The 7th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

CARTITUDE-2: PHASE 2 MULTICOHORT STUDY OF CILTACABTAGENE AUTOLEUCEL (CILTA-CEL), A B-CELL MATURATION ANTIGEN (BCMA)–DIRECTED CHIMERIC ANTIGEN RECEPTOR T (CAR-T) CELL THERAPY, IN PATIENTS WITH MULTIPLE MYELOMA (MM)

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INTRODUCTION

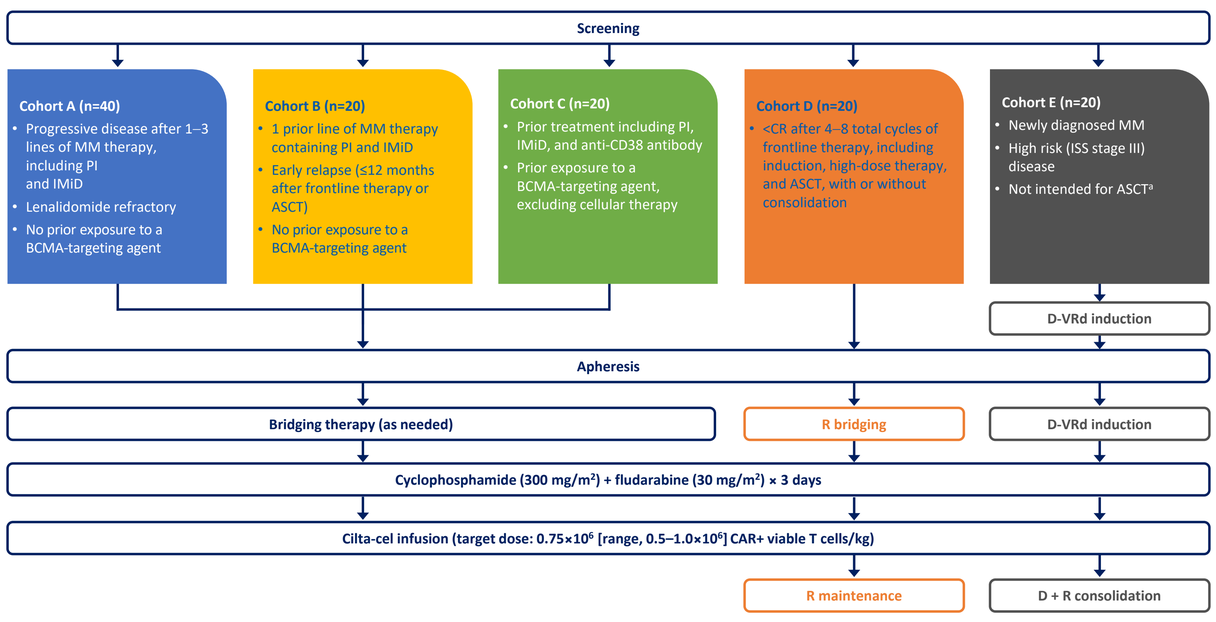
- Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is an autologous chimeric antigen receptor T-cell (CAR-T) therapy with 2 B-cell maturation antigen (BCMA)–targeting single-domain antibodies designed to confer avidity
- In the phase 1b/2 CARTITUDE-1 study (NCT03548207), a single infusion of cilta-cel yielded deep and durable responses in heavily pretreated (triple-class exposed) patients with relapsed/refractory multiple myeloma (MM)[1]
  - Overall response rate was 96.9% (95% CI, 91.2–99.4), with 67.0% achieving stringent complete response (sCR)
- Cilta-cel had a manageable safety profile at the recommended phase 2 dose of 0.75×10^6 (range, $0.5–1.0\times10^6$) CAR+ viable T cells/kg, and was generally consistent with the current understanding of CAR-T therapy
  - Cytokine release syndrome (CRS), a known CAR-T side effect, was mostly grade 1/2, with onset at a median of 7 days (range, 1–12) after cilta-cel infusion
- The characteristics of CRS in CARTITUDE-1, including the delayed onset of these events after cilta-cel infusion, suggest outpatient dosing may be feasible
- Cilta-cel may also have clinical activity in other MM populations
- The CARTITUDE-2 study (NCT04133636) will assess the efficacy and safety of cilta-cel in various clinical settings for patients with MM and explore outpatient administration in suitable patients

METHODS

Study Design

- CARTITUDE-2 is a phase 2, open-label, multicenter study including multiple cohorts of patients in varying stages of treatment for MM (**Figure 1**)
- Multiple cohorts will run in parallel
- Patients will be followed up to 2 years in Cohorts A–C, and for 2.5 years in Cohorts D and E, after the last patient in each cohort has received infusion with cilta-cel
- Eligible patients are ≥18 years of age with an MM diagnosis per International Myeloma Working Group (IMWG) criteria,[2] measurable disease (cohort specific), and an Eastern Cooperative Oncology Group performance status of 0 or 1
  - In Cohorts A–C, patients may be screened based on disease assessed via imaging, if disease is not measurable in serum or urine
- Key inclusion and exclusion criteria for each cohort are shown in **Figure 1**
- In Cohorts A–C, bridging therapy is permitted after apheresis; in Cohort D, ≥1 cycle of lenalidomide may be given as bridging therapy
- In Cohort E, patients receive induction therapy with 4 cycles of daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd) with apheresis after Cycle 1 or 2

Figure 1. CARTITUDE-2 Study Design



[a]Due to age ≥65 years, age 18–65 years with presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT, or refusal of high-dose chemotherapy with ASCT as initial treatment; ASCT, autologous stem-cell transplantation; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; D + R, daratumumab and lenalidomide; D-VRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMiD, immunomodulatory imide drug; ISS, International Staging System; MM, multiple myeloma; PI, proteasome inhibitor; R, lenalidomide.

Patients and Treatment

- Target enrollment is approximately 20–40 patients in each of the 5 cohorts
- After successful manufacturing of the cilta-cel product, patients will undergo lymphodepletion daily for 3 days with cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2
- In all cohorts, cilta-cel is given as a single infusion on Day 1 at a target dose of 0.75×10^6 (range, $0.5–1.0\times10^6$) CAR+ viable T cells/kg, 5–7 days after the start of lymphodepletion
- After the first 5 patients receive cilta-cel and the data monitoring committee completes their review, patients in Cohort D may initiate lenalidomide maintenance therapy after Day 21 post cilta-cel infusion
- Patients in Cohort E will receive consolidation treatment with daratumumab and lenalidomide, with lenalidomide starting on or after Day 21 and daratumumab starting 60–100 days post cilta-cel infusion

Outpatient Administration

- Patients are assessed for suitability for outpatient administration based on:
  - Investigator's discretion
  - Patient's willingness
  - Institutional guidance
  - Sponsor's approval
- Patients will be evaluated for suitability at the time of apheresis, prior to lymphodepletion, and again prior to cilta-cel infusion
- Key clinical considerations and monitoring guidelines for outpatient administration are described in **Table 1**

Endpoints and Assessments

- Primary, secondary, and exploratory endpoints are described in **Table 2**
- Assessments will be made according to the schedule shown in **Table 3**

Table 1. Outpatient Administration Guidelines

Key Clinical Considerations	Patient Monitoring
• No requirement for daily packed red blood cell or platelet transfusions • No presence of an indwelling central line • No fever or active infection since study enrollment • No grade ≥3 nonhematologic toxicities associated with lymphodepletion • No significant risk factors for bleeding in the setting of cytopenia and clinically significant tumor lysis syndrome requiring management • No high tumor burden defined as ≥60% plasma-cell infiltration of the marrow and/or the presence of extramedullary disease • No deterioration in neurologic status, including mental status changes (with the exception of confusion/somnolence that has resolved) • No rapidly progressing disease • Estimated glomerular filtration rate of ≥40 mL/min/1.73 m^2 • AST and ALT ≤3 times the upper limit of normal	**Days 1–4** • Patients will be clinically evaluated post infusion for ≥6 hours prior to discharge from the outpatient facility • Patients are required to stay within 30 minutes of the hospital • Patients will receive daily follow-up calls from the hospital • Hospital admission is required at any time in the event of any presenting signs and symptoms of CRS and/or neurotoxicity **Days 5–14** • Required inpatient admission • Option for discharge on Day 10 in the absence of CRS, neurotoxicity, or other significant AEs – Patients will receive daily follow-up calls through Day 14

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome.

Table 2. Study Endpoints

Primary Endpoint

- MRD-negative rate at the 10^{-5} threshold as defined by the IMWG criteria using next-generation sequencing

Secondary Endpoints

Efficacy

- Overall response rate (PR or better) as defined by the IMWG criteria
- Rate of sCR, CR, and VGPR as defined by the IMWG criteria
- Clinical benefit rate defined as overall response rate (sCR+CR+VGPR+PR) + minimal response
- Duration of response and time to response
- MRD-negative rate at 12 months for patients who achieved CR
- Time to MRD negativity and duration of MRD negativity
- MRD-negative rate across clinical response groups (sCR, CR, and VGPR)

Safety

- AEs graded by CTCAE v5.0; CRS and ICANS by ASTCT criteria[3]; and other CAR-T neurotoxicities (events not reported as ICANS) by CTCAE

Pharmacokinetics and Pharmacodynamics

- Depletion of soluble BCMA and BCMA-expressing cells
- CAR transgene levels in blood and bone marrow samples
- Levels of inflammatory cytokines
- Presence of anti–cilta-cel antibodies

Exploratory Endpoints

Efficacy

- Progression-free survival
- Overall survival
- MRD-negative rate by imaging (if PET is locally available)

Exploratory Biomarkers of Response, Relapse, and Safety

- Baseline BCMA expression in plasma cells
- T_{max}, C_{max}, and phenotypic analysis of CAR-T cells
- Neuroimaging (CT/MRI/PET)

Safety

- Qualitative changes in handwriting assessment

Patient-Reported Outcomes

- Time to worsening of symptoms using the MySIm-Q total symptom score
- Change from baseline in HRQoL outcomes as measured on EORTC QLQ-C30, MySIm-Q, PGIC, and PGIS questionnaires
- Symptomatic AEs as assessed on PRO-CTCAE using validated questions
- Medical resource utilization

AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; C_{max}, maximum concentration; CR, complete response; CRS, cytokine release syndrome; CT, computerized tomography; CTCAE, Common Terminology Criteria for Adverse Events; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL, health-related quality of life; ICANS, immune effector cell–associated neurotoxicity syndrome; IMWG, International Myeloma Working Group; MRD, minimal residual disease; MRI, magnetic resonance imaging; MySIm-Q, Multiple Myeloma Symptom and Impact Questionnaire; PET, positron emission tomography; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Symptom Severity; PR, partial response; PRO, patient-reported outcome; sCR, stringent CR; T_{max}, time to maximum concentration; VGPR, very good PR.

Table 3. Schedule of Key Assessments

Assessment	
Efficacy	
MRD-negative rate	• ≤7 days prior to first dose of lymphodepletion regimen • For all dosed patients at Day 56, and at 6, 12, 18, and 24 months (Day 744 ± 16 days), regardless of disease status measured in blood and urine • For patients with suspected CR at the time of CR and then yearly for patients that remain on study (past 24 months) up to disease progression
Overall response rate	• ≤7 days prior to first dose of lymphodepletion regimen • For all dosed patients at Days 28, 56, 78, and 100, and every 28 days up to 1 year, and then every 56 days in the post-treatment period (Day 101 and up to end of study completion); for Cohort E, assessments will also occur on Day 1 of induction Cycle 1, and when patients start consolidation treatment on or after Day 21 post infusion • Disease evaluation will continue until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first • For patients screened without measurable disease in serum or urine, imaging (PET/CT or whole-body MRI) at 6 and 12 months, and then yearly after dosing
Safety	
AEs/SAEs	• Continuous from the time of consent until 100 days after last administration of any study treatment • Study treatment-related AEs will be reported until end of study; neurologic AEs or exacerbation of existing neurologic AEs will be reported up to 1 year after cilta-cel infusion
Pharmacokinetics/Pharmacodynamics	
Soluble serum BCMA; CAR transgene levels in blood	• ≤7 days prior to first dose of lymphodepletion regimen • Predose (≤4-hour window); post dose (within 30 minutes and at 24 hours) • On Days 3, 7, 10, 14, 21, 28, 42, 56, 78, and 100 post infusion, and then every 8 weeks up to 1 year, and at disease progression or study completion (for those without disease progression)

AE, adverse event; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; CT, computerized tomography; MRD, minimal residual disease; MRI, magnetic resonance imaging; PET, positron emission tomography; SAE, serious AE.

CONCLUSION

- CARTITUDE-2 will provide insights into the efficacy and safety of cilta-cel in multiple cohorts of patients with MM who have a poor prognosis and a high unmet need

REFERENCES

1. Madduri D, et al. *Blood* 2020;136(Suppl 1):22-5. 2. Rajkumar SV, et al. *Blood* 2011;117:4691-5. 3. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25:625-38.

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Previously presented at TCT 2021