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Efficacy and Safety of Ciltacabtagene Autoleucel ± Lenalidomide Maintenance in Newly Diagnosed Multiple Myeloma With Suboptimal Response to Frontline Autologous Stem Cell Transplant: CARTITUDE-2 Cohort D

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Key Takeaway

In patients with a suboptimal response after ASCT frontline therapy, efficacy and safety with cilta-cel ± lenalidomide maintenance is promising, especially given the historically poor clinical outcomes of this patient population

Conclusions

In patients with <CR after frontline ASCT, a single cilta-cel infusion ± lenalidomide maintenance demonstrated deep and durable responses

- ORR was 94.1%, 18-month DOR was 93.3%, and MRD negativity occurred in 80.0% of patients
- 18-month PFS and OS rates were 93.8% each
- CAR-T cell expansion was robust

AEs were consistent with the known safety profile of cilta-cel

- No cases of grade 3 or 4 CRS or ICANS
- No cases of movement and neurocognitive TEAEs/parkinsonism

Incidence of prolonged neutropenia and thrombocytopenia was low

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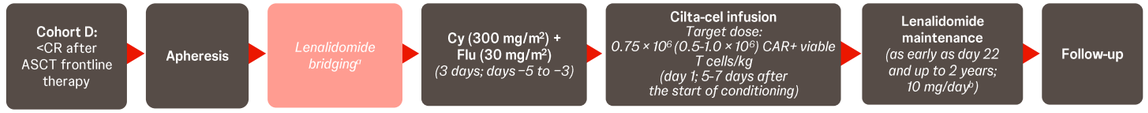
Introduction

- Ciltacabtagene autoleucel (cilta-cel), a B-cell maturation antigen (BCMA)–targeting chimeric antigen receptor (CAR)-T cell therapy, has shown deep and durable responses in heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM; CARTITUDE-1)[1,2] and significant improvement in progression-free survival (PFS) versus standard of care in lenalidomide-refractory patients with MM after 1 to 3 prior lines of therapy (LOT; CARTITUDE-4)[3]
- Cilta-cel was recently approved for the treatment of adult patients with RRMM who have received at least 1 prior LOT, including a proteasome inhibitor and an immunomodulatory agent, and who are refractory to lenalidomide[4]
- Patients with a suboptimal response after autologous stem cell transplant (ASCT) frontline therapy historically have poor outcomes[5-9]
- CARTITUDE-2 is a phase 2, multicohort study evaluating cilta-cel across various clinical settings of unmet need[10]
- CARTITUDE-2 cohort D is evaluating cilta-cel ± lenalidomide maintenance in patients with suboptimal response to frontline ASCT
- Here we report initial efficacy and safety data from CARTITUDE-2 cohort D in patients who achieved less than complete response (<CR) after frontline ASCT after a median follow-up of 22.4 months (range, 4.7-39.3)

Methods

- CARTITUDE-2 is a phase 2, multicohort, open-label study (**Figure 1**)
- The primary endpoint was minimal residual disease (MRD) negativity at 10^{-5} threshold using next-generation sequencing or next-generation flow
- Secondary endpoints included overall response rate (ORR), assessed per International Myeloma Working Group (IMWG) response criteria; duration of response (DOR); time to response; PFS and overall survival (OS); incidence and severity of adverse events (AEs), including cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), both of which were graded per American Society for Transplantation and Cellular Therapy criteria[11] (all other AEs were graded per Common Terminology Criteria for Adverse Events v5)

Figure 1: Cohort D study design



Cy, cyclophosphamide; Flu, fludarabine. [a]Bridging therapy was allowed when clinically indicated; alternative bridging regimens instead of, or in addition to, lenalidomide were allowed. [b]Per protocol, safety was assessed in the first 5 patients with cilta-cel only; subsequently, 12 patients initiated continuous lenalidomide maintenance for a minimum of 21 days post cilta-cel for ≤2 years. Dose of 10 mg daily upon adequate hematologic recovery.

Results

Baseline characteristics

- At a 22.4-month median follow-up, 17 patients had received cilta-cel (**Table 1**)

Table 1: Baseline characteristics

Characteristic		N=17
Age, median (range), y		54.0 (37-69)
Male, n (%)		14 (82.4)
Race, n (%)	White	14 (82.4)
	Black/African American	1 (5.9)
	Not reported	2 (11.8)
ECOG PS at screening, n (%)	0	13 (76.5)
	1	4 (23.5)
Time from initial diagnosis to enrollment, median (range), y		0.9 (0.6-1.4)
Myeloma type by immunofixation, n (%)	IgG	11 (64.7)
	IgA	2 (11.8)
	Light chain, kappa	2 (11.8)
	Negative immunofixation	2 (11.8)
Extramedullary plasmacytomas, n		0
High-risk cytogenetics, n (%)[a]		1 (5.9)
	Del(17p)	1 (5.9)
ISS stage I, n (%)		17 (100)
Prior ASCT, n (%)[b]		17 (100)
Prior PI and IMiD, n (%)		17 (100)
Prior anti-CD38 mAb, n (%)		3 (17.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; Ig, immunoglobulin; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor. [a]Cytogenetic risk abnormalities are based on central FISH testing, or local FISH testing and karyotype testing if central FISH is not available. One patient was unknown. [b]One patient received tandem ASCT (ie, underwent ASCT twice).

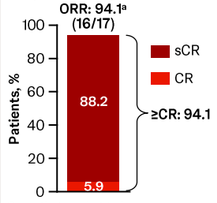
Lenalidomide maintenance

- Per protocol, the first 5 patients did not receive and the last 12 patients initiated lenalidomide maintenance after cilta-cel (10 mg daily upon adequate hematologic recovery)
  - Median time to initiation: 51.0 days (range, 21-214); median duration: 426.5 days (range, 70-716)
  - Median number of cycles: 15.0 (range, 3-26); median overall relative dose intensity: 93.4% (range, 68-100)

Efficacy

- ORR was 94.1%; all patients who responded achieved ≥CR (**Figure 2; Table 2**)
- Responses to treatment with cilta-cel were durable and deepened over time (**Figure 3**), and high rates of PFS and OS were achieved (**Figure 4**)

Figure 2: Overall response assessed using a validated computerized algorithm



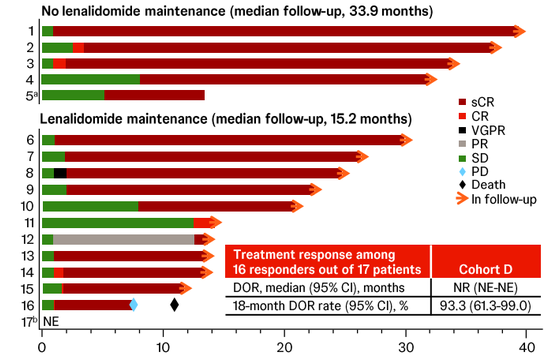
One patient was lost to follow-up and 1 patient was not evaluable for disease response. sCR, stringent CR. [a]ORR is defined as the proportion of patients who achieve a partial response or better per IMWG criteria.

Table 2: Cilta-cel efficacy outcomes

Time to response among responders, median (range), months	Cohort D (N=17)
First response	1.3 (0.9-12.5)
Best response	1.9 (0.9-12.5)
≥CR	1.7 (0.9-12.5)
MRD negativity (10^{-5}), n/N (%)	
Overall	12/17 (70.6)
MRD-evaluable patients[a]	12/15 (80.0)

[a]MRD evaluable denotes patients who had successful baseline calibration for next-generation sequencing or who were assessed by next-generation flow and had at least 1 post-baseline MRD sample with positive or negative result at the threshold of 10^{-5}.

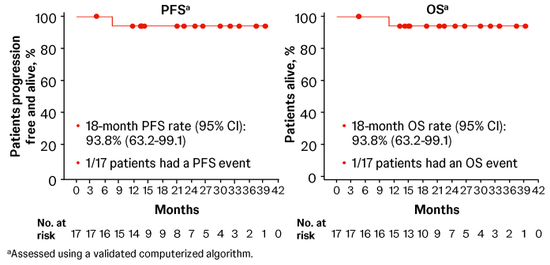
Figure 3: Duration of response



Treatment response among 16 responders out of 17 patients	Cohort D
DOR, median (95% CI), months	NR (NE-NE)
18-month DOR rate (95% CI), %	93.3 (61.3-99.0)

NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR. [a]One patient was lost to follow-up. [b]One patient was NE for disease response.

Figure 4: PFS and OS rates



[a]Assessed using a validated computerized algorithm.

Safety profile

- Treatment-emergent AEs (TEAEs) were consistent with the known safety profile of cilta-cel (**Tables 3** and **4**)
- 1 case of grade 3 myelodysplastic syndrome was reported with onset at day 353 and was not treatment related per investigator assessment
- No deaths due to TEAEs at the time of data cut-off

Table 3: Select TEAEs

n (%)		Any grade (N=17)	Grade 3 or 4 (N=17)
Any TEAE		17 (100)	17 (100)
Serious TEAE		10 (58.8)	9 (52.9)
Infections		12 (70.6)	5 (29.4)
Hematologic	Neutropenia	16 (94.1)	14 (82.4)
	Lymphopenia	11 (64.7)	10 (58.8)
	Thrombocytopenia	8 (47.1)	4 (23.5)
	Leukopenia	7 (41.2)	6 (35.3)
	Anemia	5 (29.4)	1 (5.9)

Table 4: TEAEs between patients ± lenalidomide maintenance

n (%)		Cohort D (N=17)	Cohort D without lenalidomide (n=5)	Cohort D with lenalidomide (n=12)
Prolonged cytopenias[a]	Neutropenia	1 (5.9)	0	1 (8.3)
	Lymphopenia	5 (29.4)	2 (40.0)	3 (25.0)
	Thrombocytopenia	1 (5.9)	0	1 (8.3)
Grade 3 or 4 infections		5 (29.4)	1 (20.0)	4 (33.3)

[a]Initial grade 3/4 cytopenias not recovered to grade ≤2 by day 60.

- AEs of special interest were consistent with the known safety profile of cilta-cel (**Table 5**)
- No cases of movement and neurocognitive TEAEs or parkinsonism were observed, and 1 patient experienced ICANS, which resolved

Table 5: AEs of special interest

Cohort D (N=17)	Any grade, n (%)	Grade 3 or 4, n (%)	Median time to onset, days	Median duration, days
CRS	14 (82.4)	0	8.0	2.5
ICANS	1 (5.9)	0	7.0	1.0
Other neurotoxicity[a]	6 (35.3)	1 (5.9)	21.0	111.0

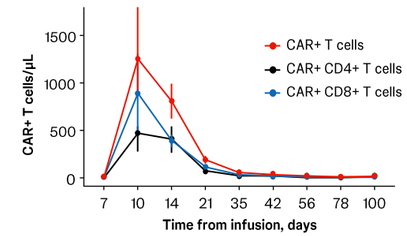
[a]Six patients experienced other neurotoxicities (mostly grade 1/2): 3 patients with cranial nerve VII disorders (grade 1 [n=1], ongoing); 1 patient with diplopia (grade 3, resolved after 43 days) and oral hypoesthesia (resolved); 1 patient with paresthesia (grade 1, ongoing); and 1 patient with peripheral motor neuropathy, dysarthria, and dysphagia (resolved).

CAR-T cell expansion profile may differ from RRMM setting

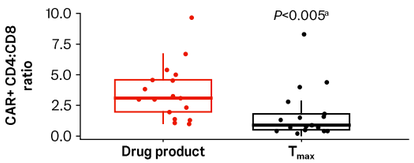
- In this population with a low tumor burden, robust CAR-T cell expansion was observed, with a mean (SD) $AUC_{(0\text{-}6m)}$ of 10,376 (7803) day × cells/μL
- CAR+ CD8+ T cells expanded more than CAR+ CD4+ T cells in blood in CARTITUDE-2 cohort D, consistent with that observed in CARTITUDE-4[12] and CARTITUDE-1[13] (**Figure 5**)

Figure 5: (A) CAR+ CD4+ and CAR+ CD8+ T cells both expanded after infusion. (B) CAR+ CD4:CD8 T-cell ratios were lower in blood at ~T_{max} than in drug product

A. CAR+ CD4+ and CAR+ CD8+ T-cell levels



B. CAR+ CD4:CD8 T-cell ratio



C_{max}, maximum observed concentration of CAR+ T cells in blood; T_{max}, sampling time (days post infusion) to reach C_{max}. [a]P value determined using the Wilcoxon test.

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Multiple Myeloma

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