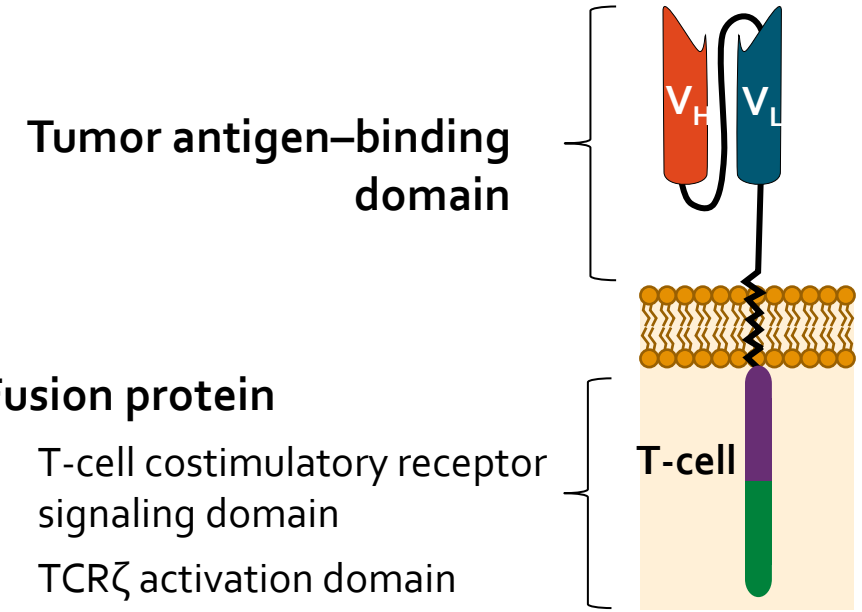
Memorial Sloan Kettering Cancer Center

Emerging and Cellular Therapeutic Options for Multiple Myeloma: Understanding Your Immune Effector Therapeutic Options in Multiple Myeloma

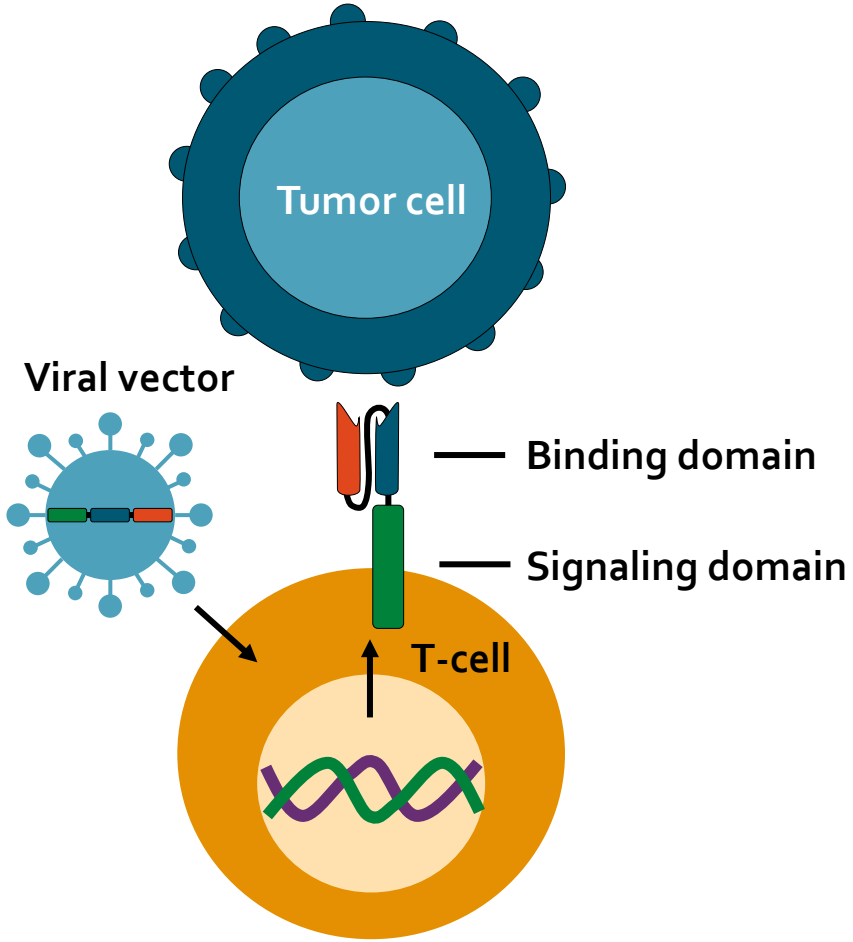
Saad Z. Usmani, MD MBA FACP FRCP FASCO
Chief of Myeloma Service
Professor, Weill Cornell Medical College, Cornell University

Memorial Sloan Kettering Cancer Center

CAR T-Cell Structure



- T-cell costimulatory receptor signaling domain
- TCRζ activation domain



BCMA-directed CAR T-cell

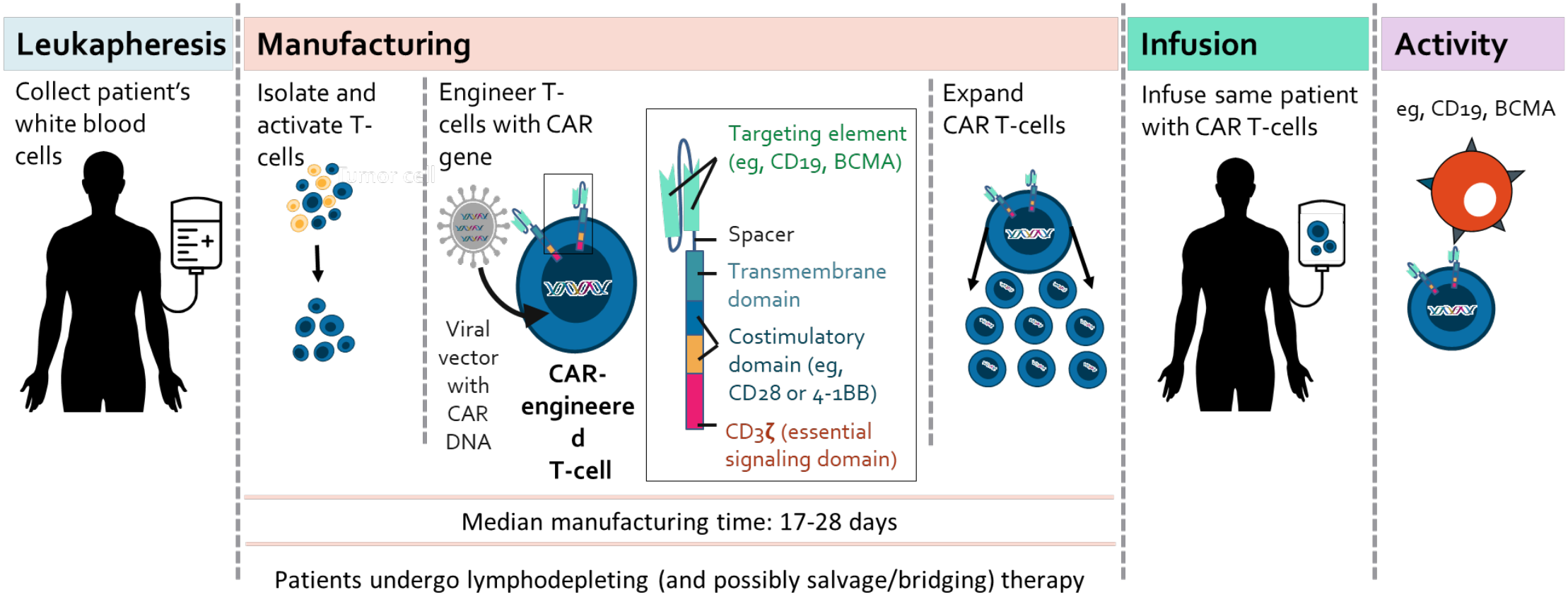
- Comprising a BCMA antigen–binding domain, a costimulatory domain (generally CD28 or 4-1BB), and CD3-ζ signaling domain

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; TCR, T-cell receptor.

Bruno. *Haematologica*. 2021;106: 2054. Morgan. *Biomedicines*. 2016;4:9.

Memorial Sloan Kettering Cancer Center

Autologous CAR T-Cell Therapy: Underlying Principles

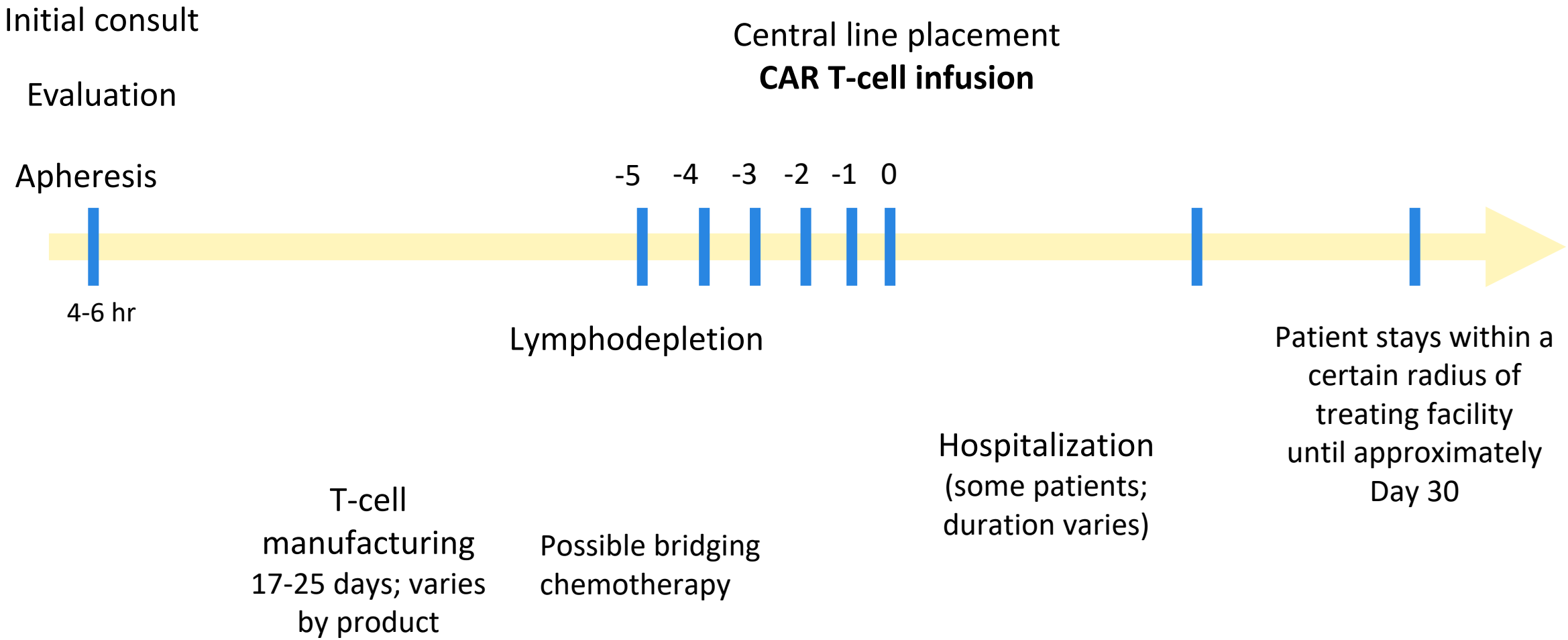


BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor.

Majors B, et al. EHA 2018. Abstract PS1156. Lim WA, June CH. *Cell*. 2017;168:724-740. Sadelain M, et al. *Nat Rev Cancer*. 2003;3:35-45. Brentjens RJ, et al. *Nat Med*. 2003;9:279-286. Park JH, et al. ASH 2015. Abstr 682. YESCARTA® (axicabtagene ciloleucel) prescribing information; 2022. TECARTUS® (brexucabtagene autoleucel) prescribing information; 2023. CARVYKTI® (ciltacabtagene autoleucel) prescribing information; 2023. ABECMA® (idecabtagene vicleucel) prescribing information; 2021. Breyanzi® (lisocabtagene maraleucel) prescribing information; 2023. KYMRIAH® (tisagenlecleucel) prescribing information; 2022.

Memorial Sloan Kettering Cancer Center

CAR T-Cell Treatment Schema



CAR, chimeric antigen receptor.

Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(suppl 3):29-40. Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135.

Memorial Sloan Kettering Cancer Center

BCMA-Targeted CAR T-Cell Therapies Indicated for MM

BCMA-Targeted Therapy	Indications
Idecabtagene vicleucel[1]	▪ **Adults with R/R multiple myeloma after ≥4 prior lines of therapy**, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
Ciltacabtagene autoleucel[2]	▪ **Adults with R/R multiple myeloma after ≥4 prior lines of therapy**, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; MM, multiple myeloma; R/R, relapsed/refractory.

1. ABECMA® (idecabtagene vicleucel) prescribing information; 2021. 2. CARVYKTI® (ciltacabtagene autoleucel) prescribing information; 2023.

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 $0.5–0.95\times10^6$)	50, 150, 450 and 800×10^6	150, 300, 450 $\times10^6$	1.5-1.8/2.5-3.0 $\times10^8$	0.75-15 $\times10^6$	1.0-3.0 $\times10^5$
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 $\times10^8$ dose, [b]0.75×10^6 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

CRS/NT Events With BCMA CAR T-Cell Therapies

- CRS and NT events were primarily grade 1/2 and manageable

	KarMMa[1] N = 128	CARTITUDE-1[2] N = 97
≥ 1 CRS event, n (%)	107 (84)	92 (95)
Grade 1/2	100 (78)	87 (95)
≥ Grade 3	7 (5)	5 (5)
Median onset (range), days	1 (1 – 12)	7 (1 – 12)
Median duration (range), days	5 (1 – 63)	4 (1 – 97)
≥ 1 NT event, n (%)	23 (18)	20 (21)
Grade 1/2	18 (12)	10 (10)
≥ Grade 3	5 (4)	10 (10)
ICANS any grade, %	-	17

Munshi et al. NEJM 2021; 384(8):705-716. Berdeja et al. Lancet 2021; 398:314

Memorial Sloan Kettering Cancer Center

Notable ASH 2023 Abstracts in RRMM CAR T-Cell Therapy

Abstract	Title	Presenter
1028	Idecabtagene vicleucel versus standard regimens in patients with triple-class–exposed relapsed and refractory multiple myeloma: updated analysis from KarMMa-3	Rodríguez-Otero
1021	The Phase 2 CARTITUDE-2 Trial: Updated Efficacy and Safety of Ciltacabtagene Autoleucel in Patients with Multiple Myeloma and 1–3 Prior Lines of Therapy (Cohort A) and with Early Relapse after First Line Treatment (Cohort B)	Hillengass
4717	A Real-World Comparison of Idecabtagene Vicleucel and Ciltacabtagene Autoleucel CAR-T Therapy: A Single Center Experience for Relapsed/Refractory Multiple Myeloma	Gill
2141	Comparative Efficacy of Ciltacabtagene Autoleucel Versus Idecabtagene Vicleucel in the Treatment of Patients with Relapsed or Refractory Multiple Myeloma Previously Treated with 2–4 Prior Lines of Therapy Using a Matching-Adjusted Indirect Comparison	Bar
219	BMS-986393 (CC-95266), a G protein–coupled receptor class C group 5 member D–targeted chimeric antigen receptor T-cell therapy for relapsed/refractory multiple myeloma: updated results from a phase 1 study	Bal

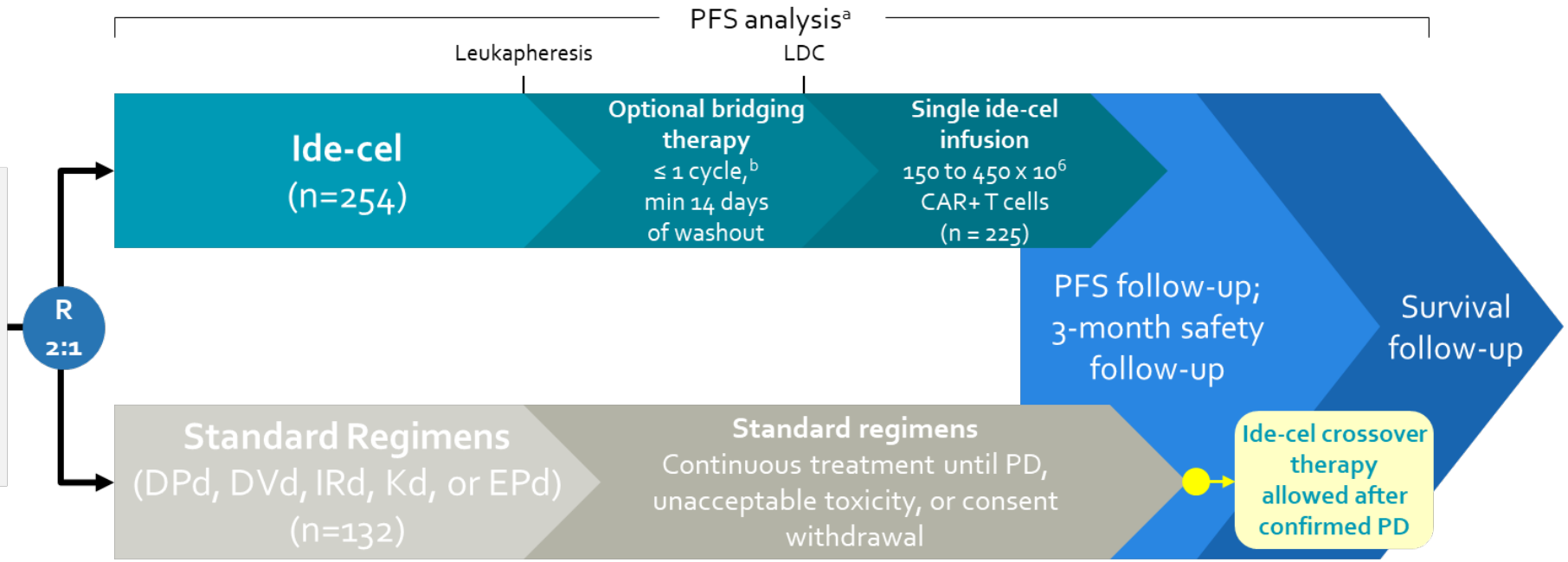
Memorial Sloan Kettering Cancer Center

BCMA-Targeted CAR T-Cell Therapy
KarMMa-3 (ide-cel)
CARTITUDE-2 (cilta-cel)

Memorial Sloan Kettering Cancer Center

KarMMa-3 Study Design (NCT03651128)

- 2–4 previous regimens (including an IMiD agent, a PI, and daratumumab)
- Refractory to the last regimen



Stratification Factors

- Age (< 65 vs ≥ 65 years)
- Number of previous regimens (2 vs 3 or 4)
- High-risk cytogenetics (yes vs no/unknown)

- **Primary endpoint:** PFS by IRC
- **Key secondary endpoints:** ORR, OS
- **Other secondary endpoints:** CR rate, DOR, MRD-negative CR, PFS2, safety

[a]Time from randomization to the first occurrence of disease progression or death from any cause according to IMWG criteria; [b]Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd may be given as bridging therapy. CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; DPd, daratumumab/pomalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; EPd, elotuzumab/pomalidomide/dexamethasone; IMWG, International Myeloma Working Group; IRC, Independent Response Committee; IRd, ixazomib/lenalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; LDC, lymphodepleting chemotherapy; min, minimum; MRD, minimal residual disease; ORR, overall response rate; PD, progressive disease; PFS2, progression-free survival on next line of therapy; R, randomization.

Rodriguez-Otero P, et al. ASH 2023. Abst 1028.

Memorial Sloan Kettering Cancer Center

Baseline Characteristics

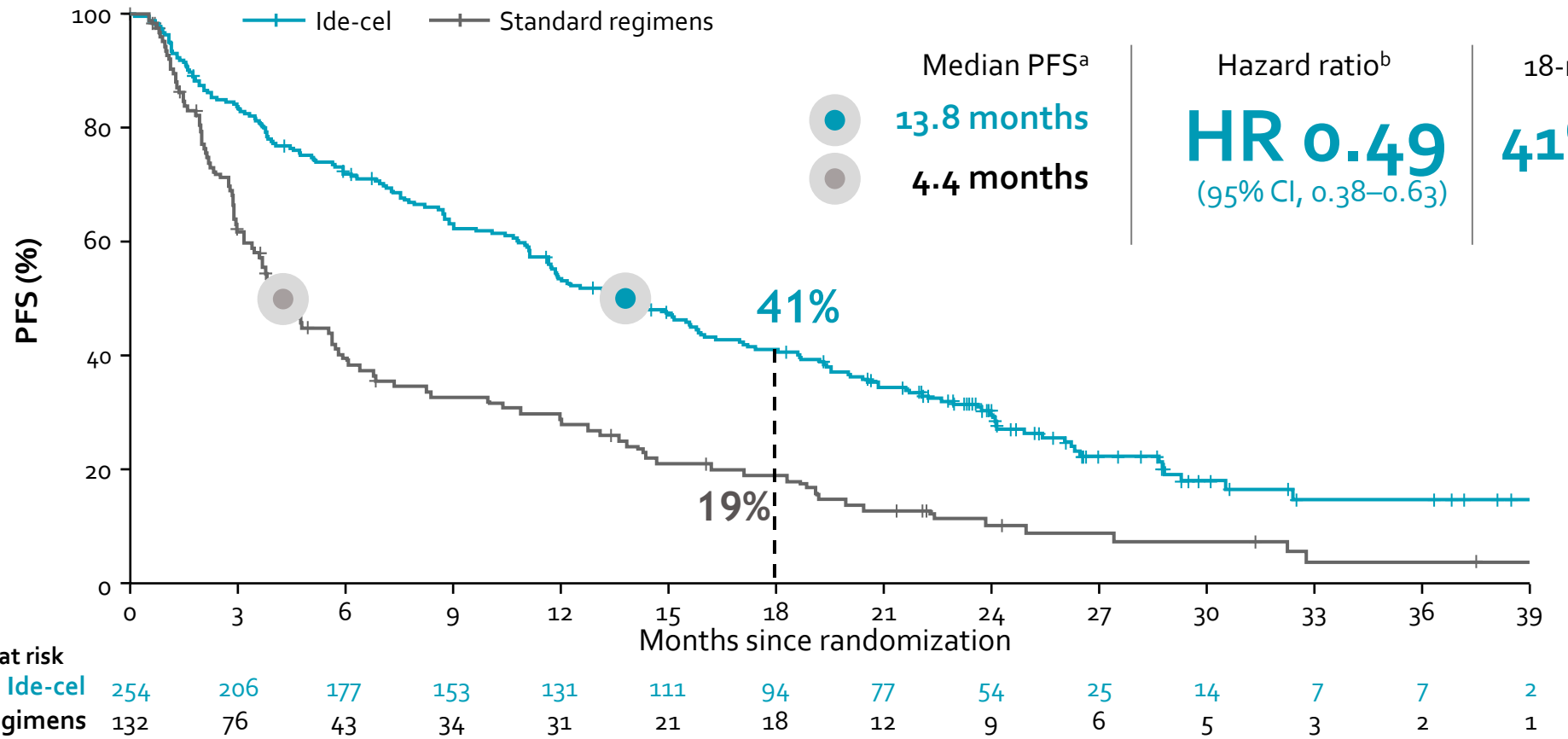
Characteristic	Ide-cel (n = 254)	Standard regimens (n = 132)
Median (range) age, years	63 (30–81)	63 (42–83)
Median (range) time from diagnosis to screening, y	4.1 (0.6–21.8)	4.0 (0.7–17.7)
Previous autologous HSCT	214 (84)	114 (86)
R-ISS disease stage		
I	50 (20)	26 (20)
II	150 (59)	82 (62)
III	31 (12)	14 (11)
EMP	61 (24)	32 (24)
High tumor burden[a]	71 (28)	34 (26)
High-risk cytogenetics[b]	166 (65)	82 (62)
del(17p)	66 (26)	42 (32)
t(4;14)	43 (17)	18 (14)
t(14;16)	8 (3)	4 (3)
1q gain/amplification	124 (49)	51 (39)
Ultra-high–risk cytogenetics[c]	67 (26)	29 (22)
Median (range) TTP on last prior antimyeloma Tx, mo	7.1 (0.7–67.7)	6.9 (0.4–66.0)
Daratumumab refractory	242 (95)	123 (93)
Triple-class–refractory[d]	164 (65)	89 (67)

- Baseline characteristics were generally balanced between treatment arms
- Overall, 66% of patients had TCR RRMM and 95% were refractory to daratumumab, indicating a difficult-to-treat patient population

Data are n (%) unless otherwise stated. [a]≥ 50% CD138+ plasma cells in bone marrow; [b]Included del(17p), t(4;14), t(14;16), or 1q gain/amplification; [c]≥ 2 of del (17p), t(4;14), t(14;16), t(14;20), or 1q gain/amplification; [d]Refractory to ≥ 1 each of an IMiD agent, a PI, and an anti-CD38 antibody.
EMP, extramedullary plasmacytoma; HSCT, hematopoietic stem cell transplantation; ide-cel, idecabtagene vicleucel; PI, proteasome inhibitor; R-ISS, revised International Staging System; RRMM, relapsed/refractory multiple myeloma; TCR, T-cell receptor; TTP, time-to-progression.
Rodriguez-Otero P, et al. ASH 2023. Abst 1028.

Memorial Sloan Kettering Cancer Center

KarMMa-3 Final PFS Analysis (ITT population)

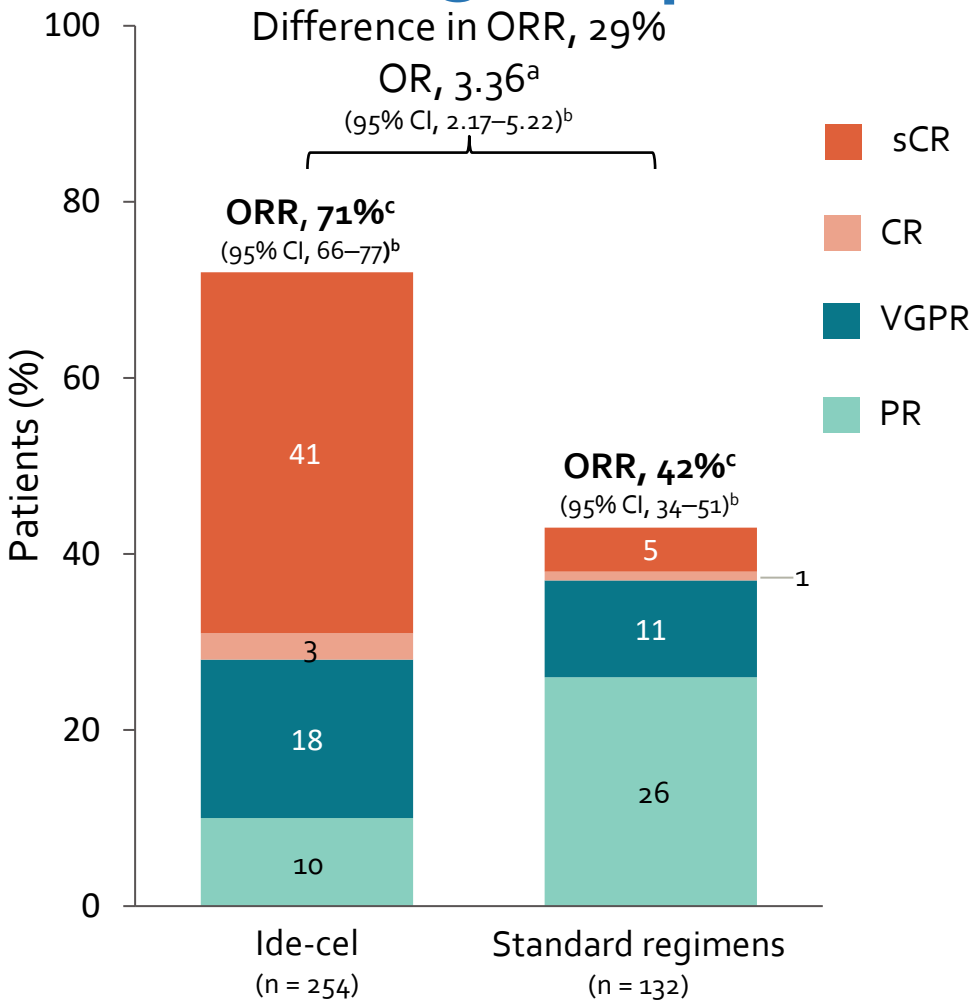


	Median PFS[a]	Hazard ratio[b]	18-month PFS rate	
Ide-cel	13.8 months	HR 0.49 (95% CI, 0.38–0.63)	41%	19%
Standard regimens	4.4 months			

PFS was analyzed in the ITT population of all randomized patients in both arms and included early PFS events occurring between randomization and ide-cel infusion. PFS based on IMWG criteria per IRC. [a]Based on Kaplan–Meier approach; [b]Stratified HR based on univariate Cox proportional hazard model. CI is 2-sided.
CI, confidence interval; HR, hazard ratio; ide-cel, idecabtagene vicleucel; ITT, intent-to-treat; PFS, progression-free survival.
Rodriguez-Otero P, et al. ASH 2023. Abst 1028.

Memorial Sloan Kettering Cancer Center

KarMMa-3: Response



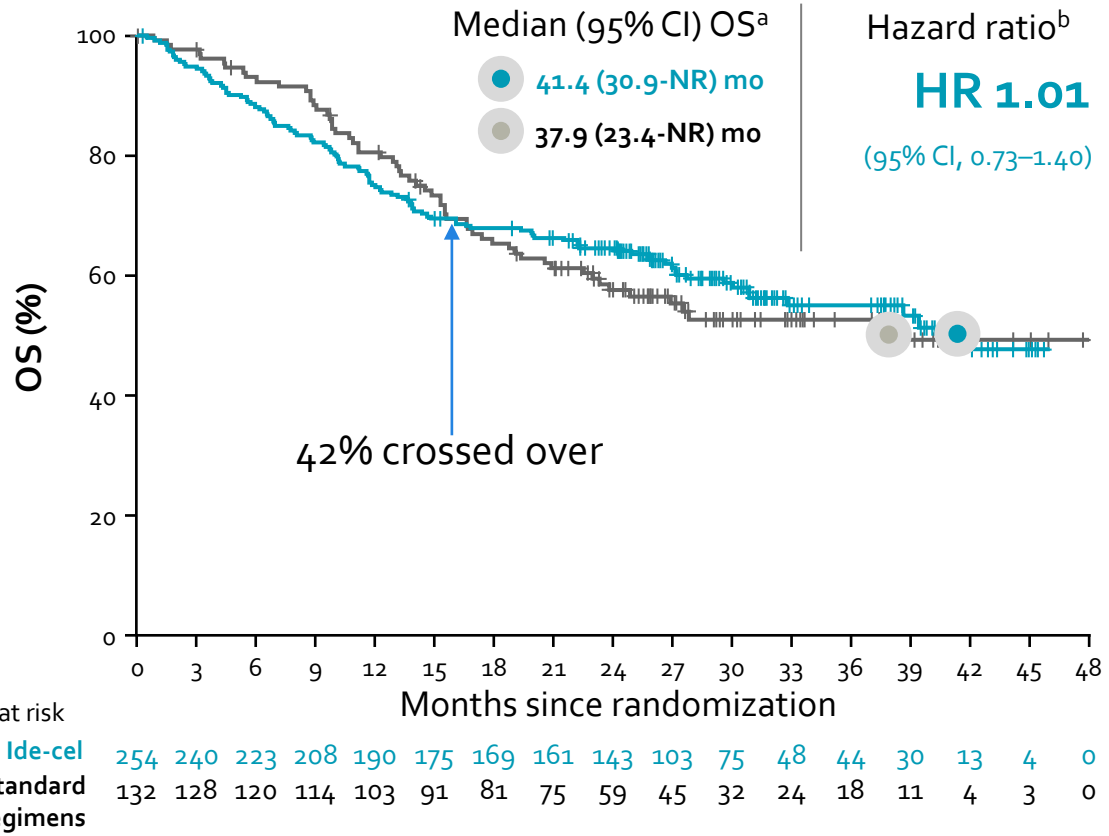
Secondary endpoint	Ide-cel (n = 254)	Standard regimens (n = 132)
CR rate (95 % CI), %[d]	44 (38–50)	5 (2–9)
MRD-negative CR rate, n/N (%) (95% CI)[e]	57/163 (35) (28–42)	1/54 (2) (0–5)
Median (95% CI) DOR, months	16.6 (12.1–19.6)	9.7 (5.5–16.1)
Median PFS2, months	23.5	16.7
HR (95% CI)	0.79 (0.60–1.04)	

Per IMWG criteria. Individual responses may not sum to ORR due to rounding. [a]OR is for ORR, calculated based on the observed response rate; [b]95% CI was calculated using 2-sided Wald interval; [c]Patients with ≥ PR; [d]Patients with CR or sCR; [e]In patients evaluable for MRD; ≥ 1 negative MRD value within 3 months prior to achieving ≥ CR until PD or death. MRD was assessed by NGS at a sensitivity of 10^{-5} per IMWG Uniform Response Criteria and as specified by the protocol.
ide-cel, idecabtagene vicleucel; NGS, next-generation sequencing; OR, odds ratio; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Rodriguez-Otero P, et al. ASH 2023. Abst 1028.

Memorial Sloan Kettering Cancer Center

KarMMa-3: OS Analysis Confounded by Crossover

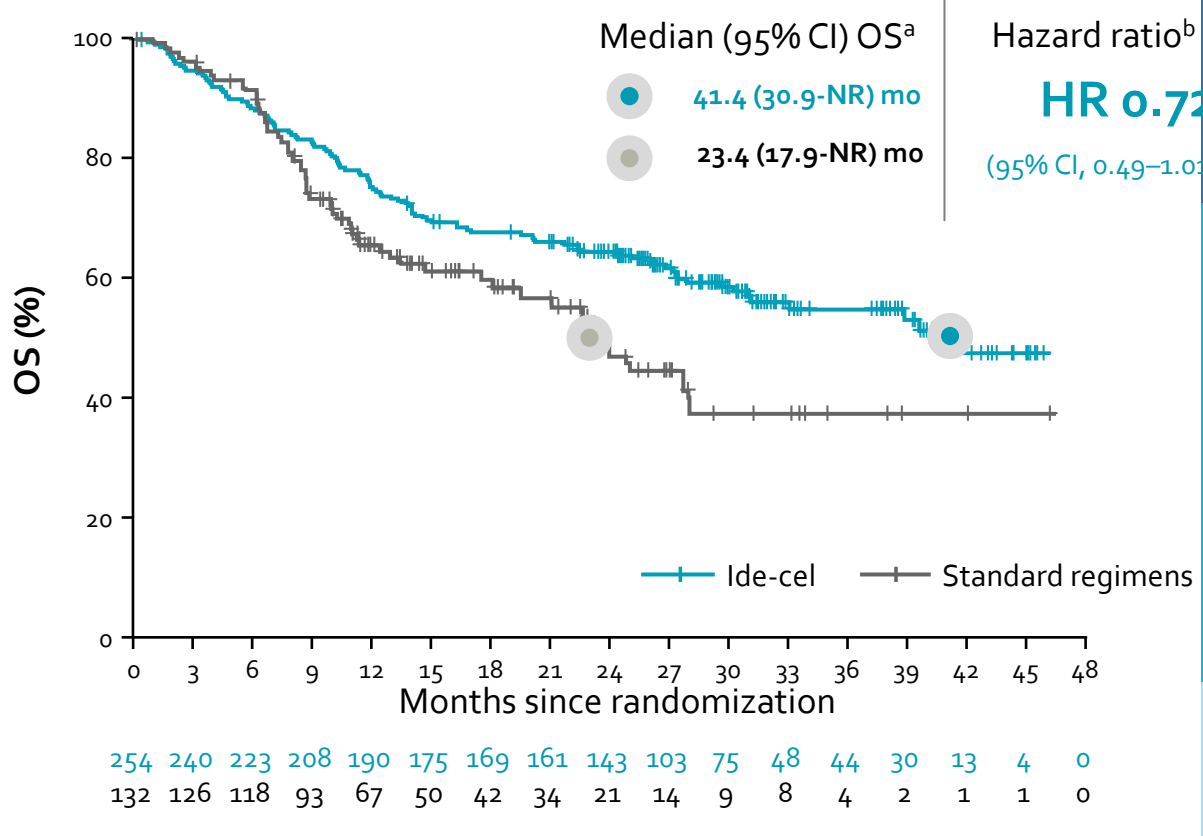
ITT population



Patients at risk

Ide-cel	254	240	223	208	190	175	169	161	143	103	75	48	44	30	13	4	0
Standard regimens	132	128	120	114	103	91	81	75	59	45	32	24	18	11	4	3	0

Sensitivity analysis adjusted for crossover[c]



Ide-cel	254	240	223	208	190	175	169	161	143	103	75	48	44	30	13	4	0
Standard regimens	132	126	118	93	67	50	42	34	21	14	9	8	4	2	1	1	0

- More than half of patients in standard regimens arm received ide-cel as subsequent therapy upon confirmed PD and the majority received ide-cel within 3–16 months of randomization
- Prespecified crossover-adjusted analysis shows OS benefit of ide-cel

Information fraction for OS was 74% (n = 164/222 required events). [a]Based on Kaplan–Meier approach; [b]Stratified HR is based on the univariate Cox proportional hazards model. CI is 2-sided and calculated by bootstrap method; [c]Two-stage Weibull model without recensoring (prespecified analysis).
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NR, not reached; OS, overall survival.
Rodriguez-Otero P, et al. ASH 2023. Abst 1028.

Memorial Sloan Kettering Cancer Center

KarMMa-3: Safety Profile[1]

Treated population, n (%)	Ide-cel (n = 225)	Standard regimens (n = 126)
Any-grade AE	225 (100)	124 (98)
Serious AE	105 (47)	52 (41)
ITT population, n (%)	**Ide-cel (n = 254)**	**Standard regimens (n = 132)**
Overall deaths	106 (42)	58 (44)
Cause of death		
Disease progression	64 (25)	37 (28)
AEs	17 (7)	8 (6)
Other causes	23 (9)	12 (9)
SPMs[a]	2 (1)	1 (1)

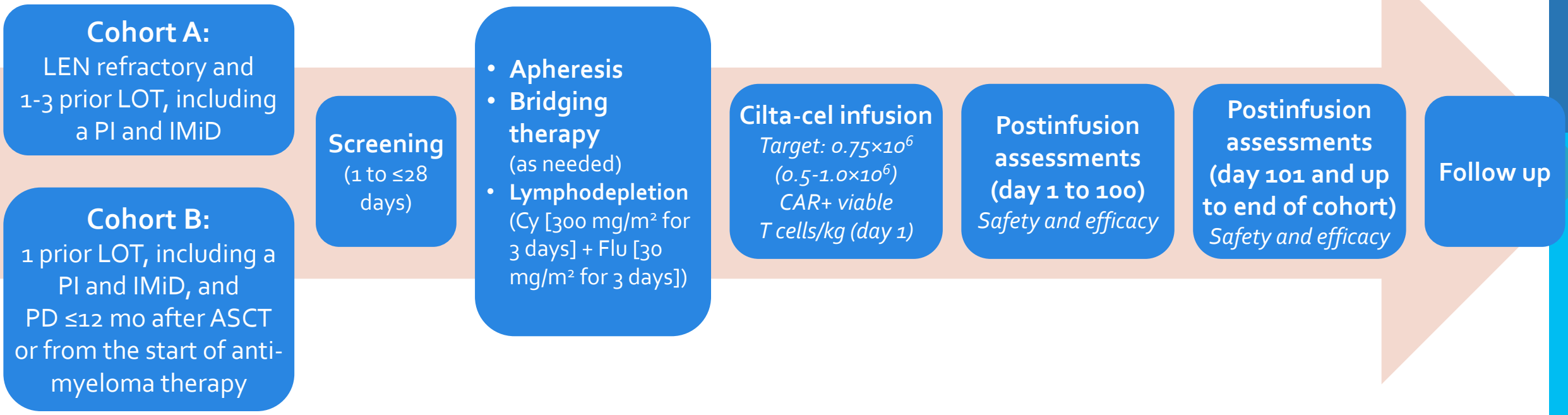
Treated population, n (%)	Ide-cel (n = 225)
CRS[b]	
Any grade	197 (88)
Grade 3/4	9 (4)
iiNT[c]	
Any grade	34 (15)
Grade 3/4	7 (3)
Infections	
Any grade	125 (56)
Grade 3/4	50 (22)

- There were no new CRS or iiNT events with ide-cel since the interim analysis1 and no parkinsonism or Guillain-Barré syndrome were reported
- No SPMs of T-cell origin were reported in the ide-cel arm
- No new safety signals

[a]Deaths due to SPMs in the ide-cel arm were leukemia (n = 1) and pancreatic adenocarcinoma (n = 1); death due to SPMs in the standard regimens arm was malignant neoplasm of unknown primary site (n = 1); [b]CRS was graded according to modified Lee's criteria;[2] maximum-grade events are reported, patients could have >1 event; [c]Includes immune effector cell–associated neurotoxicity syndrome reported by investigator as a neurologic toxicity.
CRS, cytokine release syndrome; iiNT, investigator-identified neurotoxicity; SPM, second primary malignancy.
1. Rodriguez-Otero P, et al. ASH 2023. Abst 1028. 2. Lee DW, et al. Blood. 2014;124:188–195.

Memorial Sloan Kettering Cancer Center

CARTITUDE-2 Cohorts A & B: Study Design and Methods[1]



- **Primary endpoint:** MRD negativity[a] (10^{-5} threshold) assessed by NGS or NGF
- **Secondary endpoints included:** ORR[a], DOR, tie to response, incidence and severity of AEs[b], including CRS and ICANS[2,c]
- **Exploratory endpoints included:** PFS and OS

[a]Assessed per IMWG criteria. [b]Assessed per CTCAE v 5.0. [c]Graded per ASTCT criteria. AE, adverse event; ASCT autologous stem cell transplant; ASTCT, American Society of Transplantation and Cellular Therapy; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; ICANS, immune effector cell-associated neurotoxicity syndrome; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; LEN, lenalidomide; LOT, line of therapy; MRD, minimal residual disease; NGF, next-generation flow; NGS next-generation sequencing; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor.

1. Hillengass J, et al. ASH 2023. Abst 1021. 2. Lee DW, et al. Biol Blood Marrow Transplant.2019;25:625-638.

Memorial Sloan Kettering Cancer Center

CARTITUDE-2 Cohorts A & B: Baseline Characteristics

Characteristic	Cohort A (N=20)	Cohort B (N=19)
Age, median (range), y	60 (38-75)	58 (44-67)
Male, n (%)	13 (65.0)	14 (73.7)
Race, n (%)		
White	18 (90.0)	14 (73.7)
Black/African American	2 (10.0)	2 (10.5)
Asian	0	1 (5.3)
Not reported	0	2 (10.5)
Bone marrow plasma cells[a] ≥60%, n (%)	3 (15.0)	4 (21.1)
Extramedullary plasmacytomas, n (%)	3 (15.0)	3 (15.8)
Cytogenetic high risk,[b] n (%)	7 (35.0)[c]	3 (15.8)[d]
del17p	3 (15.0)	3 (15.8)
t(14;16)	5 (25.0)	0
t(4;14)	0	0
1q	0	0

Characteristic	Cohort A (N=20)	Cohort B (N=19)
Years since initial diagnosis to enrollment, median (range)	3.5 (0.7-8.0)	1.15 (0.5-1.9)
Prior LOT, median (range)	2 (1-3)	1 (1-1)
Previous autologous SCT,[e] n(%)	17 (85.0)	15 (78.9)
Exposure status, n (%)		
Triple-class[f]	13 (65.0)	4 (21.1)
Penta-drug exposed[g]	4 (20.0)	0
Refractory status, n (%)		
Triple-class[f]	8 (40.0)	3 (15.8)
Penta-drug refractory[g]	1 (5.0)	0
To last line of prior therapy	19 (95.0)	15 (78.9)

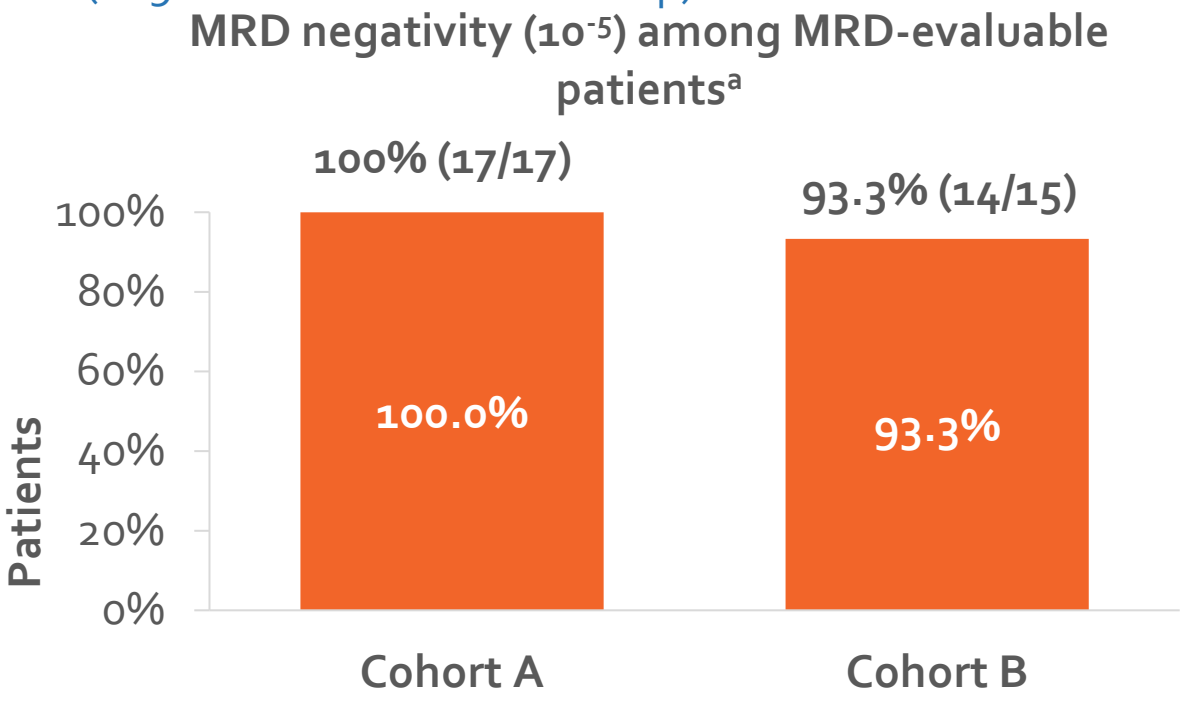
- Median follow-up for those who received cilta-cel:
  - Cohort A: 29.9 months (range, 3.3[h]-35.6)
  - Cohort B: 27.9 months (range, 5.2[h]-32.1)

[a]Maximum value from bone marrow biopsy and bone marrow aspirate is selected if both results are available. [b]Any of the following: del17p, t(14;16), t(4;14), or 1q. [c]1patient had both del17p and t(14;16); 6 (30%) patients had unknown cytogenetics. [d]3(15.8%) patients had unknown cytogenetics. [e]17 patients in cohort A and 15 patients in cohort B received prior SCT and all were autologous. [f]PI, IMiD, and anti-CD38 antibody. [g]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody. [h]Includes patients who died.
Cilta-cel, ciltacabtagene autoleucel; IMiD, immunomodulatory drug; LOT, line of therapy; PI, proteasome inhibitor; SCT, stem cell transplantation.
Hillengass J, et al. ASH 2023. Abst 1021.

Memorial Sloan Kettering Cancer Center

CARTITUDE-2 Cohorts A & B: MRD Negativity (Primary Endpoint)

(~29-month median follow-up)



Sustained MRD negativity[b]	Cohort A	Cohort B
Patients evaluable for sustained MRD negativity ≥6 mo[c]	**n=11**	**n=13**
Sustained MRD negativity (10^{-5}) ≥6 mo,[d] n (%)	8 (72.7)	10 (76.9)
Patients evaluable for sustained MRD negativity ≥12 mo[e]	**n=14**	**n=13**
Sustained MRD negativity (10^{-5}) ≥12 mo,[f] n (%)	7 (50.0)	8 (61.5)

Per protocol, bone marrow aspirate samples for MRD evaluation were collected at time of suspected CR/sCR; for all dosed patients at months 2, 6, 12, 18, and 24; and yearly thereafter for patients in CR/sCR.

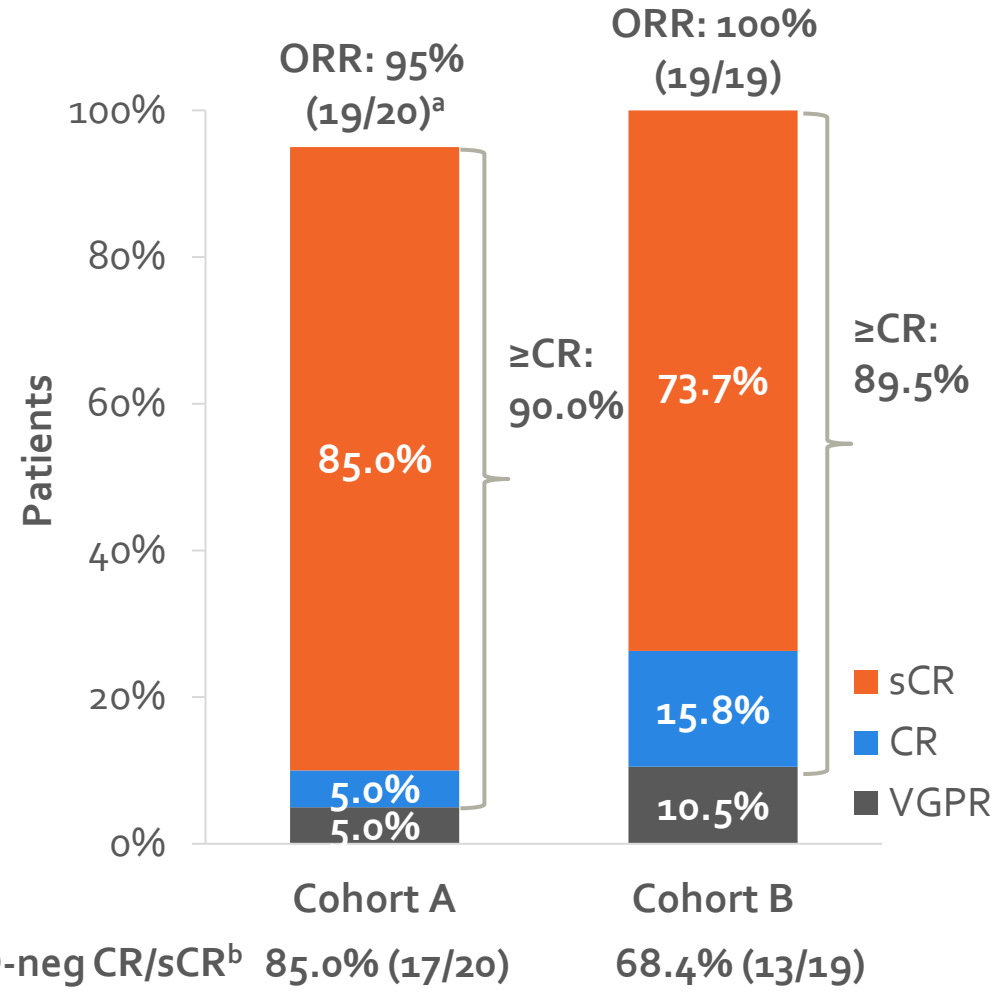
[a]Patients who were MRD evaluable had a clone identified and had ≥1 postbaseline MRD sample that included sufficient cells for evaluation at the 10^{-5} testing threshold (for NGS) or patients who had ≥1 postbaseline sample with the results of either positive or negative (for NGF). [b]Post hoc analysis. [c]Patients who achieved overall MRD negativity and had at least an evaluable MRD sample at the 10^{-5} testing threshold on or after 6 months after their first MRD negativity or progressed, started subsequent therapy, or died due to progressive disease within 6 months after their first MRD negativity. [d]MRD negative confirmed by at least 6 months apart without MRD positive in between. Percentage is calculated with number of patients evaluable for sustained MRD negativity ≥6 months as denominator. [e]Patients who achieved overall MRD negativity and had at least an evaluable MRD sample at the 10^{-5} testing threshold on or after 6 months after their first MRD negativity or progressed, started subsequent therapy, or died due to progressive disease within 6 months after their first MRD negativity. [f]MRD negative confirmed by at least 12 months apart without MRD positive in between. Percentage is calculated with number of patients evaluable for sustained MRD negativity ≥12 months as denominator.

CR, complete response; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; sCR, stringent CR.

Hillengass J, et al. ASH 2023. Abst 1021.

Memorial Sloan Kettering Cancer Center

CARTITUDE-2 Cohorts A & B: Response and Survival



Tx response among responders	Cohort A (N=19)	Cohort B (N=19)
Time (mo) to first response,[c] median (range)	0.99 (0.7-3.3)	0.95 (0.9-9.7)
Time (mo) to best response,[c] median (range)	3.25 (0.9-13.6)	5.1 (0.9-11.8)
24-mo DOR rate, % (95% CI)	73.3 (47.2-87.9)	70.5 (42.5-86.7)

Survival outcome	Cohort A (N=20)	Cohort B (N=19)
24-mo PFS rate, % (95% CI)	75.0 (50.0-88.7)	73.3 (47.2-97.9)
24-mo OS rate, % (95% CI)	75.0 (50.0-88.7)	84.2 (58.7-94.6)

[a]1 patient had a minimal response. [b]Only MRD assessments (10-5 testing threshold) within 3 months of achieving CR/sCR until death/progression/subsequent therapy (exclusive) are considered. [c]≥PR.

Cilta-cel, ciltacabtagene autoleucel; CI, confidence interval; CR, complete response; DOR, duration of response; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent CR; Tx, treatment; VGPR, very good partial response.

Hillengass J, et al. ASH 2023. Abst 1021.

Memorial Sloan Kettering Cancer Center

CARTITUDE-2 Cohorts A & B: AEs (Secondary Endpoint)

(~29-month median follow-up)

Cohort A

- Hematologic TEAEs[a] were most common
  - 95% neutropenia, all grade 3/4
- Second primary malignancies[b]:
  - Grade 3 mucoepidermoid carcinoma, n=1
- Deaths: PD, n=3[c]; sepsis, n=1[b]; pneumonia, n=1[d,e]

Cohort B

- Hematologic TEAEs[f] were most common
  - 95% neutropenia, almost all grade 3/4
- Second primary malignancies[b]:
  - Grade 2 prostate cancer, n=1
  - Grade 4 choroid melanoma, n=1[g]
- Deaths: PD, n=3; cardiac arrest, n=1[b,g]

Select TEAEs, n (%)	Cohort A (N=20)		Cohort B (N=19)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TEAE	20 (100)	19 (95)	19 (100)	18 (95)
Serious TEAE	10 (50)	–	7 (37)	–
Hematologic				
Neutropenia	19 (95)	19 (95)	18 (95)	17 (89)
Lymphopenia	16 (80)	16 (80)	9 (47)	9 (47)
Thrombocytopenia	16 (80)	8 (40)	11 (58)	5 (26)
Anemia	15 (75)	9 (45)	11 (58)	9 (47)
Leukopenia	12 (60)	12 (60)	6 (32)	6 (32)

[a]Between a median follow-up of 17.1-29.9 months, new grade 3/4 cases of leukopenia (n=1), lymphopenia (n=2), and thrombocytopenia (n=1). [b]Not treatment related. [c]1 new death on day 666 since last data cut-off. [d]Patient also had an AE of sepsis in addition to COVID-19 pneumonia. [e]Treatment related. [f]No change since previous data cut-off. [g]New event since last data cut-off.

AE, adverse event; cilta-cel, ciltacabtagene autoleucel; PD, progressive disease; TEAE, treatment-emergent AE.

Hillengass J, et al. ASH 2023. Abst 1021.

Memorial Sloan Kettering Cancer Center

CARTITUDE-2 Cohorts A & B: CRS and CAR T-Cell Neurotoxicity (Secondary Endpoint) (~29-month median follow-up)

AEs, n (%)	Cohort A (N=20)				
	Any Grade	Grade 3/4	Median time to onset, d	Median duration, d	Resolved, n
CRS	19 (95)	2 (10)	7	3	19
CAR T-cell neurotoxicity	6 (30)	1 (5)	–	–	–
ICANS	3 (15)	0	8	3	3
Other	3[a] (15)	1 (5)	30	80	2
MNT	0	0	–	–	–

AEs, n (%)	Cohort B (N=19)				
	Any Grade	Grade 3/4	Median time to onset, d	Median duration, d	Resolved, n
CRS	16 (84)	1 (5.3)	8	4	16
CAR T-cell neurotoxicity	6 (32)	1 (5)			
ICANS	1 (5)	0	11	4	1
Other[b]	5[c] (26)	1 (5)	22	128	3
MNT	1[d] (5)	1 (5)	38	–[e]	–[e]

- In both cohorts, most cases of CRS and CAR T-cell neurotoxicity resolved
  - Cohort A: 19/19 CRS cases, 3/3 ICANS cases, and 2/3 other neurotoxicity resolved
  - Cohort B: 16/16 CRS cases, 1/1 ICANS case, and 3/5 other neurotoxicity cases resolved

[a]1 case each of peripheral sensory motor neuropathy (recovering/resolving), anosmia (resolved), and facial paralysis (resolved). [b]1 new other neurotoxicity of grade 2 sensory loss (which resolved) since the last data cut-off. [c]1 case each of MNT (not resolved), hypoesthesia (not resolved), sensory loss (resolved), facial paralysis (resolved), and personality change (resolved). [d]Patient had associated risk factors for MNTs—high baseline tumor burden (95% plasma cells in BM biopsy at LD [M-protein from 5.0 g/dL at screening to 6/1 g/dL at LD chemotherapy]), worsening tumor burden despite bridging therapy, grade 4 CRS, and high CAR T-cell expansion and persistence. [e]Not recovered/resolved as of this data cut-off, patient died due to cardiac arrest on day 749 post cilta-cel.

AE, adverse event; BM, bone marrow, CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; ICANS immune effector cell-associated neurotoxicity syndrome; LD, lymphodepletion; MNT, movement and neurocognitive treatment-emergent AE.

Hillengass J, et al. ASH 2023. Abst 1021.

Memorial Sloan Kettering Cancer Center

CARTITUDE-4: Phase 3 Study of Cilta-cel vs PVd or DPd in RRMM (NCT04181827)

Primary objective

- To compare efficacy of cilta-cel to the standard treatments of PVd or DPd

Secondary objectives

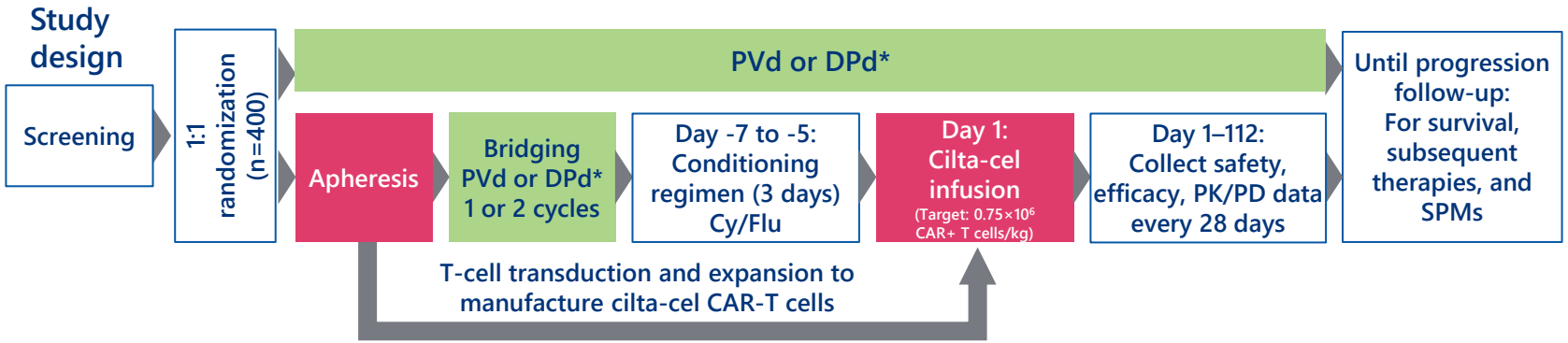
- To further compare efficacy of cilta-cel with PVd or DPd
- To further characterize the safety of cilta-cel to characterize PK/PD and immunogenicity of cilta-cel
- To evaluate the impact of cilta-cel treatment vs PVd or DPd on HRQOL

Key inclusion criteria

- Age ≥18 with diagnosed MM
- Prior 1–3 lines of therapy (must include PI+IMiD), and lenalidomide-refractory

Key exclusion criteria

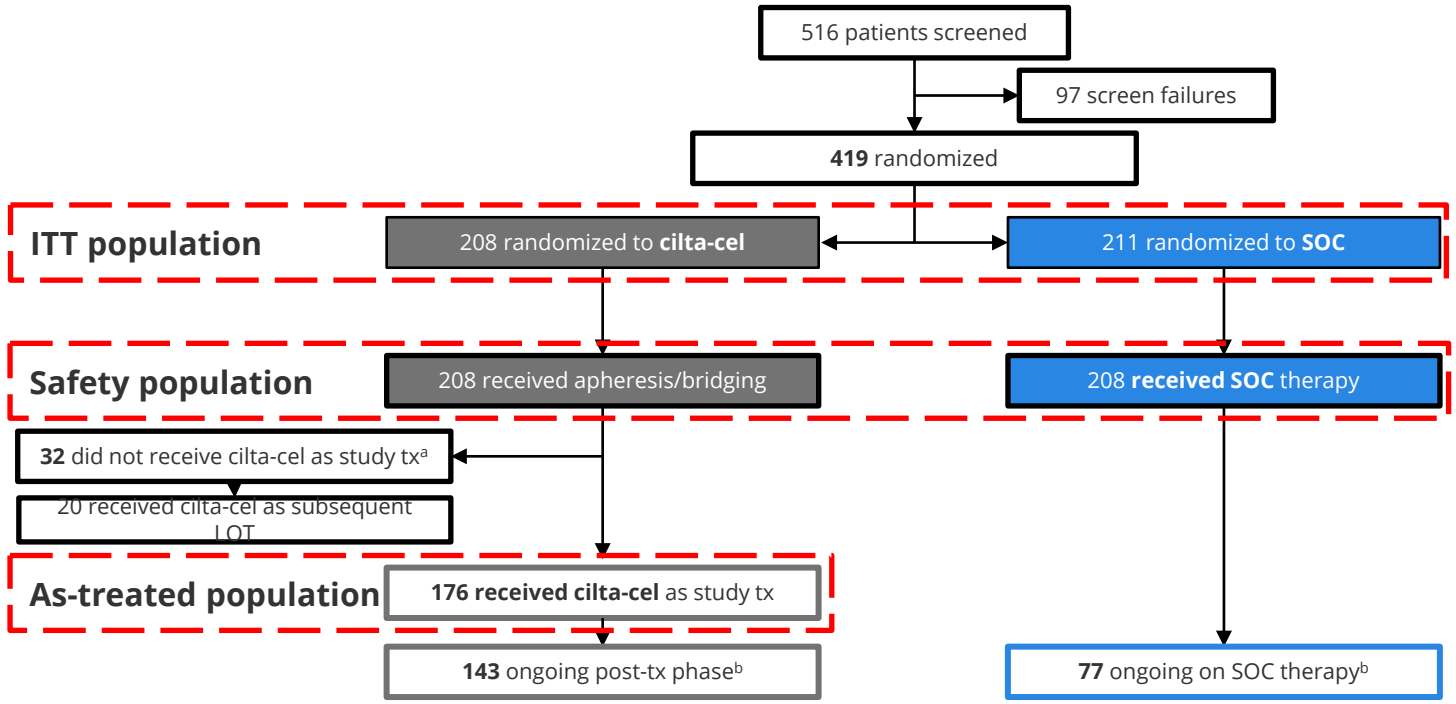
- Prior CAR-T or BCMA-targeting therapy,
- Diagnosed or treated for malignancy other than MM
- Prior allogenic SCT ≤6 months before apheresis
- Prior ASCT ≤12 weeks before apheresis



San Miguel J et al, NEJM 2023

Memorial Sloan Kettering Cancer Center

CARTITUDE-4: Patient Population and Follow-Up



- At November 1, 2022 data cut-off, median follow-up was 15.9 months (range, 0.1–27)
- First patient randomized on July 10, 2020 and last patient randomized on November 17, 2021
- Median time from first apheresis to cilta-cel infusion was 79 days

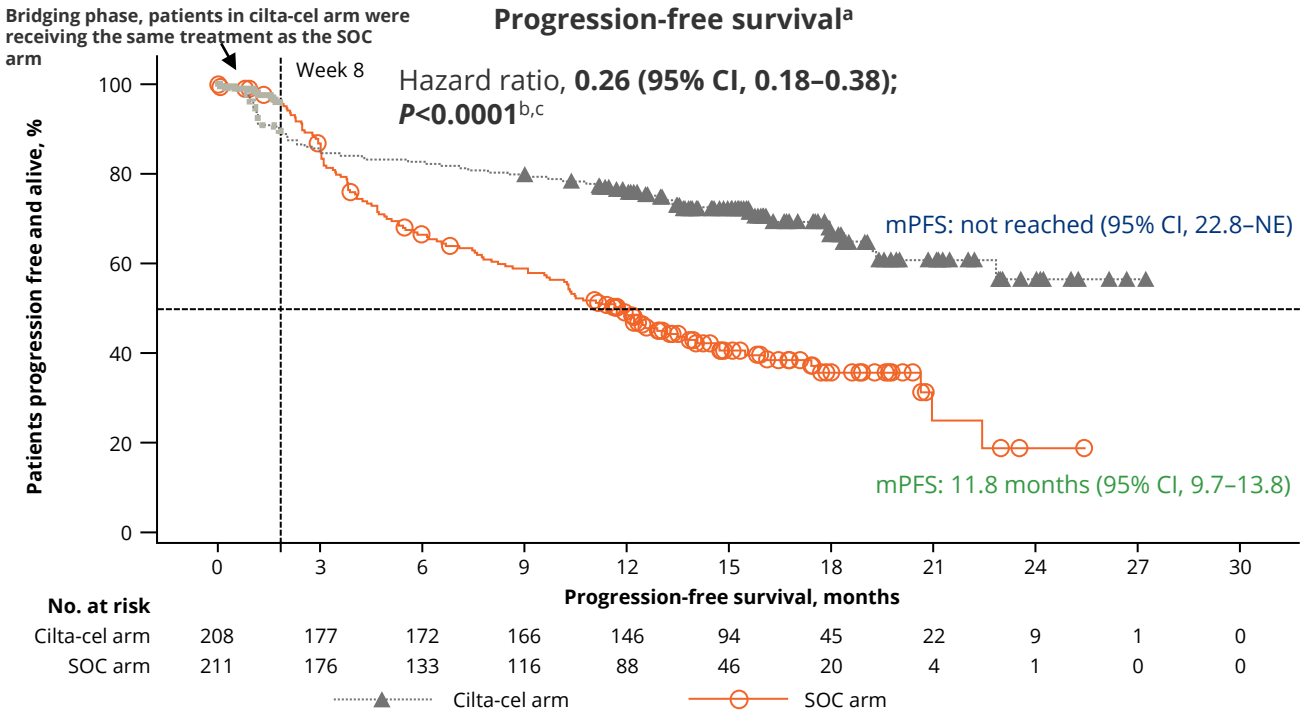
San Miguel J et al, NEJM 2023

[a]Due to disease progression (n=30) or death (n=2) during bridging therapy/lymphodepletion. [b]Have not progressed. cilta-cel, ciltacabtagene autoleucel; ITT, intent-to-treat; LOT, line of therapy; SOC, standard of care; tx, treatment.

Memorial Sloan Kettering Cancer Center

CARTITUDE-4: Primary Endpoint – PFS (ITT Population)

- Cilta-cel vs SOC
  - 12-month PFS rate: 76% vs 49%
  - SOC performed as expected



San Miguel J et al, NEJM 2023

Memorial Sloan Kettering Cancer Center

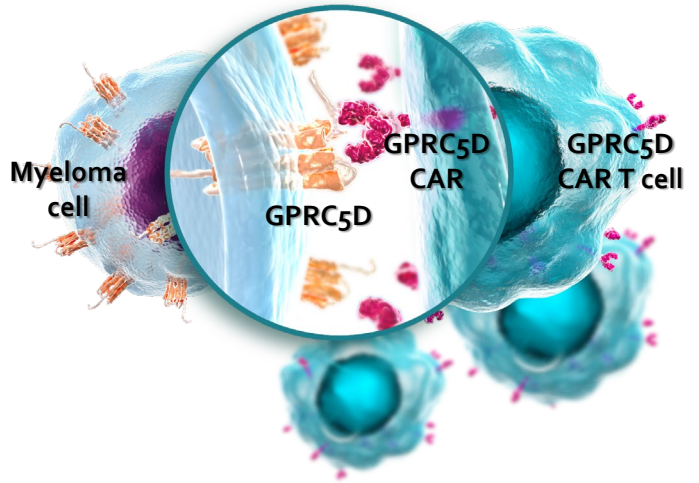
GPRC5D-Targeted CAR T-Cell Therapy

Memorial Sloan Kettering Cancer Center

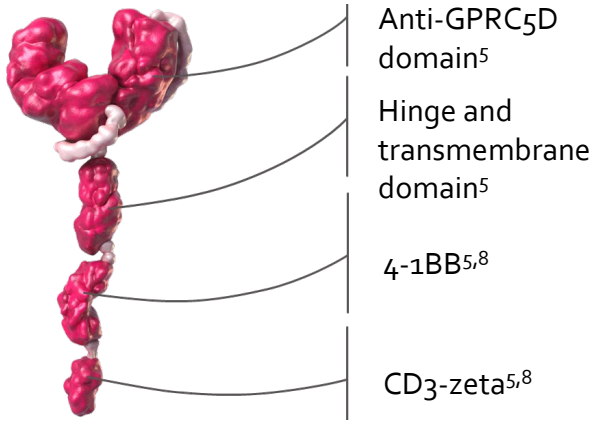
BMS-986393: a GPRC5D autologous CAR T-cell therapy

- GPRC5D is an emerging and validated target in MM, beyond IMiDs, PIs, anti-CD38 antibodies, and BCMA-targeted therapies[1-5]
- BMS-986393 (CC-95266) is a potential first-in-class autologous CAR T-cell therapy targeting GPRC5D[5] that has been granted FDA RMAT designation for RRMM
  - In the phase 1 CC-95266-MM-001 study of BMS-986393 in patients with RRMM (NCT04674813):
  - 150 × 10^6 CAR T cells has been selected as the BMS-986393 RP2D based on the totality of data[6,7]

BMS-986393 mechanism of action



GPRC5D-targeted CAR construct



BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; GPRC5D, G protein–coupled receptor class C group 5 member D; IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteosome inhibitor; RMAT, regenerative medicine advanced therapy; RP2D, recommended phase 2 dose; RRMM, relapsed and/or refractory multiple myeloma.

1. Berdeja JG, et al. Lancet. 2021;398:314–324. 2. Munshi NC, et al. N Engl J Med. 2021;384:705–716. 3. Rodriguez-Otero P, et al. N Engl J Med. 2023;388:1002–1014. 4. Mailankody S, et al. N Engl J Med. 2022;387:1196–1206. 5. Smith EL, et al. Sci Transl Med. 2019;11:eaau7746. 6. Bal S, et al. Blood. 2022;140(suppl 1):883. 7. Bal S, et al. Hemasphere. 2023;7(suppl):e9863287. 8. Song D-G, et al. Cancer Res. 2011;71:4617–4627.

Memorial Sloan Kettering Cancer Center

BMS-986393 in RRMM: Heavily Pretreated Population

Characteristic	All treated patients (n=84)	150 × 10^6 CAR T cells (n=26)
Median age, years (range)	63 (39–80)	63 (39–74)
Primary race,[a] n (%)		
American Indian or Alaska Native	1 (1.2)	1 (3.8)
Asian	4 (4.8)	2 (7.7)
Black or African American	14 (16.7)	3 (11.5)
White	56 (66.7)	19 (73.1)
High-risk cytogenetics, n (%)		
del(17p), t(4;14), and/or t(14;16)	34 (40.5)	12 (46.2)
del(17p)	24 (28.6)	11 (42.3)

Characteristic	All treated patients (n=84)	150 × 10^6 CAR T cells (n=26)
Median number of prior anti-myeloma therapies, n (range)	5 (3–15)	5 (3–13)
Prior BCMA-targeted therapy, n (%)	39 (46.4)	11 (42.3)
CAR T-cell therapy[b]	30 (35.7)	9 (34.6)
T-cell engager	2 (2.4)	0 (0)
Antibody-drug conjugate	14 (16.7)	4 (15.4)
Refractory status to prior therapies,[c] n (%)		
Triple-class refractory	62 (73.8)	22 (84.6)
Penta-drug refractory	28 (32.6)	12 (46.2)
BCMA refractory	17 (20.2)	4 (15.4)

Data cutoff: September 11, 2023. [a]Unknown/missing for 8 patients. [b]Includes investigational and approved CAR T-cell therapies. [c]Refractory definition: progression during or within 60 days of end of treatment or lack of response.

Bal S, et al. ASH 2023. Abst 219.

Memorial Sloan Kettering Cancer Center

BMS-986393 in RRMM: Safety Profile[1]

	All treated patients (n=84)		150×10^6 CAR T cells (n=26)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TEAE, n (%)	77 (91.7)	69 (82.1)	26 (100)	24 (92.3)
Hematologic TEAEs (≥ 30% of all treated patients), n (%)				
Neutropenia	54 (64.3)	52 (61.9)	20 (76.9)	18 (69.2)
Anemia	40 (47.6)	25 (29.8)	13 (50.0)	11 (42.3)
Thrombocytopenia	36 (42.9)	22 (26.2)	10 (38.5)	5 (19.2)
Non-hematologic TEAEs (≥ 30% of all treated patients), n (%)				
CRS	64 (76.2)	3 (3.6)	23 (88.5)	0 (0)
Infections and infestations	34 (40.5)	11 (13.1)	9 (34.6)	3 (11.5)
Hypokalemia	31 (36.9)	4 (4.8)	12 (46.2)	2 (7.7)
Hypocalcemia	28 (33.3)	2 (2.4)	7 (26.9)	0 (0)
Headache	27 (32.1)	1 (1.2)	8 (30.8)	0 (0)
Hypophosphatemia	26 (31.0)	2 (2.4)	11 (42.3)	1 (3.8)

- **RP2D was declared without reaching MTD**
- **Grade ≥ 3 cytopenia events resolved by median of day 46 (range, 32–129)**
- **CRS was dose-dependent,[2] with median onset on day 3 (range, 1–16) and median duration of 4 days (range, 1–13)**
  - **One patient experienced grade 5 CRS related to the study drug (450×10^6 CAR T-cell dose)**
- **No grade ≥ 3 CRS or MAS/HLH events were observed among the 26 patients at the 150×10^6 CAR T-cell dose**

Data cutoff: September 11, 2023. CAR, chimeric antigen receptor; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event.

1. *Bal S, et al. ASH 2023. Abst 219.* ***2. Bal S, et al. Hemasphere. 2023;7(suppl):e9863287.***

Memorial Sloan Kettering Cancer Center

BMS-986393 in RRMM: Transient On-Target/Off-Tumor Effects[1]

On-target/off-tumor, n (%)	All treated patients (n=84)		150 × 10^6 CAR T cells (n=26)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Dysgeusia/taste disorder	21 (25.0)	0	8 (30.8)	0
Skin[a]	17 (20.2)	0	4 (15.4)	0
Nails[b]	11 (13.1)	0	3 (11.5)	0
Dysphagia	3 (3.6)	0	1 (3.8)	0
Neurotoxicity, n (%)	**Any grade**	**Grade 3 only**	**Any grade**	**Grade 3 only**
ICANS-type neurotoxicity[c]	8 (9.5)	2 (2.4)	1 (3.8)	0
Non-ICANS-type neurotoxicity[d]	9 (10.7)	3 (3.6)	4 (15.4)	1 (3.8)

- **86% of on-target/off-tumor skin, nail, and oral AEs did not require treatment; events were transient with a median 25-day duration (range, 2–355)**
- **Low-grade[e] weight loss occurred in 7% of patients**
- **ICANS-type neurotoxicity was reversible with or without intervention**
- **Non–ICANS-type neurotoxicity appeared to be dose-related[2]**

Data cutoff: September 11, 2023. There were no cases of Parkinsonism or Guillain-Barré Syndrome. [a]Skin includes preferred terms of pruritis, maculo-papular rash, pain of skin, erythema, and vesicular rash. [b]Nails includes preferred terms of nail bed disorder and nail disorder. [c]One patient experienced cerebellar toxicity that was coded to neurotoxicity. [d]Non-ICANS-type neurotoxicity events include dizziness, ataxia, neurotoxicity, dysarthria, and nystagmus. [e]Grade 1: decrease of 5% to < 10% of baseline weight; grade 2: decrease of 10% to < 20% of baseline weight.

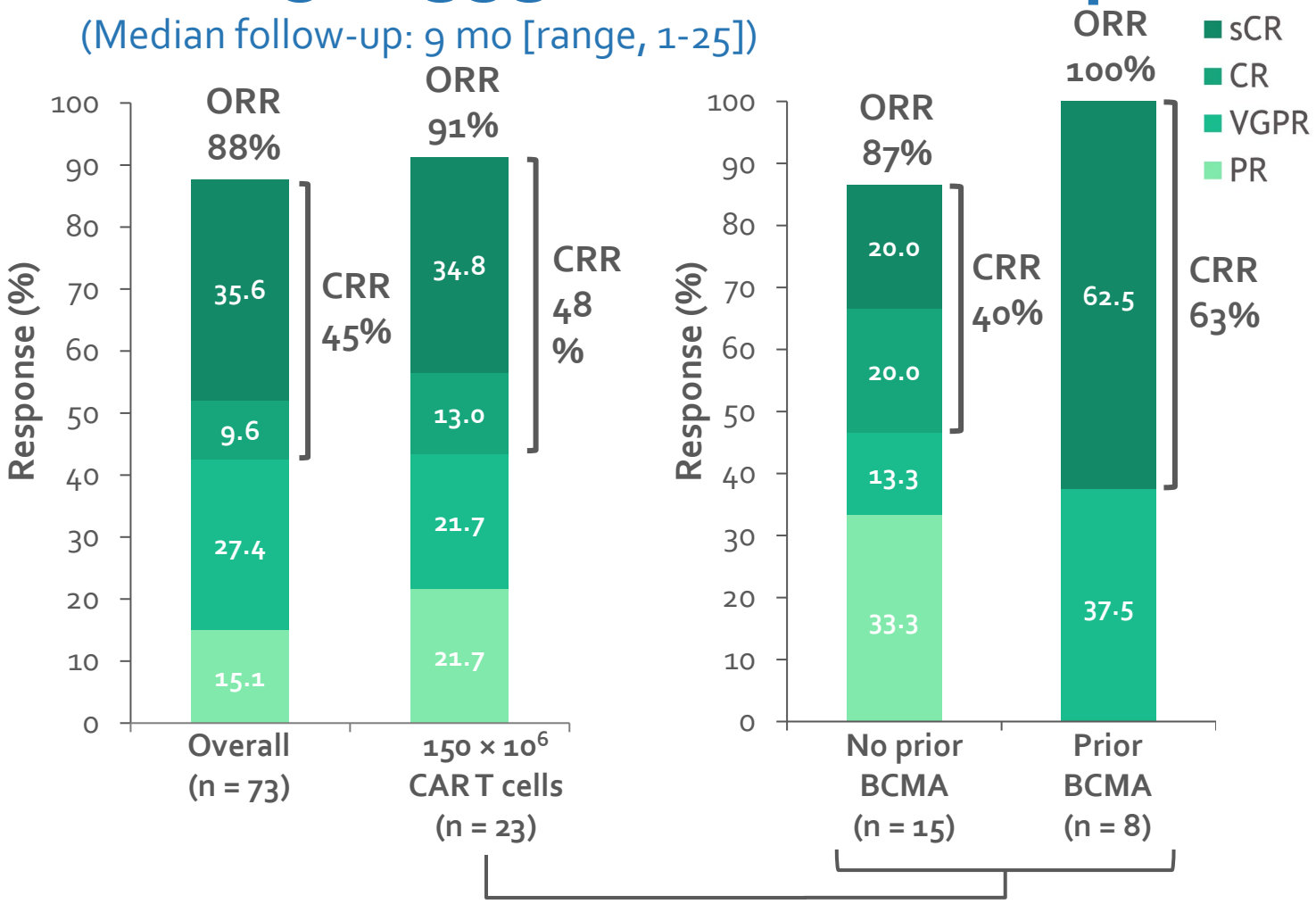
AE, adverse event; ICANS, immune effector cell–associated neurotoxicity syndrome.

1. Bal S, et al. ASH 2023. Abst 219. 2. Bal S, et al. Hemasphere. 2023;7(suppl):e9863287.

Memorial Sloan Kettering Cancer Center

BMS-986393 in RRMM: Response

(Median follow-up: 9 mo [range, 1-25])



Disease characteristic, % (n/N)	Present	Absent
Prior BCMA treatment	78% 25/32	95% 39/41
Extramedullary disease	84% 26/31	91% 38/42
High-risk cytogenetics[a]	83% 24/29	91% 40/44
Triple-class refractory	88% 50/57	88% 14/16

- **Responses observed irrespective of prior BCMA-targeted therapy or high-risk features[b]**
- **67% of responses are ongoing, yielding a median DOR of 13 months (95% CI, 10–20) at data cutoff**
- **86% (12/14) of MRD-evaluable[b] patients with ≥ CR achieved MRD negativity**

Data cutoff: September 11, 2023. [a]del(17p), t(4;14), and/or t(14;16). [b]The efficacy-evaluable analysis set includes all patients who received conforming BMS-986393 cell product, had measurable disease at the last disease assessment prior to BMS-986393 infusion, and had ≥ 1 post-infusion disease response assessment. Responses were assessed per International Myeloma Working Group criteria. CR, complete response; CRR, complete response rate; DOR, duration of response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

1. Bal S, et al. ASH 2023. Abst 219.

Memorial Sloan Kettering Cancer Center

Summary

- BCMA CAR T-cell therapies reported updated data for use in earlier lines of relapse therapy[1,2]
  - KarMMa-3: randomized comparison demonstrated significantly longer and clinically meaningful improvement in PFS for ide-cel versus standard regimens in early-line relapse and triple-class exposed RRMM[1]
  - CARTITUDE-2: long-term follow-up suggests cilta-cel is effective as early as first relapse in patients who are
    LEN-refractory or progressed within 12 months of first-line therapy[2]

- Indirect comparisons using clinical trial and real-world data suggest cilta-cel may provide improved efficacy outcomes compared with ide-cel[3,4]

- Additional targets beyond BCMA (eg, anti-GPRC5D) are under investigation with promising results[5]

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; GPRC5D, G protein–coupled receptor class C group 5 member D; ide-cel, idecabtagene vicleucel; RRMM, relapsed/refractory multiple myeloma.

1. Rodriguez-Otero P, et al. ASH 2023. Abst 1028. 2. Hillengass J, et al. ASH 2023. Abst 1021. 3. Bar N, et al. ASH 2023. Abst 2141.
4. Gill S, et al. ASH 2023. Abst 4717. 5. Bal S, et al. ASH 2023. Abst 219.