MM-153

# Phase 2 CARTITUDE-2 Study (Cohort B): Updated Clinical Data and Biological Correlative Analyses of Ciltacabtagene Autoleucel (cilta-cel), a BCMA-Directed CAR-T Cell Therapy, in Patients With Multiple Myeloma (MM) and Early Relapse After Initial Therapy


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## INTRODUCTION

- Median survival for patients with multiple myeloma (MM) who experience early clinical relapse is <2 years despite treatment with proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs)[1,2]
  - There is an unmet need for novel and durable treatment options in patients with early clinical relapse (≤12 months after start of initial treatment with anti-myeloma therapy or autologous stem cell transplant [ASCT])
- Ciltacabtagene autoleucel (cilta-cel) is a chimeric antigen receptor (CAR)-T cell therapy expressing 2 B-cell maturation antigen (BCMA)-targeting single-domain antibodies to confer avidity
- It was recently approved by the US FDA for the treatment of adult patients with relapsed/refractory MM (RRMM) after ≥4 prior lines of therapy (LOT), including a PI, an IMiD, and an anti-CD38 mAb[3]
- The Committee for Medicinal Products for Human Use (CHMP) 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 for cilta-cel is being explored
- CARTITUDE-2 cohort B consists of patients with early relapse after initial therapy with a PI and IMiD; defined as progression within 12 months after ASCT or within 12 months from the start of anti-MM therapy for patients who have not had an ASCT
  - Previous analysis (median follow-up of 10.6 months) demonstrated an overall response rate (ORR) of 95% with 79% of patients achieving complete response (CR) or better, and 90% achieving very good partial response (VGPR) or better[5]
- Here, we present updated CARTITUDE-2 cohort B efficacy and safety results, along with T cell and cytokine analyses, after a median follow-up of 13.4 months

## METHODS

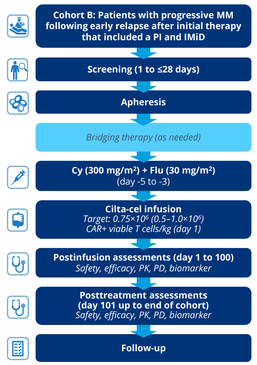
**Primary endpoint**

- 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 B study design**




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

MULTIPLE MYELOMA

## RESULTS

**Study population**

- As of January 2022, 19 patients had a median follow-up of 13.4 months (range, 5.2–21.7)
- 1 patient was treated in an outpatient setting

**TABLE 1: Patient demographics and baseline characteristics**

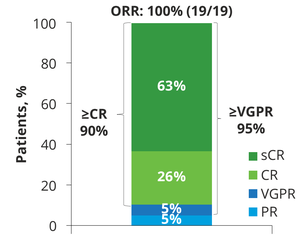
| Characteristic | N=19 |
|---|---|
| Age, years, median (range) | 58 (44–67) |
| Male, n (%) | 14 (73.7) |
| Race | |
| White | 14 (73.7) |
| Black/African American | 2 (10.5) |
| Asian | 1 (5.3) |
| Not reported | 2 (10.5) |
| Bone marrow plasma cells[a] ≥60%, n (%) | 4 (21.1) |
| Extramedullary plasmacytomas, n (%) | 3 (15.8) |
| High-risk cytogenetic profile, n (%) | 3 (15.8) |
| Del17p | 3 (15.8) |
| Years since initial diagnosis to enrollment, median (range) | 1.15 (0.5–1.9) |
| Prior LOT, median (range) | 1 (1–1) |
| Previous stem cell transplantation, n (%) | |
| Autologous | 15 (78.9) |
| Allogeneic | 0 |
| Exposure status | |
| Triple-class,[b] n (%) | 4 (21.1) |
| Penta-drug,[c] n (%) | 0 |
| Refractory status, n (%) | |
| Triple-class,[b] n (%) | 3 (15.8) |
| Penta-drug,[c] n (%) | 0 |
| To last line of therapy, n (%) | 15 (78.9) |
| Lenalidomide | 15 (78.9) |
| Bortezomib | 6 (31.6) |
| Daratumumab | 3 (15.8) |
| Thalidomide | 2 (10.5) |

[a]Maximum value from bone marrow biopsy and bone marrow aspirate is selected if both results are available. [b]≥1 PI, ≥1 IMiD, and 1 anti-CD38 antibody. [c]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody.

**Efficacy**

- ORR was 100% (95% CI, 82.4–100; **Figure 2**)
  - 90% (95% CI, 66.9–98.7) achieved ≥CR
  - 95% (95% CI, 74.0–99.9) achieved ≥VGPR
  - Responses deepened at this longer follow-up (**Supplemental Figure 2**)
- Median time to first and best response were 1.0 month (range, 0.9–9.7) and 5.1 months (range, 0.9–11.8), respectively
- Median DOR was not reached
- 12-month progression-free survival (PFS) rate was 89.5% (95% CI, 64.1–97.3)
- Of the 15 patients with MRD-evaluable samples at $10^{-5}$ threshold, 14 (93.3%, [95% CI, 68.1–99.8]) were MRD negative

**FIGURE 2: Overall response rate**




sCR, stringent CR

**Safety**

- Cilta-cel safety was manageable and predictable
- Incidence of initial grade 3/4 events not recovered to grade ≤2 by day 60 was 16% for thrombocytopenia, and 11% for lymphopenia and neutropenia
- CRS occurred in 16 patients (84%); 1 had grade 3/4 events (**Table 2, Supplemental Figure 3, Supplemental Table 1**)
  - Median time to onset was 8 days (range, 5–11), median duration was 3.5 days (range, 1–7)
  - CRS resolved in all patients
  - Tocilizumab was administered to 12 patients (63%)
  - Corticosteroids were administered to 4 patients (21%)
- Neurotoxicity was seen in 5 (26%) patients
  - 1 patient had grade 1 ICANS with time to onset of 11 days and duration of 4 days
  - 1 patient had movement and neurocognitive treatment-emergent AEs/signs and symptoms of parkinsonism with time to onset of 38 days
- The incidence of parkinsonism decreased following the implementation of patient management strategies across the CARTITUDE program (**Supplemental Figure 4**)
- 1 death occurred, due to progressive disease on day 158

**TABLE 2: Adverse events**

| AEs ≥20%, n (%) | N=19 | |
|---|---|---|
| | Any Grade | Grade 3/4 |
| **Hematologic** | | |
| Neutropenia | 18 (95) | 17 (90) |
| Anemia | 11 (58) | 9 (47) |
| Thrombocytopenia | 11 (58) | 5 (26) |
| Lymphopenia | 6 (32) | 6 (32) |
| Leukopenia | 5 (26) | 5 (26) |
| **CAR-T–related AEs** | | |
| CRS | 16 (84) | 1 (5) |
| Neurotoxicity | 5 (26) | 1 (5) |
| ICANS | 1 (5) | 0 |
| Other | 4 (21) | 1 (5) |
| Parkinsonism | 1 (5) | 1 (5) |

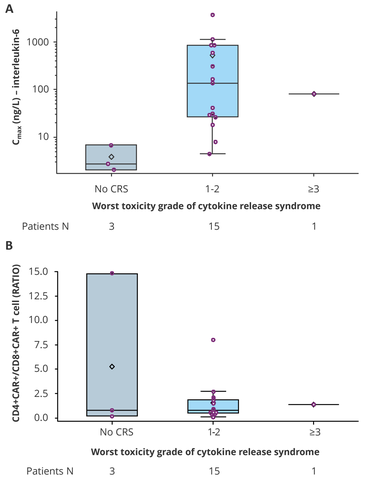
**CAR+ T cell expansion, persistence, and cytokines**

- Peak expansion of CAR-T cells occurred on day 13 (range, 9.0–209.9) and median persistence was 77 days (range, 41.0–221.8)
- 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 with respect to CRS and ICANS**

- Higher cytokine levels were associated with CRS severity (**Figure 3A**; IFNγ, IL-2Rα, and IL-10 showed similar profiles; **Supplemental Figure 6**)
- CD4+ CAR+/CD8+ CAR+ T cell ratio was not associated with CRS and ICANS severity (**Figure 3B**)

**FIGURE 3: Cytokines and CD4/CD8 ratio by CRS severity**




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

- High overall response rates 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

The efficacy and safety profile of cilta-cel in high-risk patients with MM who experienced early clinical relapse/treatment failure support the continued exploration of cilta-cel in earlier lines of treatment

## CONCLUSIONS

- Cilta-cel–treated patients who experienced early clinical relapse/treatment failure to prior therapy had an ORR of 100%, with 90% achieving ≥CR and 95% achieving ≥VGPR. The 12-month PFS rate was 89.5%
- 14 (93%) of 15 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 77 days


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### DISCLOSURES

**NWCJVDD** has served in a consulting or advisory role for Bristol-Myers Squibb/Celgene, Janssen, Amgen, Takeda, Roche, and Novartis/Bayer/Servier and has received research funding from Janssen, Amgen, Cellectis, 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, accommodation, 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. **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. **TK** has served in a consulting or advisory role for Bristol-Myers Squibb, Johnson & Johnson, Novartis, Gilead Sciences, and MSD. **JS** reports employment and stock and other ownership interests at Janssen Oncology. **KDB** reports employment at Janssen Research & Development. **HV** reports employment at and stock and other ownership interests at Janssen Oncology. **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. **EZ** reports employment at, has received travel, accommodation, and expenses from, has patents pending with, 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, accommodation, expenses, and honoraria from Legend Biotech. **DG** reports employment, stock and other ownership interests, and travel, accommodation, expenses from Legend Biotech. **TN** reports employment, stock and other ownership interests from Legend Biotech. **LP** reports employment and stock and other ownership interests at Legend Biotech. **PS** has served in a consulting or advisory role for Celgene, janssen, Amgen, Karyopharm Therapeutics, and CARsgen Therapeutics, and reports research funding from Janssen, Amgen, Skyline Diagnostics, and Bristol-Myers Squibb. **SZ** has served in a consulting or advisory role for janssen-Cilag, Takeda, Celgene, Sanofi, Oncopeptides, has received travel, accommodation, expenses from Janssen-Cilag, Takeda, and Celgene, and has received research funding from Janssen-Cilag, Takeda, and Celgene. **MAg, SA,** and **WR** have no relationships to disclose.


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