Ciltacabtagene Autoleucel vs Standard of Care in Patients With Functional High-Risk Multiple Myeloma: CARTITUDE-4 Subgroup Analysis

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CARTITUDE-4 Subgroup Analysis: Key Points

- CARTITUDE-4 evaluated cilta-cel vs SOC (DPd or PVd) in patients with lenalidomide-refractory MM after 1–3 prior LOT
- Cilta-cel was recently approved for the treatment of adult patients with RRMM who have received at least 1 prior LOT, including a PI and an IMiD, and are refractory to lenalidomide[1]
- We present data from CARTITUDE-4 for patients who received 1 prior LOT including the subset who had functionally high-risk MM (PD ≤18 months after receiving ASCT or the start of initial frontline therapy in patients with no ASCT)

In this analysis, consistently improved PFS and depth of response was observed with cilta-cel vs SOC after 1 prior LOT including the subset of patients with a functionally high-risk MM status

ASCT, autologous stem cell transplant; cilta-cel, ciltacabtagene autoleucel; DPd, daratumumab, pomalidomide, and dexamethasone; IMiD, immunomodulatory drug; LOT, line of therapy; MM, multiple myeloma; PD, progressive disease; PFS, progression-free survival; PI, proteosome inhibitor; PVd, pomalidomide, bortezomib, and dexamethasone; RRMM, relapsed/refractory multiple myeloma; SOC, standard of care.

1. CARVYKTI® (ciltacabtagene autoleucel). Package insert. Horsham, PA: Janssen Biotech, Inc; 2024.

Introduction

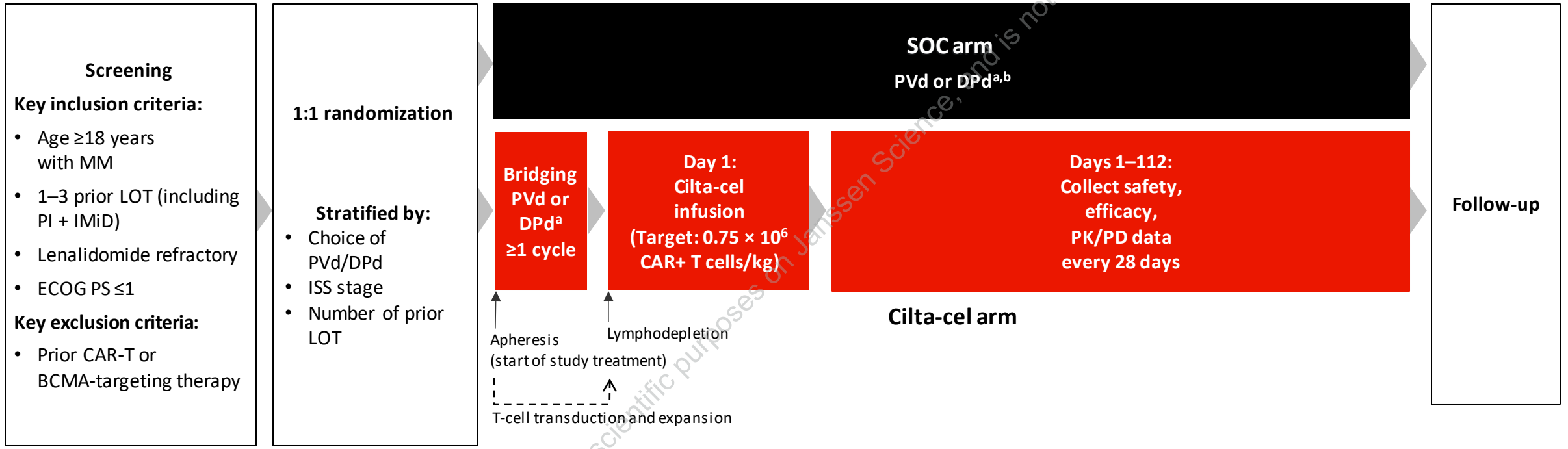
- Patients with relapse within 18 months of frontline therapy are considered to have functionally high-risk MM[1-3]
- There is a high unmet clinical need for effective and tolerable therapies in patients with functionally high-risk MM
- In the CARTITUDE-4 study, a single cilta-cel infusion improved PFS (weighted HR, 0.26; *P*<0.001), increased depth of response (≥CR, 73.1% vs 21.8%), and was associated with a manageable safety profile[4]

Objective: To report outcomes from a post hoc subgroup analysis of CARTITUDE-4 in patients who received 1 prior LOT, including the subset who had functionally high-risk MM

cilta-cel, ciltacabtagene autoleucel; CR, complete response; HR, hazard ratio; LOT, line of therapy; MM, multiple myeloma; PFS, progression-free survival.

1. Costa L, et al. *J Natl Compr Canc Netw* 2020;18:1730-7. 2. D'Agostino M, et al. *Clin Cancer Res* 2020;26:4832-41. 3. Majithia N, et al. *Leukemia* 2016;30:2208-13. 4. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47.

CARTITUDE-4 Study Design



Primary endpoint

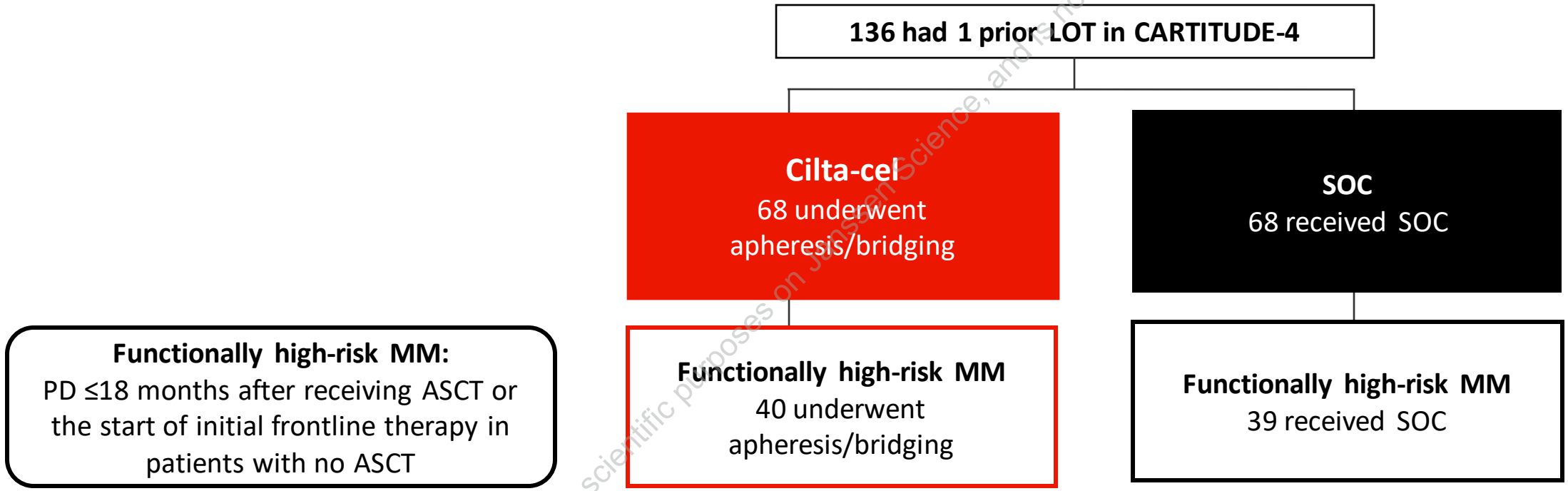
- PFS[1,c]

Secondary endpoints

- Efficacy: ≥CR,[1,2] ORR,[1,2] MRD negativity, OS
- Incidence and severity of AEs,[d] including CRS and ICANS[3,e]
- Patient-reported outcomes

[a]Physician's choice. [b]Administered until disease progression. [c]Time from randomization to disease progression/death. [d]Assessed per CTCAE version 5.0. [e]Graded per ASTCT criteria. AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ICANS, immune effector cell–associated neurotoxicity syndrome; IMiD, immunomodulatory drug; ISS, International Staging System; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PVd, pomalidomide, bortezomib, and dexamethasone; SOC, standard of care. 1. Palumbo A, et al. *N Engl J Med* 2016;375:754-66. 2. Rajkumar SV, et al. *Blood* 2011; 117;4691-5. 3. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25:625-38.

CARTITUDE-4 Subgroup Analysis: Patient Population



- At the Nov 2022, data cut-off date, the median follow-up was 15.9 months (range, 0.1–27.3)

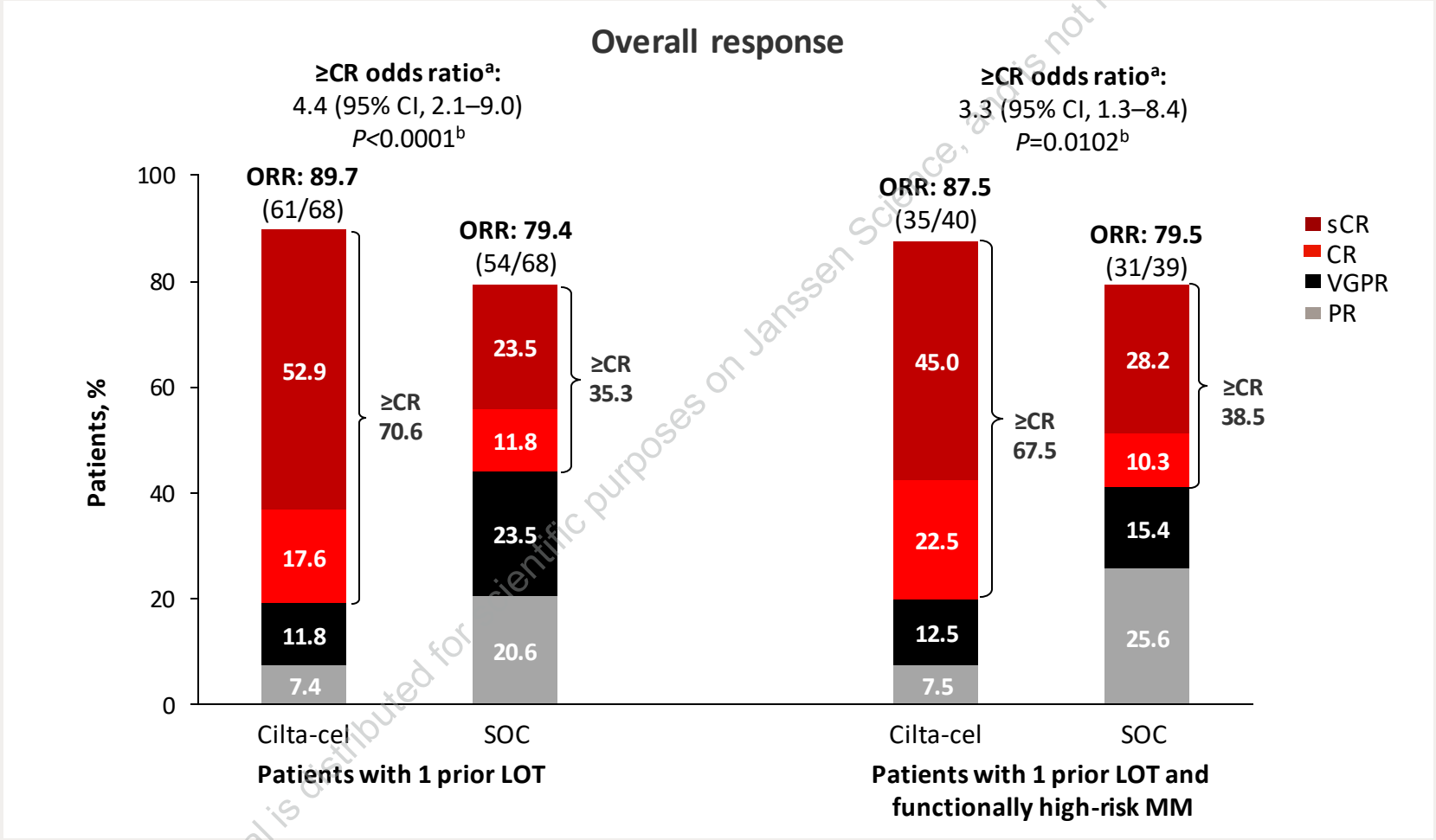
At the November 2022, data cut-off date, median follow-up was 15.9 months (range, 0.1–27.3). Among 68 patients who received 1 prior LOT in the cilta-cel arm, 60 received cilta-cel as study treatment, 5 received cilta-cel as subsequent therapy, and 3 never received cilta-cel. Among 40 patients who received 1 prior LOT and functionally high-risk MM in the cilta-cel arm, 35 received cilta-cel as study treatment. Study treatment includes any portion of the following sequence: apheresis, bridging, lymphodepletion, and cilta-cel.
ASCT, autologous stem cell transplant; cilta-cel, ciltacabtagene autoleucel; LOT, line of therapy; MM, multiple myeloma; PD, progressive disease; SOC, standard of care.

CARTITUDE-4 Subgroup Analysis:
Baseline Disease Characteristics Were Generally Balanced Between Treatment Arms in Patients With 1 Prior LOT Regardless of Functionally High-Risk MM Status

Baseline characteristic	Patients with 1 prior LOT		Patients with 1 prior LOT and functionally high-risk MM	
	Cilta-cel (n=68)	SOC (n=68)	Cilta-cel (n=40)	SOC (n=39)
Age, median (range), years	60.5 (27–78)	60.0 (35–78)	60.0 (27–71)	60.0 (40–78)
Male, n (%)	36 (52.9)	42 (61.8)	18 (45.0)	27 (69.2)
ISS stage II/III,[a] n (%)	20 (29.4)	22 (32.4)	12 (30.0)	14 (35.9)
Prior ASCT, n (%)	56 (82.4)	60 (88.2)	33 (82.5)	33 (84.6)
Prior anti-CD38 antibody exposure,[b] n (%)	2 (2.9)	3 (4.4)	2 (5.0)	1 (2.6)
High-risk cytogenetics,[c] n (%)	39 (57.4)	45 (66.2)	22 (55.0)	27 (69.2)
del17p	14 (20.6)	15 (22.1)	9 (22.5)	9 (23.1)
t(4;14)	13 (19.1)	10 (14.7)	8 (20.0)	6 (15.4)
t(14;16)	1 (1.5)	3 (4.4)	0	2 (5.1)
Gain/amp(1q)	34 (50.0)	38 (55.9)	20 (50.0)	23 (59.0)
With ≥2 high-risk abnormalities	20 (29.4)	20 (29.4)	13 (32.5)	12 (30.8)
High tumor burden,[c] n (%)	9 (13.2)	8 (11.8)	5 (12.5)	4 (10.3)
Soft tissue plasmacytoma,[d] n (%)	12 (17.6)	7 (10.3)	6 (15.0)	4 (10.3)

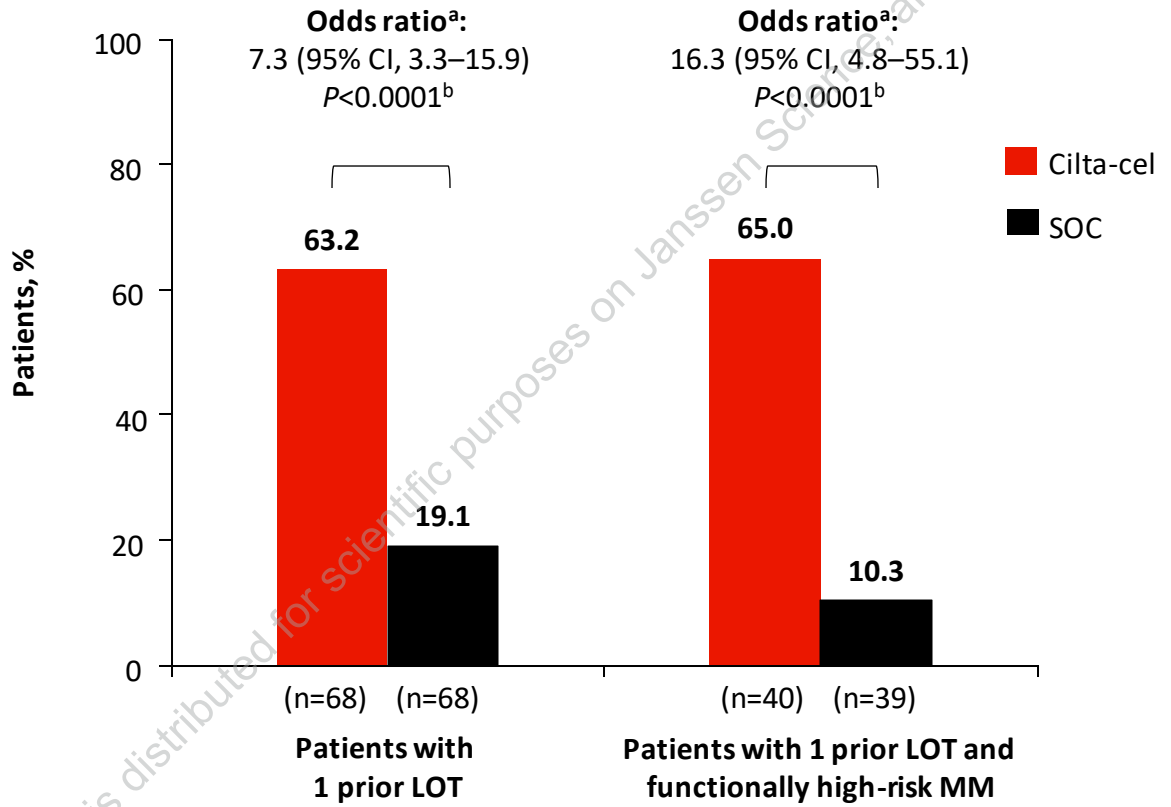
[a]Based on serum β_2-microglobulin and albumin. [b]Per study design, all patients had also received a proteosome inhibitor and immunomodulatory drug, ie, those with anti-CD38 antibody exposure were triple-class exposed. [c]High-risk cytogenetics was defined as any of the following 4 cytogenetic features abnormal: del17p, t(14;16), t(4;14), or gain/amp(1q). [d]High tumor burden defined as meeting any of the following criteria at baseline: ≥80% bone marrow plasma cells, ≥5 g/dL serum M protein level, or ≥5000 mg/L serum free light chain. [e]Soft tissue plasmacytomas include extramedullary and bone-based plasmacytomas with a measurable soft tissue component.
ASCT, autologous stem cell transplant; cilta-cel, ciltacabtagene autoleucel; ISS, International Staging System; LOT, line of therapy; MM, multiple myeloma; SOC, standard of care.

CARTITUDE-4 Subgroup Analysis: Consistently Deeper Responses Achieved With Cilta-cel vs SOC in Patients With 1 Prior LOT Regardless of Functionally High-Risk MM Status



Treatment response was assessed by a validated computerized algorithm, based on International Myeloma Working Group consensus criteria. ORR was defined as the proportion of patients who achieve a PR or better.
[a]Mantel-Haenszel estimate of the common odds ratio for unstratified tables is used. [b]*P* value from the Cochran-Mantel-Haenszel chi-squared test.
cilta-cel, ciltacabtagene autoleucel; CR, complete response; LOT, line of therapy; MM, multiple myeloma; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SOC, standard of care; VGPR, very good partial response.

CARTITUDE-4 Subgroup Analysis: Consistently Higher MRD Negativity Rates With Cilta-cel vs SOC in Patients With 1 Prior LOT Regardless of Functionally High-Risk MM Status



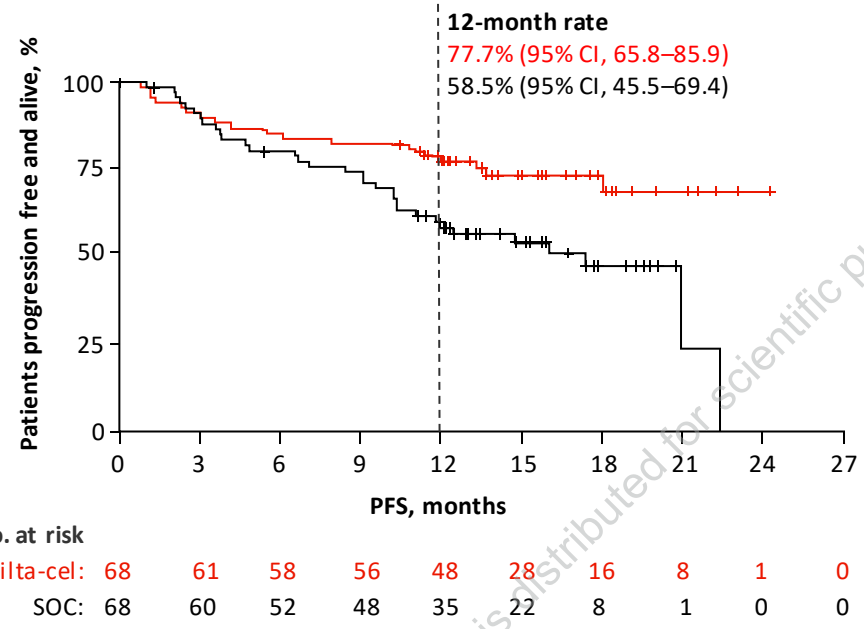
MRD negativity (10^{-5} threshold) was based on next-generation sequencing and postrandomization assessment. Overall rate reflects patients with MRD negativity by bone marrow aspirate at any time after the randomization date and before PD or subsequent antimyeloma treatment. Overall MRD negativity assessed in the ITT population.

[a]Mantel-Haenszel estimate of the common odds ratio for unstratified tables is used. [b]*P* value from Fisher's exact test.

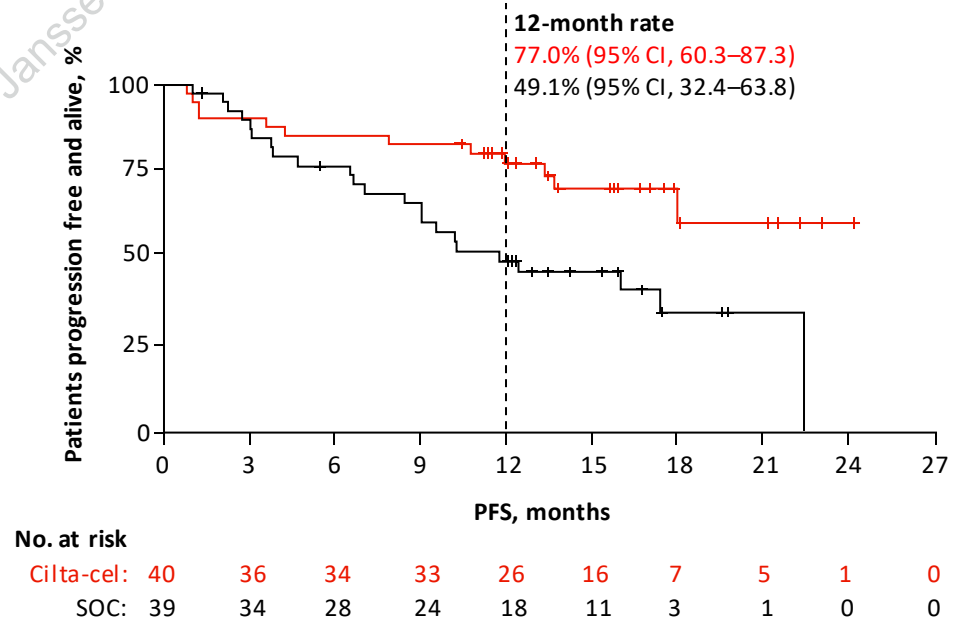
cilta-cel, ciltacabtagene autoleucel; ITT, intent to treat; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; PD, progressive disease; SOC, standard of care.

CARTITUDE-4 Subgroup Analysis: Consistently Improved PFS Observed With Cilta-cel vs SOC in Patients With 1 Prior LOT Regardless of Functionally High-Risk MM Status

	Patients with 1 prior LOT	
	Cilta-cel (n=68)	SOC (n=68)
Median PFS (95% CI), months[a]	NR (NE–NE)	17.41 (11.10–NE)
HR (95% CI); *P* value[b,c]	0.35 (0.19–0.66); 0.0007	



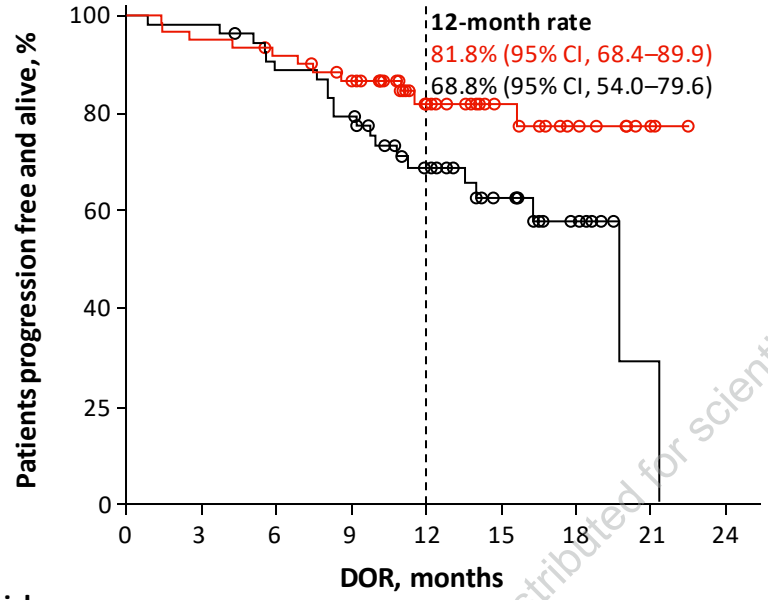
	Patients with 1 prior LOT and functionally high-risk MM	
	Cilta-cel (n=40)	SOC (n=39)
Median PFS (95% CI), months[a]	NR (18.00–NE)	11.79 (8.44–NE)
HR (95% CI); *P* value[b,c]	0.27 (0.12–0.60); 0.0006	



PFS was estimated by the Kaplan-Meier method. A stratified constant piecewise weighted log-rank test was used to compare the study groups because both groups received the same treatments during the bridging period.
[a]Assessed using a validated computerized algorithm. [b]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred >8 weeks after randomization. [c]*P* value based on the constant piecewise weighted log-rank test, where the weight equals 0 in the log-rank statistic for the first 8 weeks after randomization and 1 afterwards.
cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; LOT, line of therapy; MM, multiple myeloma; NE, not estimable; NR, not reached; PFS, progression-free survival; SOC, standard of care.

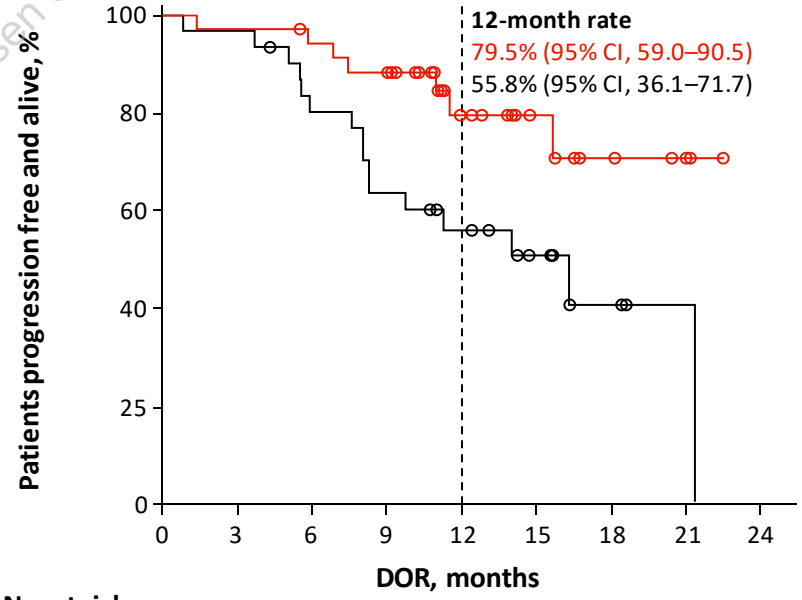
CARTITUDE-4 Subgroup Analysis: Consistently Longer DOR Achieved With Cilta-cel vs SOC in Patients With 1 Prior LOT Regardless of Functionally High-Risk MM Status

	Patients with 1 prior LOT	
	Cilta-cel (n=68)	SOC (n=68)
Median DOR (95% CI), months[a,b]	NR (NE–NE)	19.81 (14.06–NE)



No. at risk									
Cilta-cel:	61	58	55	50	29	18	9	3	0
SOC:	54	53	47	42	27	16	7	1	0

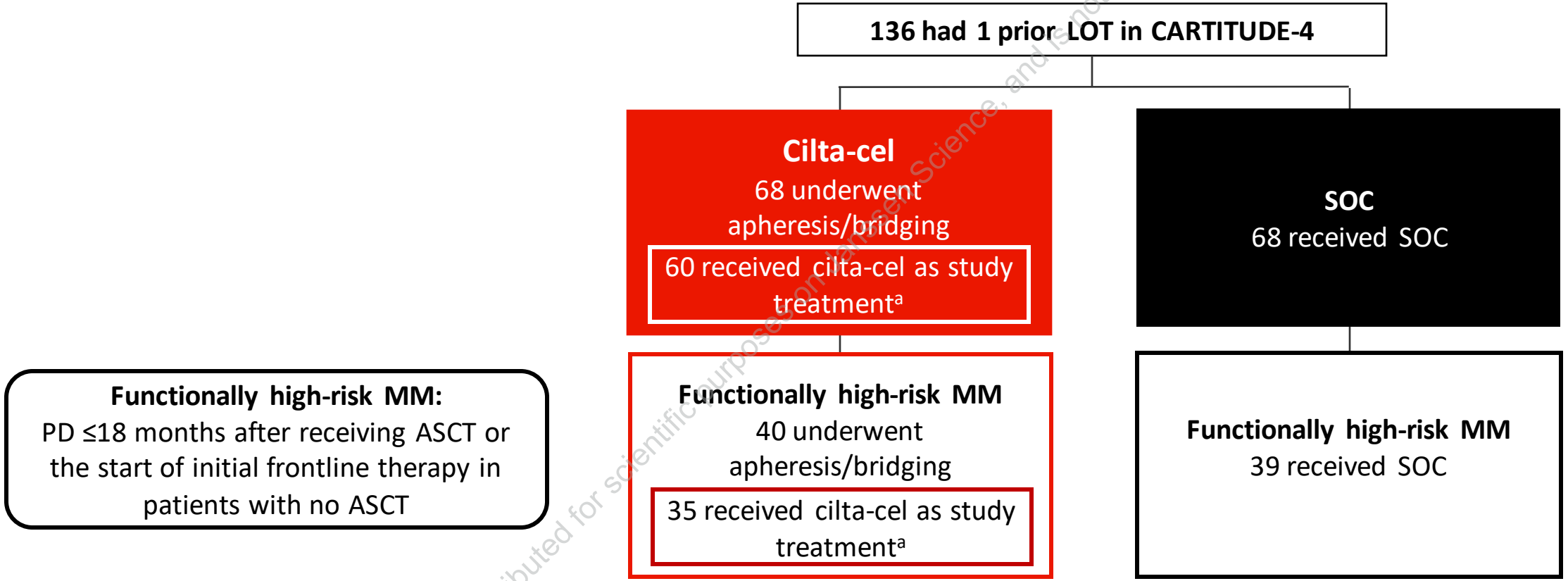
	Patients with 1 prior LOT and functionally high-risk MM	
	Cilta-cel (n=40)	SOC (n=39)
Median DOR (95% CI), months[a,b]	NR (15.70–NE)	16.36 (8.31–NE)



No. at risk									
Cilta-cel:	35	34	32	30	15	9	5	3	0
SOC:	31	30	24	19	13	8	3	1	0

[a]Assessed using a validated computerized algorithm. [b]Determined among responders.
cilta-cel, ciltacabtagene autoleucel; DOR, duration of response; LOT, line of therapy; MM, multiple myeloma; NE, not estimable; NR, not reached; SOC, standard of care.

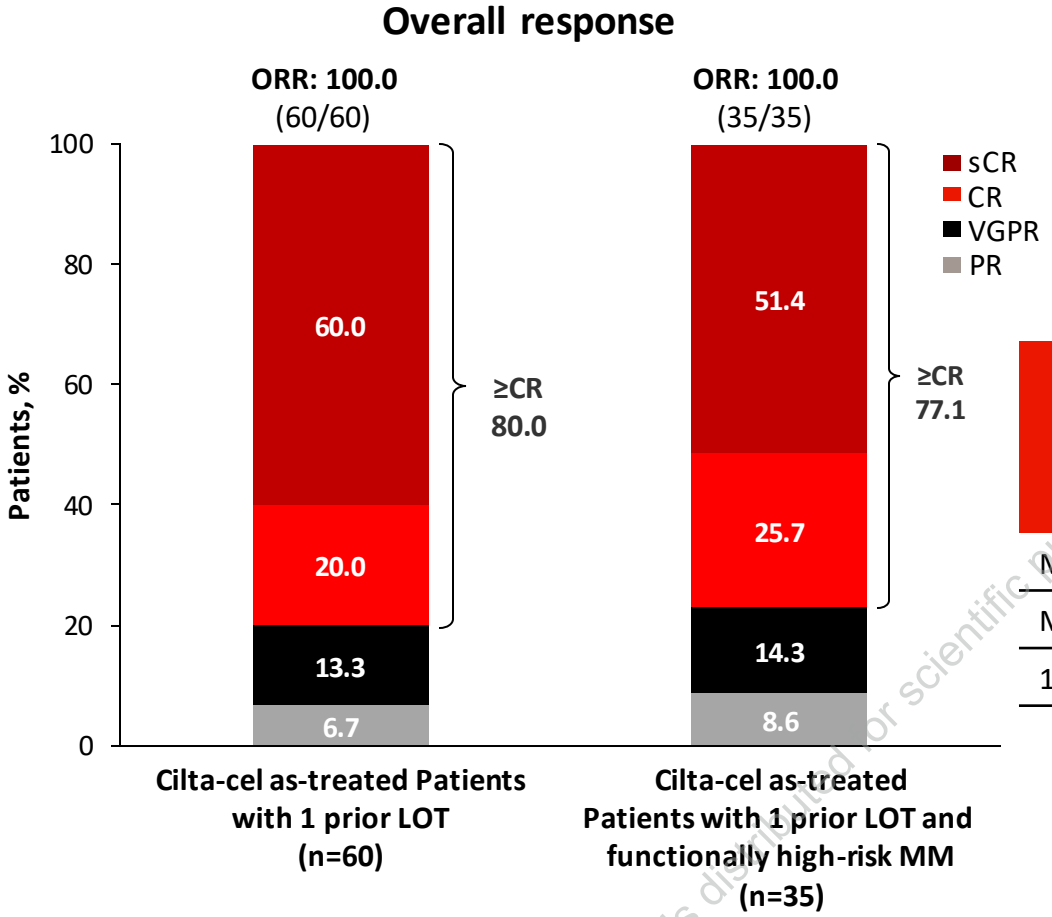
CARTITUDE-4 Subgroup Analysis: Patient Population



- At the Nov 2022, data cut-off date, the median follow-up was 15.9 months (range, 0.1–27.3)

[a]Study treatment includes any portion of the following sequence: apheresis, bridging, lymphodepletion, and cilta-cel. ASCT, autologous stem cell transplant; cilta-cel, ciltacabtagene autoleucel; ITT, intent to treat; LOT, line of therapy; MM, multiple myeloma; PD, progressive disease; SOC, standard of care.

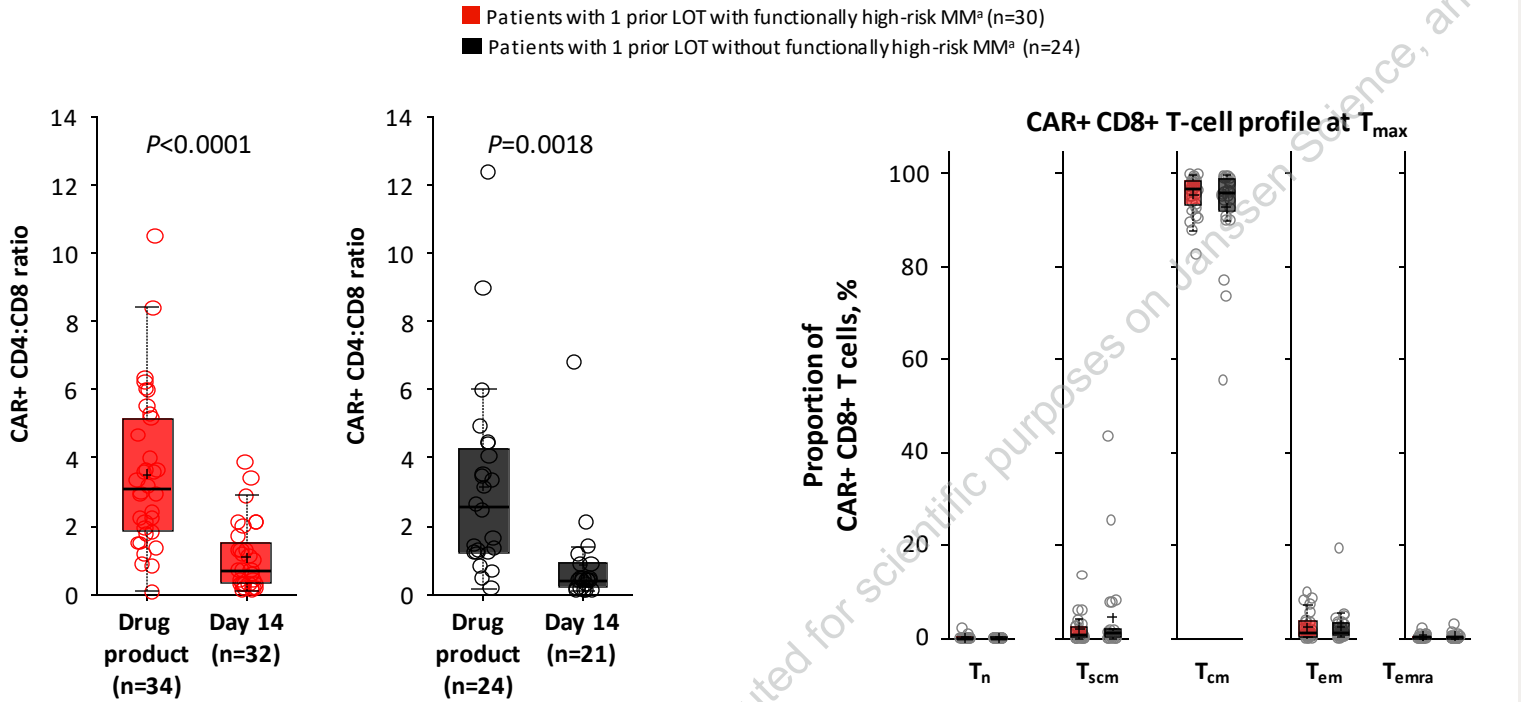
CARTITUDE-4 Subgroup Analysis:
Deep Responses and High PFS Rates in Patients Treated With Cilta-cel as Study Treatment in Those With 1 Prior LOT Regardless of Functionally High-Risk MM Status (As-Treated Population)



	Patients who received cilta-cel as study treatment	
	Patients with 1 prior LOT (n=60)	Patients with 1 prior LOT and functionally high-risk MM (n=35)
MRD negativity (10^{-5}), n (%)	43 (71.6)	26 (74.3)
Median PFS (95% CI), mo	NR (NE–NE)	NR (18.0–NE)
12-mo PFS (95% CI), mo	88.1 (76.6–94.1)	88.0 (70.9–95.3)

Treatment response was assessed by a validated computerized algorithm, based on International Myeloma Working Group consensus criteria. ORR was defined as the proportion of patients who achieve a PR or better.
MRD negativity (10^{-5} threshold) was based on next-generation sequencing and postrandomization assessment. Overall rate reflects patients with MRD negativity by bone marrow aspirate at any time after the randomization date and before PD or subsequent antimyeloma treatment. Overall MRD negativity assessed in the as-treated population.
cilta-cel, ciltacabtagene autoleucel; CR, complete response; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; NE, not estimable; NR, not reached; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; SOC, standard of care; VGPR, very good partial response.

CARTITUDE-4 Subgroup Analysis:
Preferential Expansion of CD8+ CAR+ T Cells and Dominant Central Memory Phenotype at Peak Expansion in Patients With 1 Prior LOT Who Did and Did Not Have Functionally High-Risk MM

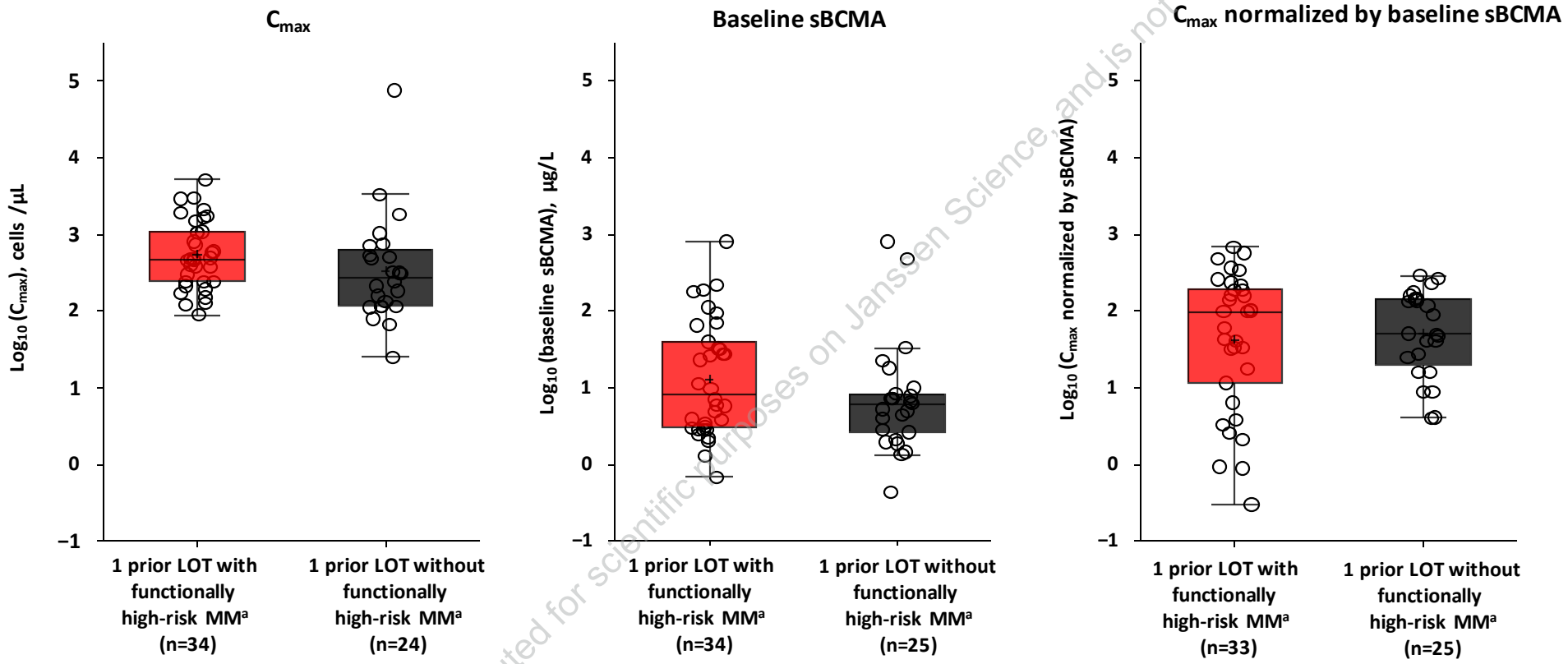


- CAR+ CD4+ T-cell profile at T_{max} also showed a dominant central memory phenotype in patients with 1 prior LOT regardless of functionally high-risk MM status
- Preferential CD8+ CAR+ T-cell expansion and dominant central memory phenotypes, which have been shown to be associated with longer PFS,[1] were comparable between patients with 1 prior LOT who did and did not have functionally high-risk MM

[A]n values are based on randomly assigned patients in the cilta-cel arm with available data on CAR+ T-cell characterization and CAR+ T-cell peak expansion.
CAR, chimeric antigen receptor; LOT, line of therapy; MM, multiple myeloma; PFS, progression-free survival; T_{cm}, central memory T cell; T_{em}, effector memory T cell; T_{emra}, terminally differentiated T cell; T_{max}, time of peak expansion; Tn, naive T cell; T_{scm}, T memory stem cell.

1. Montes de Oca R, et al. *Blood* 2023;142(supplement 1):2099.

CARTITUDE-4 Subgroup Analysis: Comparable CAR-T Peak Expansion and Baseline sBCMA in Patients With 1 Prior LOT Who Did and Did Not Have Functionally High-Risk MM



- Cilta-cel peak expansion, which has been shown to be associated with longer PFS when normalized to sBCMA, to reflect effector to target ratio,[1] was comparable between patients with 1 prior LOT who did and did not have functionally high-risk MM

[a]n values are based on randomly assigned patients in the cilta-cel arm with available data on CAR+ T-cell characterization and CAR+ T-cell peak expansion.
CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; C_{max}, maximum observed concentration of CAR+ T cells in blood; LOT, line of therapy; MM, multiple myeloma; sBCMA, soluble B-cell maturation antigen.
1. Montes de Oca R, et al. *Blood* 2023;142(supplement 1):2099.

CARTITUDE-4 Subgroup Analysis: Frequency of AEs Was Similar Between Treatment Arms in Patients With 1 Prior LOT Regardless of Functionally High-Risk MM Status

Select AEs, n (%)	Patients with 1 prior LOT		Patients with 1 prior LOT and functionally high-risk MM	
	Cilta-cel (n=68)	SOC (n=68)	Cilta-cel (n=40)	SOC (n=39)
Grade ≥3 TEAEs, n (%)	65 (95.6)	65 (95.6)	40 (100.0)	38 (97.4)
Serious TEAEs, n (%)	26 (38.2)	24 (35.3)	16.0 (40.0)	13 (33.3)

- **Deaths**
  - Among patients with 1 prior LOT, 11 each in the cilta-cel arm and SOC arm died; of these patients, 7 in the cilta-cel arm and 9 in the SOC arm died and had functionally high-risk MM
  - Of the 7 deaths in the cilta-cel arm among patients with 1 prior LOT and functionally high-risk MM, 2 did not receive cilta-cel as study treatment and 3 received cilta-cel as subsequent therapy

AE, adverse event; cilta-cel, ciltacabtagene autoleucel; LOT, line of therapy; MM, multiple myeloma; SOC, standard of care; TEAE, treatment-emergent adverse event.

CARTITUDE-4 Subgroup Analysis:
CAR-T Cell–Associated AEs Were Consistent With the Known Safety Profile of Cilta-cel in Patients With 1 Prior LOT Regardless of Functionally High-Risk MM Status

AEs of special interest,[a] n (%)	Patients with 1 prior LOT		Patients with 1 prior LOT and functionally high-risk MM	
	Cilta-cel (n=68)		Cilta-cel (n=40)	
	All	Grade 3 or 4	All	Grade 3 or 4
CRS	44 (64.7)	1 (1.5)	25 (62.5)	0
ICANS	2 (2.9)	0	2 (5.0)	0
Cranial nerve palsy	6 (8.8)	2 (2.9)	3 (7.5)	0
Movement and neurocognitive TEAEs	1 (1.5)	0	0	0
Peripheral neuropathy	2 (2.9)	0	2 (5.0)	0

- AEs of special interest were generally low grade in severity
- No grade 4 events occurred
- Second primary malignancies occurred in 3 patients in the cilta-cel arm, and 2 patients in the SOC arm among those with 1 prior LOT; all occurred in patients with functionally high-risk MM
  - 1 patient in the cilta-cel arm had peripheral T-cell lymphoma unspecified[1]

CRS and ICANS were assessed per ASTCT criteria. AEs were graded per NCI-CTCAE criteria version 5.0.
[a]AEs of special interest were evaluated in all patients receiving cilta-cel as second-line treatment (n=68) and in those with functionally high-risk MM (n=40).
AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; LOT, line of therapy; MM, multiple myeloma; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
1. Harrison SJ, et al. *Blood* 2023;142(suppl 1):6939.

Conclusions

- A single infusion of cilta-cel reduced the risk of disease progression or death vs SOC by 65% (HR, 0.35; *P*=0.0007) in patients who had received 1 prior LOT and by 73% (HR, 0.27; *P*=0.0006) in patients who had received 1 prior LOT and had functionally high-risk MM
- Consistently deeper and more durable responses and a higher frequency of MRD negativity was observed with cilta-cel vs SOC in patients with 1 prior LOT and those with 1 prior LOT and functionally high-risk MM
- CRS and neurotoxicity with cilta-cel were generally similar in patients with 1 prior LOT and those with 1 prior LOT and functionally high-risk MM, and consistent with the known mechanism of action of CAR-T cell therapy

A single cilta-cel infusion substantially improved PFS and depth of response vs SOC regardless of functionally high-risk MM status in lenalidomide-refractory patients with MM after 1 prior LOT, supporting its use in patients who relapse early after initial therapy

CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; HR, hazard ratio; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; PFS, progression-free survival; SOC, standard of care.