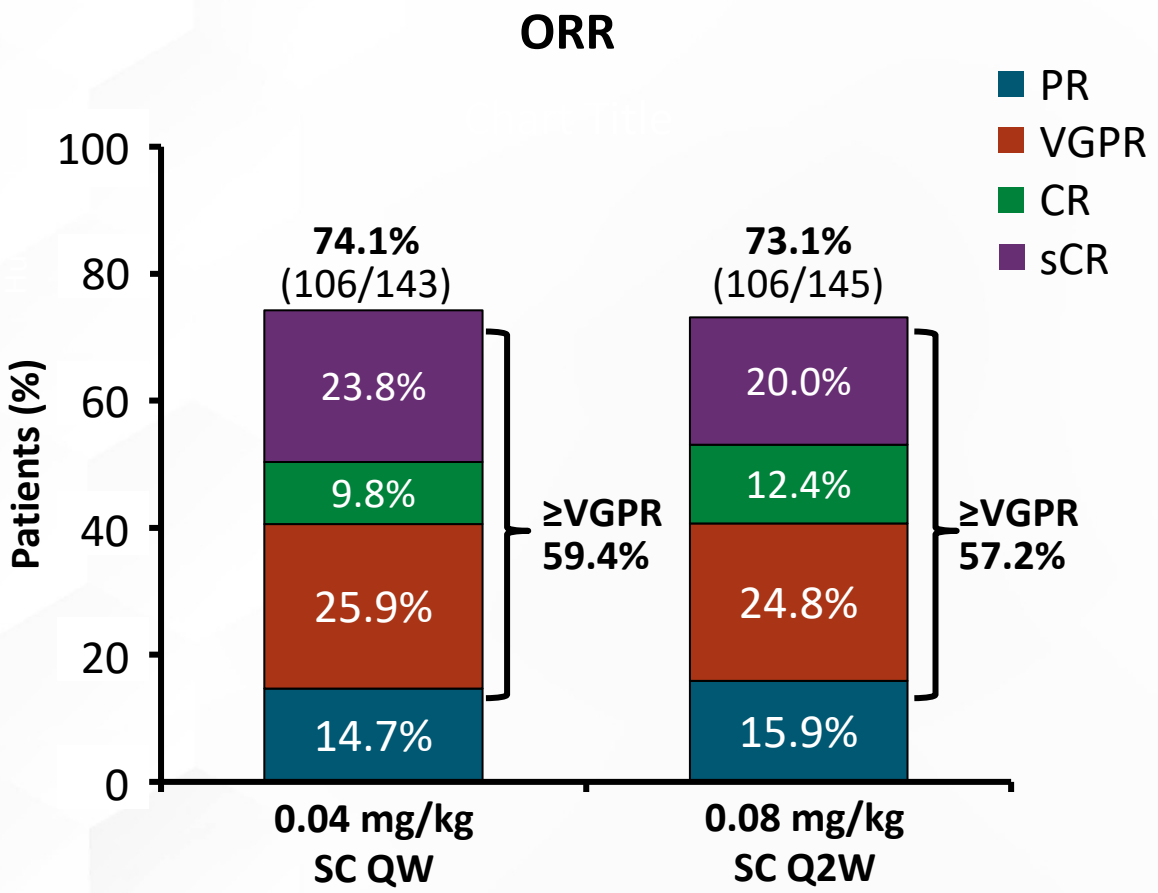
Response to Teclistamab



Median follow-up: 14.1 mo (range: 0.3-24.4)

NCT03145181. Updated July 20, 2023. Accessed July 31, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT03145181.

MonumenTAL-1: ORR



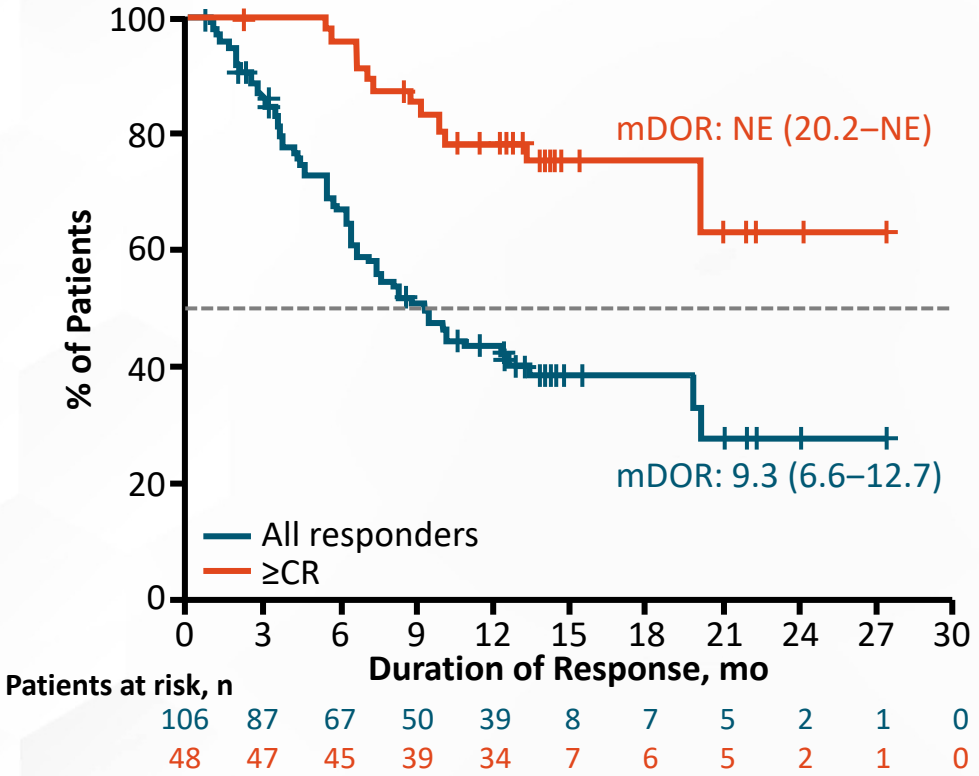
- Similar ORR among all subgroups, except for patients with BL plasmacytoma
- ORR was similar for both dosing schedules
  - Triple-class refractory: 72.6% (63.1-80.9) QW and 71.0% (61.1–79.6) Q2W
  - Penta-drug refractory: 71.4% (55.4–84.3) QW and 70.6% (52.5–84.9) Q2W

Timing	0.4 mg/kg SC QW (n = 143)	0.8 mg/kg SC Q2W (n = 145)
Median follow-up for efficacy, mo (range)	14.9 (0.5-29.0)	8.6 (0.2-22.5)
Median time to first response, mo (range) (n = 106 in each group)	1.2 (0.2-10.9)	1.3 (0.2-9.2)
Median time to best response, mo (range) (n = 106 in each group)	2.2 (0.8-12.7)	2.7 (0.3-12.5)

Chari. ASH 2022. Abstr 157. Reproduced with permission.

MonumenTAL-1: DoR

0.4 mg/kg SC QW*

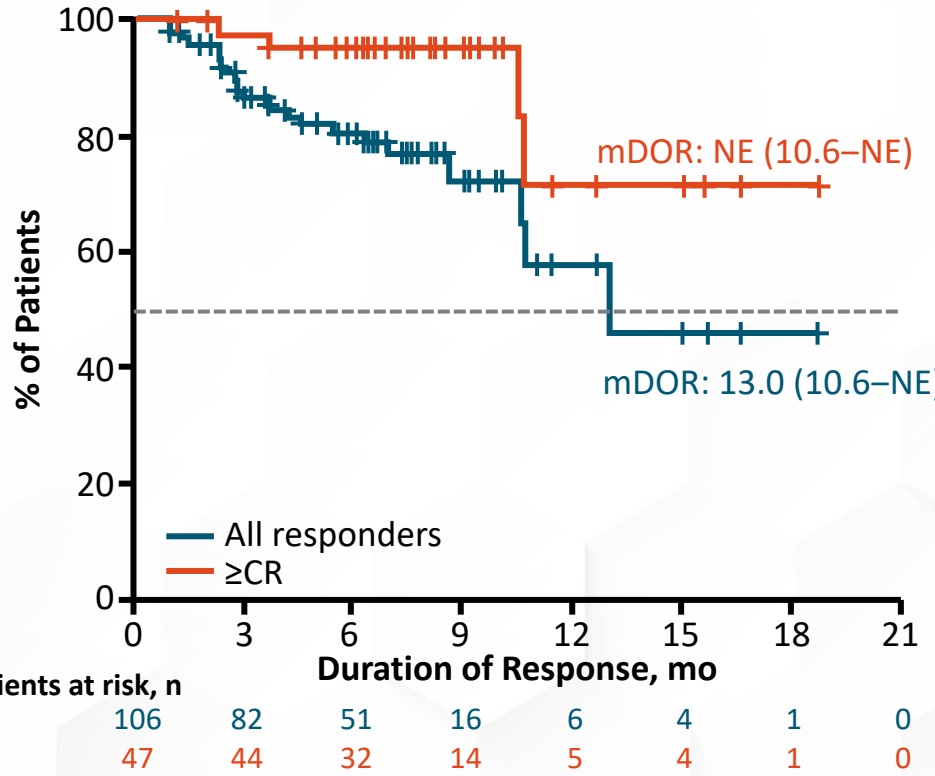


Patients at risk, n

106	87	67	50	39	8	7	5	2	1	0
48	47	45	39	34	7	6	5	2	1	0

mPFS: 7.5 mo (95% CI: 5.7-9.4)

0.8 mg/kg SC Q2W†



Patients at risk, n

106	82	51	16	6	4	1	0
47	44	32	14	5	4	1	0

mPFS: 11.9 (95% CI: 8.4-NE)

*Median follow-up (range): 14.9 (0.5-29.0). †Median follow-up (range): 8.6 (0.2-22.5).

Chari. ASH 2022. Abstr 157. Reproduced with permission.

Treatment Guidelines: CRS

Grade	Symptoms[1]	Treatment guidelines[2]
1	• Fever ≥38°C • No hypotension or hypoxia	• Supportive care (antipyretics, IV hydration) • Diagnostics to rule out infection
2	• Fever ≥38°C • Hypotension not requiring vasopressors • Hypoxia requiring low-flow nasal cannula or blow-by	• Supportive care • IV fluid boluses and/or supplemental oxygen • Tocilizumab +/- dexamethasone or methylprednisolone
3	• Fever ≥38°C • Hypotension requiring a vasopressor with/without vasopressin • Hypoxia requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	• Supportive care and monitoring in ICU • Vasopressor support and/or supplemental oxygen • Tocilizumab + dexamethasone or methylprednisolone
4	• Fever ≥38°C • Hypotension requiring multiple vasopressors (excluding vasopressin) • Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	• Supportive care and monitoring in ICU • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. 2. Neelapu SS, et al. *Hematol Oncol.* 2019;37(S1):48-52.

Treatment Guidelines: Neurological Toxicities

Symptom category[1]	Grade 1[1]	Grade 2[1]	Grade 3[1]	Grade 4[1]
ICE score	7-9	3-6	0-2	0
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad
Management[2]	• Aspiration precautions, IV hydration and seizure prophylaxis • EEG and imaging of brain • Tocilizumab if concurrent CRS	• Supportive care • Dexamethasone or methylprednisolone	• Supportive care • Dexamethasone or methylprednisolone • Anti-seizure medication	• Supportive care • High dose methylprednisolone • Anti-seizure medication • Spine imaging • Take steps to lower ICP

1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. 2. Neelapu SS. *Hematol Oncol.* 2019;37(S1):48-52.

Neurological Toxicities: ICE Score

Immune Effector Cell-Associated Encephalopathy (ICE) Score		
Category	**Description**	**Points**
Orientation	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects	3
Following commands	Ability to follow simple commands	1
Writing	Ability to write a standard sentence	1
Attention	Ability to count backwards from 100 by 10	1

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Health Equity Strategies

- ASCT
- Triple therapy
- Cellular and novel therapies
- Clinical Trials

- FDA
- Clinical trial health equity initiative
- Access
- Cost

ASCT = autologous stem cell transplant.

a. Derman BA, et al. *Blood Cancer J.* 2020;10:80, b. Ahmed N, et al. *Transplant Cell Ther*. 2022;28:358-364. c. Ailawadhi S, et al. *Blood Cancer J*. 2018;8:67.
d. Al Hadidi S, et al. *JAMA Netw Open*. 2022;5:e228161.

Clinical Trials

Early relapse

Cellular therapy

- KarMMa 2: early relapse *
- KarMMa 3: 2-4 lines of treatment *
- KarMMa 4: high risk, NDMM

- CARTITUDE 2: early relapse
- CARTITUDE 4: 1-3 lines of treatment*
- CARTITUDE 5: NDMM TI
- CARTITUDE 6: NDMM TE

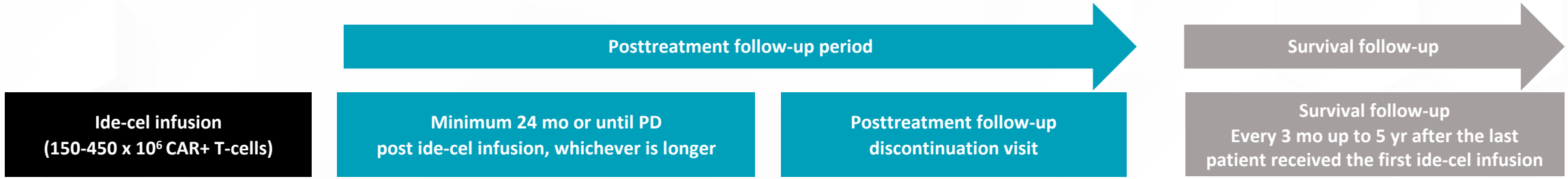
Combination

Cellular therapy

- KarMMa 7: combination with iberdomide (± low-dose dexamethasone) or BMS-986405
- Bispecific (Teclistamab)
  - TRIMM-2

- Cereblon E3 Ligase Modulators
  - Iberdomide
  - Mezigdomide

KarMMa-2 Cohort 2 Study Design



Cohort 2 (N = 99)
Clinical high-risk MM (1 regimen)

Cohort 2a (n = 37)

- **Early relapse: PD <18 mo from initiation of frontline therapy containing induction, ASCT (single or tandem) and LEN-containing maintenance**
- **≥18 yr of age**
- **Measurable disease**
- **One prior anti-myeloma treatment regimen**
- **ECOG status score ≤1**

Cohort 2b (n = 31)
Early relapse (PD <18 mo from frontline therapy without ASCT)

Cohort 2c (n = 31)
Inadequate response (< VGPR) post-ASCT

Primary endpoint

Cohort 2a: CRR (CR and sCR; by investigator per IMWG criteria)

Secondary endpoints

Cohort 2a: ORR, TTR, DOR, PFS, TTP, OS, safety, PK, immunogenicity (anti-CAR antibody response), HRQoL

Exploratory endpoints

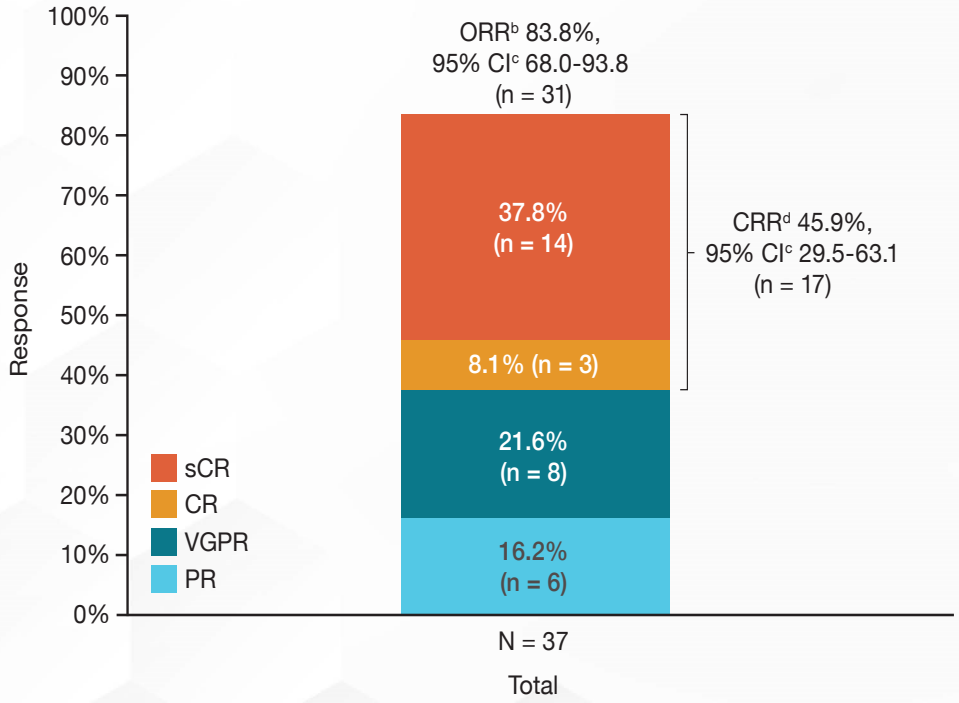
Cohort 2a: MRD, biomarkers (serum level of soluble BCMA)

- Efficacy and safety were analyzed in all patients who received ide-cel

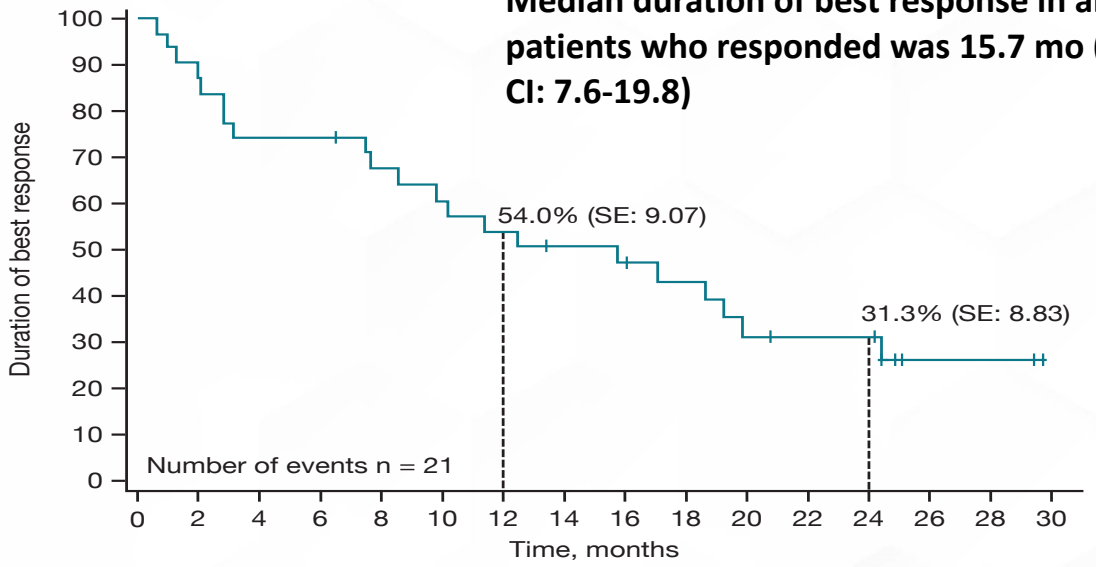
Usmani SZ, et al. Presented at: ASH;2022. Abstract 361.

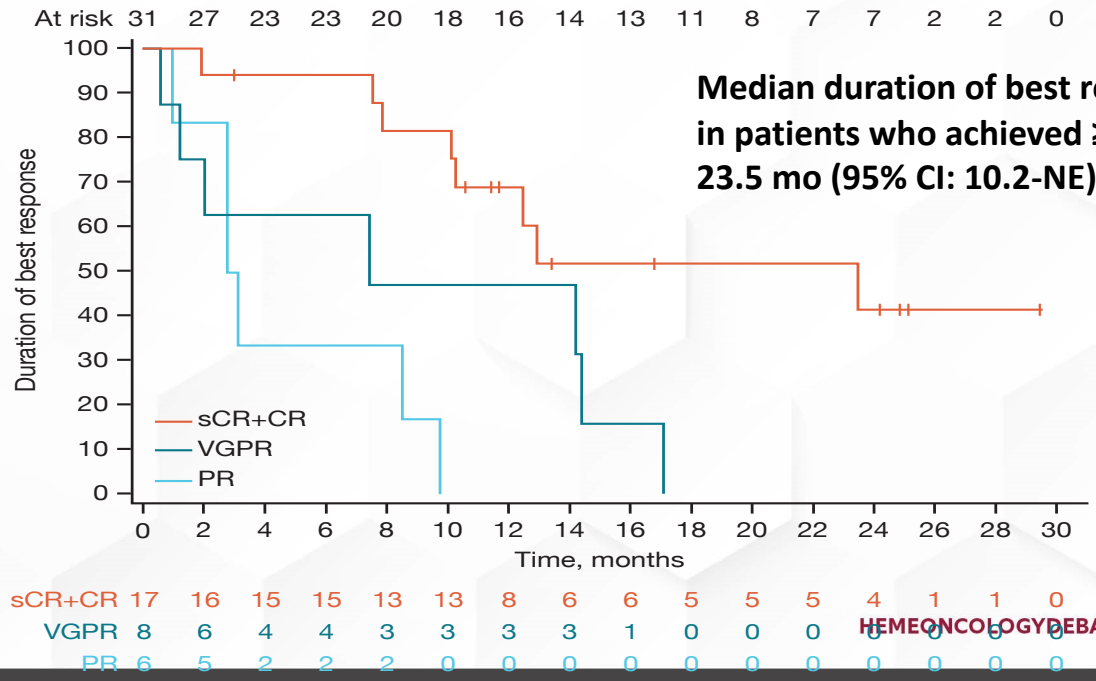
KarMMa-2 Cohort 2a: Results

- Primary endpoint met; 45.9% achieving ≥ CR (*P* <.0001)
- ORR was 83.8% (95% CI: 68.0-93.8)
- Median TTFR was 1.0 mo (range: 0.9-2.9 mo)



Median duration of best response in all patients who responded was 15.7 mo (95% CI: 7.6-19.8)





Median duration of best response in patients who achieved ≥ CR was 23.5 mo (95% CI: 10.2-NE)

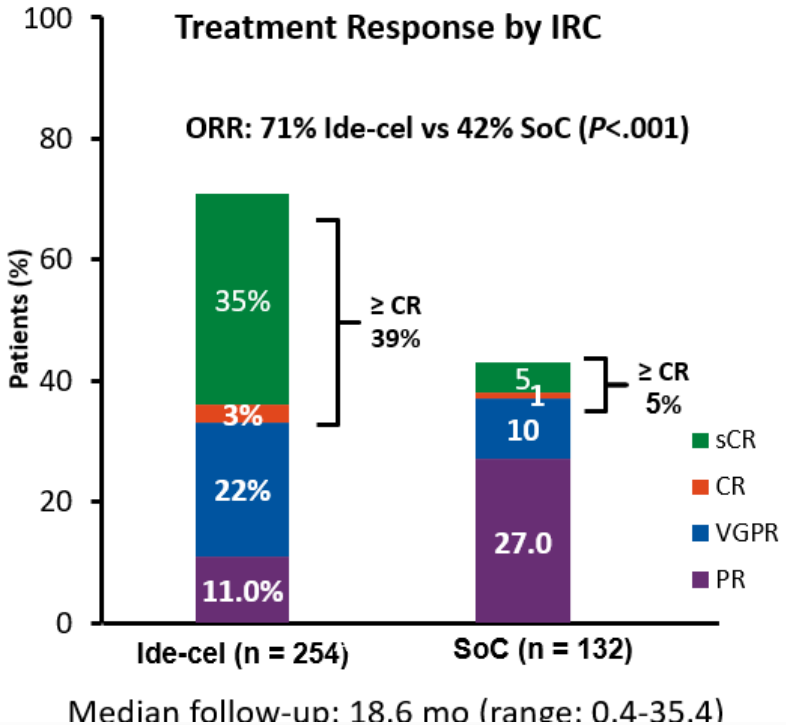
Usmani SZ, et al. Presented at: ASH;2022. Abstract 361.

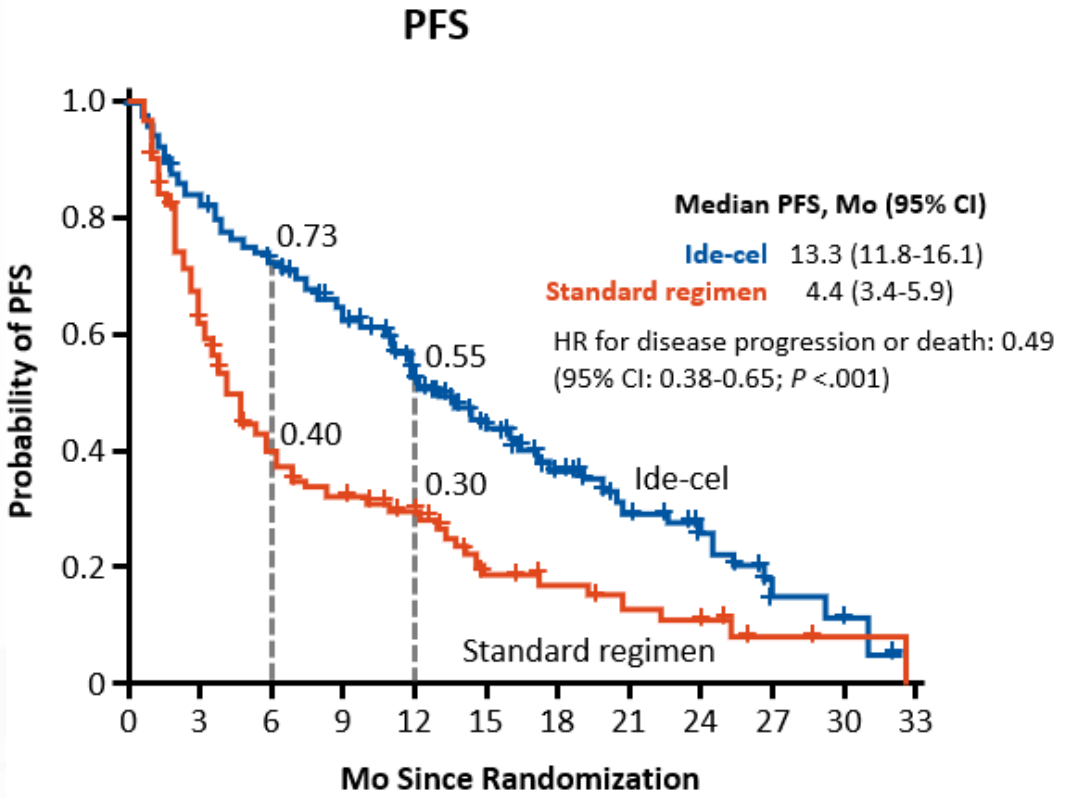
KarMMa-3: Phase III Study

2-4 lines of treatment

Triple class exposed and refractory to last line

2:1 randomization

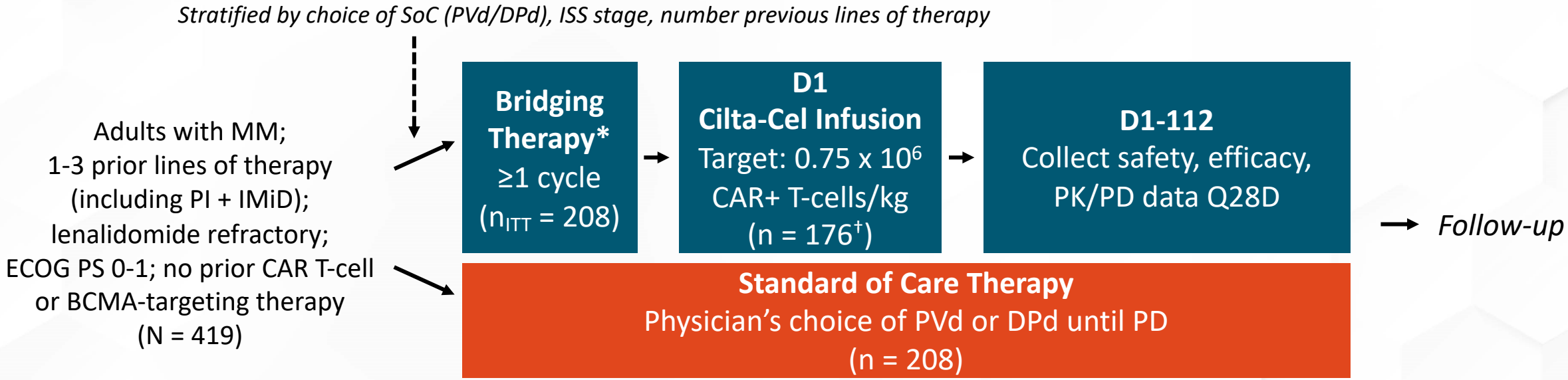




Rodriguez-Otero P, et al. *N Engl J Med*. 2023;388(11):1002-1014.

CARTITUDE-4: Phase 3 Study

- Randomized, open-label phase III trial



*Physician's choice of PVd or DPd. †As-treated population (n = 176): 32 patients did not receive cilta-cel as part of study due to PD (n = 30) or death (n = 2) during bridging therapy/lymphodepletion.

- **Primary endpoint:** PFS
- **Secondary endpoints:** ≥ CR, ORR, MRD negativity, OS, safety, PROs
- Current analysis after 15.9 mo median follow-up (range: 0.1-27 mo)

Dhakal B, et al. *J Clin Oncol*. 2023;41(17_suppl0:LBA106. San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

CARTITUDE-4: Baseline Characteristics

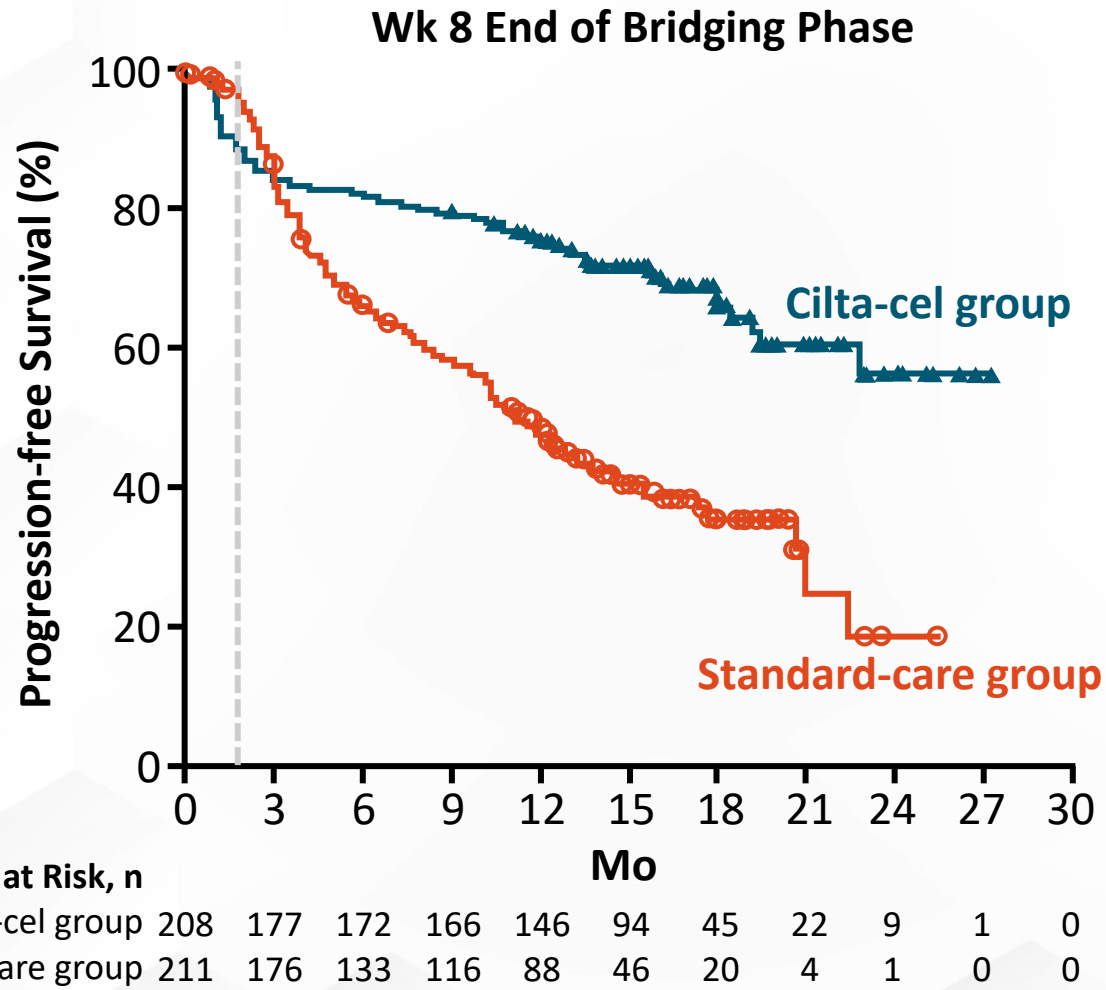
Characteristic	Cilta-Cel (n = 208)	SoC (n = 211)
Median age, yr (range)	61.5 (27-78)	61.0 (35-80)
Male, n (%)	116 (55.8)	124 (58.8)
White, n (%)	157 (75.5)	157 (74.4)
ECOG PS ≤1, n (%)*	207 (99.5)	210 (99.5)
ISS stage, n (%) ▪ I ▪ II ▪ III	 136 (65.4) 60 (28.8) 12 (5.8)	 132 (62.6) 65 (30.8) 14 (6.6)
Bone marrow plasma cells ≥60%, n (%)	42 (20.4)	43 (20.7)
Presence of soft tissue plasmacytomas, n (%)†	44 (21.2)	35 (16.6)
Median time since diagnosis, yr (range)	3 (0.3-18.1)	3.4 (0.4-22.1)
Median prior lines of therapy, n (range) ▪ 1, n (%) ▪ 2 or 3, n (%)	2 (1-3) 68 (32.7) 140 (67.3)	2 (1-3) 68 (32.2) 143 (67.8)

Characteristic, n (%)	Cilta-Cel (n = 208)	SoC (n = 211)
Cytogenetic high risk‡ ▪ del(17p) ▪ t(14;16) ▪ t(4;14) ▪ gain/amp(1q) ▪ 2+ high-risk features ▪ del(17p), t(14;16), or t(4;14)	123 (59.4) 49 (23.7) 3 (1.4) 30 (14.5) 89 (43.0) 43 (20.8) 73 (35.3)	132 (62.9) 43 (20.5) 7 (3.3) 30 (14.3) 107 (51.0) 49 (23.3) 69 (32.9)
Triple-class exposed§	53 (25.5)	55 (26.1)
Penta-drug exposed‖	14 (6.7)	10 (4.7)
Refractory status ▪ Triple-class refractory¶ ▪ Bortezomib ▪ Pomalidomide ▪ Daratumumab ▪ Any PI	 30 (14.4) 55 (26.4) 8 (3.8) 48 (23.1) 103 (49.5)	 33 (15.6) 48 (22.7) 9 (4.3) 45 (21.3) 96 (45.5)

*n = 1 per arm had ECOG PS 2. †Includes extramedullary and bone-based plasmacytomas with measurable soft tissue component. ‡In 207 (cilta-cel arm) and 210 (SoC arm) patients. §Including 1 PI, 1 IMiD, and 1 anti-CD38 mAb. ‖Including ≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 mAb. ¶n = 2 in cilta-cel arm and n = 1 in SoC arm were penta-drug refractory.

Dhakal B, et al. *J Clin Oncol*. 2023;41(17_suppl0:LBA106. San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

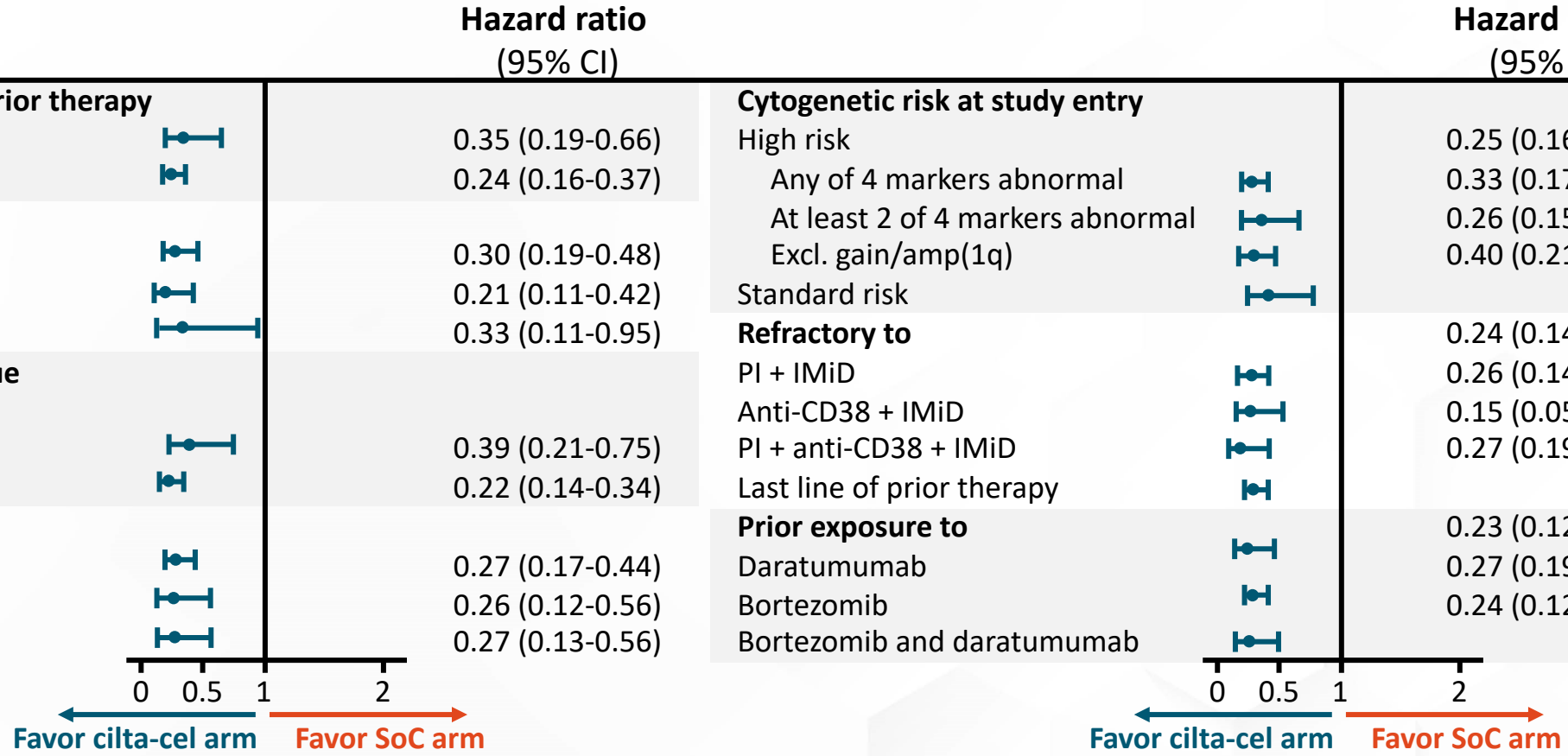
CARTITUDE-4: Progression-Free Survival (ITT Population)



	Cilta-Cel (n = 208)	SoC (n = 211)
mPFS, mo (95% CI)	NR (22.8-NE)	11.8 (9.7-13.8)
	HR: 0.26 (95% CI: 0.18-0.38; *P* <.0001)	
12-mo PFS, %	76	49

San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

CARTITUDE-4: PFS in Key Subgroups



PFS benefit consistent across all patient subgroups, including number of prior lines of therapy, ISS stage, prior drug exposure, tumor burden, and refractory status

San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

CARTITUDE-4: Key Secondary Endpoints (ITT)

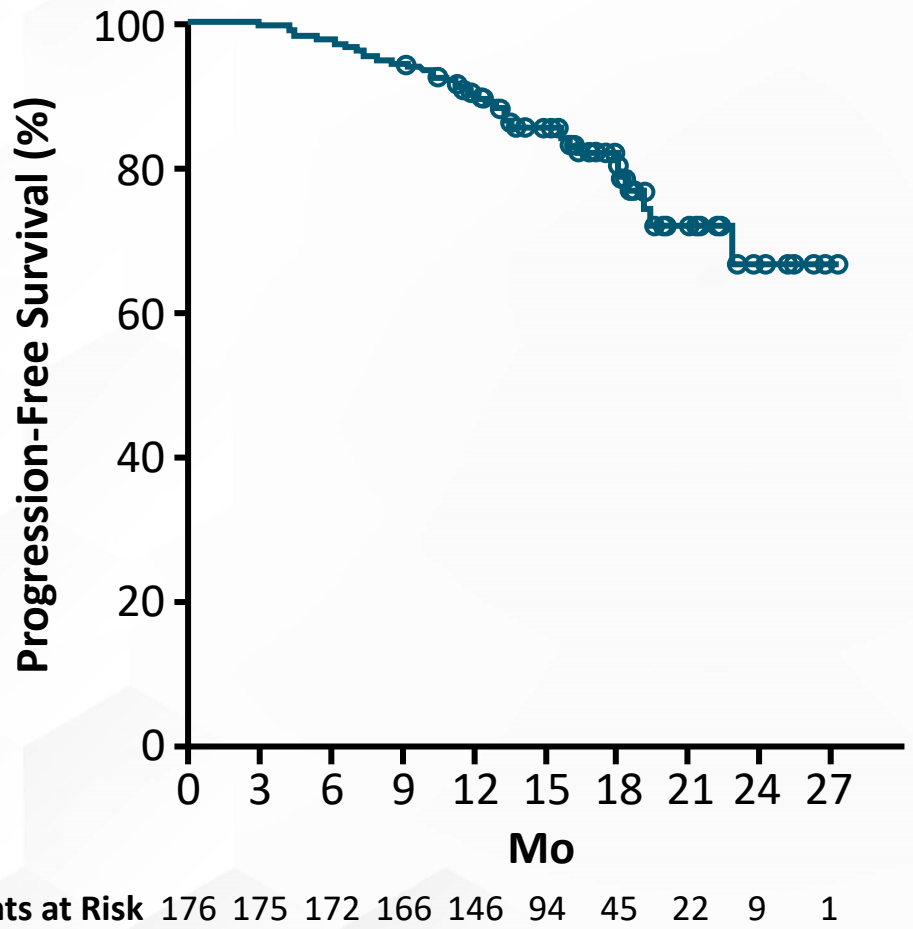
Response Parameter	Cilta-Cel (n = 208)	SoC (n = 211)
ORR, %	84.6	67.3
▪ sCR	58.2	15.2
▪ CR	14.9	6.6
▪ VGPR	8.2	23.7
▪ PR	3.4	21.8
mDoR, mo (95% CI)	NR	16.6 (12.9-NE)
12-mo DoR, % (95% CI)	84.7 (78.1-89.4)	63.0 (54.2-70.6)
MRD negativity (ITT group), %	60.6	15.6
	OR: 8.7 (*P* <.0001)	

- OS data remain immature: 39 deaths in cilta-cel arm vs 47 deaths in SoC arm; HR: 0.78 (95% CI: 0.5-1.2); *P* = .26

Dhakal B, et al. *J Clin Oncol*. 2023;41(17_suppl0:LBA106. San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

CARTITUDE-4: Efficacy Results in As-Treated Population

PFS With Cilta-Cel in As-Treated Population[1]



Outcomes in As-Treated Population[1,2]	Cilta-Cel (n = 208)
ORR, % (n = 176)	99.4
▪ sCR	68.8
▪ CR	17.6
▪ VGPR	9.7
▪ PR	3.4
MRD negative at 10^{-5}, % (n = 126/176)	72
12-mo PFS (from apheresis), %	90

Outcome, %	CARTITUDE-4 (16-Mo FU)[1,2]	CARTITUDE-1 (18-Mo FU)[3]
12-mo PFS (from cilta-cel infusion)	85	76
≥ CR	86	80
Rate of MRD negativity (10^{-5})	72	58

1. San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347. 2. Dhakal B, et al. *J Clin Oncol*. 2023;41(17_suppl0:LBA106. 3. Berdeja JG, et al. *Lancet*. 2021;398(10297):314-324.

CARTITUDE-4: TEAEs

TEAE in ≥15% of Patients, n (%)	Cilta-Cel (n = 208)		SoC (n = 208)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any AE	208 (100)	201 (96.6)	208 (100)	196 (94.2)
Serious AE	92 (44.2)	67 (32.2)	81 (38.9)	70 (33.7)
Hematologic	197 (94.7)	196 (94.2)	185 (88.9)	179 (86.1)
▪ Neutropenia	187 (89.9)	187 (89.9)	177 (85.1)	171 (82.2)
▪ Anemia	113 (54.3)	74 (35.6)	54 (26.0)	30 (14.4)
▪ Thrombocytopenia	113 (54.3)	86 (41.3)	65 (31.3)	39 (18.8)
▪ Lymphopenia	46 (22.1)	43 (20.7)	29 (13.9)	25 (12.0)
Infections	129 (62.0)	56 (26.9)	148 (71.2)	51 (24.5)
▪ Upper respiratory tract	39 (18.8)	4 (1.9)	54 (26.0)	4 (1.9)
▪ Lower respiratory tract	19 (9.1)	9 (4.3)	36 (17.3)	8 (3.8)
▪ COVID-19	29 (13.9)	6 (2.9)	55 (26.4)	12 (5.8)
Secondary primary malignancies	9 (4.3)		14 (6.7)	

- Deaths due to TEAEs: n = 10 in cilta-cel arm (7 due to COVID-19, 1 each due to neutropenic sepsis, pneumonia, and respiratory failure); n = 5 in SoC arm (1 each due to COVID-19, progressive multifocal leukoencephalopathy, respiratory tract infection, septic shock, and pulmonary embolism)

TEAEs = treatment-emergent adverse events.

Dhakal B, et al. *J Clin Oncol*. 2023;41(17_suppl0:LBA106. San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

CARTITUDE-4: CRS and Neurotoxicity Associated with Cilta-Cel

Neurotoxicity	Cilta-Cel As-Treated Patients (n = 176)				
	Any Grade n (%)	Grade 3/4 n (%)	Median Time to Onset, Days	Median Duration, Days	Resolved, n
CRS	134 (76.1)	2 (1.1)	8	3	134
Neurotoxicity	36 (20.5)	5 (2.8)			
▪ ICANS	8 (4.5)	0	10	2	8
▪ Other	30 (17.0)	4 (2.3)			
— Cranial nerve palsy	16 (9.1)	2 (1.1)	21	77	14
— Peripheral neuropathy	5 (2.8)	1 (0.6)	63	201	3
— MNT	1 (0.6)	0	85	--	0

- There were no fatal neurotoxicities
- Lower incidence/severity of CRS, ICANS, MNTs, and some hematologic AEs compared with CARTITUDE-1

Dhakal B, et al. *J Clin Oncol*. 2023;41(17_suppl0:LBA106. San-Miguel J, et al. *N Engl J Med*. 2023;389(4):335-347.

TRIMM-2: Phase IB Study

Characteristic, n (%)	SC Tec + Dara* (N = 37)
Median age, yr (range)	67 (51-79)
Female, n (%)	20 (54.1)
Extramedullary plasmacytomas ≥1, n (%)	9 (24.3)
High cytogenetic risk† (n = 27), n (%)	7 (25.9)
Median time since diagnosis, yr (range)	6.7 (0.7-14.2)
Median prior lines of tx (range)	5 (2-16)
Prior SCT, n (%)	27 (73.0)
Exposure status, n (%)	
▪ Anti-CD38‡	28 (75.7)
▪ Triple-class§	28 (75.7)
▪ Penta-drug‖	22 (59.5)
Refractory status, n (%)	
▪ Anti-CD38‡	22 (59.5)
▪ Triple-class§	20 (54.1)
▪ Penta-drug‖	7 (18.9)

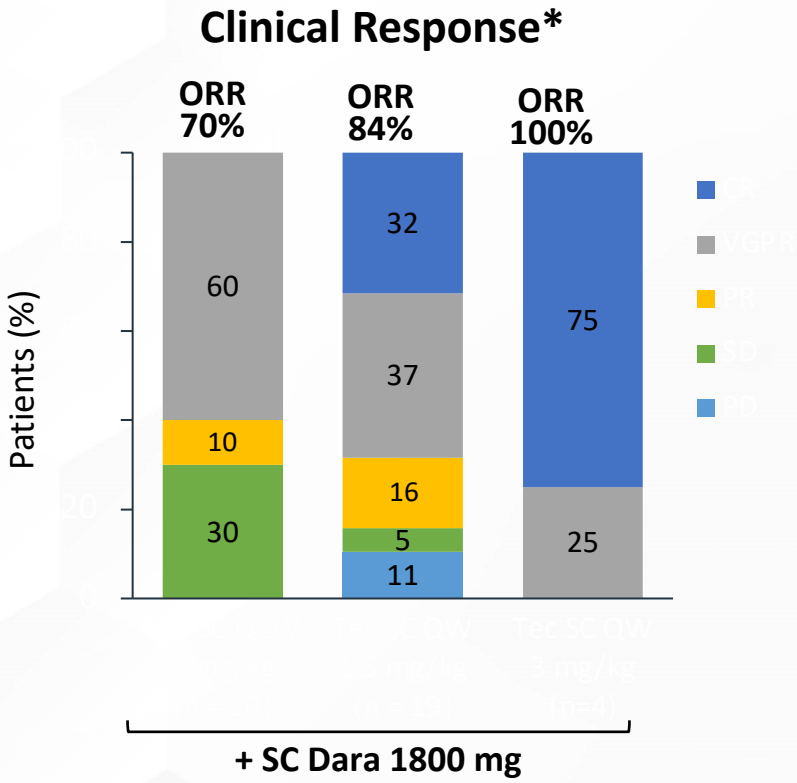
AE in ≥20% of Patients, n (%)		SC Tec + Dara* (N = 37)	
		Any Grade	Grade 3/4
Hematologic	Neutropenia	19 (51.4)	17 (45.9)
	Anemia	17 (45.9)	11 (29.7)
	Thrombocytopenia	12 (32.4)	12 (32.4)
Nonhematologic	CRS	24 (64.9)	0
	Diarrhea	13 (35.1)	1 (2.7)
	Nausea	11 (29.7)	0
	Asthenia	11 (29.7)	1 (2.7)
	Fatigue	10 (27.0)	2 (5.4)
	Pyrexia	9 (24.3)	0
	Headache	9 (24.3)	0

- First look at SC Tec/SC Dara combination
- 60% anti-CD38 refractory, 54% TCR
- Safety profile same as SC Tec

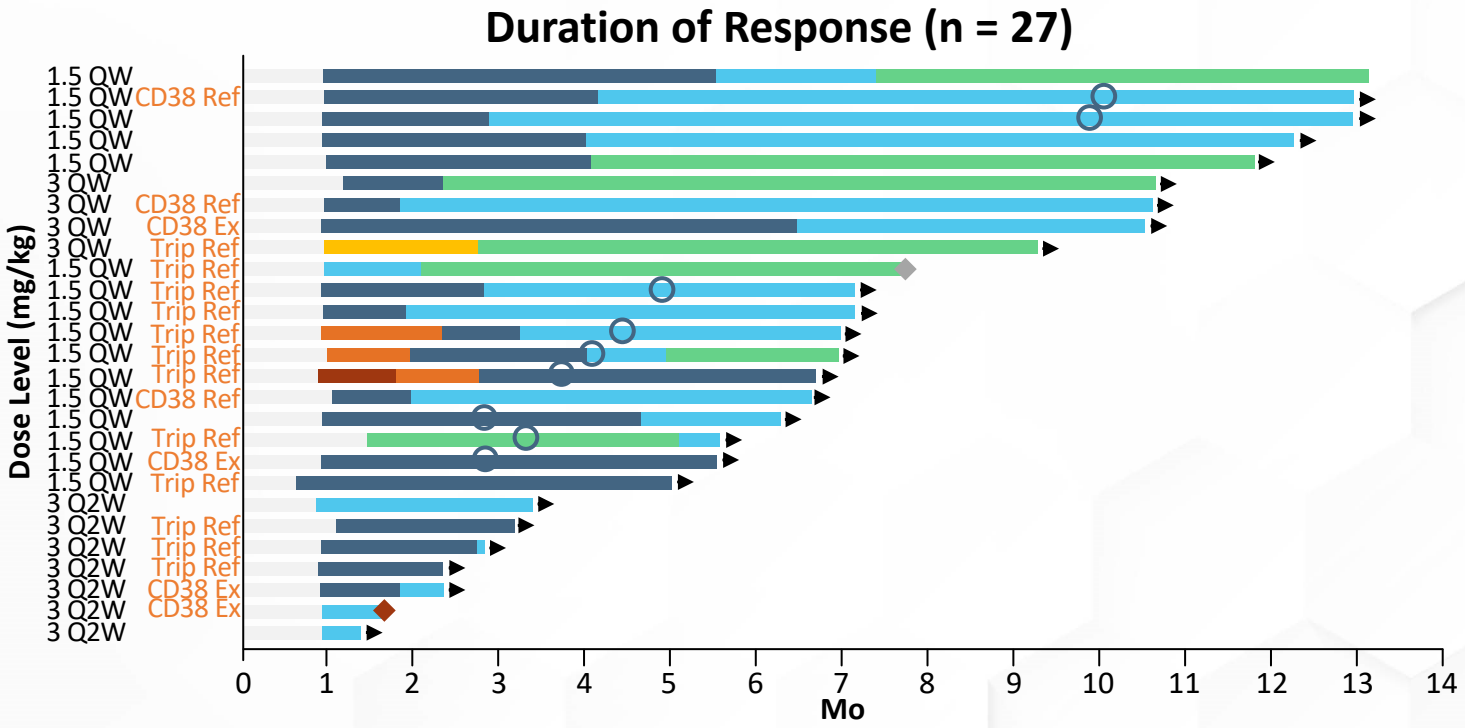
*SC Dara 1800 mg + SC Tec (1.5mg/kg QW or 3 mg/kg QW or 3mg/kg) Q2W. †del(17p), t(4:14), and/or t(14;16). ‡Dara or isatuximab. §≥1 PI, IMiD, and an anti-CD38 mAb. ‖≥2 PI, ≥2 IMiD, and ≥ 1 anti-CD38 mAb.

Rodriguez-Otero P, et al. *Blood.* 2021;138(Suppl 1):1647.

TRIMM-2: Results



*For patients who received ≥1 study drug dose and had ≥1 post BL response.

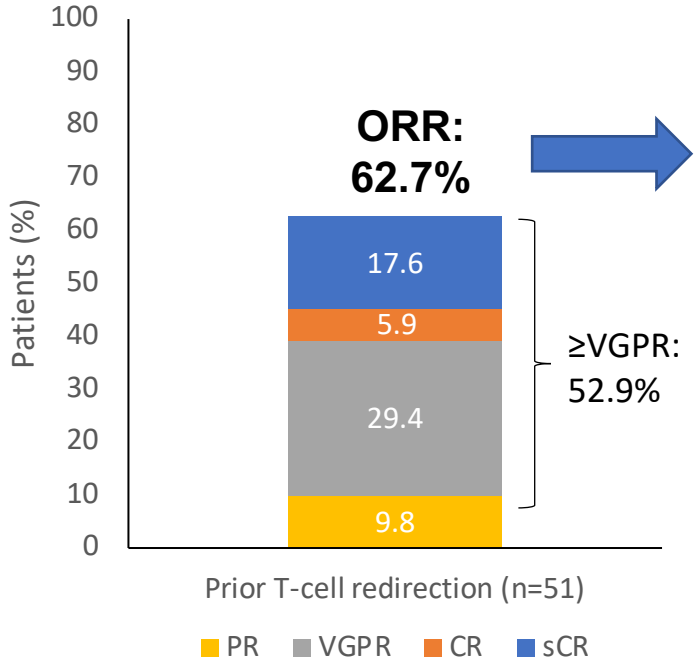


- Very impressive combination data in this refractory population
- Higher dose cohort looks most impressive
  - Need longer follow-up and perhaps explore less frequent dosing

Rodriguez-Otero P, et al. *Blood.* 2021;138(Suppl 1):1647.

In the MonumenTAL-1 trial, ORR was 63% in patients with prior T-cell redirection[1]

Response to SC talquetamab therapy[1,a]



With a median follow-up of 11.8 months (range 1.0-25.4), ORR was 62.7%[1]

mDOR was 12.7 months[b] (range 3.7-NE)

ORR was 72.2% in patients with **prior CAR T-cell therapy**

ORR was 44.4% in patients with **prior BsAb therapy**

Patients enrolled in cohort of prior T-cell–redirection therapy[1]

Were younger than patients without prior T-cell redirection therapy

Had a higher prevalence of high-risk cytogenetics: del(17p), t(4;14), and t(14;16)[2]

Had a **median of six prior LoTs** (range 3-15)

Prior CAR T-cell therapy was received in 70.6% (n=36) of patients

Prior BsAb therapy was received in 35.3% (n=18) of patients

Three patients received both prior CAR T-cell therapy and BsAb therapy

7.8% (n=4) of patients were refractory to belantamab

Most patients received QW (n=43) vs Q2W (n=8) SC talquetamab dosing

Safety profile was comparable in patients with and without prior T-cell–redirection therapy

Data cutoff date: September 12, 2022 (efficacy), May 16, 2022 (safety)

[a]Independent review committee assessment of evaluable patients per 2011 IMWG response criteria; due to rounding, individual response rates may not sum to the ORR. [b]Data are still immature.
BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR, chimeric antigen receptor; CR, complete response; IMWG, International Myeloma Working Group; LoT, line of therapy; mDOR, median duration of response; NE, not estimable; ORR, overall response rate; PR, partial response; QW, once weekly; Q2W, once every 2 weeks; sCR, stringent complete response; VGPR, very good partial response; SC, subcutaneous.
1. Chari A, et al. ASH 2022; Abstract 157 (oral presentation). 2. Chari A, et al. *N Engl J Med.* 2022; 387:2232-2244.

Synopsis of Clinical Trials of Bispecific Antibodies

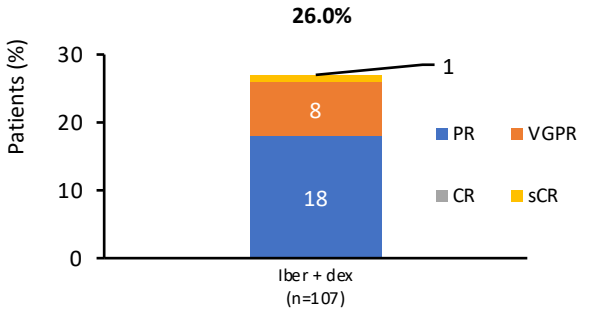
	Teclistamab[1]	Elranatamab[2,3]	ABBV-383[4]	Linvoseltamab[5]	Talquetamab[6]	Cevostamab[7]
Target	BCMA	BCMA	BCMA	BCMA	GPCR5D	FcHR5
N	165	55	60	167 (all dose levels)	143 (QW dosing)	161
P2D	1500 µg/kg SC QW	76 mg SC QW	40 mg or 60 mg IV Q3W	200 mg IV QW, then Q2W	405 µg/kg SC QW 800 µg/kg SC Q2W	--
Prior lines, median (range)	5 (2-14)	5 (2-14)	5 (3-15)	6	5 (2-13)	6 (2-18)
Triple refractory, %	100	91	80	90	74	85
Penta refractory, %	70	--	--	--	29	68
Overall response, %	63	64	60	75 (at ≥ 200 mg)	73	57 (higher doses)
Complete response, %	39	38	29	38	29	8.4
DoR, mo	18.4 mo	17.1 mo	NR (median f/u: 8.4 mo)	NR	9.3 mo	11.5 mo
Infection, %	76	52	43	--	57	--
CRS, %	72	61	72	48	79	81
Neurotoxicity, %	15 (3 ICANS)	2.2 ICANS	--	--	10 ICANS	14.3 ICANS

1 Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505. 2. Raje N, et al. Presented at: ASH;2022 Abstract 158. 3. Lesokhin AM, et al. ASCO;2022. Abstract 8006.
4. Voorhees P, et al. ASH;2022. Abstract 1919. 5. Bumma N, et al. ASH;2022. Abstract 4555. 6. Chari A, et al. ASH;2022. Abstract 157. 7. Trudel S, et al. ASH;2021. Abstract 157.

Cereblon Modulators: Iberdomide

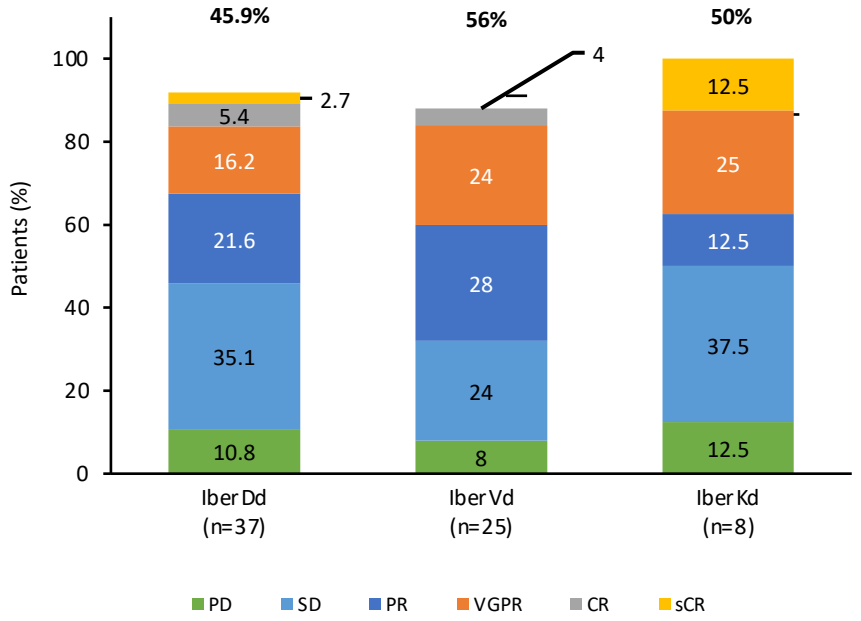
Iberdomide in combination with dexamethasone in patients with RRMM[1]

107 patients who had received at least 6 prior lines of therapy and 97% were triple-class refractory



Adverse events, %	Grades 1–2	Grade 3	Grade 4
All infections	31	24	3
Fatigue	21	2	1
Insomnia	13	1	0
Diarrhea	22	1	0
Muscle spasms	7	0	0

Iberdomide in combination with dex and daratumumab, bortezomib, or carfilzomib in patients with RRMM[2]



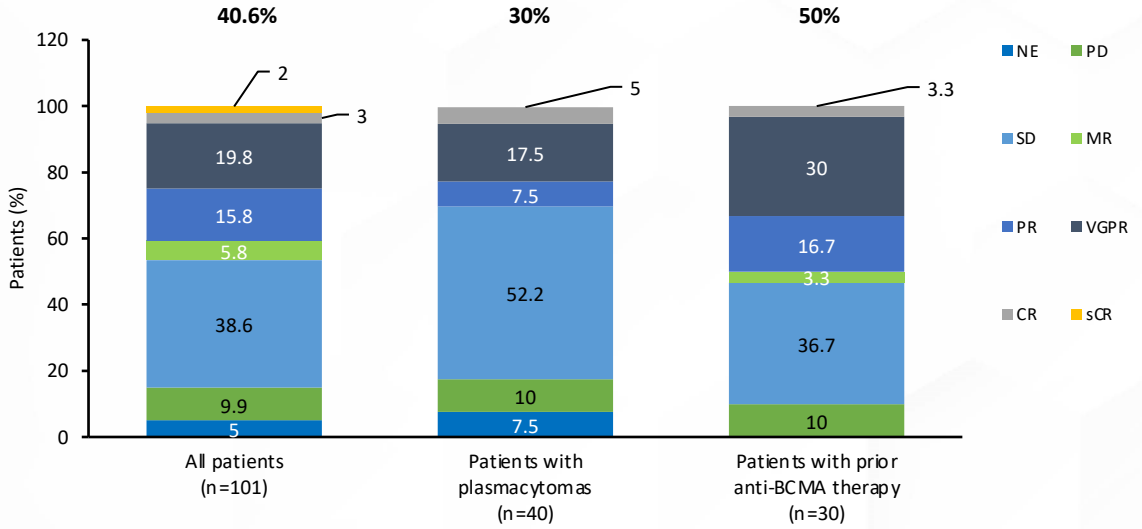
A phase 3 study is underway comparing IberDd with DVd in patients with RRMM

1. Lonial S, et al. *Lancet Haematol*. 2022;9: e822. 2. Lonial S, et al. Presented at the IMW;2021. Abstract OAB-013.

Mezigdomide: A CELMoD

A phase 1/2 study of mezigdomide combined with dex in relapsed/refractory patients

101 patients who had received at least 6 prior lines of therapy and 100% were triple-class refractory (one-third were previously exposed to anti-BCMA therapy received treatment with mezigdomide-dex.



Most frequent hematologic adverse events, %	Grade 3	Grade 4
Neutropenia	21.8	53.5
Anemia	34.7	1.0
Thrombocytopenia	13.9	13.9
Febrile neutropenia	12.9	2.0

Most frequent non-hematologic adverse events, %	Grade 3	Grade 4
Infections	28.7	5.9
Pneumonia	12.9	3.0
COVID-19	6.9	0

Two phase 3 studies are underway comparing: (1) mezigdomide + Kyprolis-dex with Kyprolis-dex; and (2) mezigdomide + Velcade-dex with Pomalyst-Velcade-dex in patients with RRMM

Richardson PG, et al. *Blood*. 2022;140:568.

Post-Session Polling Questions

- Please participate in our post-session polling questions!
- To participate:
  - Scan QR code to the right

    OR
  - Go to https://app.meet.ps/attendee/GDU_HEM_GS_Live
- Your participation is greatly appreciated and will allow us to tailor future educational programming to your needs