MM-549

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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Disclosures

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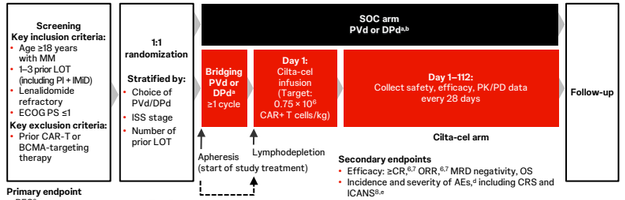
Introduction

- 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**

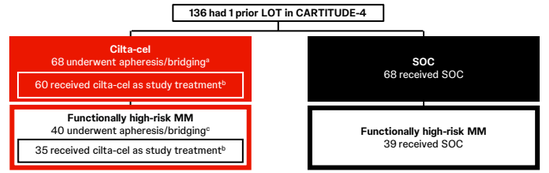
Figure 1: CARTITUDE-4 study design



[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

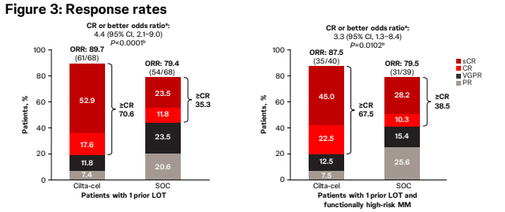
Baseline characteristic	Patients with 1 prior LOT		Patients with 1 prior LOT and functionally high-risk MM	
	Cilta-cel (n=68)	SOC (n=68)	Cilta-cel (n=40)	SOC (n=39)
Age, median (range), years	60.5 (27–78)	60.0 (35–78)	60.0 (27–71)	60.0 (40–78)
Male, n (%)	36 (52.9)	42 (61.8)	18 (45.0)	27 (69.2)
ISS stage 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: ≥50% 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**)

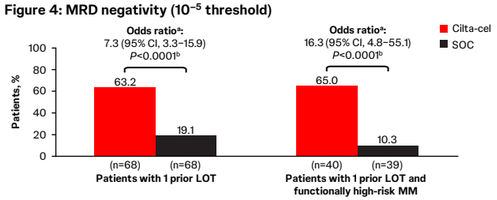
Figure 3: Response rates



[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.

- 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**)

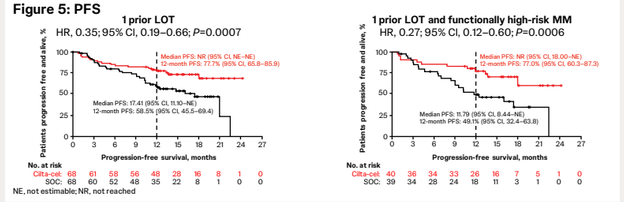
Figure 4: MRD negativity (10^{-5} threshold)



[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**)

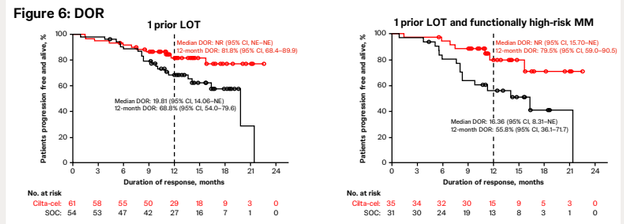
Figure 5: PFS



NE, not estimable; NR, not reached

- 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

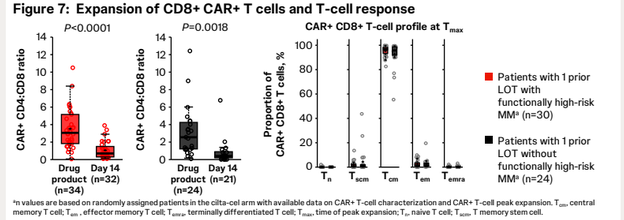


- In patients who received cilta-cel as study treatment:
  - Responses were deep regardless of functionally high-risk status
    - ORR was 100% in patients with 1 prior LOT (n=60) and those with 1 prior LOT and functionally high-risk MM (n=35)
    - ≥CR rates were 80.0% and 77.1%, respectively
  - PFS 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

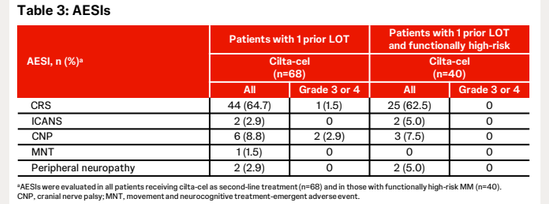
Figure 7: Expansion of CD8+ CAR+ T cells and T-cell response



[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_{scm}, 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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