Clinical Strategies for Mitigation of Cytokine Release Syndrome and Neurotoxicity With Chimeric Antigen Receptor T Cell Therapy Ciltacabtagene Autoleucel in Multiple Myeloma

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INTRODUCTION

- As chimeric antigen receptor T cell (CAR-T) therapies expand to different oncologic indications with new targets and constructs, it is crucial that patients receive the maximum benefit from treatment while mitigating serious adverse events (AEs) such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)[1]
- CARTITUDE-1 was a phase 1b/2 study investigating ciltacabtagene autoleucel (cilta-cel) in patients with relapsed or refractory multiple myeloma (MM) with ≥3 prior lines of therapy or are double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and prior exposure to PI, IMiD, and anti-CD38 antibody[2]
- In CARTITUDE-2, a multicohort phase 2 study, cilta-cel is evaluated in patients with MM in earlier-line settings
  - Cohort B consists of patients with early relapse after initial therapy with PI and IMiD or ASCT

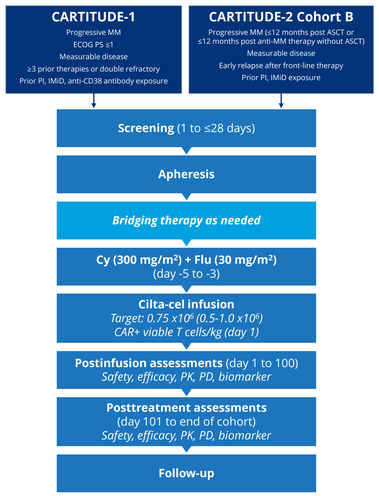
OBJECTIVES

- To characterize CRS and neurotoxicity data for the B-cell maturation antigen–targeting CAR-T cilta-cel from 2 MM clinical trials, CARTITUDE-1 and CARTITUDE-2 Cohort B
- To describe patient management strategies for movement and neurocognitive treatment-emergent AEs (MNTs) in the CARTITUDE program

METHODS

- Key CARTITUDE-1 and CARTITUDE-2 Cohort B eligibility criteria and study designs are found in **Figure 1**
  - The objectives of the phase 1b component of CARTITUDE-1 were to characterize safety and determine the recommended phase 2 dose
  - The primary endpoint of the phase 2 component of CARTITUDE-1 was overall response rate per International Myeloma Working Group criteria
  - The primary endpoint of CARTITUDE-2 was the rate of minimal residual disease negativity at the 10^{-5} threshold by next-generation sequencing
- In both studies, CRS and ICANS were graded per American Society for Transplantation and Cellular Therapy (ASTCT) criteria
  - For ICANS, phase 1b was graded by Common Terminology Criteria for Adverse Events, and phase 2 was graded by ASTCT criteria

FIGURE 1: CARTITUDE-1 and CARTITUDE-2 Cohort B study designs



ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; Cy, cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; Flu, fludarabine; IMiD, immunomodulatory drug; MM, multiple myeloma; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics.

RESULTS

CARTITUDE-1 Safety Update

- As of July 2021 (~2-year follow-up), there were no new safety signals observed relative to previously reported data at ~1 year follow-up[3]
  - 5 patients in CARTITUDE-1 experienced MNTs by the ~1-year follow-up[2]
  - There were no MNTs or treatment-related deaths since ~1-year median follow-up

Patient Management Strategies

- Patient management strategies for MNTs were implemented across the CARTITUDE development program, which decreased the overall incidence of MNTs (**Figure 2**)[4]
- Details for recognizing and grading ICANS with cilta-cel can be found in the **Table**

FIGURE 2: Management of movement and neurocognitive TEAEs in CARTITUDE program

1 **Movement and Neurocognitive TEAEs Risk Factors (2 or more)**
- High tumor burden at baseline[a]
- Grade ≥2 CRS
- ICANS
- High CAR-T cell expansion and persistence[b]

2 **Patient Management Strategies**
- Enhanced bridging therapy to reduce tumor burden[c]
- Early aggressive treatment of CRS and ICANS
- Handwriting assessments[c] and extended monitoring

3 **CARTITUDE Program Level**
- Approximately 200 patients have been dosed since implementation of these strategies in March 2020
- Implementation of patient management strategies in new and ongoing cilta-cel studies reduced overall incidence of MNTs from 5% to 0.5% as of October 2021

CAR, chimeric antigen receptor; C_{max}, maximum CAR transgene systemic level; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; MNT, movement and neurocognitive treatment-emergent adverse event; TEAE, treatment-emergent adverse event. [a]Defined as high tumor burden when any of the following parameters were met: bone marrow plasma cell ≥80%, serum, M spike ≥5 g/dL, serum-free light chain ≥5000 mg/L. [b]Patients with peripheral blood CAR-T cells C_{max} of >1000 cells/µL and CAR-T cells >300 cells/µL at day 56. [c]Enhanced bridging therapy may include therapies that a patient has not been previously exposed to and a short-term treatment (~1-2 cycles) to decrease tumor burden. [c]Assessments of qualitative changes in handwriting since baseline.

Table. Recognition and Grading of ICANS[5]

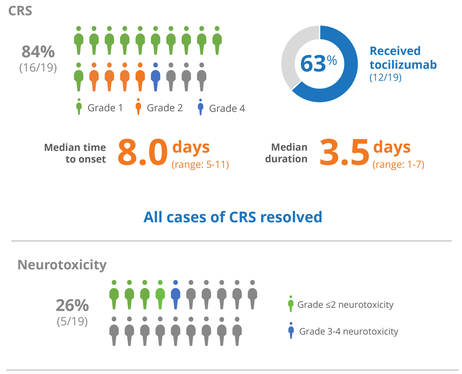
ICANS Grade	Presentation
1	ICE score 7-9[a]; depressed level of consciousness (awakens spontaneously)
2	ICE score 3-6[a] or depressed level of consciousness (awakens to voice)
3	ICE score 0-2[a,b]; depressed level of consciousness (awakens only to tactile stimulus) *Or* seizures (clinical focal or generalized seizures that resolve rapidly or nonconvulsive seizures on EEG that resolve with intervention) *Or* raised ICP with focal/local edema on neuroimaging
4	ICE score 0[a] (unarousable and unable to perform ICE) or patient is unarousable and requires repetitive tactile stimuli to arouse, or in stupor/coma) *Or* life-threatening prolonged (>5 min) or repetitive seizures without return to baseline in between *Or* motor findings (deep focal motor weakness such as hemiparesis or paraparesis) *Or* raised ICP/cerebral edema with sign/symptoms (eg, diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad)

EEG, electroencephalogram; ICE, Immune Effector-Cell Associated Encephalopathy assessment; ICP, intracranial pressure. [a]The ICE assessment assesses orientation (oriented to year, month, city, hospital = 4 points); naming (name 3 objects, eg, point to clock, pen, button = 3 points); following commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); writing (ability to write a standard sentence = 1 point); and attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points. [b]If ICE score is 0 but patient is arousable and able to perform assessment.

CARTITUDE-2 Cohort B Safety Update

- As of October 2021, 19 patients with early relapse of MM following 1 line of prior therapy including a PI and an IMiD have received cilta-cel
- Neurotoxicity and CRS incidence rates were comparable to those in CARTITUDE-1 (**Figure 3**)
- CRS occurred in 84% of patients (16 patients)
  - 1 patient had a grade 4 CRS event (5%)
  - Median time to CRS onset was 8 days (range, 5-11), with a median duration of 3.5 days (range, 1-7)
  - Tocilizumab was administered in 12 patients (63%)
  - CRS resolved in all patients
- Neurotoxicity occurred in 26% of patients (5 patients)
  - 1 patient had grade 1 ICANS with time to onset of 11 days and duration of 4 days
  - 4 patients had other neurotoxicity; 1 of these patients (male, 44 years) experienced grade 3 MNTs
    - This patient presented with bradykinesia, bradypsychia, cognitive impairment, encephalopathy, gait disturbance, and motor dysfunction on day 38 post cilta-cel
    - The patient had risk factors for MNTs (high baseline tumor burden, worsening disease burden despite bridging therapy, grade 4 CRS, high CAR-T cell expansion and persistence)
    - The patient was treated with high-dose methylprednisolone, plasmapheresis, and intravenous immunoglobulin
    - At data cutoff (July 2021), the patient was stable and achieved complete response to cilta-cel

FIGURE 3: Initial safety data for CARTITUDE-2 Cohort B (N=19)



CRS, cytokine release syndrome.

KEY TAKEAWAYS

Safety data collected in CARTITUDE studies have informed patient management strategy development that may assist nursing strategy (eg, frequent monitoring and recognizing symptoms, grading of CRS and ICANS, patient education) for management of AEs in patients receiving cilta-cel in the future

CONCLUSIONS

Since implementing patient management strategies, ~200 additional patients have been dosed, and overall MNT incidence has decreased from 5% to 0.5% (as of October 2021)

CARTITUDE-2 Cohort B neurotoxicity (including ICANS) and CRS incidence rates were comparable to those in CARTITUDE-1

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DISCLOSURES

ISM has received consultancy fees from Janssen Pharmaceuticals, Inc. JF and DM are employed by Janssen Pharmaceuticals, Inc.