Ciltacabtagene autoleucel in patients with relapsed/refractory multiple myeloma: CARTITUDE-1 (phase 2) Japanese cohort

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Abstract
Chimeric antigen receptor (CAR) T cells targeting B-cell maturation antigen have shown positive responses in patients with multiple myeloma (MM). The phase 2 portion of the CARTITUDE-1 study of ciltacabtagene autoleucel (cilta-cell) included a cohort of Japanese patients with relapsed/refractory MM. Following a conditioning regimen of cyclophosphamide (300 mg/m²) and fludarabine (30 mg/m²), patients received a single cilta-cell infusion at a target dose of 0.75 × 10⁶ (range, 0.5–1.0 × 10⁶) CAR-positive viable T cells/kg. The primary endpoint was overall response rate (ORR; defined as partial response or better) by International Myeloma Working Group criteria. A key secondary endpoint was the rate of very good partial response (VGPR) or better (defined as VGPR, complete response, stringent complete response). This first analysis was performed at 6 months after the last patient received cilta-cell. Thirteen patients underwent apheresis, nine of whom received cilta-cell infusion. Eight patients who received cilta-cell at the target dose responded, yielding an ORR of 100%. Seven of eight (87.5%) patients achieved a VGPR or better. One additional patient who received a below-target dose of cilta-cell also achieved a best response of VGPR. MRD negativity (10⁻⁵ threshold) was achieved in all six evaluable patients. Eight of nine (88.9%) patients who received cilta-cell infusion experienced a grade 3 or 4 adverse event, and eight (88.9%) patients experienced cytokine release syndrome (all grade 1 or 2). No CAR-T cell neurotoxicity was reported. A positive benefit/risk profile for cilta-cell was established for heavily pretreated Japanese patients with relapsed or refractory MM.
1 | INTRODUCTION

Multiple myeloma, which accounts for 10% of hematologic malignancies, is a B-cell malignancy characterized by uncontrolled proliferation of monoclonal plasma cells. Despite progress in MM therapeutics, including PI, IMiD, and monoclonal antibodies, and dramatically improved patient outcomes, MM remains incurable, with a high risk of relapse. Patients who become resistant to existing therapies have poor prognoses, with overall survival less than 1 year. Therefore, there is an unmet medical need for treatments with novel mechanisms of action that can provide durable responses, avoid resistance, and are well tolerated.

Activation of the immune system to target MM is a strategy driving the development of novel MM therapeutics, including CAR-T cells genetically modified to target antigens expressed on MM cells. BCMA is a cell surface protein exclusively expressed on the B-cell lineage and is involved in the differentiation and maturation of B cells into plasma cells. In MM cell lines and patient samples, BCMA has been shown to be more stably expressed on the B-cell lineage than the plasma cell marker CD138. The expression characteristics of BCMA make it an ideal therapeutic target in the treatment of MM.

Cilta-cel is a CAR-T cell product expressing two BCMA-targeting single-domain antibodies, designed to confer avidity, and a CD3ζ signaling domain with a 4-1BB costimulatory domain to optimize T-cell activation and proliferation. It was recently approved by the US Food and Drug Administration and the European Medicines Agency based on the results of CARTITUDE-1, a phase 1b/2 open-label study of cilta-cel, in which deep and durable responses and a manageable safety profile were observed in heavily pretreated non-Japanese patients with RRMM. The phase 2 portion of the study also had a protocol-specified separate Japanese cohort to characterize cilta-cel efficacy and safety in Japanese patients with RRMM, whose prior regimens included a PI, an IMiD, and an anti-CD38 antibody, and who had disease progression at time of or after the last regimen. Here, we describe the first analysis of the Japanese cohort in the phase 2 part of CARTITUDE-1.

2 | MATERIALS AND METHODS

2.1 | Study population

Male and female patients aged ≥20 years with a documented diagnosis of MM according to IMWG diagnostic criteria and an ECOG performance status score of 0 or 1 were included in the study. Patients had to have measurable disease at screening defined as serum M-protein level ≥1.0 g/dl or urine M-protein level 200mg/24h; light chain MM for patients without measurable disease in the serum or the urine (serum Ig free light chain ≥10 mg/dl and abnormal serum Ig kappa lambda free light chain ratio); received at least three prior lines of therapy or were double refractory to a PI and an IMiD, and had undergone at least one complete cycle of treatment for each regimen; received a PI, an IMiD, and an anti-CD38 antibody; and had documented disease progression during or within 12 months of their most recent antimyeloma therapy. Patients with documented disease progression within the previous 6 months and who were refractory or nonresponsive to their most recent line of therapy were also eligible.

Exclusion criteria included previous treatment with CAR-T cell-based therapy, history of therapy targeted against BCMA, diagnosis or treatment for invasive malignancy other than MM, or toxicity from previous anticancer therapy that resolved to baseline levels or grade ≤1 (except for alopecia or peripheral neuropathy).

The study protocol was approved by the institutional review board at each study site, and the study was conducted following the ethical principles of the Declaration of Helsinki, consistent with Good Clinical Practice guidelines and applicable regulatory requirements. Patients or their legal representatives provided written consent to participate after being informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment. Patients or their representatives signed consent before any study-related activity was performed.

2.2 | Study design

CARTITUDE-1 is a phase 1b and 2, open-label, multicenter study. In the protocol, in addition to the main cohort of phase 1b/2 conducted in the USA, a separate cohort of Japanese patients was enrolled in phase 2 portion to further evaluate population-specific safety and efficacy.

After screening, eligible patients underwent apheresis for collection of peripheral blood mononuclear cells. Cilta-cel was manufactured from T cells collected from the apheresis. The target dose was informed by the LEGEND-2 clinical study, and then confirmed in 29 patients enrolled in phase 1b of the CARTITUDE-1 study. If clinically indicated, bridging therapy could be chosen among previously received agents at the investigator’s discretion to maintain disease stability while waiting for manufacturing of cilta-cel. Patients achieving CR after bridging therapy were considered ineligible to receive cilta-cel.

Patients received cyclophosphamide (300 mg/m²) and fludarabine (30 mg/m²) daily for 3 days. The dose of fludarabine could be reduced to 24 mg/m² for patients with an estimated glomerular filtration rate 30–70 ml/min/1.73 m². Cilta-cel was administered on
day 1, 5–7 days after the start of the conditioning regimen. Patients received premedication with an antihistamine and an antipyretic. A single infusion of cilta-cel was given at a target dose of $0.75 \times 10^6$ CAR-positive viable T cells/kg (range, $0.5–1.0 \times 10^6$ CAR-positive viable T cells/kg). Per protocol, all patients in the Japanese cohort were required to be hospitalized from the start of the conditioning regimen until ≥2 weeks after receiving the cilta-cel infusion.

### 2.3 | Pharmacokinetic/pharmacodynamic evaluations

Cilta-cel quantifiable CAR transgene levels were measured in serial blood and bone marrow samples by validated quantitative polymerase chain reaction (TaqMan). The LLOQ of CAR transgene was 50 copies/µg host genomic DNA. Serum samples were assessed for changes in circulating sBCMA using a validated electrochemiluminescent immunoassay on the mesoscale discovery platform. The LLOQ of sBCMA was 0.25000 ng/ml. Noncompartmental analysis was applied for the PK parameter analysis for CAR transgene levels in the blood. Calculated PK parameters were $C_{\text{max}}$, $t_{\text{max}}$, $t_{\text{last}}$, and $AUC_{0-28d}$.

### 2.4 | Efficacy and safety evaluations

The primary efficacy endpoint was ORR defined as the proportion of patients who achieved PR or better assessed by an IRC according to IMWG response criteria.$^{14–17}$

Secondary efficacy endpoints included VGPR or better (defined as VGPR, CR, stringent CR), DOR, MRD-negativity rate determined by NGS with a sensitivity of at least $10^{-5}$, TTR, PFS, and OS.

AEs were collected after infusion of cilta-cel and graded using NCI CTCAE version 5.0. CRS and ICANS were graded according to American Society for Transplantation and Cellular Therapy criteria.$^{18}$ Other neurotoxicities were graded by NCI CTCAE version 5.0. Guidelines for evaluating CRS and ICANS for the CARTITUDE-1 study have been previously described.$^{11}$ Body temperature was measured with an oral thermometer at least twice a day until day 28, as with the main cohort. Treatment for CRS was at the discretion of the investigator following protocol guidelines.

### 2.5 | Statistical analysis

The primary analysis was performed at 6 months after the last patient in the Japanese cohort had received cilta-cel. The sample size of eight patients for the Japanese cohort was calculated based on the probability of showing results in the primary efficacy evaluation consistent with the non-Japanese cohort, i.e., the probability of observing an ORR of >30% with the assumption that the true ORR is 50%.$^{13,19–21}$ The mITT analysis set consisted of patients who received a cilta-cel infusion at the target dose level (i.e., within the target dose range), and was the primary analysis set for all efficacy evaluations. The all-treated analysis set consisted of all patients who received a cilta-cel infusion and was the primary analysis set for safety evaluations. The PK analysis set consisted of patients who received a cilta-cel infusion and had at least one post-dose PK assessment. The sBCMA analysis set consisted of patients who received a cilta-cel infusion and had at least one evaluable sBCMA concentration measurement.

Descriptive statistics were used to summarize means with standard deviations or medians with minimum and maximum for continuous variables and counts and percentages for categorical variables. For the primary efficacy endpoint analysis, the response and its twosided 95% Clopper–Pearson exact CI were presented, and the p-value from a one-sided exact binomial test for the null hypothesis of ORR ≤30% was provided for descriptive purpose. The secondary endpoint analyses of VGPR or better, PFS, and OS were conducted at the same cutoff as the ORR, VGPR or better and MRD-negativity rate and its two-sided 95% Clopper–Pearson exact CI were presented. The distributions of DOR, PFS, and OS were obtained using Kaplan–Meier estimates. TTR was summarized descriptively. As formal statistical testing was not planned for the Japanese cohort, and the type I error was not controlled, the presented p-values are nominal. Descriptive statistics were used to summarize transgene levels at each sampling time point. Summary statistics were tabulated for PK parameters. Pharmacodynamic evaluations were analyzed using descriptive statistics.

### 3 | RESULTS

#### 3.1 | Study population and treatments

Four sites in Japan participated in this study from December 11, 2019, to February 11, 2021. Of the 15 patients screened, 13 were enrolled (apheresed). Four patients (30.8%) discontinued from the study after apheresis (two due to disease progression; one each due to AEs [positive Cryptococcus test] and consent withdrawal). Nine patients received the conditioning regimen and cilta-cel infusion. Eight patients received a cilta-cel infusion at the target dose and were included in the mITT analysis set. One patient received a below-target dose range of cilta-cel ($0.41 \times 10^6$ CAR-positive viable T cells/kg).

Among all the-treated analysis set ($N = 9$), five (55.6%) patients were male; four (44.4%) were female. The median age was 57 (range, 45–71) years. A majority of patients (77.8%) had an ECOG performance status score of 0 prior to cilta-cel infusion (Table 1). A majority of patients (88.9%) had IgG myeloma and 33.3% of patients had bone-based plasmacytomas at baseline. The median time from diagnosis of MM to study enrollment was 5.41 years. High-risk cytogenetic profile was found in five of nine patients (55.6%) at baseline, including five patients with del17p. The median number of prior lines of therapy was 5 (range, 3–7). Eight of nine patients (88.9%) received prior stem cell transplant, of which two received prior allogeneic
One patient received prior radiotherapy. All patients had prior exposure to PIs, IMiDs, alkylating agents, and anti-CD38 antibody. Eight of nine (88.9%) patients were triple-class refractory (to PI, IMiD, and anti-CD38 antibody), and two (22.2%) were pentarefractory (including two or more PIs, two or more IMiDs, and one or more anti-CD38 antibody).

Bridging therapy was administered to all nine patients, and the most common agents were dexamethasone (all patients), carfilzomib and lenalidomide (five [55.6%] patients each), and bortezomib and daratumumab (two [22.2%] patients each). Seven (77.8%) patients who received bridging therapy had an increase in tumor burden, while two patients had a decrease in tumor burden (one patient had a decrease >50%). No patient had a CR after bridging therapy. The median turnaround time (defined as time from receipt of the apheresis material to release of product for shipment to the clinical site) was 30 days (range, 23–53 days).

After the conditioning regimen, cilta-cel was administered to nine patients, at a median dose of $0.624 \times 10^6$ CAR-positive viable T cells/kg (range, $0.41 \times 10^6$ to $0.72 \times 10^6$ CAR-positive viable T cells/kg). Acyclovir (antiviral), levofloxacin, sulfamethoxazole–trimethoprim and cefepime (antibacterial), and fluconazole (antifungal) were administered for infection prophylaxis.

### Pharmacokinetic/pharmacodynamic results

The nine patients who received the cilta-cel infusion were included in the PK analysis set and sBCMA analysis set. Quantifiable CAR transgene levels in the blood were observed from day 7 or 10 following cilta-cel infusion onward (Figure 1A). The median $t_{\text{max}}$ of CAR transgene levels in blood was 12.87 (range, 8.72–13.84) days. The mean (SD) CAR transgene values were $44,077 (39,911)$ copies/μg genomic DNA for $C_{\text{max}}$, and $592,118 (747,395)$ day × copies/μg genomic DNA for $AUC_{0-28d}$ (Table 2). Interindividual variability (expressed as % CV) was high for both $C_{\text{max}}$ (90.5%) and $AUC_{0-28d}$ (126.2%).

Comparable mean levels of CAR transgene in the bone marrow were observed on days 28 and 56; on day 184, six of nine patients...
**FIGURE 1** (A) Blood chimeric antigen receptor (CAR) transgene levels. (B) Soluble B-cell maturation antigen (sBCMA) concentration over time. LLOQ, lower limit of quantitation.

**TABLE 2** Pharmacokinetic results of CAR transgene in blood

| Pharmacokinetics of transgene                             | Japanese cohort (N = 9) | Main cohort (N = 97) |
|-----------------------------------------------------------|-------------------------|----------------------|
| C<sub>max</sub>, copies/μg genomic DNA (mean [SD])        | 44,077 (39,911)         | 48,692 (27,174)      |
| t<sub>max</sub>, day (median [range])                     | 12.87 (8.72–13.84)      | 12.71 (8.73–329.77)  |
| t<sub>last</sub>, day (median [range])                    | 129.89 (24.97–324.88)   | 125.90 (20.04–702.12) |
| AUC<sub>0-28d</sub> day × copies/μg genomic DNA (mean [SD]) | 592,118 (747,395)       | 504,496 (385,380)    |

Abbreviations: AUC<sub>0-28d</sub>, area under the concentration–time curve from dosing (time 0) to 28 days; CAR, chimeric antigen receptor; C<sub>max</sub>, maximum concentration; SD, standard deviation; t<sub>last</sub>, time of last measurable concentration; t<sub>max</sub>, time to C<sub>max</sub>.

**TABLE 3** Summary of bone marrow concentrations of CAR transgene

| CAR-T copies/μg genomic DNA | Prior to first dose of conditioning regimen (N = 9) | Day 28 (N = 7) | Day 56 (N = 9) | Day 184 (N = 9) |
|-----------------------------|-----------------------------------------------------|----------------|----------------|----------------|
| Mean [SD]                   | BQL                                                 | 9593 (16447)   | 9316 (16450)   | BQL            |
| Range                       | BQL–BQL                                             | BQL–42562      | BQL–46304      | BQL–34384      |
| % CV                        | ...                                                 | 171.5          | 176.6          | ...            |

Abbreviations: BQL, below quantification limit; CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T cell; CV, coefficient of variation. BQL: <50 CAR-T copies/μg genomic DNA.
were BQL for levels of CAR transgene in bone marrow. Similar to blood transgene levels, bone marrow transgene levels also exhibited high interindividual variability (Table 3).

Regardless of baseline value, a significant decrease in sBCMA concentration was observed within 30 days after cilta-cel infusion (Figure 1B), suggesting CAR-T cell-mediated pharmacodynamic activity.

### 3.3 | Efficacy and safety results

At the clinical cutoff date of February 11, 2021, representing 6 months after the last patient received cilta-cel and median follow-up of 8.51 months, the ORR (primary endpoint) for the mITT analysis set (n = 8) was 100% (95% CI, 63.1–100) by IRC assessment (Table 4). The ORR for all-treated analysis set (n = 9) was also 100% (95% CI, 66.4–100). Sensitivity analyses of ORR based on investigator assessment were consistent with IRC assessment. Regarding secondary endpoints, in the mITT analysis set, 87.5% of patients (95% CI, 47.3–99.7) achieved a response of VGPR or better and 25.0% (95% CI, 3.2–65.1) achieved CR or better, as adjudicated by IRC (Table 4). Responses deepened over time for seven out of the eight patients (Figure 2). In the mITT analysis set, the median (range) times to first response (PR or better), best response, and CR or better were 0.92 (0.9–1.8), 4.12 (0.9–6.9), and 5.59 (4.3–6.9) months, respectively. MRD negativity by NGS was achieved in all six patients who were evaluable for MRD at a sensitivity level of 10⁻⁵ in the mITT analysis set (Table 5). Two patients were not evaluable primarily due to insufficient material in the bone marrow sample. The median time to MRD negativity was 0.94 (range, 0.9–6.0) months at the time of clinical cutoff. In the mITT and all-treated analysis sets, all DOR, PFS, and OS data were censored at the clinical cutoff, therefore median DOR, PFS, and OS were not reached. The 9-month PFS rate was 100% (95% CI, 100–100) for both the mITT and all-treated analysis sets. The estimated 12-month OS rates were 100% (95% CI, 100–100) for both analysis sets. The patient who received a below-target dose achieved a best response of VGPR and was MRD positive.

All nine patients experienced at least one AE. No death was reported during the study. Eight (88.9%) patients experienced one or more grade 3 or 4 AEs (Table 6). Serious AEs related to cilta-cel were reported in one patient (neutropenia, thrombocytopenia, fatigue, and CRS). CRS was reported in eight (88.9%) patients (grade 1 or 2); the median time from cilta-cel infusion to CRS onset was 7.5 days (range, 4–11 days), and all CRS events recovered within 2–6 days (median 5 days). Supportive measures to treat CRS were administered to all eight patients; seven patients received tocilizumab, three patients received corticosteroids, and one patient received nasal cannula low flow oxygen. Three patients experienced a grade 3 or 4 transaminase increase; three had increased aspartate aminotransferase, one had increased alanine aminotransaminase, and one had increased gamma-glutamyl transferase. All events of increased transaminase were reported as related to CRS and resolved quickly after resolution of CRS. No patient experienced CAR-T cell neurotoxicity (including ICANS and other neurotoxicity). Grade 3 or 4 cytopenias were reported in eight (88.9%) patients; eight (88.9%) had neutropenia, seven (77.8%) had thrombocytopenia, six (66.7%) had anemia, and four (44.4%) had leukopenia. Of the patients who reported grade 3 or 4 thrombocytopenia and lymphopenia, most resolved by day 60; two (22.2%) patients continued to experience grade 3/4 neutropenia after day 60. One patient reported infections (grade 2 bacteremia and upper respiratory tract infection) that resolved. There were no second primary malignancies and no AEs of tumor lysis syndrome reported.

### Table 4 | Overall best response based on independent review committee assessment: mITT analysis set

| Best response          | mITT analysis set (N = 8) | n (%) | 95% CI for % |
|------------------------|---------------------------|-------|--------------|
| Stringent complete     | 2 (25.0)                  | 3.2–65.1 |
| Complete response      | 0                         | NE–NE |
| Very good partial      | 5 (62.5)                  | 24.5–91.5 |
| Partial response       | 1 (12.5)                  | 0.3–52.7 |
| Minimal response       | 0                         | NE–NE |
| Stable disease         | 0                         | NE–NE |
| Progressive disease    | 0                         | NE–NE |
| Not evaluable          | 0                         | NE–NE |
| Overall response       | 8 (100.0)                 | 63.1–100.0 |
| p-value                | <0.0001                   |        |
| Clinical benefit       | 8 (100.0)                 | 63.1–100.0 |
| VGPR or better         | 7 (87.5)                  | 47.3–99.7 |
| CR or better           | 2 (25.0)                  | 3.2–65.1 |
| MRD-negative CR/sCR   | 0                         | NE–NE |

Abbreviations: CI, confidence interval; CR, complete response; mITT, modified intent to treat; MR, minimal response; MRD, minimal residual disease; NE, not evaluable; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

### 4 | DISCUSSION

Consistent with the non-Japanese cohort in CARTITUDE-1,¹¹ a single-dose infusion of cilta-cel at target dose of 0.75×10⁶ CAR-positive viable T cells/kg (range, 0.5–1.0×10⁶ CAR-positive viable T cells/kg) resulted in deep and durable response in Japanese patients with RRMM. ORR was 100%, with 87.5% of patients achieving a response of VGPR or better, and 25.0% of patients achieving a response of CR or better. All six patients in the mITT dataset evaluable for MRD status achieved MRD negativity in bone marrow samples at a sensitivity level of 10⁻⁵. The results also showed initial evidence of durable response, with median follow-up of 8.51 months, in all treated patients. Responses were maintained in all patients over the follow-up period; median DOR was not reached and 100% of the patients were alive and in remission.
The efficacy results observed in the Japanese cohort are largely consistent with the non-Japanese cohort in CARTITUDE-1. The ORR, rate of VGPR or better, and MRD negativity in evaluable patients were 100%, 87.5%, and 100%, respectively, in the Japanese cohort compared with the non-Japanese cohort with 96.9%, 92.8%, and 93.0%, respectively.

The CR/sCR rate at 6-month follow-up in the Japanese cohort was 25%, but it is possible that responses will deepen over time, as they did in the main cohort (from 67% sCR at 12 months median follow-up to 83% sCR at 28 months). One of the criteria for CR is a negative result of M-protein in serum and urine; because the half-life of IgG is ~25 days, complete clearance may take several months. This clearance time may underlie a deepening response over time, as well as explain why the MRD-negativity rate is higher than the sCR rate at this early analysis. In the KarMM study of idecabtagene vicleucel (ide-cel) in patients with RRMM, it has been reported that patients with the IgG subtype tend to have a lower CR rate. The Japanese cohort of CARTITUDE-1 included more patients with IgG subtype than the main cohort (87.5% vs 58.8%), which may have impacted the CR rate in the Japanese population. Additionally, the Japanese cohort included more subjects with aggressive prognostic factors: plasmacytoma (33.3% vs 19.6%) and high cytogenetic risk (50% vs 23.7%), which could also affect CR rates. Further analysis is needed to evaluate the CR response rate in the Japanese cohort over longer follow-up.

PK parameters of the CAR transgene in peripheral blood were comparable between the Japanese cohort and main cohort. In the Japanese cohort, the median t\text{max} of CAR transgene levels in blood was very similar with that of the main cohort (12.87 and 12.71 days, respectively), as were the mean CAR transgene values (C\text{max}, 44,077 vs 48,501 copies/μg genomic DNA) (data on file). Similar to the main cohort, the comparable CAR transgene levels were observed in both peripheral blood and bone marrow. sBCMA concentration reduced rapidly after cilta-cel infusion and the decrease was sustained. Previous studies with CAR-T cell therapies noted a relationship between CAR-T cell persistence and clinical response; no such relationship was observed for cilta-cel in either cohort. However, the sustained sBCMA decrease suggests a relationship between sBCMA levels and clinical response.

Cilta-cel is among several BCMA-targeting agents used in MM. Belantamab mafodotin, an anti-BCMA monoclonal antibody conjugated to a microtubule disrupting agent, had an ORR of 31–34% depending on the dose. Teclitamab, a BCMA \times CD3 bispecific antibody had an ORR of 65%. The first-in-human study of a BCMA-targeting CAR with a CD28 costimulatory domain had an ORR of 81%. Ide-cel, a BCMA-targeting CAR with the same costimulatory domain as cilta-cel had an ORR of 73%. Although the number of enrolled patients in this study is small and the study population is different among studies, cilta-cel has a higher response rate in patients with RRMM compared with other BCMA-targeting agents.
Overall, the safety profile of cilta-cel in Japanese patients was generally within the current understanding of CAR-T cell therapy and was similar to that of the main cohort in CARTITUDE-1.11 No new safety signals were identified in the Japanese cohort. No fatal event due to AE occurred, and no second primary malignancies were observed. Only one patient experienced serious AEs related to cilta-cel. The most common AE was cytopenia, similar to non-Japanese patients in the main cohort11 and patients with RRMM treated with ide-cel.27 Grade 2 infections occurred in one patient, and no grade ≥3 infection events were reported. Careful monitoring and infection prophylaxis were key to this outcome. The incidence of CRS (88.9%) was comparable with the main cohort (95% of patients) and to patients treated with ide-cel (84%); most events were grade 1 or 2 in both studies.11,27 All CRS events in the Japanese cohort were grade 1 or 2, and CRS time to onset was consistent with those in the main cohort.

In the Japanese cohort, there were no cases of CAR-T cell neurotoxicity, including movement and neurocognitive toxicities. In contrast, the main cohort of CARTITUDE-1 reported CAR-T cell neurotoxicity in 20.6% of cilta-cel–treated patients (10% grade ≥3), including movement and neurocognitive TEAEs consistent with parkinsonism in 6% of patients.11,22 The KarMMa study of ide-cel reported 28% with neurotoxicities (4% grade ≥3).27 The use of corticosteroids and/or tocilizumab for the treatment of CRS was similar in the Japanese cohort (33% of patients) compared with the main cohort (22%; 69%) and ide-cel (15%; 52%). Notably, there was one patient in the Japanese cohort who had very high CAR-T cell expansion and persistence (Figure 1A). This patient was treated with tocilizumab and steroid therapy for grade 1 CRS and did not develop CAR-T cell neurotoxicity.

The high proportion of patients who were enrolled (31%) but were unable to receive cilta-cel reflects the advanced stage of disease of the enrolled population and highlights the need to carefully select candidates for therapy.

Although this study in Japanese patients has limitations, including a small sample size, lack of baseline tumor BCMA expression, nominal p-values, and 8.5 months of follow-up, there are several

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**TABLE 6**

| TEAEs, n (%) | All-treated analysis set (N = 9) | Total | Grade 3 or 4 | Grade 5 |
|--------------|----------------------------------|-------|--------------|--------|
| Total number of patients with TEAEs | 9 (100.0) | 8 (88.9) | 0 |

**System organ class/preferred term**

| Blood and lymphatic system disorders | 8 (88.9) | 8 (88.9) | 0 |
| Neutropenia | 8 (88.9) | 8 (88.9) | 0 |
| Thrombocytopenia | 7 (77.8) | 7 (77.8) | 0 |
| Anemia | 6 (66.7) | 6 (66.7) | 0 |
| Leukopenia | 4 (44.4) | 4 (44.4) | 0 |
| Febrile neutropenia | 3 (33.3) | 3 (33.3) | 0 |
| Hypofibrinogenemia | 2 (22.2) | 2 (22.2) | 0 |
| Lymphocytosis | 2 (22.2) | 1 (11.1) | 0 |
| Immune system disorders | 8 (88.9) | 0 | 0 |
| Cytokine release syndrome | 8 (88.9) | 0 | 0 |
| Nervous system disorders | 4 (44.4) | 0 | 0 |
| Headache | 3 (33.3) | 0 | 0 |
| Somnolence | 1 (11.1) | 0 | 0 |
| Gastrointestinal disorders | 3 (33.3) | 0 | 0 |
| Nausea | 3 (33.3) | 0 | 0 |
| Vomiting | 3 (33.3) | 0 | 0 |
| Diarrhea | 2 (22.2) | 0 | 0 |
| Investigations | 3 (33.3) | 3 (33.3) | 0 |
| Aspartate aminotransferase increased | 3 (33.3) | 3 (33.3) | 0 |
| Alanine aminotransferase increased | 2 (22.2) | 1 (11.1) | 0 |
| Blood lactate dehydrogenase increased | 1 (11.1) | 0 | 0 |
| Gamma-glutamyl transferase increased | 1 (11.1) | 1 (11.1) | 0 |
| Metabolism and nutrition disorders | 3 (33.3) | 1 (11.1) | 0 |
| Hypokalemia | 2 (22.2) | 1 (11.1) | 0 |
| Decreased appetite | 1 (11.1) | 0 | 0 |
| Fluid retention | 1 (11.1) | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 2 (22.2) | 0 | 0 |
| Arthralgia | 1 (11.1) | 0 | 0 |
| Back pain | 1 (11.1) | 0 | 0 |
| Vascular disorders | 2 (22.2) | 0 | 0 |
| Embolism | 1 (11.1) | 0 | 0 |
| Hypertension | 1 (11.1) | 0 | 0 |

**TABLE 6** (Continued)

| TEAEs, n (%) | All-treated analysis set (N = 9) | Total | Grade 3 or 4 | Grade 5 |
|--------------|----------------------------------|-------|--------------|--------|
| General disorders and administration-site conditions | 1 (11.1) | 1 (11.1) | 0 |
| Fatigue | 1 (11.1) | 1 (11.1) | 0 |
| Malaise | 1 (11.1) | 1 (11.1) | 0 |
| Infections and infestations | 1 (11.1) | 0 | 0 |
| Bacteremia | 1 (11.1) | 0 | 0 |
| Upper respiratory tract infection | 1 (11.1) | 0 | 0 |

Abbreviation: TEAE, treatment-emergent adverse event.
important findings. A single infusion of cilta-cel in the heavily pre-
treated Japanese patient resulted in deep and durable responses. The
efficacy, safety, and PK profiles observed in the Japanese cohort are
largely consistent with the main cohort of the study. Combined
with the unprecedented data from the main cohort of the study, it
is anticipated that cilta-cel will provide an important treatment op-
tion in this patient population with unmet medical need and poor
prognosis.

In conclusion, a positive benefit/risk profile for cilta-cel was es-
lished in Japanese patients with heavily pretreated RRMM. The
present study also provides evidence for a cilta-cel safety profile
generally consistent with the current understanding of CAR-T cell
therapy. The results of the Japanese cohort in the CARTITUDE-1
study suggest that cilta-cel is an effective and well tolerated treat-
ment with high therapeutic potential.

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The data sharing policy of Janssen Pharmaceutical Companies of
Johnson & Johnson is available at https://www.janssen.com/clini-
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tion of data. Tzu-Min Yeh, Tomoyoshi Hatayama, and Kensuke Aida
contributed to the analysis of data. All authors contributed to the
interpretation of data as well as critical revision of the manuscript for
important intellectual content. The authors ensured that questions related to the accuracy or integrity
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