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

# CYTOKINE RELEASE SYNDROME (CRS) IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM) TREATED WITH CILTACABTAGENE AUTOLEUCEL (CILTA-CEL) IN THE PHASE 1B/2 CARTITUDE-1 STUDY

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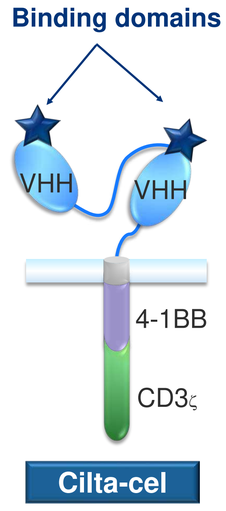
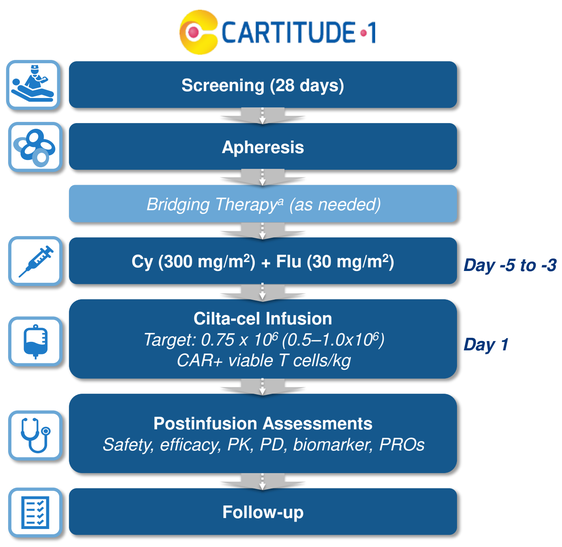
## INTRODUCTION

- Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor T cell (CAR-T) therapy
  - Contatains 2 B-cell maturation antigen (BCMA)-targeting single-domain antibodies designed to confer avidity
- The phase 1b/2 CARTITUDE-1 study (NCT03548207) is investigating the efficacy and safety of cilta-cel in relapsed/refractory multiple myeloma (MM)
  - A single, low-dose infusion of cilta-cel yielded early, deep, and durable responses in heavily pretreated patients with MM[1]
- Cytokine release syndrome (CRS) is a known side effect of CAR-T therapy; it can be mild to life-threatening and requires careful monitoring and management
- Here, we analyzed CRS and cytokine profiles in CARTITUDE-1




VHH, single variable domain on a heavy chain

### Figure 1. CARTITUDE-1 Study Design




**Key Eligibility Criteria**
- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- ≥3 prior therapies or double refractory
- Prior PI, IMiD, anti-CD38 therapy

ClinicalTrials.gov number NCT03548207; 01 Sept 2020 data cutoff; [a]Treatment with previously used agent resulting in at least stable disease. ASTCT, American Society for Transplantation and Cellular Therapy; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; Cy, cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; PI, proteasome inhibitor; PD, pharmacodynamic; PK, pharmacokinetic; PROs, patient-reported outcomes.

**Primary Objectives**
- Phase 1b: Characterize the safety of cilta-cel and confirm the recommended phase 2 dose
- Phase 2: Evaluate the efficacy (by ORR) of cilta-cel

**CRS Monitoring**
- Patients were admitted for inpatient monitoring from day of infusion (day 1) through day 14 post infusion; body temperature was monitored twice daily for 28 days post infusion
- Patients were to be monitored and hospitalized for evaluation at first sign of CRS

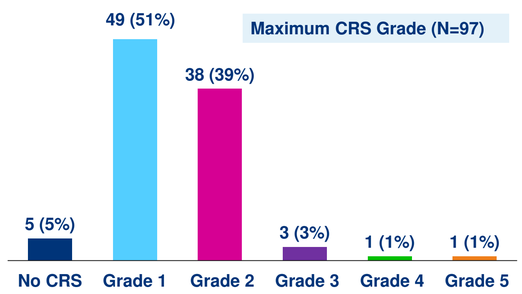
**CRS Grading**
- Lee et al (*Blood* 2014) criteria were used in the phase 1b portion and ASTCT in the phase 2 portion
- In this combined analysis, Lee et al criteria were mapped to ASTCT criteria for patients in the phase 1b portion

**Cytokine Sampling**
- Serum samples for cytokine profiling were collected prior to lymphodepletion, prior to cilta-cel infusion, and 2 hours post infusion on day 1, and on the following days until Day 100: Days 2, 3, 7, 10, 14, 21, 28, 42, 56, and 78
- Samples were also collected if CRS was suspected or reported

## RESULTS

- Of 92 patients with CRS, majority (94.6%) had grade 1/2 events
- CRS onset:
  - Day 4 or later: 89.1% (n=82)
  - Day 6 or later: 73.9% (n=68)
- CRS resolved in 91 (98.9%) patients within 14 days of onset
- Cilta-cel CAR+ T cells showed maximum peripheral expansion at a median of 13 days (range, 9–55)

### Figure 2. CRS Grades




CRS, cytokine release syndrome.

### Table 1. CRS Events in Cilta-cel–Treated Patients With RRMM

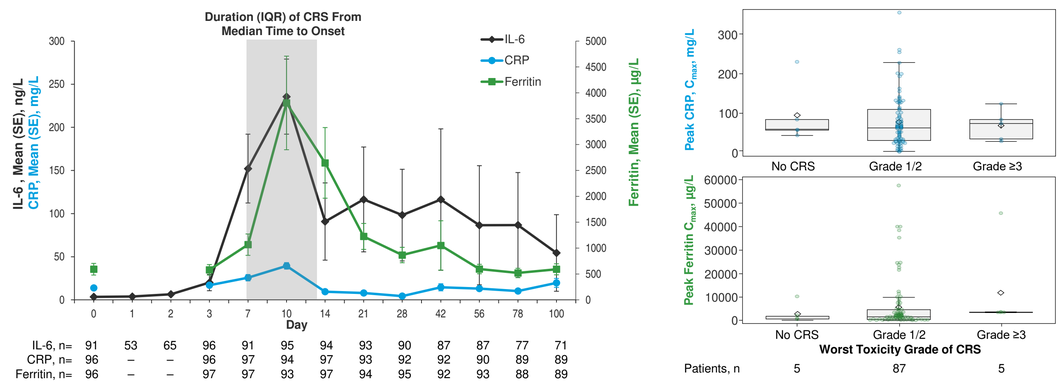
| | N=97 |
|---|---|
| Patients with a CRS event,[a] n (%) | 92 (94.8) |
| Median time to onset (range), days | 7.0 (1–12) |
| Median duration (range), days | 4.0 (1–97)[b] |
| Supportive measures, n (%) | 88 (90.7) |
| Tocilizumab | 67 (69.1) |
| Corticosteroids | 21 (21.6) |
| Anakinra | 18 (18.6) |
| Vasopressor used | 4 (4.1) |
| Intubation/mechanical ventilation | 1 (1.0) |
| Other | |
| Cyclophosphamide | 1 (1.0) |
| Etanercept | 1 (1.0) |

[a]CRS was graded using Lee et al (*Blood* 2014) in the phase 1b portion of the study and ASTCT in phase 2. In this combined analysis, Lee et al criteria were mapped to ASTCT criteria for patients in the phase 1b portion. [b]The patient with 97-day duration died due to CRS/HLH. ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; MM, multiple myeloma; R/R, relapsed/refractory.

## RESULTS *(cont.)*

- Across all patients, interleukin (IL)-6 levels peaked at Days 7–14 post–cilta-cel infusion (**Figure 3**), as did IL-10 and interferon (IFN)-γ levels
- C-reactive protein (CRP) and ferritin trends follow cytokine levels and can be useful in monitoring CRS
- No association was observed between CRS severity and baseline (data not shown) or peak levels of CRP or ferritin

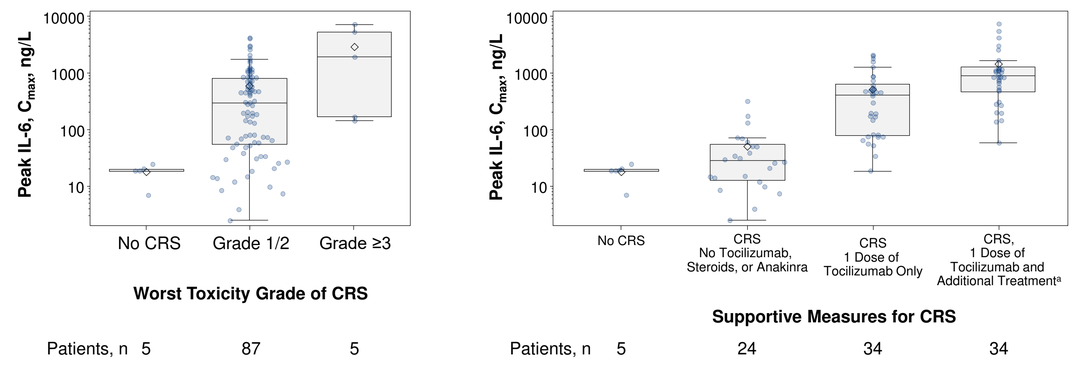
### Figure 3. IL-6, CRP and Ferritin Levels in Cilta-cel–Treated Patients




Cilta-cel, ciltacabtagene autoleucel; $C_{max}$, maximum concentration; CRP, C-reactive protein; CRS, cytokine release syndrome; IL, interleukin; IQR, interquartile range; SE, standard error.

- CRS severity and supportive measures were associated with peak IL-6 levels (**Figure 4**), as well as peak levels of IL-10 and IFN-γ (data not shown)

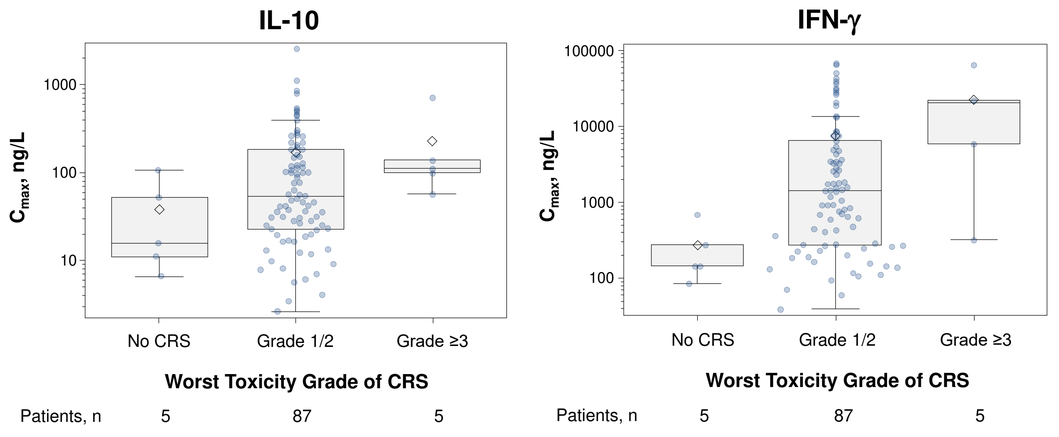
### Figure 4. Peak IL-6 Levels by CRS Severity and Supportive Measures




[a]Additional dose of tocilizumab, steroids, and/or anakinra. $C_{max}$, maximum concentration; CRS, cytokine release syndrome; IL, interleukin.

- CRS severity was associated with peak IL-10 and IFN-γ levels (**Figure 5**)
- Results were similar for other cytokines including IL-2, IL-8, soluble IL-2Rα, and tumor necrosis factor-γ (data not shown)

### Figure 5. Peak IL-10 and IFN-γ Levels by CRS Severity




$C_{max}$, maximum concentration; CRS, cytokine release syndrome; IFN, interferon; IL, interleukin.

## CONCLUSIONS

- CRS after cilta-cel treatment was low grade and manageable in most patients with RRMM
- Increasing severity of CRS and supportive measures for CRS
  - Were associated with peak IL-6, IL-10 and IFN-γ cytokine levels
  - Were not associated with baseline or peak CRP and ferritin levels
- CRP and ferritin trends follow cytokine levels and can be useful in monitoring CRS
- Due to the low rate (5%) of grade ≥3 CRS and median time to CRS onset of 7.0 days, outpatient dosing of cilta-cel is being explored in the phase 2 CARTITUDE-2 (NCT04133636) and phase 3 CARTITUDE-4 (NCT04181827) studies

## REFERENCES

1. Madduri, D et al. Cartitude-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/Refractory Multiple Myeloma. Oral Presentation. Presented at 2020 American Society of Hematology Annual Meeting.

**https://comylive.cme-congresses.com/**

*Previously presented at ASH 2020*