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

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Key Takeaway

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

Conclusions

A single infusion of cilta-cel reduced the risk of disease progression or death by 65% in patients who received 1 prior LOT and by 73% in patients who received 1 prior LOT and had functionally high-risk MM (relapse ≤18 months of frontline therapy)

- 1 prior LOT: HR, 0.35 (95% CI, 0.19–0.66); *P*=0.0007
- 1 prior LOT and functionally high-risk MM: HR, 0.27 (95% CI, 0.12–0.60); *P*=0.0006

Consistently deeper and 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

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Acknowledgments

The authors, Janssen, and Legend Biotech USA Inc. thank the patients who participated in this study, the staff members at the study sites, the data and safety monitoring committee, and the staff members involved in data collection and analyses. This study was funded by Janssen Research & Development, LLC, and Legend Biotech USA Inc. The authors also thank Qingxuan Song, PhD (of Janssen Research & Development, Raritan, NJ, USA), for substantially contributing to data analysis, and Feng Wang, PhD (of Janssen Research & Development, Shanghai, China), for support with translational correlative analyses. Medical writing support was provided by Rebekah Dedrick, PhD, of Eloquent Scientific Solutions, and funded by Janssen Global Services, LLC.

Disclosures

KW has received honoraria, serves on a board of directors or advisory committee, and has received research funding for Adaptive Biotechnologies, Amgen, BMS, Celgene, GSK, Janssen, Karyopharm, Oncopeptides, Roche, Sanofi, and Takeda. **LJC** has received honoraria, serves on a board of directors or advisory committee, received research funding, or is on a speaker's bureau member for AbbVie, Adaptive Biotechnologies, Amgen, BMS, Caribou Biosciences, Celgene, Janssen, Karyopharm Therapeutics, Pfizer, and Sanofi. **NWCJvdD** has served in a consulting/advisory role for or has received research funding from AbbVie, Adaptive Biotechnologies, Amgen, Bayer, BMS, Celgene, Cellectis, Janssen, Novartis, Pfizer, Roche, Servier, and Takeda. **SS** has served in a consulting/advisory role for BMS/Celgene, Janssen, Magenta Therapeutics, Oncopeptides, and Sanofi; and has received research funding from Allogene Therapeutics, BMS/Celgene, Janssen, and Magenta Therapeutics. **YCC** has received honoraria, is a speaker's bureau member, has received research funding, or has received travel accommodation and expenses from AbbVie, BMS, GSK, Janssen, Roche, Sanofi, and Takeda. **DP** has received research funding from Atara Biotherapies, Janssen, Novartis, and Takeda. **CT** has received honoraria from and served in a consulting/advisory role for AbbVie, Amgen, BMS, GSK, Janssen, Novartis, Pfizer, and Sanofi; and has received research funding from GSK and Sanofi. **CFdL** has received honoraria, serves in a consultancy/advisory role, and received research funding or travel and accommodation expenses from Amgen, Amgen, Beigene, BMS, GSK, Janssen, and Pfizer. **JM-L** has served in a consultancy/advisory role, is a speaker's bureau member, has received research funding, or travel and accommodation expenses from Astellas, BMS, Gilead, Janssen, Menarini, Novartis, Pfizer, and Roche. **NL**, **AS**, **CL**, **KL**, and **MV** are employees of Janssen and may own stock in Janssen. **MZ** is an employee of IQVIA. **MK**, **NP**, **EF**, and **OCF** are employees of Legend Biotech and may hold stock in Legend Biotech. **M-VM** has received honoraria or serves on a consulting/advisory board for AbbVie, Amgen, Celgene, GSK, Janssen-Cilag, Pfizer, Regeneron, Roche, Sanofi, and Takeda.

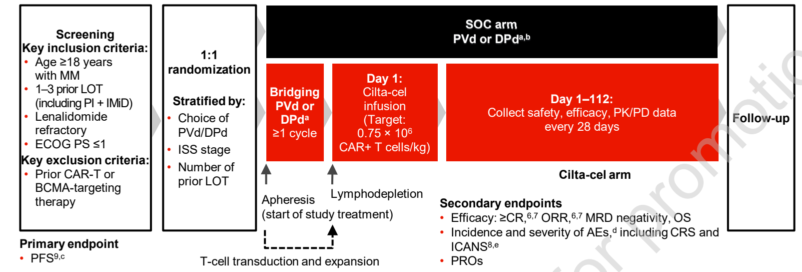
Introduction

- The phase 3 CARTITUDE-4 study evaluated ciltacabtagene autoleucel (cilta-cel) vs standard of care (SOC) in patients with lenalidomide-refractory multiple myeloma (MM) after 1–3 prior lines of therapy (LOT)[1]
  - A single cilta-cel infusion improved progression-free survival (PFS) with a prespecified hazard ratio (HR; weighted) of 0.26; *P*<0.001 and increased depth of response (complete response [CR] or better, 73.1% vs 21.8%) and was associated with a manageable safety profile[1]
- Cilta-cel was recently approved for the treatment of patients with relapsed/refractory MM who have received ≥ 1 prior LOT, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), and are refractory to lenalidomide[2]
- Patients with relapse within 18 months of frontline therapy are considered to have functionally high-risk MM[3-5]
- There is a high unmet clinical need for effective and tolerable therapies in patients with functionally high-risk MM
- We 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

Methods

- CARTITUDE-4 study design is shown in **Figure 1**

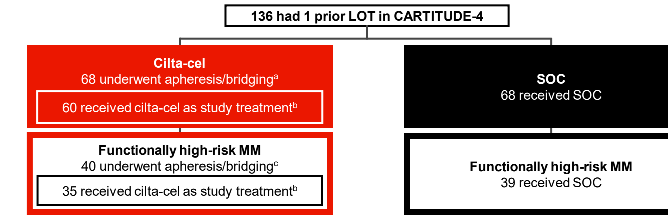
Figure 1: CARTITUDE-4 study design



[a]Physicians' 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; 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; ISS, International Staging System; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PK, pharmacokinetics; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib, and dexamethasone.

- Efficacy and safety were assessed in patients with 1 prior LOT and in patients with 1 prior LOT and functionally high-risk MM (**Figure 2**)
  - **Functionally high-risk MM was defined as progressive disease ≤18 months after receiving autologous stem cell transplant (ASCT) or the start of initial frontline therapy in patients with no ASCT**

Figure 2: CARTITUDE-4 subgroup analysis patient population



[a]Among the 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. [b]Study treatment includes any portion of the following sequence: apheresis, bridging, lymphodepletion, and cilta-cel. [c]Among the 40 patients who received 1 prior LOT and had functionally high-risk MM in the cilta-cel arm, 35 received cilta-cel as study treatment.

Results

Study population

- As of Nov 2022, median follow-up was 15.9 months (range, 0.1–27.3)
- Demographic and baseline characteristics were balanced (**Table 1**)

Table 1: Baseline characteristics

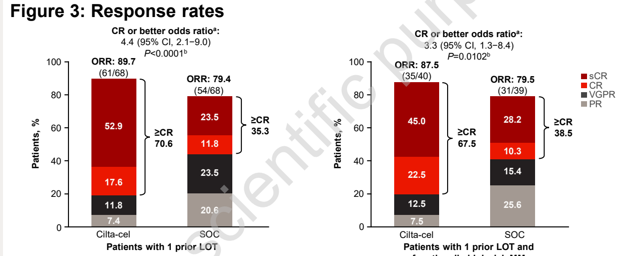
Baseline characteristic	Patients with 1 prior LOT		Patients with 1 prior LOT and functionally high-risk MM	
	Cilta-cel (n=68)	SOC (n=68)	Cilta-cel (n=40)	SOC (n=39)
Age, median (range), years	60.5 (27–78)	60.0 (35–78)	60.0 (27–71)	60.0 (40–78)
Male, n (%)	36 (52.9)	42 (61.8)	18 (45.0)	27 (69.2)
ISS stage 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,[d] n (%)	9 (13.2)	8 (11.8)	5 (12.5)	4 (10.3)
Soft tissue plasmacytoma,[e] 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 PI and IMiD, 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: 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, or ≥5000 mg/L serum free light chain. [e]Soft tissue plasmacytomas include extramedullary and bone-based plasmacytomas with a measurable soft tissue component.

Efficacy

- Consistently deeper responses were achieved with cilta-cel vs SOC in patients with 1 prior LOT and those with 1 prior LOT and functionally high-risk MM (**Figure 3**)

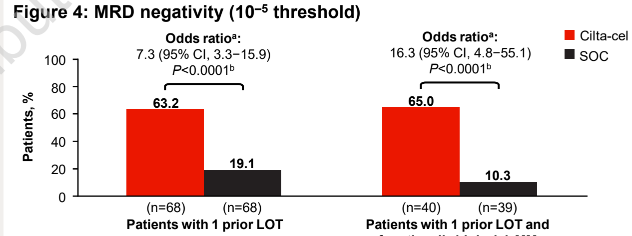
Figure 3: Response rates



[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. PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

- Consistently higher MRD-negativity rates occurred with cilta-cel vs SOC in patients with 1 prior LOT and those with 1 prior LOT and functionally high-risk MM (**Figure 4**)

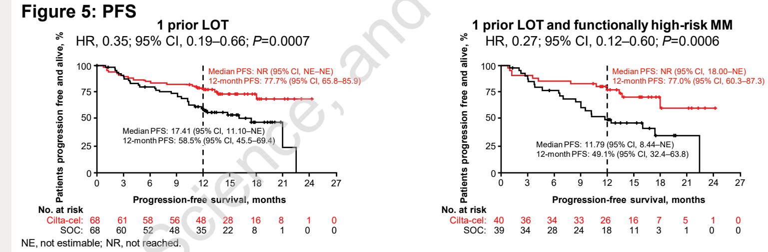
Figure 4: MRD negativity (10^{-5} threshold)



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

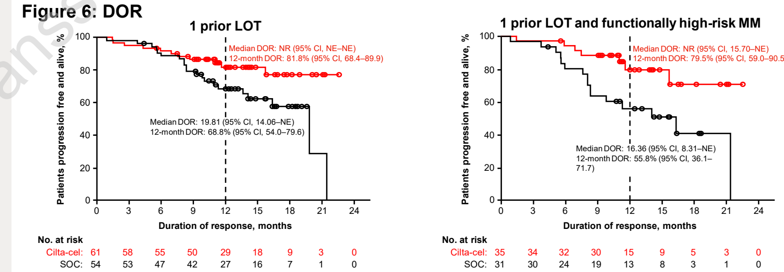
- PFS was consistently improved with cilta-cel vs SOC in patients with 1 prior LOT and those with 1 prior LOT and functionally high-risk MM (**Figure 5**)

Figure 5: PFS



- Consistently longer duration of response (DOR) was achieved with cilta-cel vs SOC in patients with 1 prior LOT and those with 1 prior LOT and functionally high-risk MM (**Figure 6**)

Figure 6: DOR

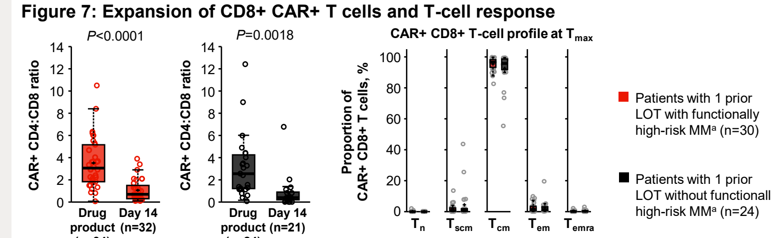


- In patients who received cilta-cel as study treatment:
  - Responses were deep regardless of functionally high-risk status
    - ORR was 100% in patients with 1 prior LOT (n=60) and those with 1 prior LOT and functionally high-risk MM (n=35)
    - ≥CR rates were 80.0% and 77.1%, respectively
  - PFS and MRD-negativity rates were high regardless of functionally high-risk status
    - 12-month PFS rate was 88.1% (95% CI, 76.6–94.1) in patients with 1 prior LOT and 88.0% (95% CI, 70.9–95.3) in patients with 1 prior LOT and functionally high-risk MM
    - MRD-negativity (10^{-5}) rate was 71.6% in patients with 1 prior LOT and 74.3% in patients with 1 prior LOT and functionally high-risk MM

CAR+ T-cell pharmacokinetics and biomarkers

- Preferential CD8+ CAR+ T-cell expansion and dominant central memory phenotypes, which have been shown to be associated with longer PFS,[9] were comparable between patients with 1 prior LOT regardless of functionally high-risk MM (**Figure 7**)
  - 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 status

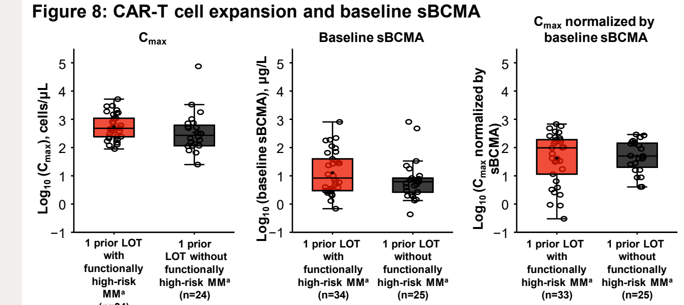
Figure 7: Expansion of CD8+ CAR+ T cells and T-cell response



[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. T_{cm}, central memory T cell; T_{em}, effector memory T cell; T_{emra}, terminally differentiated T cell; T_{max}, time of peak expansion; T_n, naive T cell; T_{scm}, T memory stem cell.

- CAR-T peak expansion and baseline levels of soluble BCMA (sBCMA) were comparable in patients with 1 prior LOT who did or did not have functionally high-risk MM (**Figure 8**)
  - Cilta-cel peak expansion, which has been shown to be associated with longer PFS when normalized to sBCMA (to reflect effector to target ratio),[9] was comparable between patients with 1 prior LOT regardless of functionally high-risk MM status

Figure 8: CAR-T cell expansion and baseline sBCMA



[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. C_{max}, maximum observed concentration of CAR+ T cells in blood.

Safety

- The frequency of AEs was similar between arms in patients with 1 prior LOT and those with 1 prior LOT and functionally high-risk MM (**Table 2**)

Table 2: TEAEs

Select AEs, n (%)	Patients with 1 prior LOT		Patients with 1 prior LOT and functionally high-risk	
	Cilta-cel (n=68)	SOC (n=68)	Cilta-cel (n=40)	SOC (n=39)
Grade ≥3 TEAEs	65 (95.6)	65 (95.6)	40 (100.0)	38 (97.4)
Serious TEAEs	26 (38.2)	24 (35.3)	16 (40.0)	13 (33.3)

TEAE, treatment-emergent adverse event.

- Among patients with 1 prior LOT, 11 each in the cilta-cel arm and the SOC arm died; of these patients, 7 in the cilta-cel arm and 9 in the SOC arm had functionally high-risk MM
  - Of the 7 patients with functionally high-risk MM in the cilta-cel arm who died, 2 had not received cilta-cel and 3 received cilta-cel as subsequent therapy
- AEs of special interest (AESIs) were consistent with the known safety profile of cilta-cel in patients with 1 prior LOT and functionally high-risk MM (**Table 3**)
  - AESIs 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[10]

Table 3: AESIs

AESI, n (%)[a]	Patients with 1 prior LOT		Patients with 1 prior LOT and functionally high risk	
	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
CNP	6 (8.8)	2 (2.9)	3 (7.5)	0
MNT	1 (1.5)	0	0	0
Peripheral neuropathy	2 (2.9)	0	2 (5.0)	0

[a]AESIs were evaluated in all patients receiving cilta-cel as second-line treatment (n=68) and in those with functionally high-risk MM (n=40). CNP, cranial nerve palsy; MNT, movement and neurocognitive treatment-emergent adverse event.

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Multiple Myeloma

Presented by K Weisel at the Annual Meeting of the German, Austrian and Swiss Associations of Hematology and Medical Oncology (DGHO); October 11–14, 2024; Basel, Switzerland