Efficacy and Safety in Patients With Lenalidomide-Refractory Multiple Myeloma and 1–3 Prior Lines Who Received a Single Infusion of Ciltacabtagene Autoleucel as Study Treatment in the Phase 3 CARTITUDE-4 Trial

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Disclosure of Conflicts of Interest

HE has served in a consulting/advisory role for Amgen, BMS/Celgene, GSK, Janssen, and Sanofi; and has received honoraria and research funding from Amgen, BMS/Celgene, GSK, Janssen, and Sanofi. **MHS** has served on speakers' bureaus for Antengene, BMS, Gilead, and Janssen; and has served on the board of directors/advisory committees for Janssen and Pfizer. **PC** has served in a consulting/advisory/lecturer role and received honoraria from AbbVie, ADC Therapeutics (DSMB), Amgen, Celgene, Daiichi Sankyo, Gilead/Kite, GSK, Incyte, Kyowa Kirin, Nerviano Medical Science, Janssen, Novartis, Pfizer, Roche, Sanofi, SOBI, and Takeda; has received honoraria from BeiGene; and has received travel and accommodations from AbbVie, Amgen, BMS, Celgene, Gilead/Kite, Janssen, Novartis, Roche, and Takeda. **DP** has received honoraria from BMS Celgene, Gilead, and Jazz. **HE** has served in a consulting/advisory role and has received honoraria, travel, and accommodations from Amgen, BMS/Celgene, GSK, Janssen, Novartis, Sanofi, and Takeda. **BD** has served in speakers' bureaus/consulting roles and has received honoraria from Arcellx, Genentech, GSK, Janssen, Karyopharm, Sanofi, and Pfizer. **LK** has served in a consulting role for Amgen, Celgene, GSK, Janssen, and Takeda; and has received honoraria from AbbVie, Amgen, Celgene, Janssen, Sanofi, and Takeda. **SM** has served on the board of directors/advisory committees for AbbVie, Amgen, Celgene/BMS, GSK, Janssen, Novartis, Pfizer, Regeneron, Roche, Sanofi, and Takeda. **SI** has served in a consulting role for AbbVie, BMS, GSK, Janssen, Novartis, Otsuka, Pfizer, Regeneron, Sanofi, and Takeda; has received honoraria from BMS, Janssen, Ono, Sanofi, and Takeda; and has received research funding from AbbVie, Alexion, Amgen, BMS, Chugai, Daiichi Sankyo, GSK, Janssen, Novartis, Ono, Otsuka, Pfizer, Sanofi, Shinogi, and Takeda. **SG** has served in speakers' bureaus/consulting roles and has received honoraria from AbbVie, Amgen, AstraZeneca, Gilead, Janssen, Novartis, Pfizer, and Roche; and has served in speakers' bureaus/received honoraria from Angelini, BMS, Servier, Swixx, and Zentiva. **SJH** has served in a consulting role for AbbVie, Amgen, Celgene/BMS, Eusa, F. Hoffmann-La Roche Ltd/Genentech, GSK, Haemalogix, Janssen Cilag, Novartis, and Terumo BCT; has received research funding from Celgene/BMS, GSK, Haemalogix, and Janssen Cilag; has served on speakers' bureaus for AbbVie, Amgen, Celgene/BMS, Eusa, F. Hoffmann-La Roche Ltd/Genentech, GSK, Janssen Cilag, and Novartis; and has served on the board of directors/advisory committees for Haemalogix. **BL** has served in a consulting role for AbbVie, BMS, GSK, and Janssen. **AMK** has received honoraria from Janssen; research funding from BMS and Secura Bio; has served in a consulting role for Secura Bio; and has served on speakers' bureaus for Amgen and Sanofi. **JMS** is employed by and holds patents/royalties from Janssen. **CCJ** was an employee/holds stock and other ownership interests in Janssen Research & Development. **T-mY**, **AB**, **NL**, **AS**, **KL**, and **TR** are employed by/have stock and other ownership interests in Janssen. **WD**, **CL**, **DC**, **JG**, and **MZ** are employed by Janssen. **NP**, **EF**, and **OCF** are employed by/have stock and other ownership interests in Legend Biotech. **MK** and **DG** are employed by Legend Biotech. **JS-M** has received honoraria and has served in a consulting/advisory role for AbbVie, Amgen, BMS, Celgene, GSK, Haemalogix, Karyopharm, MSD, Pfizer, Roche, Regeneron, Sanofi, SecuraBio, and Takeda; and has received honoraria/served in a consulting role for Janssen and Novartis. **KY** has no disclosures to report.

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Introduction: CARTITUDE-4

- Cilta-cel is a dual-binding, BCMA-directed CAR-T cell therapy approved for the treatment of RRMM after ≥4 and ≥3 prior LOT in the US and Europe, respectively[1,2]
- The phase 3 CARTITUDE-4 study (NCT04181827) is comparing cilta-cel with SOC in patients with lenalidomide-refractory MM after 1–3 prior LOT[3]
- At the 15.9-month median follow-up in the ITT population, a single infusion of cilta-cel vs SOC:
  - Significantly improved PFS (HR, 0.26; *P*<0.001)[3]
  - Resulted in a higher ORR (84.6% vs 67.3%) and a higher rate of ≥CR (73.1% vs 21.8%)[3]
- The ITT analysis included all patients who were randomized; in the cilta-cel arm, study treatment included treatments prior to infusion, ie, apheresis, bridging therapy, and lymphodepletion
- To describe outcomes in the patients who received cilta-cel, we report the efficacy and safety in patients who received cilta-cel as study treatment in CARTITUDE-4

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; HR, hazard ratio; ITT, intent-to-treat; LOT, line of therapy; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; SOC, standard of care; US, United States.

1. CARVYKTI® (ciltacabtagene autoleucel). Prescribing information. Janssen Biotech, Inc.; 2022. 2. CARVYKTI® (ciltacabtagene autoleucel). European Medicines Agency. Orphan maintenance assessment report. June 7, 2022. Accessed September 19, 2023. https://www.ema.europa.eu/en/documents/orphan-maintenance-report/carvykti-orphan-maintenance-assessment-report-initial-authorization_en.pdf. 3. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47.

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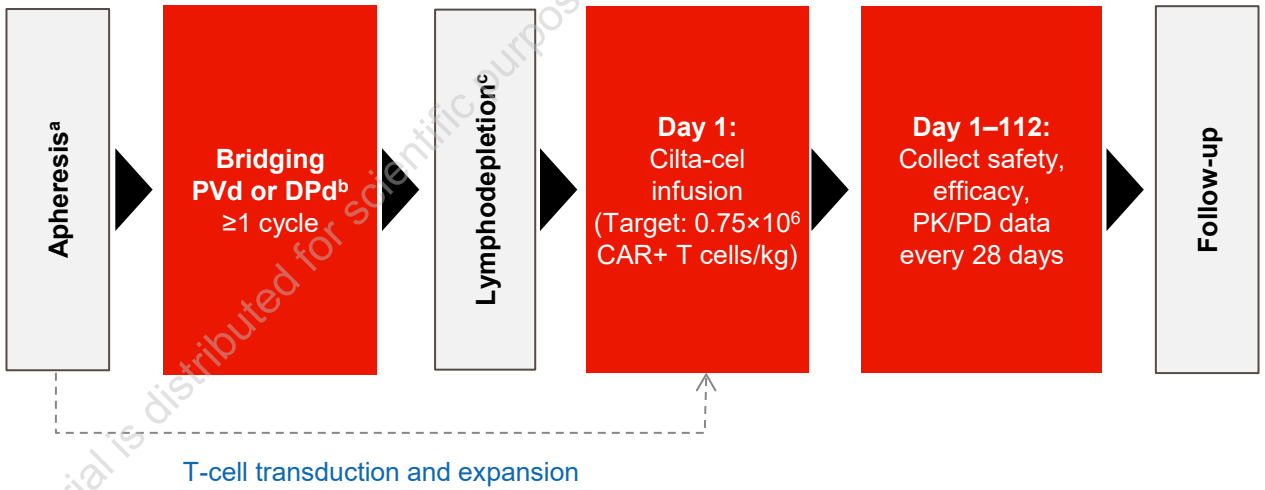
CARTITUDE-4 Cilta-cel Arm Patients and Study Treatments

- Key eligibility criteria:
  - Lenalidomide-refractory RRMM
  - 1–3 prior LOT, including a PI and IMiD
  - ECOG PS ≤1
  - No prior CAR-T or BCMA-directed therapy

CARTITUDE-4 study treatments (cilta-cel as-treated population)



[a]Start of study treatment. [b]Physicians' choice. [c]Cyclophosphamide 300 mg/m^2 plus fludarabine 30 mg/m^2 daily for 3 days.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; LOT, line of therapy; PD, pharmacodynamics; PK, pharmacokinetics; PI, proteasome inhibitor; PVd, pomalidomide, bortezomib, and dexamethasone; RRMM, relapsed/refractory multiple myeloma.

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CARTITUDE-4 Cilta-cel Arm Assessments

- Treatment responses and disease progression were assessed per IMWG criteria using a validated computer algorithm[1]
- MRD negativity (10^{-5} threshold) was assessed by next-generation sequencing starting at day 56 post infusion
- Post-infusion PFS and OS endpoints were evaluated using the Kaplan-Meier method
- CRS and ICANS were assessed per ASTCT criteria[2]
- Individual symptoms of CRS and ICANS were graded per NCI-CTCAE[3]
- Other AEs were graded per NCI-CTCAE criteria

AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity; IMWG, International Myeloma Working Group; MRD, minimal residual disease; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; PFS, progression-free survival.

1. Palumbo A, et al. *N Engl J Med* 2016;375:754-66. 2. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25:625-38. 3. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). Version 5.0; 2017.

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CARTITUDE-4 Cilta-cel Arm Population and Baseline Characteristics

- 208 patients were randomized to the cilta-cel arm (ITT) and 176 received cilta-cel as study treatment (as-treated population)[1]
- As of November 1, 2022, median follow-up from randomization in the as-treated population was 16 months (range, 3.8–27.3)
- Median time from apheresis to cilta-cel infusion was 79 days (range, 45–246)[1]
- 21.6% of patients in the as-treated population received 1 bridging therapy cycle, 58.5% received 2 cycles, and 19.9% received 3–6 cycles

Characteristic	As-treated population (n=176)	ITT population (n=208)
Age, median (range), years	61 (27–78)	61.5 (27–78)
Male, n (%)	101 (57.4)	116 (55.8)
Race, n (%)		
Asian	15 (8.5)	16 (7.7)
Black or African American	6 (3.4)	6 (2.9)
White	136 (77.3)	157 (75.5)
Not reported	19 (10.8)	28 (13.5)
ECOG PS, n (%)		
0	103 (58.5)	114 (54.8)
1	73 (41.5)	93 (44.7)
ISS stage, n (%)		
I	121 (68.8)	136 (65.4)
II	45 (25.6)	60 (28.8)
III	10 (5.7)	12 (5.8)
Bone marrow plasma cells ≥60%,[a] n (%)	33 (18.9)	42 (20.4)
Presence of soft tissue plasmacytomas,[b] n (%)	30 (17.0)	44 (21.2)
Number of prior LOT, n (%)		
1	60 (34.1)	68 (32.7)
2	66 (37.5)	83 (39.9)
3	50 (28.4)	57 (27.4)
High-risk cytogenetics,[c] n (%)	105 (60.0)[d]	123 (59.4)[e]
Triple-class refractory,[f] n (%)	20 (11.4)	30 (14.4)

[a]Maximum value from bone marrow biopsy and bone marrow aspirate selected if both results are available. [b]Including extramedullary and bone-based plasmacytomas with measurable soft tissue component. [c]Cytogenetics data for the as-treated and ITT populations were available for 175 and 207 patients, respectively. [d]39 (22.3%) patients with del(17p); 23 (13.1%) with t(4;14), 3 (1.7%) with t(14;16), 77 (44.0%) with gain/amp(1q), 34 (19.4%) with ≥2 high-risk abnormalities, and 11 (6.3%) with unknown cytogenetic risk. [e]49 (23.7%) patients with del(17p), 30 (14.5%) with t(4;14), 3 (1.4%) with t(14;16), 89 (43.0%) with gain/amp(1q), 43 (20.8%) with ≥2 high-risk abnormalities, and 15 (7.2%) with unknown cytogenetic risk. [f]Including 1 PI, 1 IMiD, and 1 anti-CD38 monoclonal antibody. ECOG PS, Eastern Cooperative Oncology Group performance status; LOT, line of therapy; ISS, International Staging System; ITT, intent-to-treat. 1. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47.

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Efficacy in the Cilta-cel As-Treated Population

- ORR was 99.4% (≥CR, 86.4%)
- Responses deepened over time
- Median DOR and median PFS were not reached
- MRD-evaluable patients (n=144) with MRD-negative ≥CR had improved PFS from infusion vs those who remained MRD positive and/or had <CR (*P*=0.0196)

	n=176
ORR after randomization, n (%)	175 (99.4)
≥CR, %	152 (86.4)
Time to first response after randomization, mo (range)	2.1 (0.9–11.1)
PFS rate 12 mo after infusion, % (95% CI)	84.9 (78.2–89.7)
OS rate 12 mo after infusion, % (95% CI)	91.9 (86.6–95.1)
MRD negative at 10^{-5} threshold after infusion, n (%)	126 (71.6)
In MRD evaluable,[a] n/N (%)	126/144 (87.5)
MRD-negative ≥CR, n/N (%)	111/144 (77.1)

[a]Patients with a bone marrow sample evaluable for MRD at 10^{-5} threshold.
cilta-cel, ciltacabtagene autoleucel; CR, complete response, DOR, duration of response, mo, month(s); MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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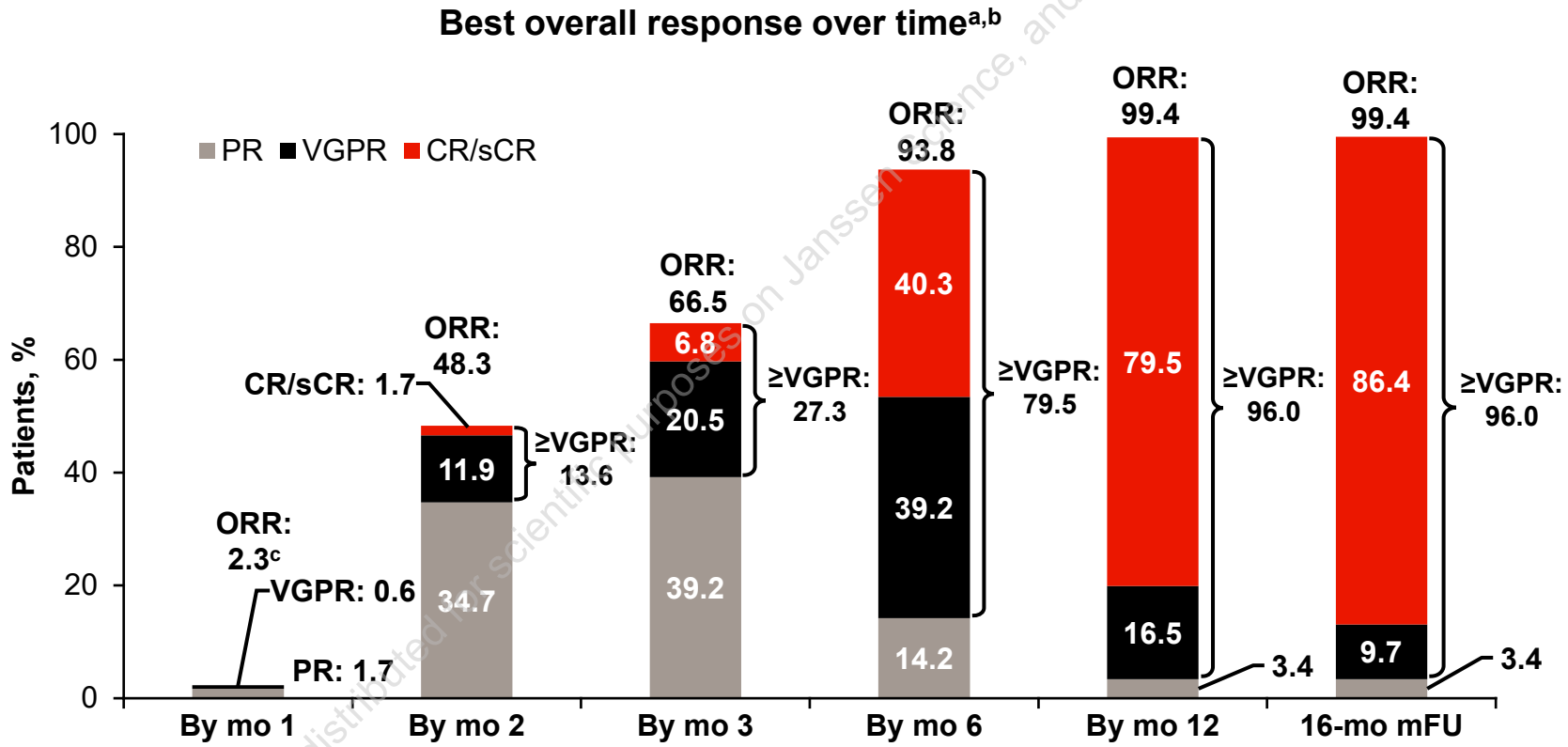
Responses Deepened Over Time in the Cilta-cel As-Treated Population



[a]Best overall response by each time point post randomization and at CCO in the as-treated population (n=176). [b]Sum of best response rates may not be equal to ORR due to rounding. [c]No patients had ≥CR by month 1 post randomization. CCO, clinical cut-off; cilta-cel, ciltacabtagene autoleucel; CR, complete response; mFU, median follow-up; mo, month; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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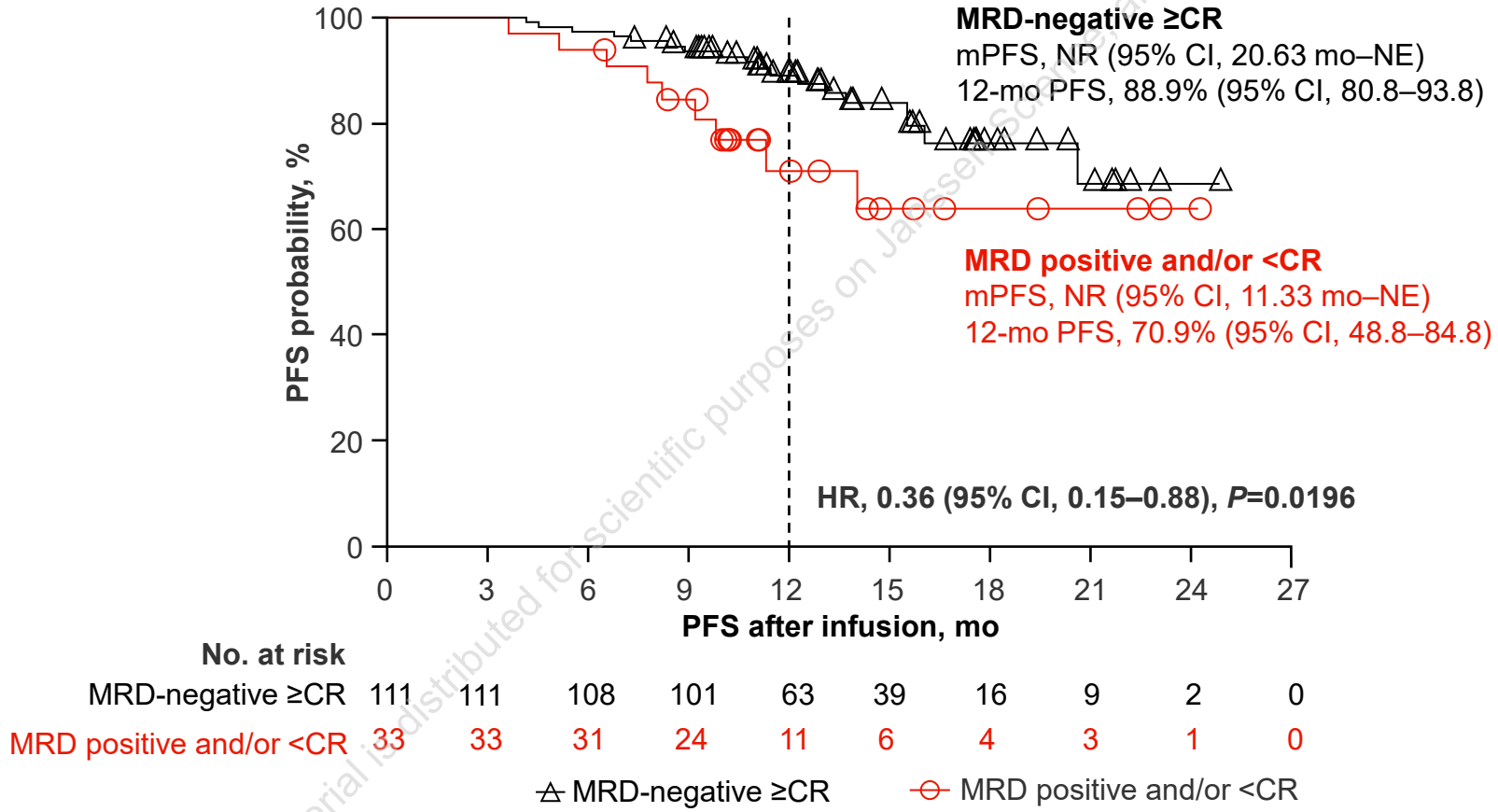
MRD-Negative ≥CR was Associated With Improved PFS

PFS after infusion in patients by achievement of MRD negativity and best response in MRD-evaluable patients



PFS from infusion in MRD-evaluable patients in the cilta-cel as-treated population.
cilta-cel, ciltacabtagene autoleucel; CR, complete response; HR, hazard ratio; mo, month(s); mPFS, median progression-free survival; MRD, minimal residual disease, NE, not estimable; NR, not reached; PFS, progression-free survival.

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Safety in the Cilta-cel As-Treated Population

- CRS occurred in 76.1% of patients and were mostly grade 1/2; all cases resolved[1,2]
- CAR-T cell neurotoxicity occurred in 20.5% of patients; none were fatal[1,2]
  - ICANS occurred in 4.5% of patients; all were grade 1/2 and resolved[1,2]
  - Cranial nerve palsy (9.1%), peripheral neuropathy (2.8%), and MNTs (0.6%) were mostly grade 1/2[1,2]
  - By the CCO, all but 2 of the cranial nerve palsy and 2 of the peripheral neuropathy cases had resolved; the MNT case (grade 1) had not yet resolved by the CCO[3,4]

AE, n (%)	As-treated population (n=176)			
	Any Grade	Grade 3/4	Median time to onset,[a] days	Median duration,[b] days
CRS	134 (76.1)	2 (1.1)	8	3
Neurotoxicity	36[c] (20.5)	5 (2.8)	–	–
ICANS	8 (4.5)	0[d]	10	2
Other[e]	30 (17.0)	4 (2.3)	–	–
Cranial nerve palsy	16 (9.1)[f]	2 (1.1)	21	77
Peripheral neuropathy	5 (2.8)	1 (0.6)	63	201
MNT	1 (0.6)	0	85	253[g]

[a]Time to onset from cilta-cel infusion. [b]Calculated regardless of resolution of event. [c]Several patients had both ICANS and ''other" neurotoxicity. [d]Grade 3 syncope reported as a symptom of grade 2 ICANS.
[e]Other neurotoxicities include AEs reported as CAR-T cell neurotoxicity that are not ICANS or associated symptoms. These included (but were not limited to) MNTs, cranial nerve palsy, and peripheral neuropathy.
[f]All cases involved cranial nerve VII; 2 cases involved a second cranial nerve (cranial nerves III and V; each n=1). [g]Ongoing at CCO; last known date alive is October 17, 2022 (day 337 post infusion) in this patient.
AE, adverse event; CAR, chimeric antigen receptor; CCO, clinical cut-off; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity; MNT, movement/neurocognitive treatment-emergent adverse event.

1. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47. 2. Dhakal B, et al. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA.

Conclusions

- The PFS rate of 85% at 12 months post infusion in patients who received a single cilta-cel infusion as study treatment compares favorably with the median PFS of 6 months in real-world patients with lenalidomide-refractory MM after 1–3 prior LOT who were treated with SOC regimens including, but not limited to, DPd[1]
- Cilta-cel rapidly led to treatment responses that deepened over time, resulting in a **99%** ORR (≥CR, **86%**) and a 72% MRD-negativity rate at the CCO
- The PFS rate at 12 months post infusion in patients who achieved MRD-negative ≥CR was 89%
- CARTITUDE-4 results, reinforced by longer-term outcomes in a similar patient population from CARTITUDE-2 Cohort A,[2] highlight the potential for prolonged disease control with cilta-cel as early as after first relapse

Rapid, deep responses and high 12-month PFS and OS rates of 85% and 92%, respectively, together with a manageable AE profile after a single cilta-cel infusion reinforce the potential of cilta-cel to be a new SOC for lenalidomide-refractory MM as early as after first relapse

AE, adverse event; cilta-cel, ciltacabtagene autoleucel; CCO, clinical cut-off; CR, complete response; DPd, daratumumab, pomalidomide, and dexamethasone; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

1. Dhakal B, et al. Presented at International Myeloma Society (IMS) Annual Meeting; August 25–27, 2022; Los Angeles, CA, USA. 2. Hillengass J, et al. Presented at the 65th American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023; San Diego, CA, USA.

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