MM-183

CARTITUDE-2 Cohort A: Updated Clinical Data and Biological Correlative Analyses of Ciltacabtagene Autoleucel (cilta-cel) in Lenalidomide-Refractory Patients with Progressive Multiple Myeloma (MM) After 1–3 Prior Lines of Therapy (LOT)

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INTRODUCTION

- Patients who have progressive multiple myeloma (MM) after 1–3 lines of treatment and are refractory to lenalidomide and/or proteasome inhibitors (PIs), have limited treatment options[1,2]
- Ciltacabtagene autoleucel (cilta-cel) is a chimeric antigen receptor (CAR)-T cell therapy expressing 2 B-cell maturation antigen (BCMA)-targeting single-domain antibodies designed to confer avidity
- Cilta-cel was recently approved by the US Food and Drug Administration for the treatment of adult patients with relapsed/refractory MM (RRMM) after ≥4 prior lines of therapy (LOT), including a PI, an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody[3]
- The Committee for Medicinal Products for Human Use of the European Medicines Agency has recommended cilta-cel for authorization in a similar indication, but in patients with ≥3 prior LOT[4]
- In CARTITUDE-2 (NCT04133636), a multicohort phase 2 study, cilta-cel is being evaluated in patients with MM in earlier-line settings (**Supplemental Figure 1**)
  - Suitability of outpatient administration is being explored
- CARTITUDE-2 cohort A consists of patients who are lenalidomide refractory with 1–3 prior LOT
  - Previous analysis (median follow-up 14.3 months) demonstrated an overall response rate (ORR) of 95%, with 85% achieving complete response (CR) or better and 90% achieving very good partial response (VGPR) or better[5]
- Here, we present updated CARTITUDE-2 cohort A efficacy and safety results, along with T cell and cytokine analysis after a median follow-up of 17.1 months

METHODS

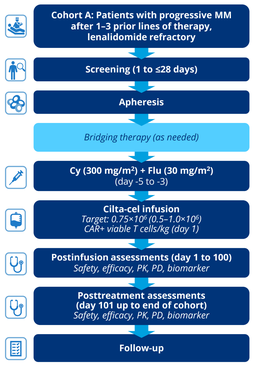
Primary endpoint

- Minimal residual disease (MRD) 10^{-5} negativity (assessed by next-generation sequencing or next-generation flow)

Secondary endpoints

- ORR, per International Myeloma Working Group response criteria
- Duration of response (DOR)
- Time to response
- Incidence and severity of adverse events (AEs)
  - Assessed per CTCAE version 5.0
  - Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) graded per ASTCT criteria

FIGURE 1: CARTITUDE-2 cohort A study design



Cy, cyclophosphamide; Flu, fludarabine; PD, pharmacodynamics; PK, pharmacokinetics

MULTIPLE MYELOMA

RESULTS

Study population

- As of January 2022, 20 patients had a median follow-up of 17.1 months (range, 3.3–23.1)
- 1 patient was treated in an outpatient setting

TABLE 1: Patient demographics and baseline characteristics

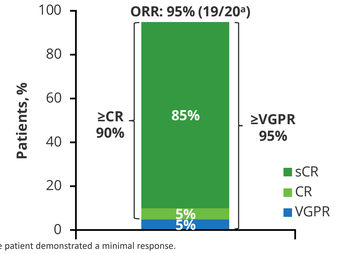
Characteristic	N=20
Age, years, median (range)	60 (38–75)
Male, n (%)	13 (65.0)
Race	
White	18 (90)
Black/African American	2 (10)
Bone marrow plasma cells[a] ≥60%, n (%)	3 (15)
Extramedullary plasmacytomas ≥1, n (%)	3 (15)
High-risk cytogenetic profile, n (%)	7 (35)[b]
del17p	3 (15)
t(14;16)	5 (25)
t(4;14)	0
Years since diagnosis, median (range)	3.5 (0.7–8.0)
Prior lines of therapy, median (range)	2 (1–3)
Previous stem cell transplantation, n (%)	
Autologous	17 (85)
Allogeneic	0
Exposure status	
Triple-class,[c] n (%)	13 (65)
Penta-drug,[d] n (%)	4 (20)
Refractory status, n (%)	
Triple-class,[c] n (%)	8 (40)
Penta-drug,[d] n (%)	1 (5)
To last line of therapy, n (%)	19 (95)
Bortezomib	8 (40)
Carfilzomib	2 (10)
Pomalidomide	7 (35)
Daratumumab	12 (60)

[a]Maximum value from bone marrow biopsy and bone marrow aspirate is selected if both results are available. [b]One patient had both del17p and t(14:16). [c]≥1 PI, ≥1 IMiD, and 1 anti-CD38 antibody. [d]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody.

Efficacy

- ORR was 95% (95% CI, 75.1–99.9; **Figure 2**)
  - 85% (95% CI, 62.1–96.8) achieved ≤CR
  - 90% (95% CI, 68.3–98.8) achieved ≥CR
  - 95% (95% CI, 75.1–99.9) achieved ≥VGPR
  - Responses deepened at this longer follow-up (**Supplemental Figure 2**)
- Median times to first and best response were 1.0 month (range, 0.7–3.3) and 2.6 months (range, 0.9–13.6), respectively
- Median DOR was not reached
  - Estimated 90% of responders remained in response for 12 months
- 15-month progression-free survival rate was 70% (95% CI, 45.1–85.3)
- All patients with MRD-evaluable samples at 10^{-5} threshold (n=16) were MRD negative (95% CI, 79.4–100.0)

FIGURE 2: Overall response rate



[a]One patient demonstrated a minimal response.
sCR, stringent CR

Safety

- Cilta-cel safety was manageable and predictable
- Incidence of initial grade 3/4 cytopenias not recovered to grade ≤2 by day 60 was 20% for neutropenia, 15% for thrombocytopenia, and 5% for lymphopenia
- CRS occurred in 19 patients (95%); 2 (10%) had grade 3/4 events (**Table 2, Supplemental Figure 3, Supplemental Table 1**)
  - Median time to onset was 7 days (range, 5–9), median duration was 3 days (range, 2–12)
  - CRS resolved within 7 days in 90% of patients at data cutoff
  - Tocilizumab was administered to 14 patients (70%)
  - Corticosteroids were administered to 6 patients (30%)
- 3 patients had ICANS (2 grade 1; 1 grade 2)
  - Median time to onset was 8 days (range, 7–10), and median duration was 3 days (range, 1–3)
- There were no cases of movement and neurocognitive treatment-emergent AEs/signs and symptoms of parkinsonism
- The incidence of parkinsonism decreased following implementation of patient management strategies across the CARTITUDE program (**Supplemental Figure 4**)

TABLE 2: Adverse events

AEs ≥20%, n (%)	N=20	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	19 (95)	19 (95)
Thrombocytopenia	16 (80)	7 (35)
Anemia	15 (75)	9 (45)
Lymphopenia	14 (70)	14 (70)
Leukopenia	11 (55)	11 (55)
CAR-T–related AEs		
CRS	19 (95)	2 (10)
Neurotoxicity	6 (30)	1 (5)
ICANS	3 (15)	0
Other	3 (15)[a]	1 (5)

[a]One patient had peripheral sensorimotor neuropathy, one had anosmia and dysgeusia, and one had facial paralysis.

- 4 deaths occurred post cilta-cel infusion
  - 1 due to COVID-19 (treatment related, day 100)
  - 1 due to sepsis (not treatment related, day 394)
  - 2 due to progressive disease (days 426 and 550)

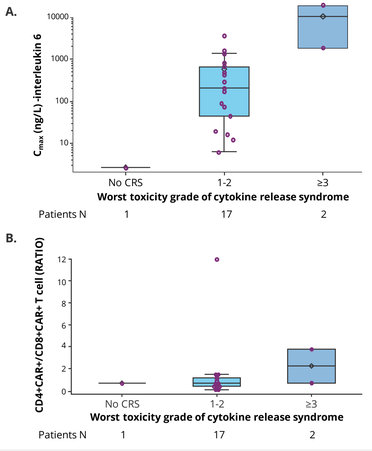
CAR+ T cell expansion, persistence, and cytokines

- Peak expansion of CAR-T cells occurred on day 11 (range, 8.7–42.9) and median persistence was 153 days (range, 57.1–336.8)
- Levels of interleukin-6 (IL-6), interferon gamma (IFNγ), IL-2Rα, and IL-10 increased post infusion, peaked at days 7–14, and returned to baseline levels within 2–3 months post infusion (**Supplemental Figure 5**)

Cytokines and CD4/CD8 ratio with respect to CRS and ICANS

- Higher cytokine levels were associated with severity of CRS (**Figure 3A**; IFNγ, IL-2Rα, and IL-10 showed similar profiles; **Supplemental Figure 6**)
- Trend of increasing CD4+ CAR+/CD8+ CAR+ T cell ratio associated with CRS and ICANS severity (**Figure 3B**)

FIGURE 3: Cytokines and CD4/CD8 ratio by CRS



Cytokines and CD4/CD8 ratio with respect to response (≥CR responders vs other responders)

- High ORRs precluded meaningful analysis of correlation between cytokine levels and response (**Supplemental Figure 7A**)
- No association of CD8+ enrichment with response at peak CAR+ T cell expansion (**Supplemental Figure 7B**)

KEY TAKEAWAY

At a longer median follow-up of 17.1 months, a single infusion of cilta-cel led to deepening and durable responses in patients with MM who received 1–3 lines of therapy and were lenalidomide refractory

CONCLUSIONS

- Cilta-cel–treated patients who had received a median of 2 prior LOT and were lenalidomide refractory had an ORR of 95%, with 90% achieving ≥CR, and 95% achieving ≥VGPR; all 16 patients with MRD-evaluable samples at 10^{-5} threshold were MRD negative
- The safety profile was manageable and predictable, including in the patient treated in an outpatient setting
- CAR-T cells had a median persistence of 153 days
- This patient population is also being investigated in the phase 3 CARTITUDE-4 (NCT04181827) study comparing cilta-cel to pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd)

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DISCLOSURES

HE has served in a consulting or advisory role for Amgen, Celgene, Bristol-Myers Squibb, Takeda, Janssen, Novartis, has received travel, accommodations, expenses from Amgen, Janssen, Celgene, Bristol-Myers Squibb, Takeda, has received honoraria from Janssen, Amgen, Celgene, Bristol-Myers Squibb, Takeda, Novartis, and has received research funding from Celgene, Janssen, Amgen, and Bristol-Myers Squibb. **AC** has served in a consulting or advisory role for Celgene, Janssen Oncology, Oncopeptides, Takeda, Seattle Genetics, GlaxoSmithKline, Novartis, Bristol-Myers Squibb, AstraZeneca, and Roche/Genentech, has received travel, accommodations, expenses from GlaxoSmithKline, Takeda, Celgene, and Janssen Oncology, has provided expert testimony for Janssen Oncology, has received research funding from Novartis, and GlaxoSmithKline, and holds patents, royalties, other intellectual property related to CAR-T cells and biomarkers of Cytokine Release Syndrome. **MD** has served in a consulting or advisory role for Amgen, Celgene, and Janssen, and has received honoraria from Amgen, Celgene, and Janssen. **JH** has served in a consulting or advisory role for Sanofi, Skyline Diagnostics, Oncopeptides, Janssen Biotech, Intellisphere, GlaxoSmithKline, Axxess Network, and Bristol-Myers Squibb/Celgene, has received travel, accommodations, expenses from Amgen, Janssen Biotech, Rocket Medical, Celgene, Takeda, Adaptive Biotechnologies, and Bristol-Myers Squibb, has received honoraria from Janssen Biotech, Takeda, Adaptive Biotechnologies, and Amgen, and has received research funding from Celgene. **HG** has served in a consulting or advisory role for Celgene, Janssen-Cilag, Bristol-Myers Squibb, Amgen, Takeda, Adaptive Biotechnologies, and Sanofi, has received travel, accommodations, expenses from Janssen-Cilag, and Sanofi, reports other relationships with Amgen, Celgene/Bristol-Myers Squibb, Chugai Pharma Europe, Janssen, and Sanofi, has received honoraria from Janssen-Cilag, Novartis, Bristol-Myers Squibb, Celgene, Chugai Pharma, Sanofi, Amgen, and GlaxoSmithKline, and reports research funding from Bristol-Myers Squibb, Janssen, Novartis, Chugai Pharma Europe, Celgene, Amgen, Sanofi, Mundipharma, Takeda, Molecular Partners, MSD, and Incyte. **KW** has served in a consulting or advisory role for Amgen, Adaptive Biotechnologies, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen-Cilag, Karyopharm Therapeutics, Sanofi, Takeda, Oncopeptides, and Roche, reports travel, accommodations, expenses from Amgen, Celgene, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline, and Takeda, reports honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen-Cilag, GlaxoSmithKline, Adaptive Biotechnologies, Karyopharm Therapeutics, Takeda, Sanofi, Roche/Genentech, Oncopeptides, AbbVie, GlaxoSmithKline, Novartis, and Pfizer, and reports research funding from Amgen, Celgene, Sanofi, Janssen-Cilag, Bristol-Myers Squibb/Celgene and GlaxoSmithKline. **M-SR** has served in a consulting or advisory role for Bristol-Myers Squibb, Amgen, GlaxoSmithKline, Janssen, Sanofi, Pfizer, and Oncopeptides, has received honoraria from AbbVie, Bristol-Myers Squibb, Takeda, and GlaxoSmithKline and has received research funding from Bristol-Myers Squibb, Janssen, Sanofi, and Novartis. **CS** has served in a consulting or advisory role for Amgen, Roche, Janssen Oncology, and Bristol-Myers Squibb/Celgene, has received travel, accommodations, expenses from Bristol-Myers Squibb/Celgene, Janssen Oncology, and Amgen, has received honoraria from Amgen, Bristol-Myers Squibb/Celgene, Janssen Oncology, Novartis, Pfizer, and Takeda, and has received research funding from Janssen Oncology, Takeda, and Novartis. **JMS** reports employment and stock and other ownership interests at Janssen Oncology. **KDB** reports employment at Janssen Research & Development. **HV** reports employment and stock and other ownership interests at Janssen Oncology. **TmY** reports employment at Janssen Research & Development. **PM** reports employment at and stock and other ownership interests at Janssen Oncology. **TR** reports employment at and stock and other ownership interests at Janssen Oncology. **CC** reports employment at Janssen and stock other ownership interests at Bristol Myers Squibb Foundation. **MAk** reports employment, stock and other ownership interests, travel, accommodations, expenses, and honoraria from Legend Biotech. **LP** reports employment and stock and other ownership interests at Legend Biotech. **TN** reports employment and stock and other ownership interests at Legend Biotech. **YC** has served in a consulting or advisory role for Janssen, Amgen, Medison, and GlaxoSmithKline, has received honoraria from Janssen, Amgen, Takeda, GlaxoSmithKline, NeoPharm, and Medison, and has received research funding from Karyopharm Therapeutics, Takeda, and Amgen. **MAg** has no relationships to disclose.

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