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CILTACABTAGENE AUTOLEUCEL FOR THE TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA WHO HAVE RECEIVED AT LEAST 1 PRIOR LINE OF THERAPY, INCLUDING A PROTEASOME INHIBITOR AND AN IMMUNOMODULATORY AGENT, AND ARE REFRACTORY TO LENALIDOMIDE

SPONSOR BRIEFING DOCUMENT

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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ADVISORY COMMITTEE BRIEFING MATERIALS AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Abbreviation	Definition
AE(s)	Adverse event(s)
AESI(s)	Adverse event(s) of special interest
ALC	Absolute lymphocyte count
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T (cells)
CMH	Cochran-Mantel-Haenszel
CPW	Constant piecewise weighted (log-rank test)
CR	Complete response
CRS	Cytokine release syndrome
DoR	Duration of response
DPd	Daratumumab, pomalidomide, and dexamethasone
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item
FDA	Food and Drug Administration
GHS	Global health status
HLH	Hemophagocytic lymphohistiocytosis
HR	Hazard ratio
HRQoL	Heath-related quality of life
ICANS	Immune Effector Cell-associated Neurotoxicity Syndrome
ICF	Informed consent form
IHC	Immunohistochemistry
IMiD	Immunomodulatory agent
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
ISS	International Staging System
ITT	Intent-to-treat
IVIG	Intravenous immunoglobulin

LLOQ	Lower limit of quantification
LS	Least squares
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimally important difference
MNT	Movement and neurocognitive toxicity
MRD	Minimal residual disease
MySIm-Q	Multiple Myeloma Symptom and Impact Questionnaire
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NGS	Next-generation sequencing
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PFS2	PFS on next-line therapy
PI	Proteasome inhibitor
PK	Pharmacokinetic
PR	Partial response
PRIME	PRIority Medicines
PRO(s)	Patient-reported outcome(s)
PVd	Pomalidomide, bortezomib, and dexamethasone
SAE(s)	Serious adverse event(s)
sBCMA	Soluble B-cell maturation antigen
sBLA	Supplemental biologics license application
sCR	Stringent complete response
SoC	Standard of care
US	United States
USPI	United States Prescribing Information
VGPR	Very good partial response

1 EXECUTIVE SUMMARY

1.1 Introduction

Multiple myeloma is a malignant disorder of plasma cells, characterized by uncontrolled and progressive proliferation, and accounts for approximately 10% of hematological malignancies (Rodriguez-Abreu et al 2007; Rajkumar et al 2011). The disease leads to significant morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), renal insufficiency, anemia, hyperviscosity, and secondary amyloidosis (Orlowski 2013). Despite advances in available therapies, multiple myeloma remains largely incurable. Most patients eventually relapse and become refractory to existing treatments. There is also a high attrition rate with 85% of patients unable to receive treatment beyond third line (Dhakal et al 2023), underscoring the importance of applying effective treatments earlier in the disease course.

CARVYKTI® (ciltacabtagene autoleucel, hereafter referred to as cilta-cel), is a one-time infusion treatment that employs chimeric antigen receptor (CAR) technology to genetically engineer autologous peripheral blood T cells to target and eliminate cells that express B-cell maturation antigen (BCMA). All multiple myelomas express BCMA making it an ideal therapeutic target (Darce et al 2007; Tai and Anderson 2015).

Cilta-cel is currently approved in the United States (US) for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody based on data from the Phase 1b/2 CARTITUDE-1 study (MMY2001; CARVYKTI® USPI 2023). The Sponsor is seeking to expand the cilta-cel indication to include adult patients with relapsed or refractory multiple myeloma, who have received at least one prior therapy, including an IMiD and a PI, and are refractory to lenalidomide.

The pivotal CARTITUDE-4 study randomized 419 patients with relapsed lenalidomide-refractory multiple myeloma who had received 1 to 3 prior lines of therapy in a 1:1 ratio to either cilta-cel (n=208) or standard of care (SoC; n=211). In this Phase 3 study, a single infusion of cilta-cel showed superior efficacy compared to Investigator's choice of pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd). Progression-free survival (PFS), the primary endpoint, was superior in the cilta-cel arm over the SoC arm. The hazard ratio (HR) based on Intent-to-Treat (ITT) analysis, including all PFS events after randomization, was 0.40 (95% confidence interval [CI]: 0.29–0.55), p<0.0001; by the pre-specified weighted methodology that included PFS events that occurred after 8 weeks post-randomization, HR was 0.26 (95% CI: 0.18–0.38), p<0.0001. Median PFS was not estimable (NE; [95% CI: 22.8–NE]) for the cilta-cel arm and 11.8 months (95% CI: 9.7–13.8) for the SoC arm. Key secondary endpoints of complete response (CR) or better rate, overall response rate (ORR), and overall minimal residual disease (MRD)

negativity rate also met statistical significance, all favoring the cilta-cel arm. The deep and durable responses observed with cilta-cel have translated into a strong trend towards improved overall survival (OS) that has further strengthened as data matures (HR=0.57 [95% CI: 0.40–0.83]). Health-related quality of life (HRQoL) as measured by the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item (EORTC QLQ-C30) showed improvement with cilta-cel treatment compared to SoC.

Comprehensive analyses were performed to assess the early imbalance of PFS and OS events. This imbalance was driven by disease progression in patients on the experimental arm who had not yet received cilta-cel and was therefore not due to cilta-cel toxicity. Demographics, baseline disease characteristics, treatment history, study-related procedures, including apheresis, timing of bridging therapy, choice of bridging therapy, relative dose intensity of study drugs given as part of bridging, and chimeric antigen receptor T (CAR-T) manufacturing time were evaluated among other variables for any potential role in the observed imbalance in early PFS events. We found an imbalance of relative dose intensity of pomalidomide and bortezomib which may have contributed to the imbalance of early PFS events although the extent of this contribution is unknown. No specific patient population was identified as driving this early imbalance.

The clinical efficacy of cilta-cel is robust and consistent across all patient subgroups. Safety findings from CARTITUDE-4 were consistent with previous cilta-cel experience and the current understanding of the mechanism of CAR-T therapies.

1.2 Background and Unmet Need

Patients with lenalidomide-refractory multiple myeloma have shorter survival times (Lecat et al 2021) and receive burdensome SoC, generally until disease progression, that requires continuous daily, weekly, biweekly, or monthly dosing with no treatment-free interval. With each successive relapse, the depth and duration of response (DoR) typically decreases, HRQoL worsens, the disease becomes increasingly refractory, and patients experience increasing immune system dysregulation (Kawano et al 2017).

Therefore, there remains a significant need for new therapeutic options with alternative mechanisms of action and without the need for ongoing treatment.

Interviews with patients treated with cilta-cel on the CARTITUDE-1 study showed that patients considered the break from continuous treatment as meaningful. Reasons included fewer treatment-related symptoms while being off-treatment and the benefits of a treatment-free period allowing for greater independence, improved social functioning, and an opportunity to return to work (Cohen et al 2023).

1.2.1 Current Standard of Care

It has become standard to use lenalidomide as part of frontline and maintenance therapies. As a result, patients increasingly have lenalidomide-refractory disease as early as in first relapse. Refractoriness to lenalidomide is associated with poorer outcomes (Lecat et al 2021) with median PFS around 12 months in patients who have relapsed after ≥1 prior line of therapy (Table 1). Additionally, the response shown in these studies relies on ongoing therapy until progression of disease, potentially resulting in cumulative toxicity and significant treatment burden. While patients in the CANDOR and IKEMA studies had longer median PFS, it should be noted that only a third of patients in these studies were lenalidomide-refractory.

Table 1: Summary of Median Progression-free Survival and Minimal Residual Disease for Pomalidomide or Carfilzomib Based Regimens

Study Name	Publication Year	Percent of Lenalidomide-refractory Patients	mPFS, months	MRD Negativity Rate
ICARIA[1] (IsaPd)	2019	94%	11.5	5%
APOLLO[2] (DaraPd)	2021	79%	12.4	9%
OPTIMISMM[3] (PVd)	2019	71%	11.2	N/A
CANDOR[4] (DaraKd)	2023	32%	28.4	28%
IKEMA[5] (IsaKd)	2023	32%	35.7	34%

1. Attal et al 2019 (isatuximab, pomalidomide, and low-dose dexamethasone) 2. Dimopoulos et al 2021 (pomalidomide, dexamethasone, and daratumumab) 3. Richardson et al 2019 (pomalidomide, bortezomib, and dexamethasone) 4. Usmani et al 2023 (carfilzomib, dexamethasone, and daratumumab) 5. Martin et al 2023a (isatuximab, carfilzomib, and dexamethasone).
mPFS=median progression-free survival; MRD=minimal residual disease; N/A=not available.

1.3 Overview of Cilta-cel

Cilta-cel consists of patient-derived T cells genetically modified to target and eliminate cells that express BCMA. BCMA is an ideal therapeutic target due to its highly restricted expression, primarily on late-stage B cells, plasma cells, and malignant B-lineage cells (Bu et al 2018; Carpenter et al 2013; Darce et al 2007; Novak et al 2004; Tai and Anderson 2015). The cilta-cel CAR protein features two BCMA-targeting single-domain antibodies designed to confer high avidity against human BCMA, along with a 4-1BB co-stimulatory domain and a signaling cytoplasmic domain.

1.3.1 Global Approvals

1.3.1.1 Approval for Current Indication

Cilta-cel was approved by the Food and Drug Administration (FDA) on 28 February 2022 for the treatment of adult patients with relapsed or refractory multiple myeloma after ≥4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody (CARVYKTI® USPI 2023). In addition to the US approval, cilta-cel is approved

in 40 countries worldwide. Cilta-cel was granted Breakthrough Therapy Designation by the FDA in December 2019 and PRIority Medicines (PRIME) designation by the European Medicines Agency (EMA) in April 2019.

1.4 Clinical Development Program of Cilta-cel

The cilta-cel clinical development program consists of 8 clinical trials across the spectrum of adult patients with multiple myeloma (Table 7). The pivotal results demonstrating efficacy and safety of cilta-cel in adults with relapsed and lenalidomide-refractory multiple myeloma treated with 1 to 3 prior lines of therapy are from the global, randomized, controlled, Phase 3 CARTITUDE-4 (MMY3002) study, as outlined in Sections 6 and 7.

1.5 Pivotal CARTITUDE-4 Study (MMY3002)

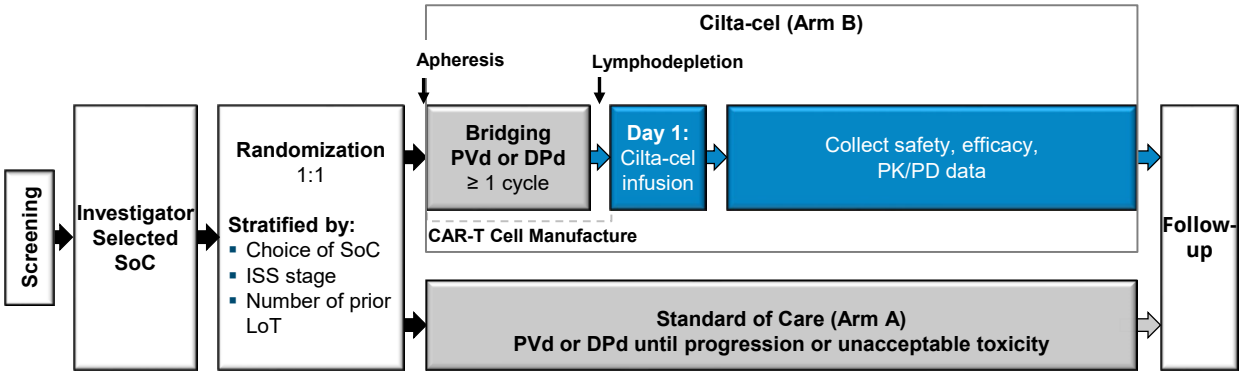
1.5.1 Study Design

CARTITUDE-4 is an ongoing, global, randomized, open-label trial designed to evaluate the efficacy and safety of a one-time infusion of 0.75 x10^6 CAR-positive viable T cells/kg vs SoC. The eligibility criteria for CARTITUDE-4 were selected to enroll a population of adults that reflected a significant unmet need in multiple myeloma (additional details provided in Section 6.1.2).

Janssen Research & Development, LLC (Janssen) sought input and agreement from the FDA regarding the design of CARTITUDE-4, including advice on the choice of comparator regimens and endpoint selection (Table 8). Through these interactions, the study protocol was refined, and the choice of the comparator regimens and endpoint selection were endorsed.

During the CARTITUDE-4 study, the selection for each patient of either pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd) was made by the Investigator prior to randomization. Patients were randomized (1:1) to Arm A (SoC arm) or Arm B to receive cilta-cel (Figure 1).

Figure 1: CARTITUDE-4: Study Design



CAR-T=chimeric antigen receptor T (cells); DPd=daratumumab, pomalidomide, and dexamethasone; ISS=International Staging System; LoT=line of therapy; PD=pharmacodynamic; PK=pharmacokinetic; PVd=pomalidomide, bortezomib, and dexamethasone; SoC=standard of care.

Per protocol, patients randomized to the cilta-cel arm were to undergo:

- **Apheresis**: performed 3 to 6 days after randomization
- **Bridging therapy**: starting after apheresis but no more than 7 days after randomization
  - At least one cycle of either PVd (21-day cycle) or DPd (28-day cycle)
  - Additional cycles of bridging therapy could be given based on the patient's status and availability of cilta-cel
  - Cycle 2+ of bridging therapy could be truncated to allow for adequate washout prior to lymphodepletion
- **Wash-out period**: from the last dose of bridging therapy until prior to lymphodepletion (daratumumab: 21 days, bortezomib: 14 days, pomalidomide and dexamethasone: 7 days)
- **Lymphodepletion**: given daily for 3 days, consisting of fludarabine and cyclophosphamide
- **Cilta-cel**: given 5 to 7 days after the start of lymphodepletion, at the target dose of 0.75 x 10^6 CAR-positive viable T cells/kg
- **Follow-up**: patients continued to be monitored for efficacy and safety until confirmed progressive disease (PD), withdrawal of consent, or death
- **After confirmed PD**: patients are followed for survival, subsequent anti-myeloma therapies, PFS on next-line therapy (PFS2), delayed adverse events (AEs)
- **Long-term follow-up after cilta-cel**: all patients are monitored for long-term safety for up to 15 years.

1.5.1.1 Key Endpoints

The primary endpoint was PFS, defined as the time from the date of randomization to the date of first documented disease progression using the International Myeloma Working Group (IMWG) criteria, or death due to any cause, whichever occurred first. The protocol-specified interim analysis of PFS with the clinical cutoff date of 1 November 2022 occurred based on 187 events (75% information fraction of the total 250 planned PFS events).

Key secondary endpoints included, by the pre-specified hierarchy, rate of complete response or better (CR/stringent CR [sCR]; as defined by IMWG criteria [Kumar et al 2016]), ORR, overall MRD negativity rate, OS, and time to worsening of symptoms in the MySIm-Q total symptom score. Additional endpoints included DoR, patient-reported outcomes (PROs), and safety.

The primary analysis set for all efficacy endpoints was the ITT analysis set, consisting of all 419 patients randomized: 208 patients in the cilta-cel arm and 211 patients in the SoC arm. The safety analysis set is described in Section 7.

1.5.2 Baseline Demographics and Disease Characteristics

Patient demographic and baseline disease characteristics were well balanced between the two arms (Table 9; Table 10). The median age of patients was 61 years with a slightly greater proportion of males in both arms. Most patients were white (75%), had a baseline Eastern Cooperative Oncology Group (ECOG) score of 0, and an International Staging System (ISS) stage of I. Soft tissue plasmacytomas were present in 21% of cilta-cel patients and 17% of SoC patients. The median time from multiple myeloma diagnosis to randomization was 3 years with approximately one third of patients exposed to 1 prior line of therapy, and two thirds of patients exposed to 2 to 3 prior lines of therapy. Approximately 60% of patients had high-risk cytogenetics. All patients were refractory to lenalidomide, as per study entry criteria, and 23% of patients were refractory to an anti-CD38 monoclonal antibody.

Among the 64 patients enrolled in the US, 9 patients (14.1%; 4 patients in the cilta-cel arm and 5 patients in the SoC arm) were Black or African American.

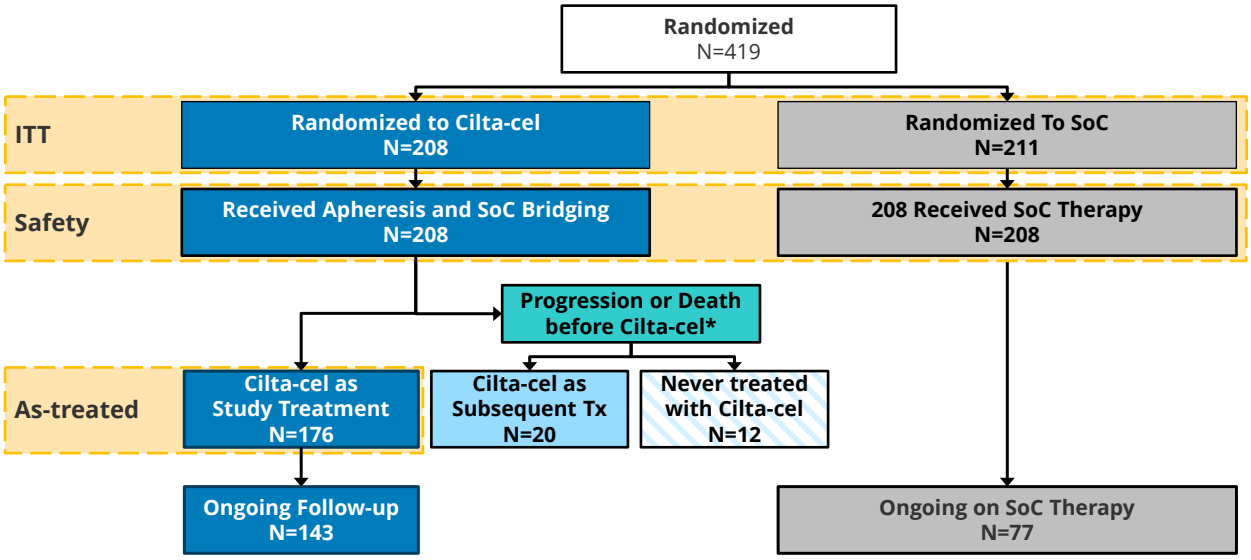
1.5.3 Summary of Disposition

The ITT analysis set consists of the 419 patients randomized (1:1): 208 patients to the cilta-cel arm and 211 patients to the SoC arm (Figure 2). Of the randomized patients, 416 received any part of study treatment and comprised the protocol-defined safety analysis set. Three patients were randomized to SoC but were not treated. The safety analysis set presented is described in Section 7.

Of the 208 patients randomized to cilta-cel, 32 patients experienced a PFS event prior to receiving cilta-cel as study treatment. Of the 32 patients, 20 patients went on to receive cilta-cel as subsequent therapy after disease progression. A total of 176 patients were in the as-treated population and received cilta-cel as study treatment. As

of the clinical cutoff date of 1 November 2022, 143 cilta-cel treated patients were in ongoing follow-up for PFS compared to 77 patients who were ongoing on SoC study treatment.

Figure 2: CARTITUDE-4 Study: CONSORT Diagram



*31 patients progressed and 1 died prior to cilta-cel infusion.
CONSORT=Consolidated Standards of Reporting Trials; ITT=Intent-to-Treat; SoC=standard of care; Tx=treatment.

1.5.4 Efficacy Findings

1.5.4.1 Primary Endpoint: Progression-free Survival

A one-time infusion of cilta-cel demonstrated clinically meaningful and statistically significant improvement in the primary endpoint of PFS as compared with continuous treatment with standard therapy. After a median follow-up of 15.9 months, at the clinical cutoff of 1 November 2022, a PFS event had occurred for 31.3% of patients randomized to cilta-cel and 57.8% of patients randomized to SoC. Median PFS for the cilta-cel arm was NE (95% CI: 22.8 months–NE) vs a median PFS of 11.8 months (95% CI: 9.7–13.8) with SoC (Figure 3).

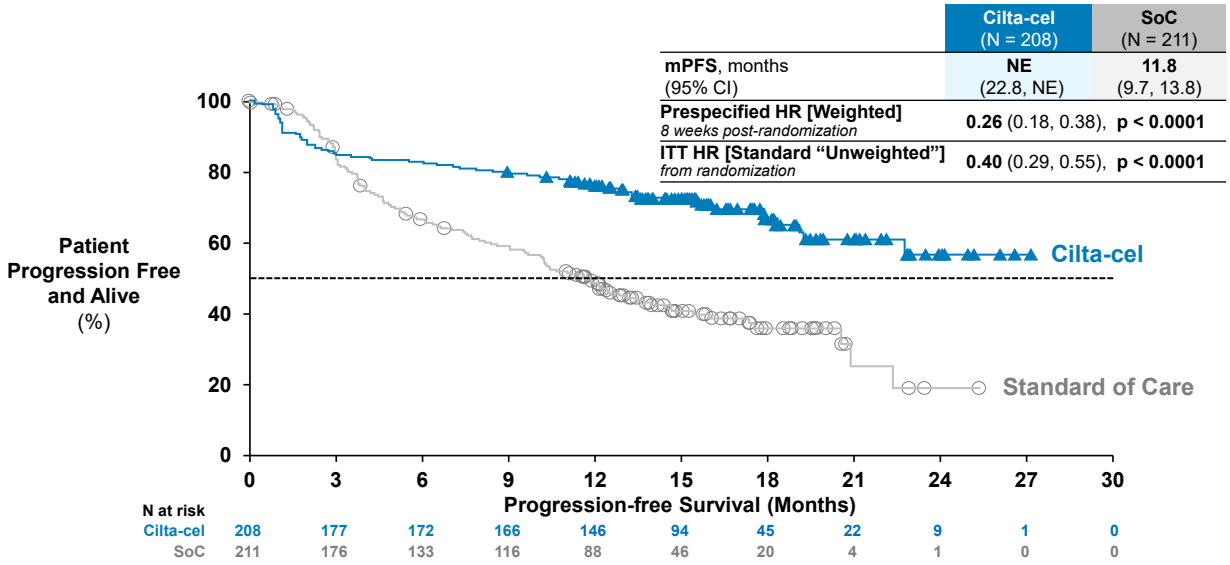
The standard “unweighted” stratified log-rank test and the HR for the ITT analysis set, including all PFS events from the time of randomization, strongly favored cilta-cel (HR=0.40 [95% CI: 0.29–0.55], p<0.0001), demonstrating a 60% reduction in the risk of progression or death for cilta-cel.

The pre-specified constant piecewise weighted (CPW) stratified log-rank test and the corresponding HR that included PFS events that occurred after 8 weeks post-randomization also strongly favored cilta-cel (HR=0.26 [95% CI: 0.18–0.38], p<0.0001), indicative of a 74% reduction in the risk of progression or death for cilta-cel.

Both the standard stratified log-rank test and the CPW stratified log-rank test results were statistically significant, crossing the conservative O'Brien-Fleming stopping boundary, and demonstrated robust PFS benefit. Additional details on the statistical analysis of the primary endpoint are provided in Section 6.1.4.1.

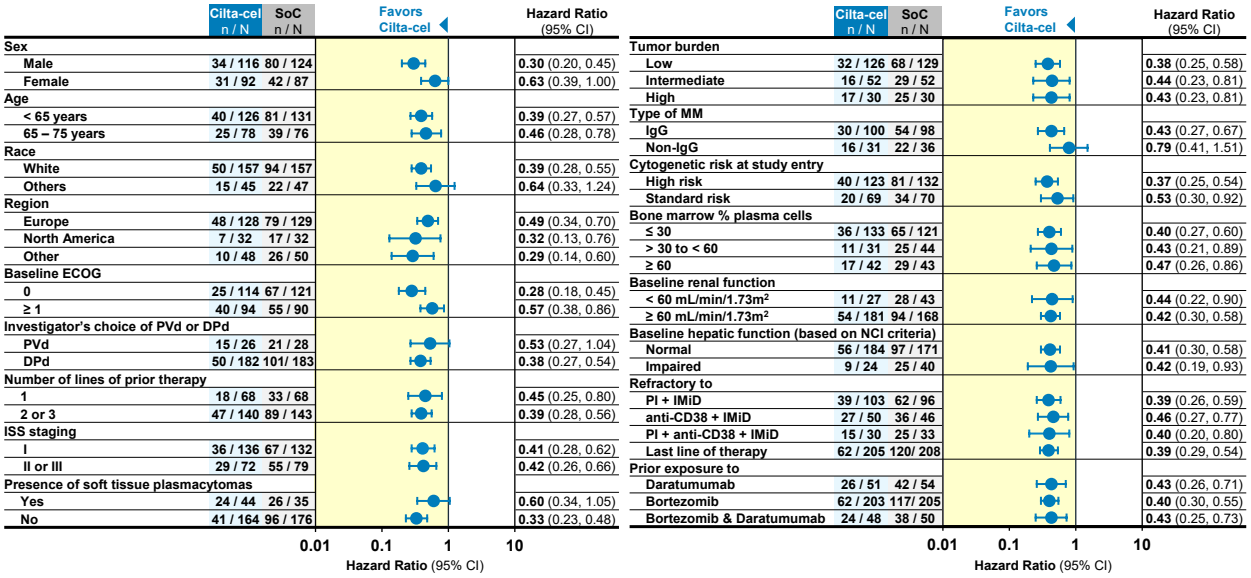
The PFS benefit of cilta-cel over SoC was consistent across all pre-specified subgroups (Figure 4).

Figure 3: CARTITUDE-4 Study: Kaplan-Meier Plot of Progression-free Survival (ITT Analysis Set)



ITT=Intent-to-Treat; NE=not estimable; mPFS=median progression-free survival; SoC=standard of care.

Figure 4: CARTITUDE-4 Study: Progression-free Survival by Subgroup (ITT Analysis Set)



Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.
DPd=daratumumab, pomalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; IMiD=immunomodulatory agent; ISS=International Staging System; ITT=Intent-to-Treat; MM=multiple myeloma; NCI=National Cancer Institute; PI=proteasome inhibitor; PVd=pomalidomide, bortezomib, and dexamethasone; SoC=standard of care.

1.5.4.2 Key Secondary Endpoints

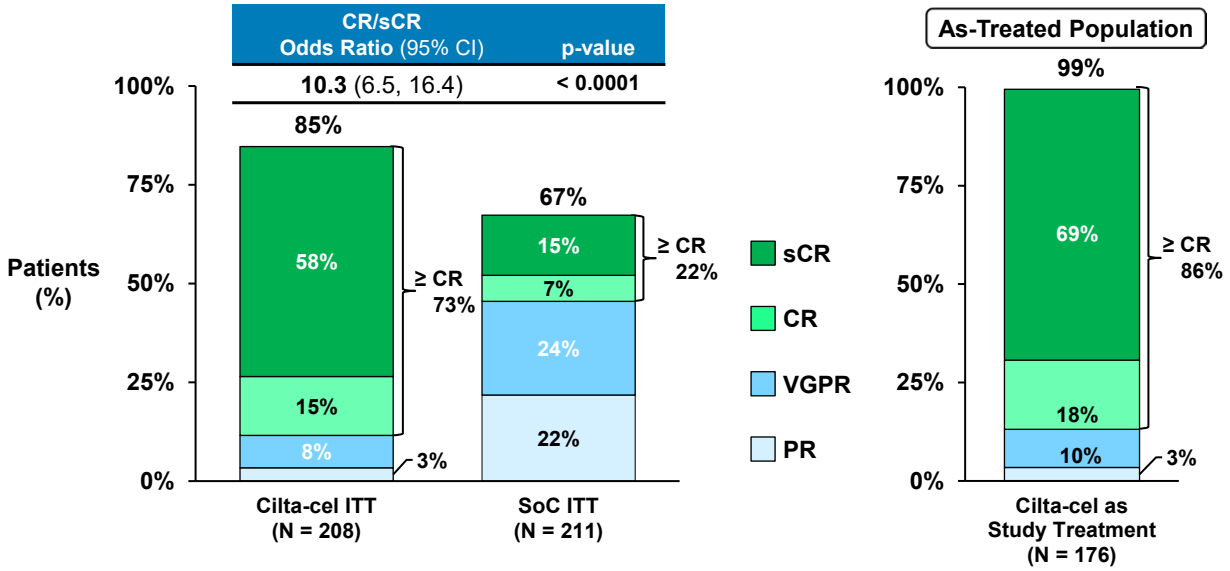
1.5.4.2.1 Complete Response or Better (CR/sCR) Rate, Overall Response Rate, and Overall Minimal Residual Disease Negativity Rate

Key secondary endpoints demonstrated a consistent, highly significant treatment effect favoring cilta-cel vs SoC (Figure 5; Table 12; Figure 6). The CR or better rate was 73.1% (95% CI: 66.5–79.0) for the cilta-cel arm and 21.8% (95% CI: 16.4–28.0; Table 12) for the SoC arm; the stratified Cochran-Mantel-Haenszel (CMH) estimate of odds ratio was 10.3 (95% CI: 6.5–16.4; p<0.0001; Figure 5).

The ORR was 84.6% (95% CI: 79.0–89.2) for the cilta-cel arm and 67.3% (95% CI: 60.5–73.6) for the SoC arm. The stratified CMH estimate of odds ratio was 3.0 (95% CI: 1.8–5.0; p<0.0001; Figure 5). These responses were durable in the cilta-cel arm with the median DoR of NE (95% CI: NE–NE) vs 16.6 months (95% CI: 12.9–NE) in the SoC arm (Figure 25), with most responders in the cilta-cel arm (81.3%) censored as of the time of clinical cutoff, as compared with 56.3% in the SoC arm.

Importantly, considering the 176 patients that were treated with cilta-cel as study treatment, 99% of patients achieved a response and 86% achieved a CR or better response (Figure 5).

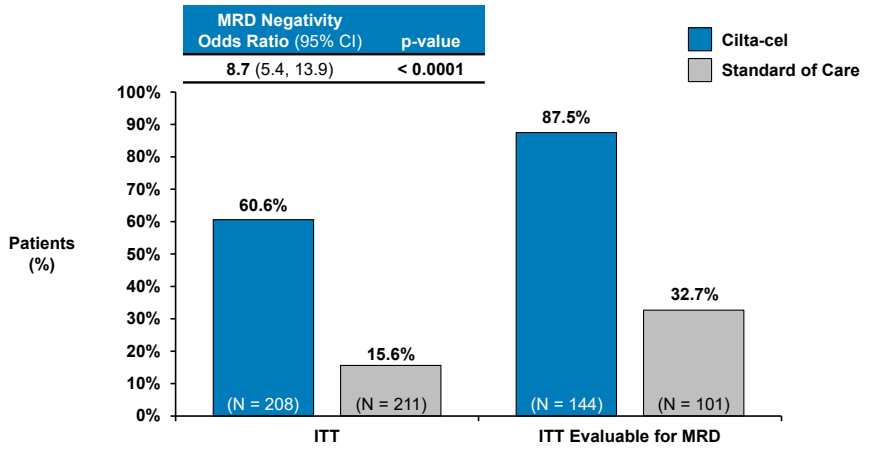
Figure 5: CARTITUDE-4 Study: Overall Response Rate (ITT Analysis Set and As-treated Population)



CR=complete response; ITT=Intent-to-Treat; PR=partial response; sCR=stringent complete response; SoC=standard of care; VGPR=very good partial response.

MRD negativity rate is highly indicative of long-term outcomes (Munshi et al 2020; Paiva et al 2024). In the ITT population, the MRD negativity rate (at a threshold of 10^{-5}) in the cilta-cel arm as measured by next-generation sequencing (NGS) was approximately 4-fold the rate in the SoC arm (cilta-cel arm: 60.6% [95% CI: 53.6–67.3], SoC arm: 15.6% [95% CI: 11.0–21.3]; odds ratio=8.7 [95% CI: 5.4–13.9]; p<0.0001; Figure 6). Among patients with an evaluable sample, the MRD negativity rate (at a threshold of 10^{-5}) was higher for the cilta-cel arm (87.5% [95% CI: 81.0–92.4]) as compared with the SoC arm (32.7% [95% CI: 23.7–42.7]).

Figure 6: CARTITUDE-4 Study: Minimal Residual Disease Negativity Rate (ITT and Evaluable for Minimal Residual Disease Analysis Set)



ITT=Intent-to-Treat; MRD=minimal residual disease.

1.5.4.2.2 Overall Survival

At the interim analysis clinical cutoff of 1 November 2022, the OS data were yet to be mature (HR=0.78 [95% CI: 0.50–1.20], p=0.2551, based on the ITT analysis set and standard stratified log-rank test, at 34% information fraction of the planned 250 OS events). As of 17 April 2023, for an FDA requested analysis based on the ITT analysis set, deaths had occurred for 45 patients in the cilta-cel arm and 67 patients in the SoC arm (Table 2). The most recent descriptive update of OS was based on the 13 December 2023 survival sweep at the request of the EMA for the ITT analysis set. At this analysis date, corresponding to a median follow-up of 28.7 months, 48 deaths in the cilta-cel arm and 77 deaths in the SoC arm had occurred with a HR of 0.57 (95% CI: 0.40–0.83; Figure 7). The estimated OS rates at 24 months were 78.8% (95% CI: 72.6–83.8) for the cilta-cel arm and 66.2% (95% CI: 59.3–72.2) for the SoC arm (Table 3).

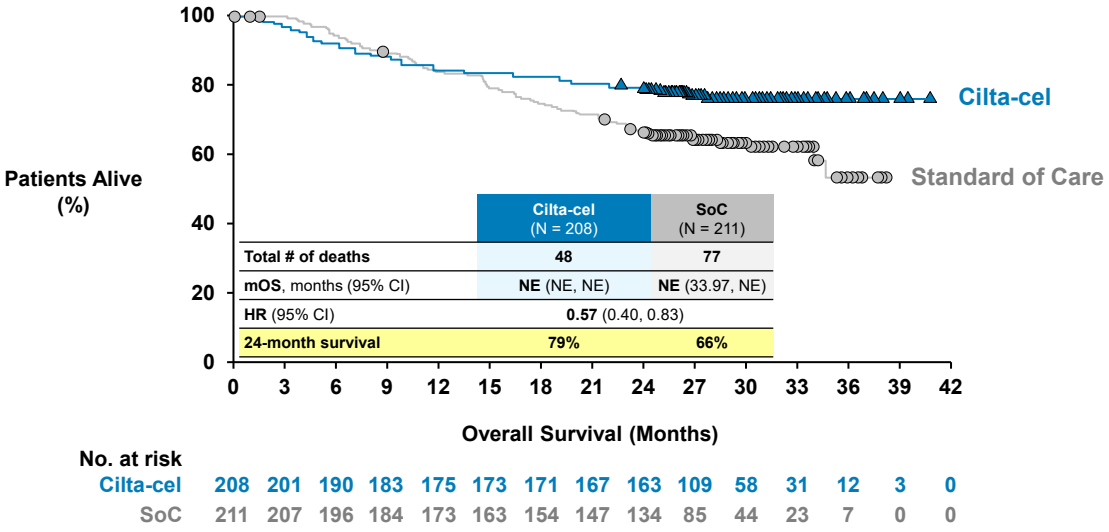
In addition, OS by pre-specified subgroups demonstrated a consistent trend favoring cilta-cel over SoC (Figure 8).

Table 2: CARTITUDE-4 Study: Summary of Overall Survival by Analysis Date

	1 November 2022 (Interim Analysis)	17 April 2023 (120-Day Safety Update)	13 December 2023 (Survival Sweep)
Median follow-up (months)	15.9	21.5	28.7
Total deaths	86	112	125
Cilta-cel	39	45	48
SoC	47	67	77
Hazard ratio[a] (95% CI)	0.78 (0.50–1.20)	0.63 (0.43–0.92)	0.57 (0.40–0.83)
p-value[b]	0.2551	N/A	N/A

a. Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with Investigator's choice (PVd or DPd), ISS staging (I, II, III), and number of prior lines (1 vs 2 or 3) as randomized. A hazard ratio <1 indicates an advantage for the cilta-cel arm.
b. p-value based on a standard log-rank test stratified with Investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs 2 or 3) as randomized.
DPd=daratumumab, pomalidomide, dexamethasone; ISS=International Staging System; N/A=not applicable; OS=overall survival; PVd= pomalidomide, bortezomib, dexamethasone; SoC=standard of care.

Figure 7: CARTITUDE-4 Study: Kaplan-Meier Plot for Overall Survival (ITT Analysis Set; 13 December 2023 Survival Sweep)



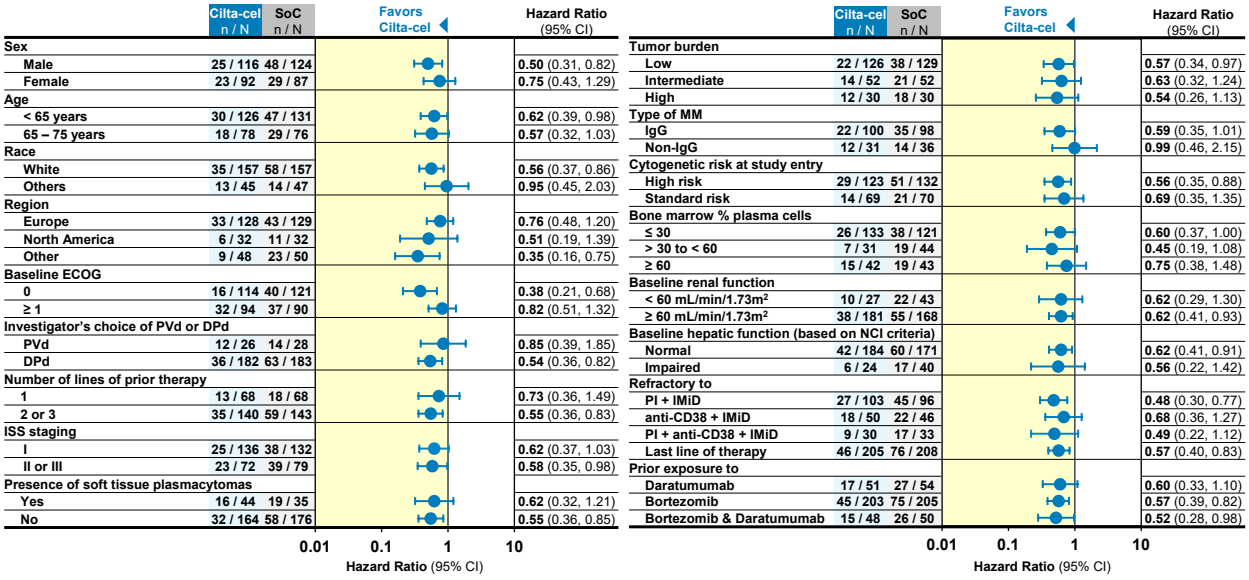
ITT=Intent-to-Treat; mOS=median overall survival; NE=not estimable; SoC=standard of care.

Table 3: CARTITUDE-4 Study: Summary of Overall Survival (ITT Analysis Set; 13 December 2023 Survival Sweep)

	Cilta-cel (N=208)	SoC (N=211)
Overall Survival (months)		
Number of events (%)	48 (23.1)	77 (36.5)
Number of censored (%)	160 (76.9)	134 (63.5)
Median (95% CI)	NE (NE, NE)	NE (33.97, NE)
Hazard ratio (95% CI)[a]	0.57 (0.40, 0.83)	
Survival Rate, % (95% CI)		
6-month	91.3 (86.6, 94.5)	94.2 (90.1, 96.7)
12-month	84.1 (78.4, 88.4)	83.6 (77.9, 88.0)
18-month	82.2 (76.3, 86.8)	74.4 (67.9, 79.8)
24-month	78.8 (72.6, 83.8)	66.2 (59.3, 72.2)

a. Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with Investigator's choice (PVd or DPd), ISS staging (I, II, III), and number of prior lines (1 vs 2 or 3) as randomized. A hazard ratio <1 indicates an advantage for the cilta-cel arm.
DPd=daratumumab, pomalidomide, and dexamethasone; ISS=Internal Staging System; ITT=Intent-to-Treat; NE=not estimable; PVd=pomalidomide, bortezomib, and dexamethasone; SoC=standard of care.

Figure 8: CARTITUDE-4 Study: Overall Survival by Subgroup (ITT Analysis Set; 13 December 2023 Survival Sweep)



Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.
DPd=daratumumab, pomalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; IMiD=immunomodulatory agent; ISS=International Staging System; ITT=Intent-to-Treat; MM=multiple myeloma; NCI=National Cancer Institute; PI=proteasome inhibitor; PVd=pomalidomide, bortezomib, and dexamethasone; SoC=standard of care.

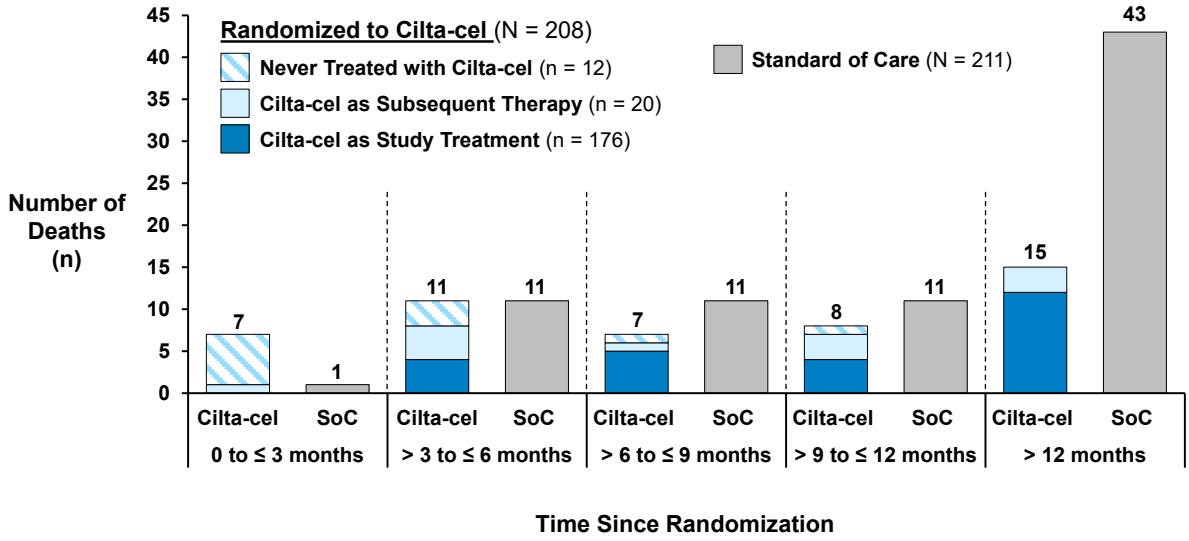
1.5.5 Imbalance in Early Overall Survival Events

The Kaplan-Meier curves for overall survival cross at around 10 months after randomization. Evaluating OS by time period from randomization, the only period in which there were more deaths in the cilta-cel arm (n=7) than in the SoC arm (n=1) occurred within the first three months after randomization. This imbalance is the reason the OS Kaplan-Meier curves are initially unfavorable. However, 6 of the 7 deaths in this period were in patients randomized to cilta-cel who progressed prior to cilta-cel infusion and had never received cilta-cel. The remaining patient received cilta-cel as subsequent therapy following progression on bridging therapy (Figure 9).

Thereafter, OS events are balanced between months 3 to 6 and then trend towards improvement with fewer deaths observed in the cilta-cel arm compared to the SoC arm (Figure 9).

Primary causes of all deaths are provided in Appendix 11.1.

Figure 9: CARTITUDE-4 Study: Deaths Over Time Across Treatment Groups (13 December 2023 Survival Sweep)



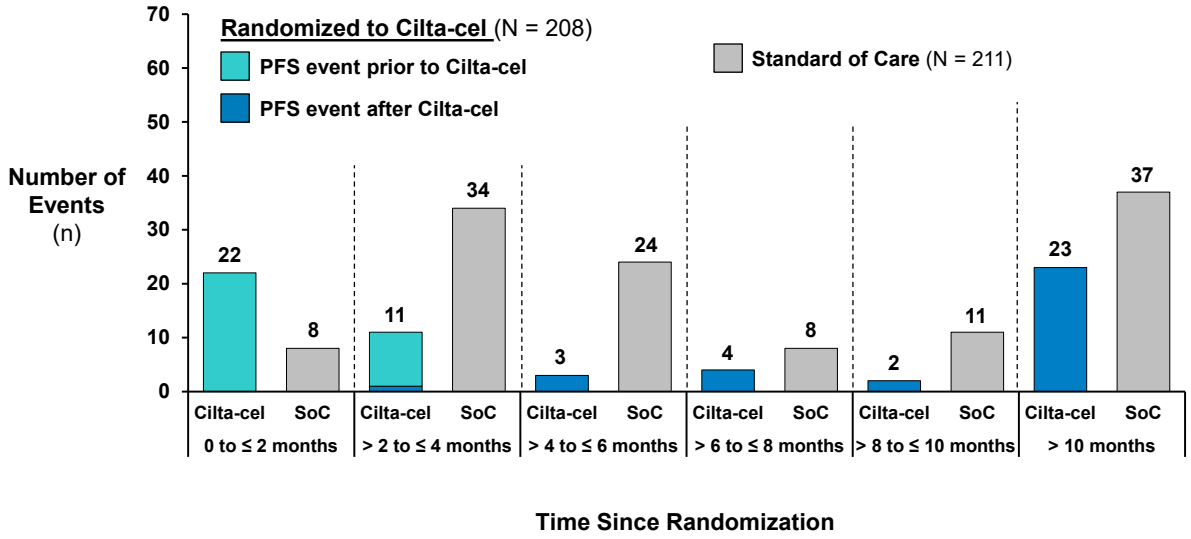
SoC=standard of care.

1.5.6 Imbalance in Early Progression-free Survival Events

The PFS curves cross, depicting an early imbalance of PFS events, as shown in Figure 3. In the first 8 weeks, 22 PFS events were observed in the cilta-cel arm compared with 8 events in the SoC arm. All 22 events in the cilta-cel arm occurred prior to cilta-cel infusion (Figure 10). Therefore, the imbalance is not related to toxicity associated with cilta-cel. Additionally, these early progression events led to deaths which in turn resulted in an imbalance in early deaths during the first 3 months post randomization (Figure 9). In-depth analysis of factors potentially contributing to the imbalance of early PFS events

did not identify a definite underlying cause (additional details provided in Section 6.1.8.2). Patients in the cilta-cel arm received a lower relative dose intensity of pomalidomide and bortezomib as part of bridging therapy, which may have contributed to the imbalance, however the extent of this impact is unclear. Therefore, no subpopulations have been identified where cilta-cel should be avoided.

Figure 10: CARTITUDE-4 Study: Progression-free Survival Events Over Time Across Treatment Groups



PFS=progression-free survival; SoC=standard of care.

1.5.7 Patient-reported Outcomes

1.5.7.1 Time to Worsening Symptoms in MySIm-Q Total Symptom Score

The MySIm-Q total symptom score measures the severity of pain, neuropathy, fatigue, digestive symptoms, and cognitive symptoms. Most patients (cilta-cel arm: 85.6%; SoC arm: 78.2%) were censored as of the time of clinical cutoff (Table 13). The median time to worsening of multiple myeloma symptoms was longer for the cilta-cel arm than for the SoC arm: 23.7 months (95% CI: 22.1–NE) vs 18.9 months (95% CI: 16.8–NE); HR=0.42 (95% CI: 0.26–0.68).

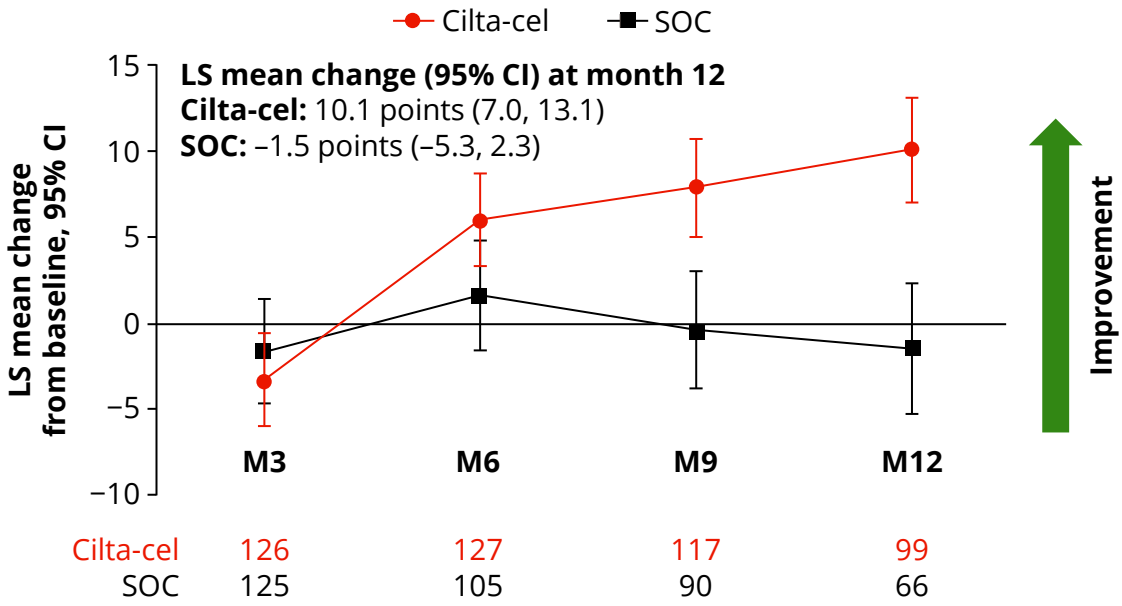
1.5.7.2 EORTC QLQ-C30

EORTC QLQ-C30 was used to assess HRQoL, symptoms, and functioning. The proportion of patients that achieved clinically meaningful improvement at any timepoint prior to disease progression in HRQoL, pain, fatigue, and physical functioning was greater for the cilta-cel arm than the SoC arm. Data showed improvement across multiple symptom and functional scales suggesting a positive impact on HRQoL following cilta-cel.

1.5.7.2.1 Global Health Status

Global health status (GHS) reflects the overall HRQoL. Patients treated with cilta-cel reported a slight decrease in GHS at Month 3 (28 days post-infusion), but quickly reported an improvement over time with the least-squares (LS) mean change from baseline at Month 12 equal to 10.1 (95% CI: 7.0–13.1), compared to no change from baseline being reported by patients treated with SoC (Figure 11). For additional results see Section 6.1.7.3.3.

Figure 11: CARTITUDE-4 Study: EORTC QLQ-C30 Global Health Status Change from Baseline[a]



a. LS means are derived based on the mixed effects model with repeated measures in which the dependent variable is change from baseline in score and independent variables baseline score and visit as fixed effects with individual subject as random effect. Assessments after the start of subsequent therapy were excluded.
Sully et al 2019.
EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; GHS=global health status; LS=least squares; M=month; SoC=standard of care.

1.5.8 Safety Findings

Safety analysis is presented based on the FDA-proposed safety analysis set (N=188), including patients who received conforming cilta-cel as study treatment (170 out of 176 patients) and patients who received conforming cilta-cel as subsequent therapy (18 out of 20 patients). Conforming product is cilta-cel drug product that meets all pre-specified release criteria for clinical supply.

Per FDA's guidance, the Sponsor compared post-infusion AEs for patients who received conforming cilta-cel either as study treatment or as subsequent therapy (N=188), against patients in the SoC arm (N=208). Post-infusion AEs were defined as any AE that occurred on or after cilta-cel infusion (Day 1) until Day 112 post-cilta-cel infusion or the start of subsequent therapy, whichever occurred first, or at any time if

related to cilta-cel. AEs for patients in the SoC arm (N=208) were defined as any AE from Day 1 of study treatment until 30 days after the last dose of study treatment or the start of subsequent therapy, whichever occurred first, or at any time if related to study treatment. Further details are provided in Section 7.

The clinical cutoff date for safety analyses was 1 November 2022 unless otherwise specified. AE summaries are presented by grouped terms as provided by the FDA as well as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

1.5.8.1 Safety Overview

All patients in the safety population experienced ≥1 AE and most experienced ≥1 Grade 3 or 4 AE (Table 4). Hematologic AEs were the most common, and most high-grade cytopenias resolved to Grade ≤2 by Day 60.

Incidence of Grade 3 or 4 infections was similar across both arms (Table 4). Urgent safety measures were implemented in June 2022 following identification of an imbalance of COVID-19 deaths in the cilta-cel vs SoC arm (additional details provided in Section 7.5.2). No fatal COVID-19 infections were reported in the cilta-cel arm after mitigation measures were implemented.

Presentation of second primary malignancies in this document is based on the 4-month safety update cutoff date of 17 April 2023 in order to include recent cases of myelodysplastic syndrome (MDS) that occurred after the primary analysis cutoff date. Seventeen patients (9.0%) who received conforming cilta-cel and 17 patients (8.2%) in the SoC arm had a second primary malignancy during the study. No patients in the SoC arm and 5 patients (2.7%) in the cilta-cel arm had a hematologic second primary malignancy, including MDS (3 patients), acute myeloid leukemia (AML; 1 patient), and one case of CAR-positive peripheral T-cell lymphoma (1 patient) (Harrison et al 2023). Of note, all five patients had previous exposure to melphalan and lenalidomide, including 4 patients with high-dose melphalan followed by stem cell transplantation.

Table 4: CARTITUDE-4 Study: Overall Summary of Adverse Events

	Safety Population			
	Conforming Cilta-cel (n=188) n (%)		SoC (n=208) n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any AE	188 (100.0)	173 (92.0)	208 (100.0)	196 (94.2)
Hematologic	172 (91.5)	169 (89.9)	185 (88.9)	179 (86.1)
Infections	111 (59.0)	35 (18.6)	151 (72.6)	47 (22.6)
SAE	71 (37.8)	71 (37.8)	81 (38.9)	70 (33.7)

SAE=serious adverse event; SoC=standard of care.

CAR-T-specific AEs were largely as expected (Table 5). Most cytokine release syndrome (CRS) events were low grade and resolved in about 3 days after onset. Rates

of neurologic toxicity including Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS), cranial nerve palsy, peripheral neuropathy, and movement and neurocognitive toxicity (MNT) were all relatively low and most resolved by data cutoff. The safety profile was consistent with the known safety of approved cilta-cel and the mechanism of action of CAR-T therapy.

Table 5: CARTITUDE-4 Study: Summary of Adverse Events of Special Interest

	Conforming Cilta-cel (n=188)				
	Any Grade	Grade 3/4	Median time to onset, days	Median duration, days	Resolved[a]
CRS	146 (77.7)	6 (3.2)	8	3	99%
ICANS	14 (7.4)	1 (0.5)	9	2	93%
Cranial nerve palsy	16 (8.5)	2 (1.1)	21	77	88%
Peripheral neuropathy	14 (7.4)	1 (0.5)	51	168	57%
MNT	2 (1.1)	0	60	265	Ongoing at clinical cutoff

a. Percentage resolved were calculated based on the number of patients with the events as the denominator.
AEs=adverse events; CRS=cytokine release syndrome; ICANS=Immune Effector Cell-associated Neurotoxicity Syndrome; MNT=movement and neurocognitive toxicity.

1.5.8.2 *Adverse Events as Primary Cause of Death*

At the request of EMA, an unplanned assessment of survival status was performed using an analysis date of 13 December 2023. This analysis showed that AEs were the primary cause of death for 23 patients (12.2%) post-infusion in the cilta-cel arm and 28 patients (13.5%) in the SoC arm. Of note, these events include all AEs as primary cause of death, including AEs that occurred outside of the AE reporting period (as defined in Section 7.1) or after the start of subsequent therapy.

AEs (FDA grouped terms or MedDRA preferred terms) as the primary cause of death for more than 1 patient in the cilta-cel arm included pneumonia (9 patients [4.8%], of which 7 [3.7%] were COVID-19 pneumonia), hemorrhage (4 patients [2.1%]), sepsis (3 patients [1.6%]), and hematologic malignancies (3 patients [1.6%], 2 AML; 1 MDS). AEs as the primary cause of death for more than 1 patient in the SoC arm included pneumonia (5 patients [2.4%], of which 2 [1.0%] were pneumocystis jirovecii pneumonia and 2 [1.0%] were COVID-19 pneumonia), sepsis (5 patients [2.4%], of which 2 [1.0%] were septic shock), viral infection (4 patients [1.9%] of which 2 [1.0%] were COVID-19), renal failure (3 patients [1.4%], of which 2 [1.0%] were acute kidney injury), upper respiratory tract infection (2 patients [1.0%]), hemorrhage (2 patients [1.0%]), and multiple organ dysfunction syndrome (2 patients [1.0%]).

Additional details on all deaths are provided in Appendix 11.2.

1.5.9 Overview of Patients Receiving Cilta-cel as Subsequent Therapy

Twenty patients randomized to the cilta-cel arm progressed on bridging therapy (considered a PFS event for the primary analysis) and received cilta-cel as subsequent therapy at the Investigator's request. These 20 patients represent a distinct and higher-risk population compared with patients who received cilta-cel as study treatment. Most of these patients had high-risk features and were rapidly progressing on bridging therapy. Nine of these 20 patients received cilta-cel after 4 or more prior lines of therapy by the time of cilta-cel infusion. Importantly, as a result these patients would not have been eligible for the CARTITUDE-4 study by protocol specified inclusion criteria.

For these 20 patients, median PFS from cilta-cel infusion was 7.4 months, CR or better rate was 40% (95% CI: 19.1–63.9), and the ORR was 65% (95% CI: 40.8–84.6) following cilta-cel infusion. Overall, 6 patients died of AEs, 6 patients progressed, and 8 patients were progression-free at the data cutoff with a median follow-up of 13.8 months (range: 11.5 to 20.4 months) from randomization. Median OS from randomization for the 20 patients was 13.4 months (95% CI: 4.93–NE).

Although these patients were more likely to experience early death post-infusion and higher rates and higher severity of AEs (additional details provided in Section 8), approximately one third of these patients had sustained response and survival as of the most recent data cut.

1.6 Benefit-Risk Summary

Cilta-cel demonstrates superior outcomes (PFS, ORR, CR/sCR, and MRD negativity rate) in patients with 1 to 3 prior lines of therapy who are lenalidomide-refractory. This treatment effect was consistently observed across all subgroups. Patients who received cilta-cel as study treatment derived even greater clinical benefit with ORR of 99% and CR/sCR of 86%, which suggests the importance of effective disease control prior to cilta-cel infusion.

Cilta-cel has a safety profile consistent with the mechanism of action of CAR-T therapy, with clinically manageable AEs in the target population.

Based on the overwhelmingly positive PFS, ORR, CR, and MRD negativity rate data, a strong trend toward OS benefit, and a clinically manageable safety profile, in the context of a significant unmet need for lenalidomide-refractory patients, the Sponsor considers that a positive benefit-risk profile has been demonstrated for cilta-cel.

2 BACKGROUND ON MULTIPLE MYELOMA

Summary

- Multiple myeloma remains a largely incurable disease. Each relapse typically results in shorter DoR to the subsequent line of therapy and worsening HRQoL.
- High attrition rate with 85% of patients not receiving treatment beyond the fourth line necessitates the need for highly effective treatments in the earlier line setting.
- Lenalidomide-refractory relapsed multiple myeloma confers a worse prognosis than lenalidomide-sensitive or -naïve myeloma, with fewer treatment options.
- Expected PFS for patients with relapsed and lenalidomide-refractory multiple myeloma is approximately 12 months.

2.1 Epidemiology of Multiple Myeloma

In 2023, an estimated 35,730 adults (19,860 men and 15,870 women) in the US were expected to be diagnosed with multiple myeloma. It was estimated that 12,590 deaths (7,000 men and 5,590 women) from this disease would occur in the US in 2023 (Cancer.net 2023).

2.2 Current Treatment Options for Early Relapsed or Refractory Multiple Myeloma and Unmet Need

Lenalidomide is a key backbone agent in the treatment of multiple myeloma in the frontline setting and as maintenance following autologous stem cell transplantation (ASCT) resulting in an increasing number of patients who are lenalidomide-refractory as early as their first relapse.

Lenalidomide-refractory patients have a worse prognosis than lenalidomide-sensitive or -naïve myeloma, with fewer effective treatment options (Lecat et al 2021).

Among patients treated with the triplet regimens, median PFS was 11.2 months for the OPTIMISMM study (bortezomib, pomalidomide, and dexamethasone; Richardson et al 2019), 11.5 months for the ICARIA study (isatuximab, pomalidomide, dexamethasone; Attal et al 2019), and 12.4 months for the APOLLO study (daratumumab, pomalidomide, dexamethasone; Dimopoulos et al 2021). Longer median PFS was reported for the CANDOR (28.4 months) and IKEMA studies (35.7 months), both of which used an anti-CD38 monoclonal antibody in combination with carfilzomib and dexamethasone in a mostly lenalidomide-sensitive patient population (Usmani et al 2023; Martin et al 2023a; Table 6). The response shown in these studies relies on ongoing therapy until disease progression, potentially resulting in cumulative toxicity and significant treatment burden.

Table 6: Summary of Median Progression-free Survival and Minimal Residual Disease for Pomalidomide or Carfilzomib Based Regimens

Study Name	Publication Year	Percent of Lenalidomide-refractory Patients	mPFS, months	MRD Negativity Rate
ICARIA[1] (IsaPd)	2019	94%	11.5	5%
APOLLO[2] (DaraPd)	2021	79%	12.4	9%
OPTIMISMM[3] (PVd)	2019	71%	11.2	N/A
CANDOR[4] (DaraKd)	2023	32%	28.4	28%
IKEMA[5] (IsaKd)	2023	32%	35.7	34%

1. Attal et al 2019 (isatuximab, pomalidomide, and low-dose dexamethasone) 2. Dimopoulos et al 2021 (pomalidomide, dexamethasone, and daratumumab) 3. Richardson et al 2019 (pomalidomide, bortezomib, and dexamethasone) 4. Usmani et al 2023 (carfilzomib, dexamethasone, and daratumumab) 5. Martin et al 2023a (isatuximab, carfilzomib, and dexamethasone).
mPFS=median progression-free survival; MRD=minimal residual disease; N/A=not available.

2.3 BCMA Expression in Multiple Myeloma

BCMA (also known as CD269 and TNFRSF17) is a 20 kDa, Type III membrane protein that is part of the tumor necrosis receptor family (Tai and Anderson 2015). BCMA is predominantly expressed in B lineage cells and selectively induced during plasma cell differentiation associated with the loss of B-cell activating factor receptor (Avery et al 2003; Carpenter et al 2013; Darce et al 2007; Maus and June 2013). Immunohistochemistry (IHC) on normal tissues demonstrated that BCMA is a highly restricted target, with expression limited to normal B cells and plasma cells in lymph node, spleen, bronchial-associated lymphoid tissue, and mucosa-associated lymphoid tissue (Bu et al 2018). BCMA mRNA and protein were universally detected in multiple myeloma cell lines and in all malignant plasma cells from patients with multiple myeloma in studies conducted by the Sponsor (Study DD16321) and others (Carpenter et al 2013; Novak et al 2004). These expression characteristics make BCMA an ideal therapeutic target for the treatment of multiple myeloma (Darce et al 2007; Tai and Anderson 2015).

3 CILTA-CEL PRODUCT DESCRIPTION

Summary

- Cilta-cel is a BCMA-directed genetically modified autologous T cell immunotherapy.
- Cilta-cel is administered by intravenous infusion as a single-dose treatment.
- Cilta-cel is differentiated from other approved CAR-T in that it contains two distinct BCMA binding domains to confer high antigen binding avidity.

3.1 Proposed Indication and Recommended Dose

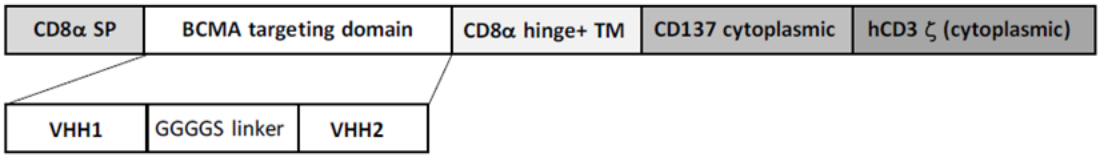
The proposed indication is *"for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor, and an immunomodulatory agent, and are refractory to lenalidomide."*

The recommended target dose of single-infusion cilta-cel is 0.75 x10^6 CAR-positive viable T cells/kg.

3.2 Product Overview

Cilta-cel is a BCMA-directed genetically modified autologous T cell immunotherapy. It is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and genetically modified ex vivo by transduction with a replication-incompetent lentiviral vector to express a CAR comprising an anti-BCMA targeting domain, which is differentiated from other CAR-T in that it consists of two single-domain antibodies linked to a 4-1BB (CD137) costimulatory domain and a CD3-zeta signaling domain (Figure 12).

Figure 12: Lentiviral Vector Coding Region



The LV vector coding sequence is composed of a human CD8α SP, VHH1 and VHH2 variable region of heavy chain antibodies.
BCMA=B-cell maturation antigen; CD8α SP=human CD8 alpha signal peptide; CD8α hinge+TM=human CD8 alpha hinge and transmembrane domain; GGGGS=4 glycines and 1 serine.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Cilta-cel (CARVYKTI®) is approved for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody.
- The primary evidence supporting this supplemental biologics license application (sBLA) for cilta-cel in patients with relapsed and lenalidomide-refractory multiple myeloma who have had at least 1 prior line of therapy is from the pivotal randomized, controlled, multicenter, Phase 3, CARTITUDE-4 study.

4.1 Initial Approval for Late Stage Relapsed or Refractory Multiple Myeloma

Cilta-cel received initial marketing authorization in the US by the FDA on 28 February 2022 for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody based on data from the Phase 1b/2 study (CARTITUDE-1; MMY2001) (CARVYKTI® USPI 2023). In addition to the US approval, cilta-cel is approved in 40 countries worldwide. Cilta-cel was granted Breakthrough Therapy Designation by FDA in December 2019 and PRIME (PRIority Medicines) designation by the EMA in April 2019.

4.1.1 Efficacy Data Supporting Initial Approval

Ninety-seven patients received a cilta-cel infusion in CARTITUDE-1. After a median follow-up of 27.7 months (protocol-specified final analysis corresponding to 2 years after last patient dosed), the Independent Review Committee (IRC) assessed ORR was 97.9% (95% CI: 92.7–99.7) and 82.5% (95% CI: 73.4–89.4) of patients achieved a sCR. Median DoR was not reached (95% CI: 23.3–NE). Median PFS and OS were not reached; 27-month PFS and OS rates were 54.9% (95% CI: 44.0–64.6) and 70.4% (95% CI: 60.1–78.6), respectively (Martin et al 2023b). At an updated analysis, median PFS was approximately 3 years (Lin et al 2023). For historic context prior to cilta-cel initial approval, standard therapy in a similar population lead to an ORR of approximately 30%, median PFS of 3 to 5 months, and median OS of 10 to 12 months (Gandhi et al 2019; Mateos et al 2022; Costa et al 2022; Mateos et al 2023).

4.1.2 Safety Data Supporting Initial Approval

The safety profile is consistent with the known mechanism of action of CAR-T therapy as communicated in the current label.

4.2 Clinical Development Program for Earlier Line Relapsed or Refractory Multiple Myeloma

The overall clinical development program of cilta-cel consists of 8 clinical trials in patients with multiple myeloma (Table 7).

The pivotal results demonstrating the efficacy and safety of cilta-cel in adult patients with relapsed and lenalidomide-refractory multiple myeloma treated with 1 to 3 prior lines of therapy are from a Phase 3, randomized, open-label, multicenter study (CARTITUDE-4) as outlined in Sections 6 and 7.

Table 7: Clinical Development Program for Cilta-cel in Adult Patients with Multiple Myeloma

Phase	Study Number (Name)	Study Design	Status	Study population
Studies Supporting the Current Supplemental Indication				
Phase 3 (Pivotal)	68284528MMY3002 (CARTITUDE-4)	Global, Randomized, Open-label, Multicenter Study	Ongoing	Relapsed after 1 to 3 prior lines of treatment and lenalidomide-refractory MM
Phase 2 (Supportive)	68284528MMY2003 (CARTITUDE-2)	Global, Multi-cohort, Open-label, Multicenter Study	Ongoing	Multiple cohorts with different MM populations, including RRMM and NDMM
Other Completed and Ongoing Studies				
Phase 3	EMN28/ 68284528MMY3005 (CARTITUDE-6)	Global, Randomized Open-label, Multicenter Study	Ongoing	NDMM eligible for ASCT as initial therapy
Phase 3	68284528MMY3004 (CARTITUDE-5)	Global, Randomized Open-label, Multicenter Study	Ongoing	NDMM for whom ASCT is not planned as initial therapy
Long-term Follow-up	68284528MMY4002	Long-term, Safety Follow-up Study	Ongoing	Patients previously enrolled in a clinical trial of cilta-cel
Phase 2	68284528MMY2002 (CARTIFAN-1)	Open-label Study	Enrollment ongoing for Additional Cohort	RRMM (China)
Phase 1b-2	68284528MMY2001 (CARTITUDE-1)	Open-label Study	Completed	RRMM after 3 or more prior lines of therapy
Investigator-initiated Study				
Phase 1	Legend-2	Single-arm, Open-label, Multicenter, First-in-Human Study	Enrollment completed	RRMM (China)

ASCT=Autologous stem cell transplantation; NDMM=newly diagnosed multiple myeloma; RRMM=relapsed or refractory multiple myeloma.

4.3 Key Regulatory Interactions and Milestones for Supplemental Indication

Key regulatory interactions and milestones between FDA and Janssen in the clinical development of cilta-cel for the treatment of adult patients with relapsed or refractory

multiple myeloma after at least 1 prior line of therapy, including a PI, an IMiD, and are refractory to lenalidomide, are included in Table 8.

Table 8: Key Regulatory Interactions and Milestones in Cilta-cel Clinical Development for the Treatment of Relapsed/Refractory Multiple Myeloma in Adults Who Have Received at Least One Prior Line of Therapy

Date	Milestone
11 September 2019	Type B EOP2 meeting to obtain Agency's review and agreement on the Phase 3 registration study in patients with multiple myeloma (Study MMY3002)
30 June 2020	Study MMY3002 initiated
29 March 2021	Type C meeting to discuss the MySIm-Q Patient Reported Outcome Instrument and the Psychometric Analysis Plan
24 June 2022	Type B meeting to obtain agreement with the Agency regarding the proposed content, format, and planned efficacy and safety analyses for the sBLA for cilta-cel
24 August 2022	Final SAP for Study MMY3002 submitted to IND application 18080 (Amendment 2)
19 January 2023	IDMC recommendation submitted for Study MMY3002 and request for Agency feedback (IND 18080)
28 March 2023	Type B pre-sBLA meeting to obtain the Agency's review of the topline results from Study MMY3002 and guidance on sBLA submission plans

EOP2=End-of-Phase 2; IDMC=Independent Data Monitoring Committee; IND=Investigational New Drug; MySIm-Q=Multiple Myeloma Symptom and Impact Questionnaire; SAP=statistical analysis plan; sBLA=supplemental biologics license application.

5 CLINICAL PHARMACOLOGY

Summary

- Cilta-cel pharmacokinetics (PK) were characterized by transgene levels and CAR-positive T cells in peripheral blood and bone marrow.
  - The median time to reach peak levels of cilta-cel expansion in peripheral blood was 12.8 days post-infusion.
  - Persistence phase of the cilta-cel transgene levels was observed with median t_{last} cilta-cel transgene level of 83 days (range: 13 to 631 days).

5.1 Brief Overview of Pharmacokinetics

PK measurements using both transgene and CAR-positive T cell levels in peripheral blood were concordant and showed similar expansion and persistence profiles. The key PK findings for the CARTITUDE-4 study based on transgene level data are summarized below:

- The median time to reach peak levels of cilta-cel expansion in peripheral blood was 12.8 days post-infusion. High interindividual variability was observed for cilta-cel transgene exposure including C_{max} and $AUC_{0\text{-}28d}$ of transgene levels in blood. After cell expansion, the persistence phase of the cilta-cel transgene levels was observed. The mean $t_{1/2}$ of cilta-cel was 21.8 days. The median t_{last} cilta-cel transgene level was 83 days (range: 13 to 631 days).

5.2 Brief Overview of Pharmacodynamics

5.2.1 BCMA Levels in Serum

After a single cilta-cel infusion, soluble BCMA (sBCMA) decreased in all patients with mean serum concentrations reaching nadir levels around the lower limit of quantification (LLOQ) value at Day 56. Increases from nadir were seen in some patients, but levels remained lower than baseline sBCMA. The reversal of sBCMA levels may reflect the reappearance of normal $BCMA^+$ plasma cells or may be associated with recurrence in patients with PD.

6 CLINICAL EFFICACY

Summary

- The pivotal Phase 3 CARTITUDE-4 study is an ongoing, global, randomized, controlled study that evaluated the efficacy and safety of cilta-cel administered as a one-time intravenous infusion in patients with relapsed and lenalidomide-refractory multiple myeloma treated with 1 to 3 prior lines of therapy.
- Cilta-cel met the primary efficacy endpoint of PFS. At a median follow-up of 15.9 months, a PFS event was reported for 31.3% of patients in the cilta-cel arm and 57.8% of patients in the SoC arm (HR=0.40 [95% CI: 0.29–0.55], p<0.0001).
    - All planned sensitivity analyses resulted in statistically significant improvement in PFS with cilta-cel treatment compared to SoC demonstrating the robustness of the primary efficacy results.
    - PFS benefit of cilta-cel over SoC was consistent across all pre-specified subgroups, including patients with soft tissue plasmacytoma, ISS Stage II or III, high tumor burden, and high-risk cytogenetics.
- Pre-specified secondary endpoints of CR or better (CR/sCR) rate, ORR, and overall MRD negativity rate demonstrated clinically meaningful, deep and durable responses that were highly statistically significant compared to SoC.
    - The CR or better rate was 73.1% (95% CI: 66.5–79.0) for the cilta-cel arm and 21.8% (95% CI: 16.4–28.0) for the SoC arm (odds ratio=10.3 [95% CI: 6.5–16.4], p<0.0001).
    - The ORR was 84.6% (95% CI: 79.0–89.2) for the cilta-cel arm and 67.3% (95% CI: 60.5–73.6) for the SoC arm (odds ratio=3.0 [95% CI: 1.8–5.0], p<0.0001). Median DoR was not reached for the cilta-cel arm and 16.6 months for the SoC arm.
    - The overall MRD negativity rate (at a threshold of 10^{-5}) in the cilta-cel arm was approximately 4-fold the rate in the SoC arm (cilta-cel arm: 60.6%, SoC arm: 15.6%; odds ratio=8.7 [95% CI: 5.4–13.9], p<0.0001).
- The OS data shows a strengthening trend in favor of cilta-cel vs SoC across 3 sequential timepoints (most recent analysis, HR=0.57 [95% CI: 0.40–0.83]).
    - The estimated OS rates at 24 months based on a 13 December 2023 analysis date was 78.8% (95% CI: 72.6–83.8) in the cilta-cel arm and 66.2% (95% CI: 59.3–72.2) for the SoC arm.
- EORTC QLQ-C30 was used to assess HRQoL, symptoms, and functioning. The proportion of patients that achieved clinically meaningful improvement at any timepoint prior to disease progression in HRQoL, pain, fatigue, and physical functioning was greater for the cilta-cel arm than the SoC arm.

6.1 Pivotal Phase 3 CARTITUDE-4 Study

6.1.1 Study Design

CARTITUDE-4 is an ongoing global, randomized, open-label, Phase 3 study in patients with relapsed and lenalidomide-refractory multiple myeloma treated with 1 to 3 prior lines of therapy to assess the efficacy and safety of one-time infusion of cilta-cel compared to Investigator's choice of pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd). The study was conducted in 3 phases: Screening, Treatment, and Follow-Up (Figure 1).

Patients were randomized (1:1) to receive either Investigator's choice of PVd or DPd (Arm A; SoC arm) or cilta-cel (Arm B; cilta-cel arm). Randomization was stratified by Investigator's choice (PVd or DPd), ISS (I vs II vs III), and number of prior lines of therapy (1 vs 2 or 3).

The Investigator determined prior to randomization if the patient would be treated with PVd or DPd based on the patient's prior exposure to anti-myeloma therapies. If randomized to the cilta-cel arm, patients would receive Investigator's choice of PVd/DPd as bridging therapy. If randomized to the SoC arm, patients would receive Investigator's choice of PVd/DPd as SoC treatment.

DPd is considered a clinically relevant comparator for the CARTITUDE-4 study based on its regulatory approval status and clinical use in the target population of patients with lenalidomide-refractory disease. DPd is considered as a category 1 recommendation per National Comprehensive Cancer Network (NCCN) guidelines after 2 prior therapies including lenalidomide and a PI based on results from the Phase 3 APOLLO study (Dimopoulos et al 2021). PVd is a category 1 recommended treatment regimen in the NCCN treatment guidelines for patients whose multiple myeloma has relapsed after 2 or more therapies including an IMiD and a PI based on results from the Phase 3 OPTIMISMM study (Richardson et al 2019).

After meeting eligibility criteria, patients randomized to the SoC arm started either PVd or DPd within 7 days. In the cilta-cel arm, eligible patients underwent apheresis, performed 3–6 days after randomization, followed by at least 1 cycle of bridging therapy with either PVd or DPd (determined by the Investigator prior to randomization) for disease stabilization, initiated no more than 7 days after randomization. A standard lymphodepleting regimen of cyclophosphamide and fludarabine was administered daily for 3 days, starting 5–7 days prior to cilta-cel administration at the target dose of 0.75 x 10^6 CAR-positive viable T cells/kg.

6.1.2 Key Enrollment Criteria

Patients in CARTITUDE-4 were enrolled at 81 centers in Europe, North America, and other regions including Australia, Israel, Japan, and Republic of Korea. Enrollment criteria included:

- ≥18 years of age,

- a documented diagnosis of multiple myeloma according to IMWG diagnostic criteria,
- refractory to lenalidomide per IMWG consensus guidelines (Kumar et al 2016),
- received 1 to 3 prior lines of therapy including a PI and an IMiD,
- documented evidence of PD by IMWG criteria based on Investigator's determination on or within 6 months of their last regimen,
- measurable disease at screening as defined by any of the following: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or light chain multiple myeloma without measurable M-protein in the serum or the urine: serum free light chain ≥10 mg/dL and abnormal serum free light chain ratio,
- an ECOG performance status score of 0 or 1, and
- patients with prior treatment with CAR-T therapy directed at any target or any BCMA-targeted therapy were excluded.

6.1.3 Endpoint Definitions and Testing Hierarchy

The primary endpoint of the study was PFS, defined as the time from the date of randomization to the date of first documented disease progression, as defined by IMWG criteria, or death due to any cause, whichever occurs first.

If the primary endpoint PFS was statistically significant, the key secondary endpoints were sequentially tested for superiority utilizing a hierarchical procedure to control familywise Type I error rate at a 2-sided significance level of 0.05 (overall), in the following order:

- CR or better (CR/sCR) rate,
- ORR (defined as sCR, CR, very good partial response [VGPR], or PR),
- Overall MRD negativity rate,
- OS, and
- time to worsening of symptoms in the MySIm-Q total symptom score.

Additional endpoints included DoR, PROs, and safety.

6.1.4 Statistical Analyses

6.1.4.1 Analysis of the Primary Endpoint

The Kaplan-Meier method was used to estimate the distribution of overall PFS for each treatment arm.

As both arms were expected to receive the same therapy (DPd or PVd) for approximately 2 cycles after randomization (approximately 8 weeks), no initial separation of the Kaplan-Meier curves was expected. For this reason, in consultation

with the FDA, the pre-specified primary analysis of PFS utilized a CPW stratified log-rank test, where the weight was 0 for the first 8 weeks post-randomization, and 1 afterwards. Accordingly, the “weighted” HR was estimated based on a stratified Cox regression model, where this analysis included only PFS events that occurred after 8 weeks post-randomization. Stratification factors used in the stratified analyses included Investigator’s choice of PVd or DPd, ISS staging (I, II, III), and number of prior lines (1 vs 2 or 3).

A standard stratified log-rank test, based on ITT analysis set including all PFS events from the time of randomization, was a pre-specified sensitivity analysis for the comparison of PFS distribution between the 2 treatment arms. The treatment effect in terms of HR and its 2-sided 95% CI were estimated using a stratified Cox’s regression model with treatment as the sole explanatory variable.

In addition, per FDA feedback, a post-hoc sensitivity analysis for PFS was performed, utilizing the composite strategy for one missed disease evaluation (i.e., patients will be considered as having PFS event at the last disease evaluation right before one missed disease assessment followed by an immediate PD or death) and the hypothetical strategy for two or more consecutive missed disease evaluations (i.e., patients who missed two or more consecutive disease assessments immediately preceding the PD or death will be censored at the date of last disease assessment prior to the missing assessments). Standard stratified log-rank test and stratified Cox’s regression model were used. Numerous sensitivity analyses were also pre-specified for this endpoint.

6.1.4.2 Analysis of Key Secondary Endpoints

The CR of better (CR/sCR) rate, ORR, and overall MRD negativity rate were calculated for each treatment arm with the corresponding 95% Clopper-Pearson exact CI. The stratified CMH estimate of odds ratio and its 95% CI were used to estimate the treatment effect for CR/sCR, ORR, and overall MRD negativity rate. The stratified CMH Chi-Squared test was used for the comparison of CR or better (CR/sCR) rate and ORR between the two arms and the Fisher’s exact test for overall MRD negativity rate. Stratification factors used in the stratified analyses included Investigator’s choice of PVd or DPd, ISS (I vs II vs III), and number of prior lines of therapy (1 vs 2 or 3).

The Kaplan-Meier method was used to estimate OS distribution for each treatment arm. A standard stratified log-rank test was used for the comparison of OS distribution between the 2 treatment arms. The treatment effect in terms of HR and its 2-sided 95% CI were estimated using a stratified Cox’s regression model with treatment as the sole explanatory variable.

Analysis methods for time to worsening of symptoms in the MySIm-Q total symptom score were similar to those for OS.

6.1.5 Baseline Characteristics and Patient Disposition

6.1.5.1 Baseline Demographics and Characteristics

As shown in Table 9 and Table 10, demographic and baseline disease characteristics were well balanced between the two arms and representative of the target population.

Among the 64 enrolled patients in the US, 9 patients (14.1%; 4 patients in the cilta-cel arm and 5 patients in the SoC arm) were Black or African American. An additional four Black or African American patients were enrolled at sites outside the US (2 patients in each arm).

Table 9: CARTITUDE-4 Study: Baseline Demographics and Characteristics (ITT Analysis Set)

Characteristic	Cilta-cel (N=208)	SoC (N=211)
Age, median (range), years	61.5 (27–78)	61.0 (35–80)
Age group, n (%)		
< 65 years	126 (60.6)	131 (62.1)
65–75 years	78 (37.5)	76 (36.0)
> 75 years	4 (1.9)	4 (1.9)
Male, n (%)	116 (55.8)	124 (58.8)
Race, n (%)		
White	157 (75.5)	157 (74.4)
Asian	16 (7.7)	20 (9.5)
Black or African American[a]	6 (2.9)	7 (3.3)
American Indian or Alaska Native	1 (0.5)	1 (0.5)
Not reported	28 (13.5)	26 (12.3)
Ethnicity, n (%)		
Not Hispanic or Latino	152 (73.1)	165 (78.2)
Hispanic or Latino	18 (8.7)	10 (4.7)
Not reported	38 (18.3)	36 (17.1)
Baseline ECOG score[b]		
0	114 (54.8)	121 (57.3)
1	93 (44.7)	89 (42.2)
2	1 (0.5)	1 (0.5)

a. For the 64 patients enrolled in the US, race was captured as follows: White, 51 patients (79.7%; 24 patients in cilta-cel arm and 27 patients in SoC arm); Black or African American, 9 patients (14.1%; 5 patients in cilta-cel arm and 4 patients in SoC arm); Asian, 1 patient (1.6%) in cilta-cel arm and 0 patients in SoC arm; American Indian or Alaska Native, 1 patient (1.6%) in cilta-cel arm and 0 patients in SoC arm; Not Reported, 2 patients (3.1%; 1 patient in cilta-cel arm and 1 patient in SoC arm).
b. The latest non-missing ECOG score on or prior to Apheresis/Cycle 1 Day 1 is used. All patients met the inclusion criteria of ECOG score of 0 or 1 prior to randomization.
ECOG=Eastern Cooperative Oncology Group; ITT=Intent-to-Treat; SoC=standard of care; US=United States.

Table 10: CARTITUDE-4 Study: Baseline Disease Characteristics (ITT Analysis Set)

Characteristic	Cilta-cel (N=208)	SoC (N=211)
ISS staging at study baseline[a], n (%)		
N	208	211
I	136 (65.4)	132 (62.6)
II	60 (28.8)	65 (30.8)
III	12 (5.8)	14 (6.6)
Bone marrow plasma cells ≥60%[b]	42 (20.4)	43 (20.7)
Presence of soft tissue plasmacytomas, n (%)	44 (21.2)	35 (16.6)
Years since diagnosis, median (range)	3.0 (0.3, 18.1)	3.4 (0.4, 22.1)
Cytogenetic risk[c], n (%)		
N	207	210
Standard risk	69 (33.3)	70 (33.3)
High risk (any of the 4 markers abnormal)	123 (59.4)	132 (62.9)
del17p	49 (23.7)	43 (20.5)
t(4;14)	30 (14.5)	30 (14.3)
t(14;16)	3 (1.4)	7 (3.3)
gain/amp (1q)	89 (43.0)	107 (51.0)
At least 2 of the 4 markers abnormal	43 (20.8)	49 (23.3)
Excluding gain/amp(1q)	73 (35.3)	69 (32.9)
Unknown	15 (7.2)	8 (3.8)
Number of lines of prior therapies for multiple myeloma, n (%)		
1	68 (32.7)	68 (32.2)
2	83 (39.9)	87 (41.2)
3	57 (27.4)	56 (26.5)
Prior ASCT, n (%)	171 (82.2)	185 (87.7)
Prior radiotherapy, n (%)	59 (28.4)	54 (25.6)
Prior PI, n (%)	208 (100.0)	211 (100.0)
Bortezomib	203 (97.6)	205 (97.2)
Carfilzomib	77 (37.0)	66 (31.3)
Ixazomib	21 (10.1)	21 (10.0)
Prior IMiD, n (%)	208 (100.0)	211 (100.0)
Lenalidomide	208 (100.0)	211 (100.0)
Pomalidomide	8 (3.8)	10 (4.7)
Thalidomide	100 (48.1)	82 (38.9)
Prior PI and IMiD, n (%)	208 (100.0)	211 (100.0)
Prior anti-CD38 antibodies	53 (25.5)	55 (26.1)

Characteristic	Cilta-cel (N=208)	SoC (N=211)
Prior PI+IMiD+anti-CD38 antibodies	53 (25.5)	55 (26.1)
Prior penta-exposed (at least 2 PIs + at least 2 IMiDs + 1 anti-CD38 antibody)	14 (6.7)	10 (4.7)
Refractory status		
N	208	211
Any PI	103 (49.5)	96 (45.5)
Any IMiD	208 (100.0)	211 (100.0)
Any anti-CD38 antibody	50 (24.0)	46 (21.8)
PI+IMiD	103 (49.5)	96 (45.5)
PI+anti-CD38 antibody	30 (14.4)	33 (15.6)
IMiD+anti-CD38 antibody	50 (24.0)	46 (21.8)
PI+IMiD+anti-CD38 antibody	30 (14.4)	33 (15.6)
At least 2 PIs + at least 2 IMiDs + 1 anti-CD38 antibody	2 (1.0)	1 (0.5)

a. ISS staging is derived based on serum β-2 microglobulin and albumin.
b. Cilta-cel arm, n=206; SoC arm, n=208.
c. Cytogenetic risk abnormalities are based on central FISH testing, or local FISH and karyotype testing if central FISH not available.
Note: The ITT analysis set consists of patients who were randomized in the study.
ASCT=Autologous stem cell transplantation; FISH=fluorescence in situ hybridization; IMiD(s)=immunomodulatory agent(s); ISS=International Staging System; ITT=Intent-to-Treat; PI(s)=proteasome inhibitor(s); SoC=standard of care.

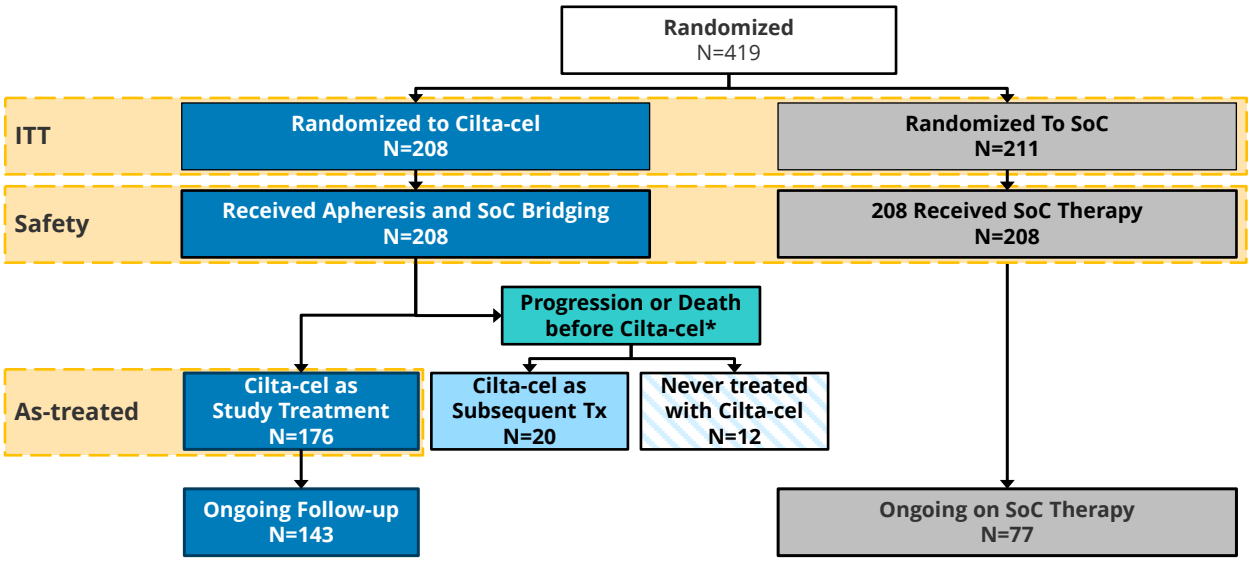
6.1.5.2 Patient Disposition

The ITT analysis set for CARTITUDE-4 consisted of the 419 patients randomized (1:1): 208 patients to the cilta-cel arm and 211 patients to the SoC arm (Figure 13). Of these, 416 patients received any part of study treatment and comprised the safety analysis set (cilta-cel arm: 208 patients; SoC arm: 208 patients). Three patients were randomized to the SoC arm but not treated.

Of note, 32 patients randomized to the cilta-cel arm had disease progression (n=31) or died (n=1) after apheresis and prior to infusion of cilta-cel. Twenty (20) of these patients received cilta-cel as subsequent therapy, and the other 12 never received cilta-cel. The remaining 176 patients (84.6%) randomized to cilta-cel received the conditioning regimen of cyclophosphamide and fludarabine infusion followed by cilta-cel infusion as planned for study treatment. This “As-treated” population is comprised of all patients that received cilta-cel as study treatment (n=176).

Of the patients in the cilta-cel arm, 39 patients discontinued from the study, all due to death. As of the efficacy clinical cutoff of 1 November 2022, 143 cilta-cel treated patients were still in ongoing follow-up for PFS compared to 77 patients who were ongoing on SoC study treatment.

Figure 13: CARTITUDE-4 Study: CONSORT Diagram



*31 patients progressed, and 1 patient died prior to access to cilta-cel infusion.
CONSORT=Consolidated Standards of Reporting Trials; ITT=Intent-to-Treat; SoC=standard of care; Tx=treatment.

6.1.6 Treatment Exposure

All 208 patients (100.0%) randomized to the cilta-cel arm received bridging therapy of either PVd (n=26 [12.5%]) or DPd (n=182 [87.5%]). In total, 196 patients received the single cilta-cel infusion, 176 as study treatment and another 20 as subsequent therapy, including eight patients who received non-conforming product (6 patients as study treatment and 2 patients as subsequent therapy).

The median number of bridging cycles started in the cilta-cel arm was 2.0 (range: 1–6 cycles). One hundred and sixty-eight patients (80.8%) started 1–2 cycles of bridging therapy and 40 patients (19.2%) started 3–6 cycles of bridging therapy (3 cycles: 34 patients [16.3%], 4 cycles: 5 patients [2.4%], 6 cycles: 1 patient [0.5%]).

The median number of treatment cycles started in the SoC arm was 12.0 (range: 1–28 cycles). Thirteen patients (6.3%) started 1 or 2 cycles of treatment, 58 patients (27.9%) started 3–6 cycles of treatment, and 137 patients (65.9%) started ≥7 cycles of treatment.

6.1.7 Efficacy Results

6.1.7.1 Primary Endpoint – Progression-free Survival

A one-time infusion of cilta-cel demonstrated clinically meaningful and statistically significant improvement in the primary endpoint of PFS as compared with continuous treatment with standard therapy. At a median follow-up of 15.9 months, at the clinical cutoff of 1 November 2022, a PFS event was reported for 31.3% of patients randomized to cilta-cel and 57.8% of patients randomized to SoC. Median PFS for the cilta-cel arm

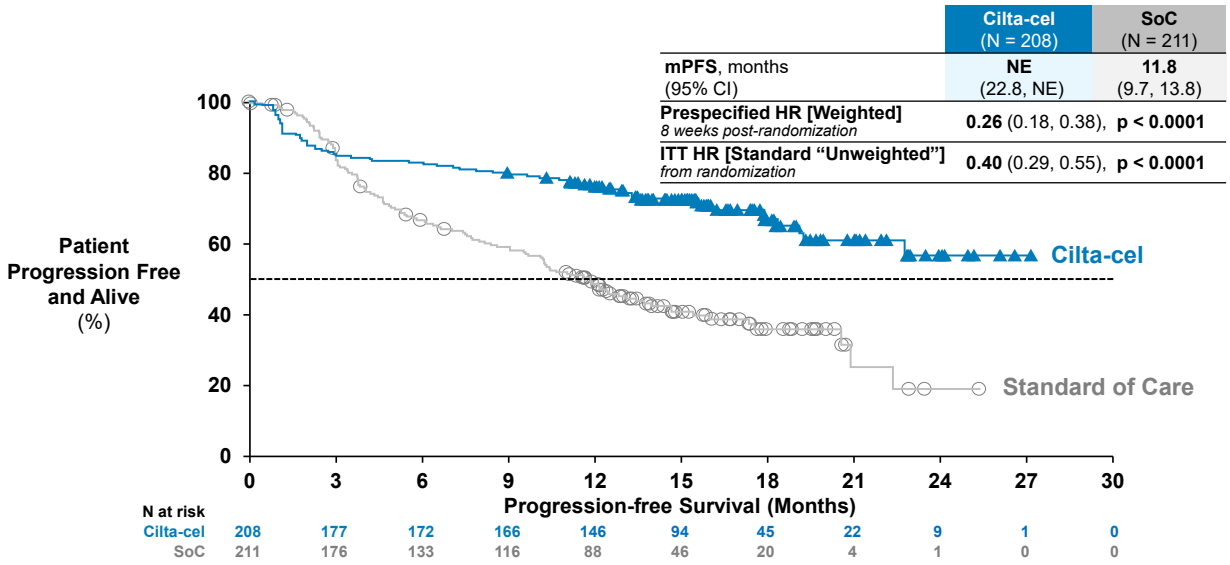
was NE (95% CI: 22.8 months–NE) vs a median PFS of 11.8 months (95% CI: 9.7–13.8) with SoC (Figure 14).

The standard stratified log-rank test and the HR for the ITT analysis set, including all PFS events from the time of randomization, strongly favored cilta-cel (HR=0.40 [95% CI: 0.29–0.55], p<0.0001; Table 11).

The pre-specified CPW stratified log-rank test and the corresponding HR that included PFS events that occurred after 8 weeks post-randomization also strongly favored cilta-cel (HR=0.26 [95% CI: 0.18–0.38], p <0.0001).

Both the standard stratified log-rank test and the CPW stratified log-rank test results were statistically significant and demonstrated robust PFS benefit.

Figure 14: CARTITUDE-4 Study: Kaplan-Meier Plot for Progression-free Survival (ITT Analysis Set)



ITT=Intent-to-Treat; mPFS=median progression-free survival; NE=not estimable; SoC=standard of care.

Table 11: CARTITUDE-4 Study: Summary of Progression-free Survival (ITT Analysis Set)

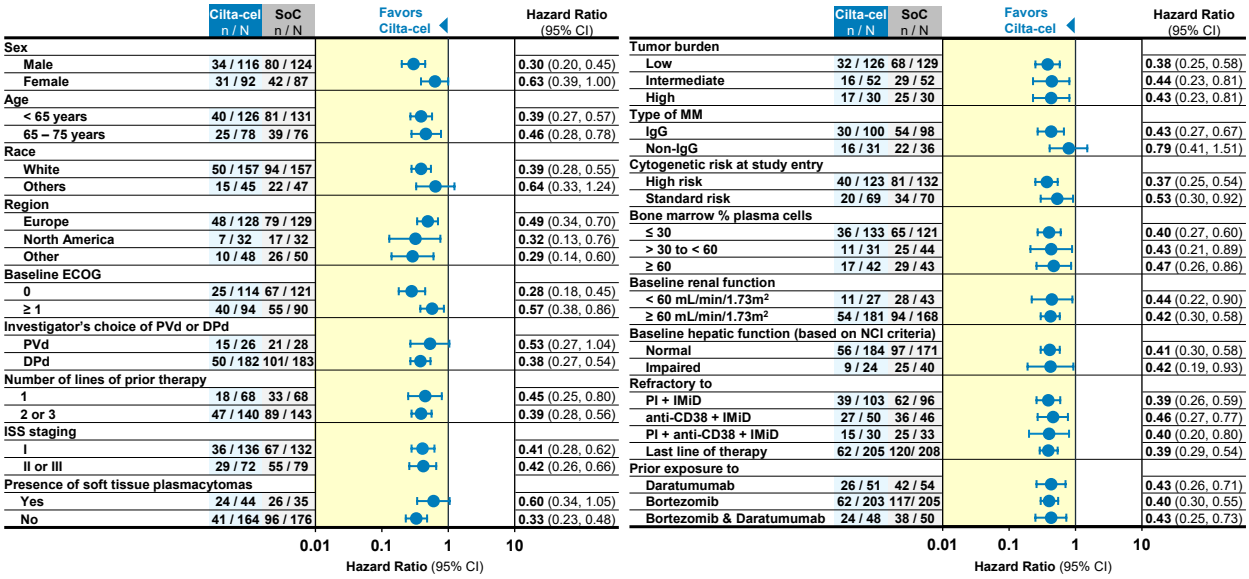
	Cilta-cel (N=208)	SoC (N=211)
PFS (months)		
Number of events (%)	65 (31.3)	122 (57.8)
Number of censored (%)	143 (68.8)	89 (42.2)
Median (95% CI)	NE (22.8, NE)	11.8 (9.7, 13.8)
P-value	< 0.0001	
Hazard ratio (95% CI)	0.40 (0.29, 0.55)	
PFS Rate, % (95% CI)		
6-month	82.7 (76.8, 87.2)	66.5 (59.5, 72.5)
12-month	75.9 (69.4, 81.1)	48.6 (41.5, 55.3)
18-month	67.8 (60.0, 74.5)	35.7 (28.0, 43.4)

Note: p-value is based on the standard log-rank test stratified with Investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs 2 or 3) as randomized.
Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with Investigator's choice (PVd or DPd), ISS staging (I, II, III), and number of prior lines (1 vs 2 or 3) as randomized.
DPd=daratumumab, pomalidomide, and dexamethasone; ISS=International Staging System; ITT=Intent-to-Treat; NE=not estimable; PFS=progression-free survival; PVd=pomalidomide, bortezomib, and dexamethasone; SoC=standard of care.

6.1.7.1.1 Progression-free Survival by Subgroups

The PFS benefit of cilta-cel over SoC was consistent across all pre-specified subgroups, including the following key subgroups: patients with soft tissue plasmacytomas (HR=0.60 [95% CI: 0.34–1.05]), ISS Stage III (HR=0.38 [95% CI: 0.14–1.01]), high tumor burden (HR=0.43 [95% CI: 0.23–0.81]), and high-risk cytogenetics (HR=0.37 [95% CI: 0.25–0.54]; Figure 15).

Figure 15: CARTITUDE-4 Study: Progression-free Survival by Subgroup (ITT Analysis Set)



Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.
DPd=daratumumab, pomalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; IMiD=immunomodulatory agent; ISS=International Staging System; ITT=Intent-to-Treat; MM=multiple myeloma; NCI=National Cancer Institute; PI=proteasome inhibitor; PVd=pomalidomide, bortezomib, and dexamethasone; SoC=standard of care.

6.1.7.2 Sensitivity Analyses

All planned sensitivity analysis results, including PFS comparison based on Investigator assessment of disease progression (HR: 0.39 [95% CI: 0.28–0.52], p<0.0001) and the FDA requested sensitivity analysis (HR: 0.41 [95% CI: 0.30–0.56], p<0.0001), demonstrated the robustness of the PFS results from the primary analysis.

Analysis was conducted to determine the level of agreement on disease progression assessment (PD and no PD) between IRC assessment and assessment by computerized algorithm. This assessment demonstrated complete concordance between the two approaches, as indicated by Prevalence Adjusted and Bias Adjusted Kappa (PABAK)=1.00 (95% CI: 1.00–1.00) and observed agreement of 100.0%.

6.1.7.3 Secondary Endpoints

6.1.7.3.1 CR or Better (CR/sCR) Rate, ORR, and Overall MRD Negativity Rate

Key secondary endpoints demonstrated a consistent, highly significant treatment effect favoring cilta-cel vs SoC, further supporting the efficacy of cilta-cel compared with standard therapy.

The CR or better (CR/sCR) rate was 73.1% (95% CI: 66.5–79.0) for the cilta-cel arm and 21.8% (95% CI: 16.4–28.0) for the SoC arm; the stratified CMH estimate of odds

ratio was 10.3 (95% CI: 6.5–16.4; p<0.0001) demonstrating deep responses in patients randomized to cilta-cel vs SoC (Table 12; Figure 16).

The ORR was 84.6% (95% CI: 79.0–89.2) for the cilta-cel arm and 67.3% (95% CI: 60.5–73.6) for the SoC arm. The stratified CMH estimate of odds ratio was 3.0 (95% CI: 1.8–5.0; p<0.0001; Table 12; Figure 16).

The overall MRD negativity rate (at a threshold of 10^{-5}) as measured by NGS for patients in the cilta-cel arm was approximately 4-fold the rate in the SoC arm (cilta-cel arm: 60.6%, SoC arm: 15.6%; odds ratio=8.7; 95% CI: 5.4–13.9; p<0.0001; Figure 17). Among patients with an evaluable sample, the overall MRD negativity rate (at a threshold of 10^{-5}) was higher for the cilta-cel arm (87.5% [95% CI: 81.0–92.4]) as compared with the SoC arm (32.7% [95% CI: 23.7–42.7]; Figure 17)

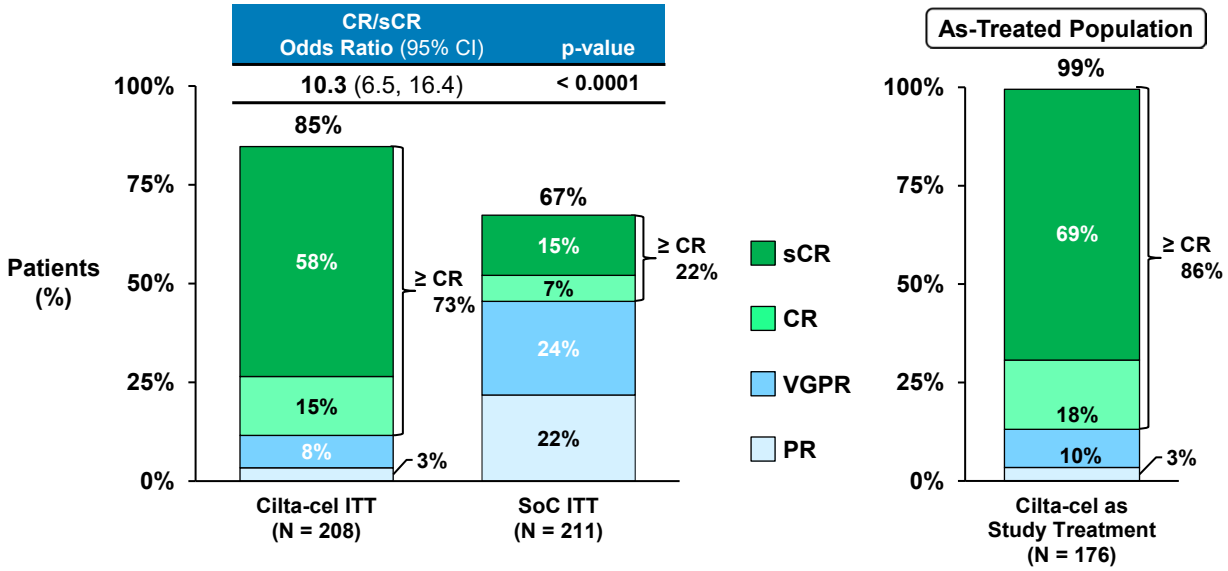
In the 176 patients who received cilta-cel as study treatment, the ORR was 99.4% (95% CI: 96.9–100.0) and the CR or better rate (CR/sCR) was 86.4% (95% CI: 80.4–91.1; Figure 16).

Table 12: CARTITUDE-4 Study: Summary of Best Confirmed Response (ITT Analysis Set)

Response Category	Cilta-cel (N=208)	SoC (N=211)
Overall response (sCR + CR + VGPR + PR)	84.6%	67.3%
95% CI	(79.0%, 89.2%)	(60.5%, 73.6%)
Odds ratio (95% CI)[a]	3.00 (1.81, 4.97)	
p-value[b]	<0.0001	
CR or better (sCR + CR)	73.1%	21.8%
95% CI	(66.5%, 79.0%)	(16.4%, 28.0%)
Odds ratio (95% CI)[a]	10.30 (6.48, 16.35)	
p-value[b]	<0.0001	

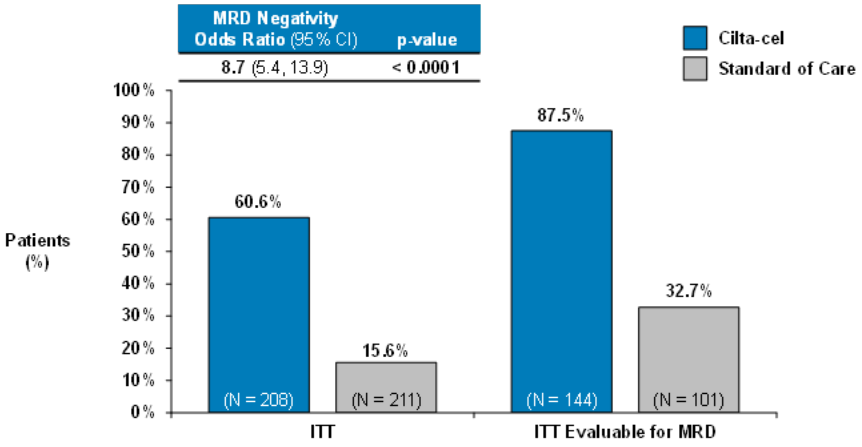
a. Mantel-Haenszel estimate of the common odds ratio for stratified tables was used. An odds ratio > 1 indicates an advantage for the cilta-cel arm. The stratification factors were: Investigator's choice (PVd or DPd), ISS staging (I, II, III), and number of prior lines of therapy (1 vs 2 or 3) as randomized.
b. p-value from the stratified Cochran-Mantel-Haenszel Chi-Squared test.
DPd=daratumumab, pomalidomide, and dexamethasone; ISS=Internal Staging System; ITT=Intent-to-Treat; PR=partial response; PVd=pomalidomide, bortezomib, and dexamethasone; sCR=stringent complete response; SoC=standard of care; VGPR=very good partial response.

Figure 16: CARTITUDE-4 Study: Overall Response Rate (ITT Analysis Set and As-treated Population)



ITT=Intent-to-Treat; PR=partial response; sCR=stringent complete response; SoC=standard of care; VGPR=very good partial response.

Figure 17: CARTITUDE-4 Study: Minimal Residual Disease Negativity Rate (ITT and Evaluable for Minimal Residual Disease Analysis Set)



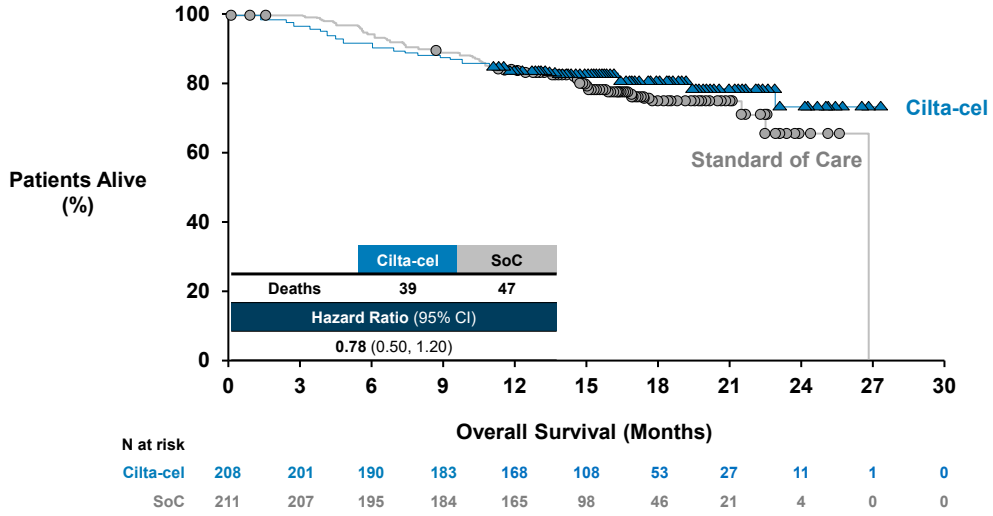
ITT=Intent-to-Treat; MRD=minimal residual disease.

6.1.7.3.2 Overall Survival

OS was analyzed using a standard stratified log-rank test and is based on the ITT analysis set. At the time of the efficacy clinical cutoff date of 1 November 2022, 39 patients (18.8%) in the cilta-cel arm and 47 patients (22.3%) in the SoC arm had died. OS data may suggest a trend towards improved survival in the cilta-cel arm vs SoC arm (HR=0.78; 95% CI: 0.50–1.20; p=0.2551); however, the OS data were yet to be mature. A Kaplan-Meier plot for OS is provided in Figure 18.

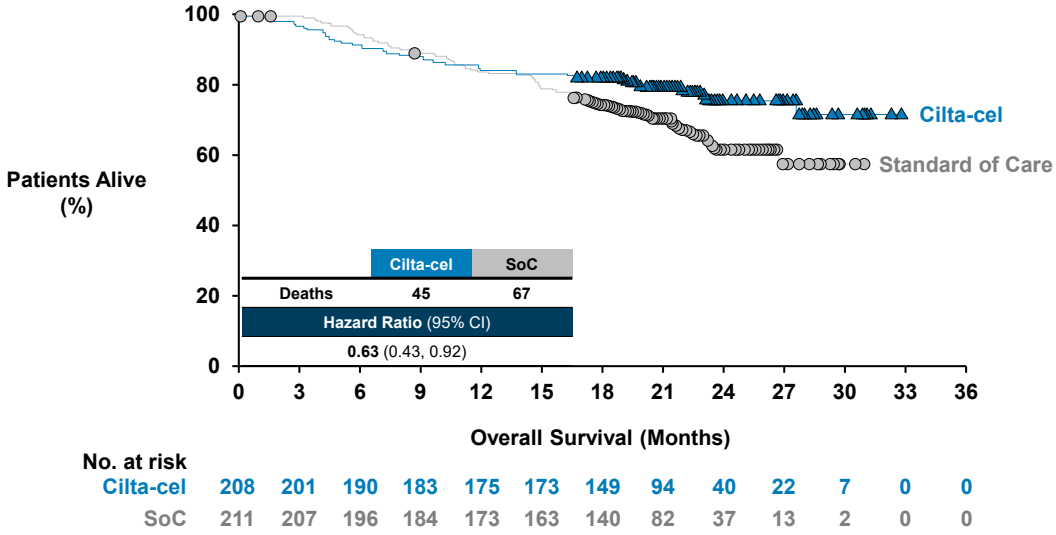
Two additional descriptive OS analyses were conducted using clinical cutoff dates of 17 April 2023 and 13 December 2023. The analysis of OS of 17 April 2023 was conducted at the request of the FDA. The most recent analysis conducted on 13 December 2023 was at the request of the EMA. Over time, the HR has strengthened as data continue to mature (Figure 19; Figure 20). The most recent analysis from 13 December 2023, corresponding to a median follow-up of 28.7 months, showed 48 deaths in the cilta-cel arm and 77 deaths in the SoC arm had occurred with a HR of 0.57 (95% CI: 0.40–0.83).

Figure 18: CARTITUDE-4 Study: Kaplan-Meier Plot for Overall Survival (ITT Analysis Set; Clinical Cutoff Date of 01 November 2022)



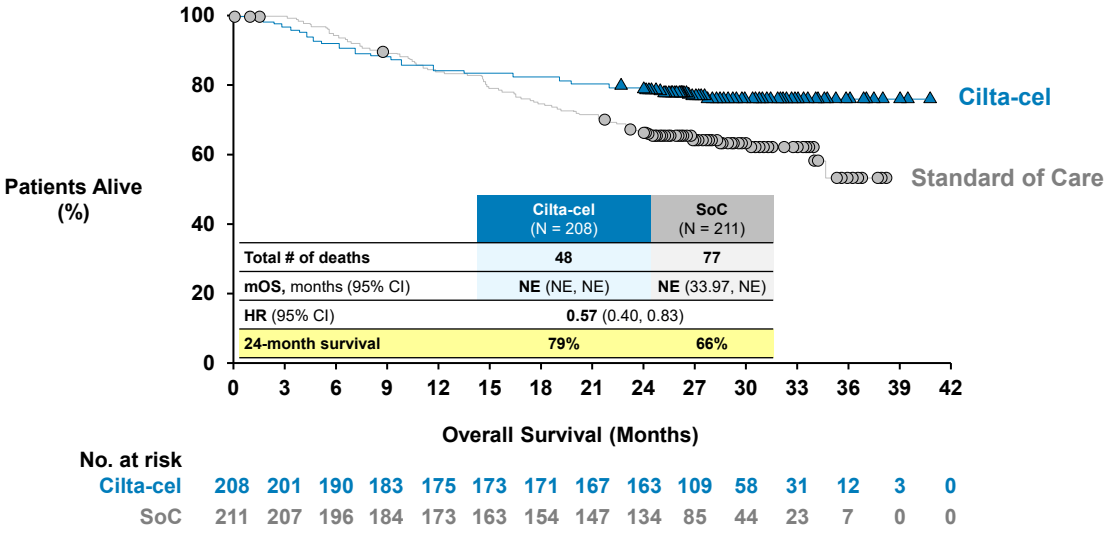
ITT=Intent-to-Treat; SoC=standard of care.

Figure 19: CARTITUDE-4 Study: Kaplan-Meier Plot for Overall Survival (ITT Analysis Set; Clinical Cutoff Date of 17 April 2023)



ITT=Intent-to-Treat; SoC=standard of care.

Figure 20: CARTITUDE-4 Study: Kaplan-Meier Plot for Overall Survival (ITT Analysis Set; 13 December 2023 Survival Sweep)

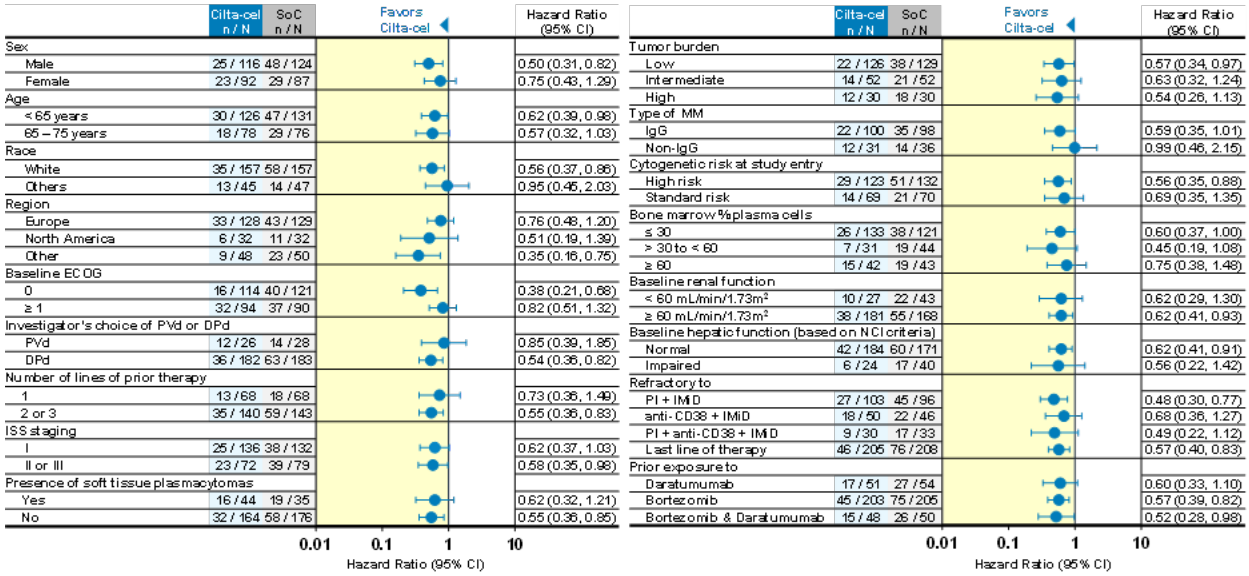


ITT=Intent-to-Treat; mOS=median overall survival; NE=not estimable; SoC=standard of care.

Overall Survival by Subgroup

Across all pre-specified subgroups, the positive trend towards OS benefit of cilta-cel over SoC was consistent (Figure 21).

Figure 21: CARTITUDE-4 Study: Overall Survival by Subgroup (ITT Analysis Set; 13 December 2023 Survival Sweep)



Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.
DPd=daratumumab, pomalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; IMiD=immunomodulatory agent; ISS=International Staging System; ITT=Intent-to-Treat; MM=multiple myeloma; NCI=National Cancer Institute; PI=proteasome inhibitor; PVd=pomalidomide, bortezomib, and dexamethasone; SoC=standard of care.

6.1.7.3.3 Patient-reported Outcomes

Time to Worsening of Symptoms in the MySIm-Q Total Symptom Score

While time to worsening of symptoms in the MySIm-Q total symptom score is considered a key secondary endpoint for the study, this endpoint could not be tested formally at the interim analysis because it follows OS in the hierarchical testing order. Nonetheless, the totality of PRO data from CARTITUDE-4 supports an improvement in patients' overall HRQoL, functioning, and reduction in symptoms with cilta-cel treatment.

Patient-reported multiple myeloma symptom severity was assessed using the MySIm-Q total symptom score, where the total score measures severity of pain, neuropathy, fatigue, digestive symptoms, and cognitive symptoms. The median time to worsening of multiple myeloma symptoms was longer for the cilta-cel arm than for the SoC arm: 23.7 months (95% CI: 22.1–NE) vs 18.9 months (95% CI: 16.8–NE); HR=0.42 (95% CI: 0.26–0.68; Table 13). Time to worsening was defined as a worsening by the minimally important difference (MID) threshold compared to baseline without subsequent improvement to a score above this level.

Table 13: CARTITUDE-4 Study: Time to Worsening in MySIm-Q Total Symptom Subscale (ITT Analysis Set)

	Cilta-cel (N=208)	SoC (N=211)
Time to Worsening in MySIm-Q Total Symptom Score (months)		
Number of events (%)	30 (14.4)	46 (21.8)
Number of censored (%)	178 (85.6)	165 (78.2)
Median (95% CI)	23.66 (22.11, NE)	18.86 (16.76, NE)
Hazard ratio (95% CI)[a]	0.42 (0.26, 0.68)	
Worsening Event-free Rate, % (95% CI)		
6-month	91.5 (86.2, 94.8)	84.5 (77.7, 89.3)
12-month	84.6 (77.7, 89.6)	65.6 (55.2, 74.2)
18-month	79.8 (69.6, 86.9)	51.9 (34.5, 66.8)

a. Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with Investigator's choice (PVd or DPd), ISS staging (I, II, III), and number of prior lines (1 vs 2 or 3) as randomized. A hazard ratio <1 indicates an advantage for the cilta-cel arm.
Note: Time of worsening is defined as an increase (≥0.5 standard deviation of pooled baseline values) without a subsequent reduction in score.
DPd=daratumumab, pomalidomide, and dexamethasone; ITT=Intent-to-Treat; ISS=International Staging System; MySIm-Q=Multiple Myeloma Symptom and Impact Questionnaire; NE=not estimable; PVd=pomalidomide, bortezomib, and dexamethasone; SoC=standard of care.

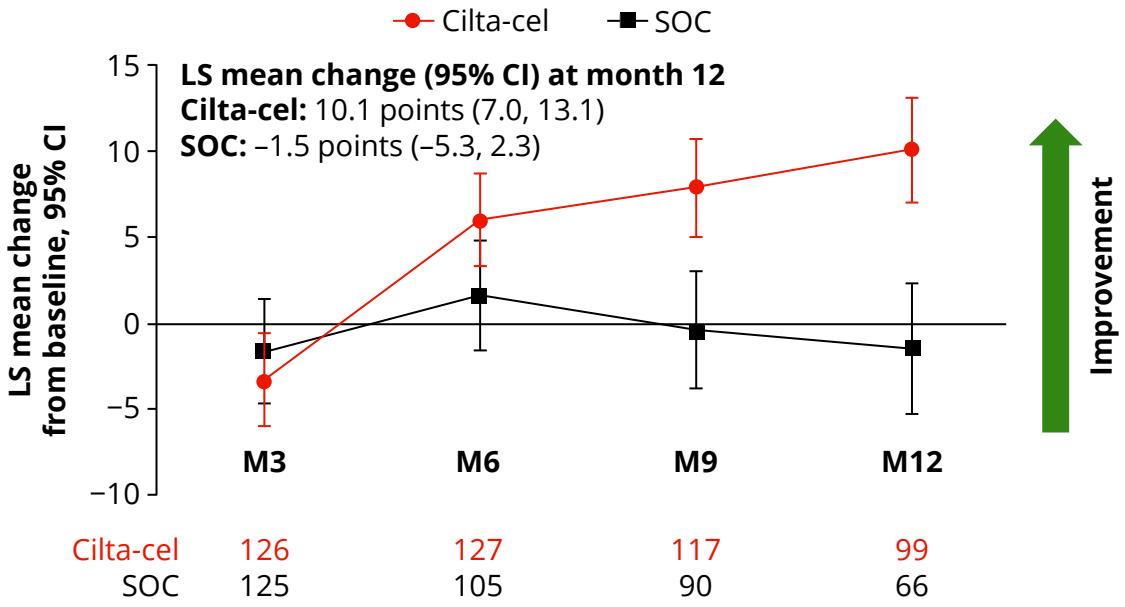
EORTC QLQ-C30 Results

Patients' overall HRQoL, symptoms, and functioning were also assessed using the EORTC QLQ-C30. The EORTC QLQ-C30 contains an overall HRQoL scale (global health status), 3 symptom scales (pain, fatigue, nausea/vomiting), and 5 functional scales (physical, role, emotional, cognitive, and social functioning).

Global health status

GHS reflects the overall HRQoL. Patients treated with cilta-cel reported a slight decrease in GHS at Month 3 (28 days post-infusion), but quickly reported an improvement over time with the LS mean change from baseline at Month 12 equal to 10.1 (95% CI: 7.0–13.1), compared to no change from baseline being reported by patients treated with SoC (Figure 22).

Figure 22: CARTITUDE-4 Study: EORTC QLQ-C30 Global Health Status Change from Baseline[a]

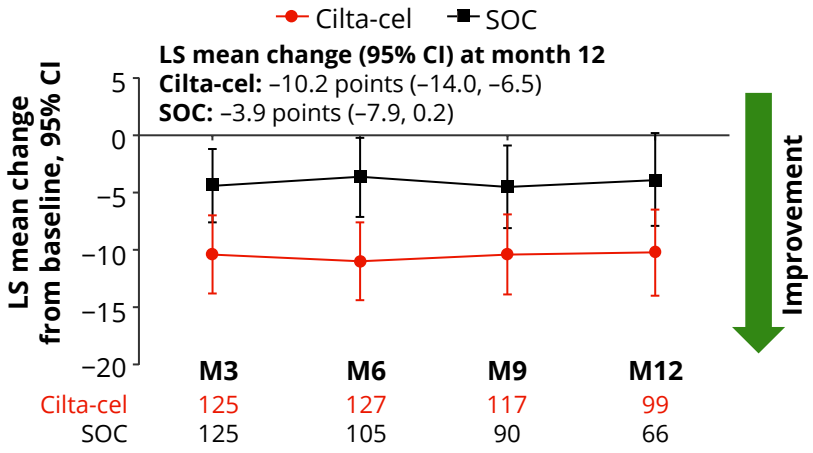


a. LS means are derived based on the mixed effects model with repeated measures in which the dependent variable is change from baseline in score and independent variables baseline score and visit as fixed effects with individual subject as random effect. Assessments after the start of subsequent therapy were excluded.
Sully et al 2019.
EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; GHS=global health status; LS=least squares; M=month; PRO=patient-reported outcome; SoC=standard of care.

Symptom scales

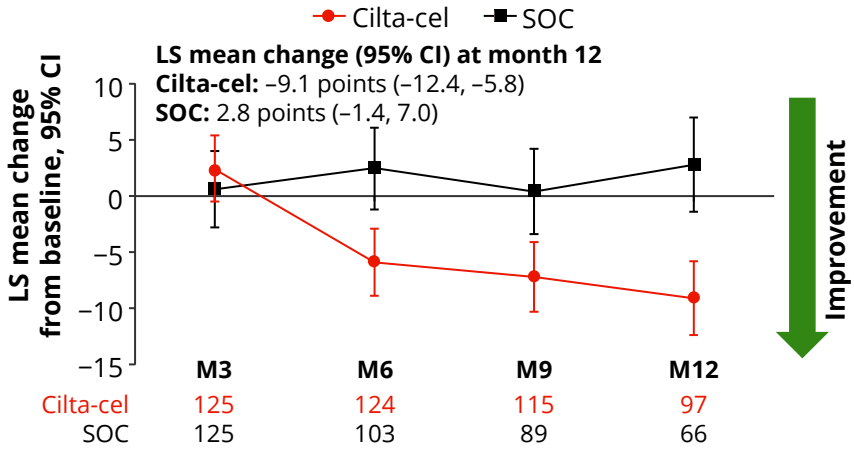
Patients treated with cilta-cel reported improvement in pain and fatigue to a greater degree than patients treated with SoC. Pain improved as early as the first assessment post-cilta-cel infusion and patients continued to report reduction in pain severity over time. Reduction in fatigue in patients treated with cilta-cel was noted starting at 6 months and continued to improve with time. Fatigue remained unchanged from baseline for patients in the SoC arm (Figure 23; Figure 24). The EORTC QLQ-C30 nausea and vomiting baseline mean values were low and there was little change over time for both the cilta-cel and SoC treated patients.

Figure 23: CARTITUDE-4 Study: EORTC QLQ-C30 Symptom Scale Change from Baseline in Pain[a]



a. LS means are derived based on the mixed effects model with repeated measures in which the dependent variable is change from baseline in score and independent variables baseline score and visit as fixed effects with individual subject as random effect. Assessments after the start of subsequent therapy were excluded.
King et al 1996; Osoba et al 1998.
EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30-item; M=month; PRO=patient-reported outcome; SoC=standard of care.

Figure 24: CARTITUDE-4 Study: EORTC QLQ-C30 Symptom Scale Change from Baseline in Fatigue[a]



a. LS means are derived based on the mixed effects model with repeated measures in which the dependent variable is change from baseline in score and independent variables baseline score and visit as fixed effects with individual subject as random effect. Assessments after the start of subsequent therapy were excluded.
King et al 1996; Osoba et al 1998.
EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30-item; M=month; PRO=patient-reported outcome; SoC=standard of care.

Functional scales

Patients on the cilta-cel arm experienced improvements through Month 12 in all 5 functional domains (cognitive, emotional, physical, role and social functioning; Table

14). In contrast, patients on the SoC arm experienced worsening in 4 of 5 functional scales at 12 months, especially on the cognitive functioning scale. Notably, for patients on the cilta-cel arm there was no discernable decline from baseline on the cognitive functioning scale.

Table 14: CARTITUDE-4 Study: EORTC QLQ-C30 Functional Scale Change from Baseline at Month 12[a]

Scale	LS Mean Change (95% CI)	
	Cilta-cel (N=99)	SoC (N=66)
EORTC QLQ-C30 Functional Scales		
Cognitive functioning	0.5 (-2.4, 3.5)	-7.5 (-11.2, -3.9)
Emotional functioning	9.5 (6.6, 12.5)	2.2 (-1.3, 5.7)
Physical functioning	6.5 (3.8, 9.1)	-2.1 (-5.0, 0.7)
Role functioning	7.7 (3.7, 11.7)	-1.7 (-6.3, 2.9)
Social functioning	6.1 (2.1, 10.0)	-0.1 (-4.2, 4.0)

a. LS means are derived based on the mixed effects model with repeated measures in which the dependent variable is change from baseline in score and independent variables baseline score and visit as fixed effects with individual subject as random effect. Assessments after the start of subsequent therapy were excluded.
EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30-item; LS=least squares; M=month; SoC=standard of care.

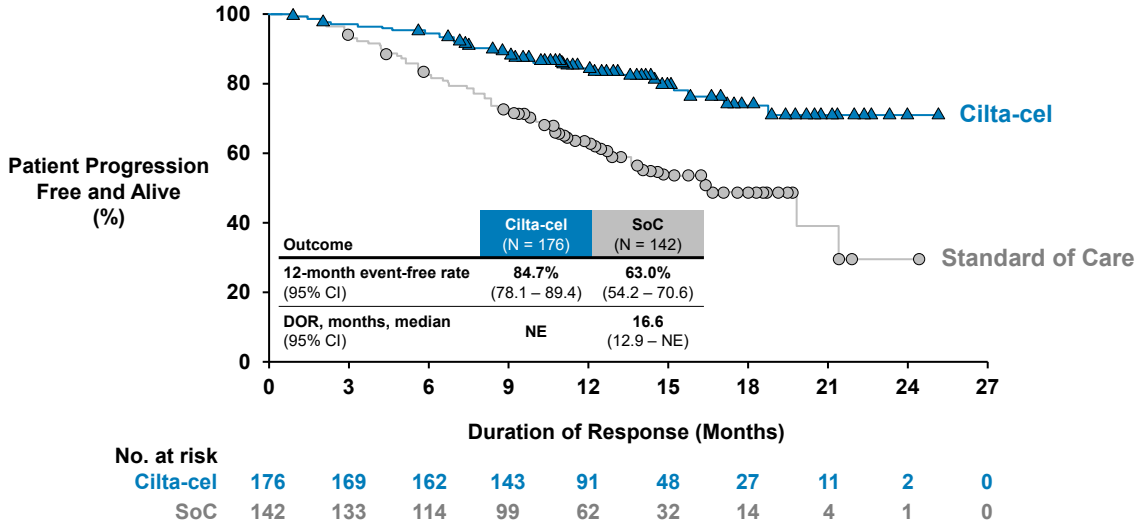
6.1.7.4 Additional Endpoint

6.1.7.4.1 Duration of Response

DoR was calculated among responders (with a partial response [PR] or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of disease progression, or death due to any cause, whichever occurred first.

Most responders (81.3% of patients in the cilta-cel arm and 56.3% of patients in the SoC arm with PR or better) were censored as of the time of clinical cutoff on 1 November 2022. Median DoR was NE (95% CI: NE–NE) for the cilta-cel arm and was 16.6 months (95% CI: 12.9–NE) for the SoC arm. Twelve-month event-free rates were 84.7% (95% CI: 78.1–89.4) for the cilta-cel arm and 63.0% (95% CI: 54.2–70.6) for the SoC arm. Kaplan-Meier curves for DoR are provided in Figure 25.

Figure 25: CARTITUDE-4 Study: Kaplan-Meier Plot for Duration of Response; Responders (Partial Response or Better) in ITT Analysis Set



DOR=duration of response; ITT=Intent-to-Treat; NE=not estimable; SoC=standard of care.

6.1.8 Comprehensive Analyses of Early Imbalance in Overall Survival and Progression-free Survival Events

The Sponsor has conducted an in-depth analysis of possible factors that may have contributed to the early progression events prior to cilta-cel, which in turn led to the early deaths. The exploratory nature of the analysis and the small number of events, as well as potential unmeasured confounding factors, warrant cautious interpretation of the results. The Sponsor recognizes that early progression events were likely multi-factorial and may not be attributable to one single factor nor due to random variability alone. In the context of clinically meaningful and highly statistically significant improvement in PFS as well as ORR, CR or better rate, MRD negativity rate, and strong trend toward OS improvement consistently seen in the cilta-cel arm over SoC arm in all pre-specified subgroups, no patient subpopulations were identified where cilta-cel should be avoided.

6.1.8.1 Imbalance in Early Overall Survival Events

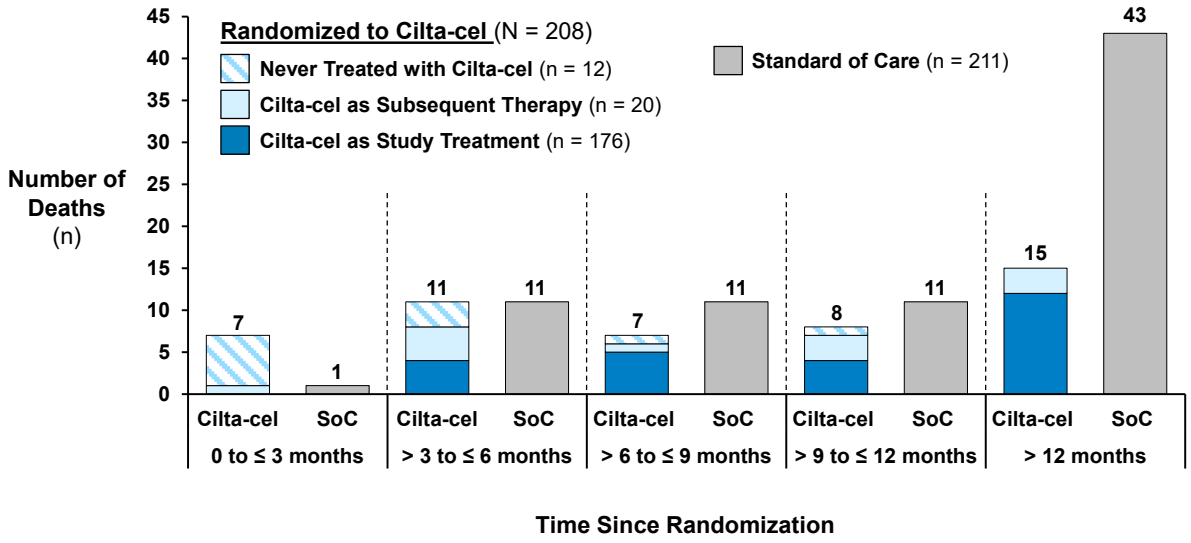
The only period in which there were more deaths in the cilta-cel arm (n=7) than in the SoC arm (n=1) occurred within the first three months after randomization. This imbalance is the reason the OS Kaplan-Meier curves are initially unfavorable (Figure 20). However, 6 of these 7 deaths were in patients randomized to cilta-cel who progressed prior to cilta-cel infusion and had never received cilta-cel. The remaining patient received cilta-cel as subsequent therapy following progression on bridging therapy (Figure 26; Table 15).

In summary, the higher number of deaths in the cilta-cel arm during the first 3-month period post randomization was attributable to progression in patients prior to receiving cilta-cel. Between 3 and 6 months, an equal number of deaths was observed on both

arms. In the cilta-cel arm, deaths during this period were primarily due to (1) deaths in patients who progressed prior to receiving cilta-cel, (2) COVID-19 in patients following cilta-cel, and (3) AEs in patients who rapidly progressed on bridging therapy, had poorly controlled disease, and generally had poorer performance status but were allowed to receive cilta-cel as subsequent therapy (Figure 26; Table 15).

Primary causes of all deaths during the CARTITUDE-4 study are provided in Appendix 11.1.

Figure 26: CARTITUDE-4 Study: Deaths Over Time Across Treatment Groups (13 December 2023 Survival Sweep)



SoC=standard of care.

Table 15: CARTITUDE-4 Study: Total Deaths and Causes of Deaths at 0–≤3 and >3–≤6 Months (ITT Analysis Set)

Cause of Death	0–≤3 Months				>3–≤6 Months			
	Never Treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never Treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)
Total Deaths	6	1	0	1	3	4	4	11
PD	4	-	-	1	3	-	1	5
AE[a]	2	1	-	-	-	4	3[b]	6

a. AEs listed by preferred term are presented in Appendix 11.1.
b. All 3 due to COVID-19 pneumonia.
AE=adverse event; ITT=Intent-to-Treat; PD=progressive disease; SoC=standard of care.

6.1.8.2 Imbalance in Early Progression-free Survival Events

A comprehensive analysis was carried out to determine if any parameters could be identified that may have contributed to the imbalance in early PFS events between the cilta-cel arm compared to the SoC arm (as described below). No subpopulation was identified where cilta-cel should be avoided.

6.1.8.2.1 Demographics and Baseline Disease Characteristics and Treatment History

Baseline demographics and disease characteristics were well balanced at baseline (Table 9; Table 10). A subgroup identification analysis was performed in all randomized patients to explore whether there was a potential subgroup of patients with specific baseline features that may be associated with a higher risk of having an early PFS event. Once these subgroups were identified, the Sponsor looked for any imbalance in the covariates between the two arms to assess whether these covariates and their imbalanced distributions across arms may have contributed to the subsequent imbalance in early PFS events. Baseline covariates evaluated in the analysis are listed in Table 16.

Table 16: Baseline Covariates

- Number of lines of prior therapy
- Tumor burden (low, intermediate, high)[1]
- Bone marrow plasma cells (%)
- Disease tempo (percent change in disease burden from screening to baseline[2])
- Duration-adjusted disease tempo (disease tempo per week)[3]
- Presence of soft tissue plasmacytomas
- Cytogenetics risk (high vs standard risk)
- Cytogenetics high risk abnormality del(17p)
- Cytogenetics high risk abnormality t(4;14)
- Cytogenetics high risk abnormality t(14;16)
- Cytogenetics high risk abnormality gain/amp 1q
- Cytogenetics high risk abnormality double hit (at least 2 abnormalities)
- del(17p), t(4;14) or (14;16)
- Refractory to anti-CD38 monoclonal antibody
- Refractory to pomalidomide
- Refractory to bortezomib
- Refractory to carfilzomib
- Triple-class refractory (PI+IMiD+anti-CD38)
- Penta drug refractory
- Refractory to anti-CD38 monoclonal antibody in last line of prior therapy
- Refractory to carfilzomib in last line of prior therapy
- Refractory to bortezomib in last line of prior therapy
- Refractory to lenalidomide in last line of prior therapy
- Refractory to pomalidomide in last line of prior therapy
- Prior ASCT
- Time from last ASCT to progression
- Baseline platelet count, neutrophil count, hemoglobin
- Time from start of last line of prior therapy to randomization
- Time from end of last line of prior therapy to randomization
- ISS staging (I, II, III)
- ECOG (0, 1 or 2)
- Investigator's choice of regimen (PVd or DPd)
- Country
- Region
- Beta-2 microglobulin
- Receiving bridging therapy to which the patient is refractory
- Revised ISS (I, II, III)

1. High tumor burden is defined as meeting any of the following: bone marrow % plasma cell ≥ 80%, serum M-protein ≥5g/dL, serum free light chain ≥5000 mg/L. Low tumor burden is defined as meeting all of the following: bone marrow % plasma cell <50%, serum M-protein <3g/ dL, serum free light chain <3000 mg/L. Intermediate tumor burden is defined as not meeting either high or low tumor burden.
2. The percent change between screening and baseline of serum M-protein, urine M-protein, or difference between involved and uninvolved free light chain according to the measurable disease at screening, reflecting kinetics of disease during the screening period.
3. Disease tempo divided by the duration from screening to baseline (in weeks).
ASCT=autologous stem cell transplantation; DPd=daratumumab, pomalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; IMiD=immunomodulatory agent; ISS=International Staging System; PI=proteasome inhibitor; PVd=pomalidomide, bortezomib, and dexamethasone.

The results suggest certain subgroups of patients among all randomized patients might be at higher risk of early PFS events: patients who had higher disease tempo during screening, were refractory to anti-CD38 antibody, were triple-class refractory, progressed faster after their last ASCT, or had lower hemoglobin at baseline. Distributions of the identified subgroups were further evaluated between the two randomized arms, revealing no substantial differences between the two arms with respect to the percentage of patients having the identified covariates. Therefore, patients with these features may be at higher risk of early progression, but the presence of these factors does not account for the imbalance of early PFS events.

6.1.8.2.2 Study Factors

To further assess the potential impact of various study-related procedures on the imbalance of early PFS events, the cilta-cel and SoC arms were compared where applicable. In addition, a comparison was made of patients on the cilta-cel arm with early PFS events (n=22), defined as PFS events in the first 8 weeks after randomization, to those without early PFS events (n=186).

Impact of apheresis

All patients randomized to cilta-cel underwent apheresis. Apheresis is a standard procedure required in the manufacturing of all autologous CAR-T products and has not been reported to impact tumor progression in published data from other CAR-T products. The median duration of apheresis was 240 minutes (range: 83 to 455 minutes) with a median of 212.5 mL collected (range: 60 to 394 mL).

Hematologic parameters (absolute lymphocyte count [ALC], absolute neutrophil count [ANC], hemoglobin, platelet count) were assessed before and after apheresis in patients randomized to the cilta-cel arm. Small, expected decreases in ALC, hemoglobin, and platelet counts were noted after apheresis; however, these were not considered to be clinically meaningful.

Timing of study procedures

Median time from signing informed consent form (ICF) to randomization was not appreciably different between patients in the cilta-cel arm (19 days) vs those in the SoC arm (20 days). Median time from signing ICF to randomization was also not substantially different between patients on the cilta-cel arm with early PFS (22.5 days) vs those without (19.0 days).

Median time from randomization to apheresis for all patients on the cilta-cel arm was 6 days (range: 2 to 8). The time from randomization to apheresis in patients with early PFS events was similar (5 days, range: 2 to 7) to that in patients without early PFS events (6 days, range: 2 to 8).

The median time from randomization to the start of study treatment in the SoC arm was 6 days (range: 1 to 14). Median time from randomization to start of bridging therapy was 7 days (range: 2 to 19). The median time from randomization to start of bridging therapy was 7 days in patients with and without early PFS events.

The protocol-prescribed treatment and schedule of assessments for patients receiving bridging therapy on the cilta-cel arm was the same as for patients on the SoC arm receiving standard therapy.

Therefore, in terms of time to starting therapy, no substantial difference between either the two arms or between patients with early PFS events and those without could be identified that may have accounted for the observed early imbalance in PFS events.

Choice of DPd or PVd

Investigator's choice of DPd or PVd was made prior to randomization and based on prior treatment exposure and refractoriness. There was no substantial difference between the cilta-cel arm (18.3%) and the SoC arm (16.1%) in terms of the number of patients who were refractory to at least 1 component (daratumumab, bortezomib or pomalidomide) of the Investigator's choice of DPd/PVd.

CAR-T manufacturing time

The median duration of vein-to-vein time in the cilta-cel group was 79 days (interquartile range [IQR]: 68–90), and apheresis-to-release time was 57 days (IQR: 45–65). Ten of the 22 early PFS events occurred within 4 weeks of apheresis, with 19 of the 22 occurring within 5 weeks of apheresis. The median time from apheresis to product release for patients with early PFS events vs those without was 59 days (IQR: 47–66) and 57 days (IQR: 44–65), respectively. The median number of days patients with early PFS event spent off bridging therapy prior to progression was 0 (range: 0 to 15), indicating that most patients were actively receiving bridging therapy at the time of PD. Therefore, it is unlikely that manufacturing time played a major role in early PFS events.

6.1.8.2.3 Dose of bridging therapy

The Sponsor evaluated the relationship between dose of bridging therapy and occurrence of early PFS events. For this purpose, a relative dose intensity of bridging therapy was calculated to account for PFS events mid-cycle and any washout periods on the cilta-cel arm prior to cilta-cel infusion (Table 17). Data for relative dose intensity evaluation showed that the median relative dose intensity of pomalidomide and bortezomib were lower in the cilta-cel arm than in the SoC arm. The relative dose intensities for daratumumab and dexamethasone were similar between the two arms.

Table 17: Difference in Relative Dose Intensity of Bridging Therapy

Relative Dose Intensity	Cilta-cel (N=208)	SoC (N=208)
Pomalidomide, n	207	208
Median	81.0%	94.5%
Bortezomib, n	26	26
Median	73.2%	87.5%
Dexamethasone, n	207	208
Median	90.0%	90.0%
Daratumumab, n	181	182
Median	81.3%	80.0%

SoC=standard of care.

To determine whether a possible association between early PFS events and bridging therapy dosing existed, the Sponsor ranked patients across both arms based on their relative dose intensity of pomalidomide, focusing on the 25% of the patients with the

lowest relative dose intensity (Quartile 1). For pomalidomide, this included 104 patients in the lowest quartile (Q1). Twelve of 104 (11.5%) patients in Q1 for pomalidomide had an early PFS event vs 16 out of 311 (5.1%) among those without this level of dose reduction, indicating twice the rate of early PFS among patients in Quartile 1 vs those without this level of dose reduction (patients in Quartiles 2 through 4 [Q2–Q4], Table 18). Out of the 104 patients, 67 were from the cilta-cel arm and 37 were from the SoC arm. The cutoff for Quartile 1 was 68.5% relative dose intensity; the equivalent of receiving approximately 2 weeks instead of 3 weeks of pomalidomide as part of a cycle of DPd.

Table 18: Pomalidomide Relative Dose Intensity and Early Progression-free Survival Events

Pomalidomide Relative Dose Intensity	Number of Patients		Early PFS Event (Both Arms)
	Cilta-cel (N=207)	SoC (N=208)	
Q1 (n=104)	67	37	12 (11.5%)
Q2–Q4 (n=311)	140	171	16 (5.1%)

PFS=progression-free survival; SoC=standard of care.

Similarly, for bortezomib there were 13 patients in the lowest quartile (Q1). Seven of 13 (53.8%) patients in Q1 for bortezomib had an early PFS event vs 4 out of 39 (10.3%) among those without this level of dose reduction, indicating five times the rate of early PFS among patients in Quartile 1 vs those without this level of dose reduction (patients in Quartiles 2 through 4 [Q2–Q4], Table 19). Out of the 13 patients, 9 were from the cilta-cel arm and 4 were from the SoC arm. The cutoff for Q1 was 68% relative dose intensity; the equivalent of receiving approximately 5 doses of bortezomib instead of 8 during 2 cycles of PVd.

Table 19: Bortezomib Relative Dose Intensity and Early Progression-free Survival Events

Bortezomib Relative Dose Intensity	Number of Patients		Early PFS Event (Both Arms)
	Cilta-cel (N=26)	SoC (N=26)	
Q1 (n=13)	9	4	7 (53.8%)
Q2–Q4 (n=39)	17	22	4 (10.3%)

PFS=progression-free survival; SoC=standard of care.

This may have contributed to the imbalance of early PFS events although the extent of this contribution is unknown.

6.1.8.2.4 Lymphodepleting conditioning therapy

Among 22 patients with early PFS events in the first 8 weeks, none of the patients received lymphodepletion prior to disease progression, eliminating lymphodepleting chemotherapy as a reason for early disease progression.

6.2 Efficacy Conclusions

In the Phase 3, global, randomized, controlled CARTITUDE-4 study, cilta-cel demonstrated clinically meaningful, statistically significant improvement in PFS and key secondary endpoints compared to continuous treatment with SoC therapy. Deep and durable responses translated into a strong trend towards improved OS that has strengthened as data mature. Consistent PFS benefit and trend toward OS benefit in favor of cilta-cel was seen in all pre-specified subgroups. Efficacy results are further supported by data from PROs showing clinically meaningful improvements in GHS scores, emotional, social, physical and role functioning, and reductions in pain and fatigue.

Overall, the efficacy data supports the use of cilta-cel for the treatment of patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a PI and IMiD, and are refractory to lenalidomide.

7 CLINICAL SAFETY

Summary

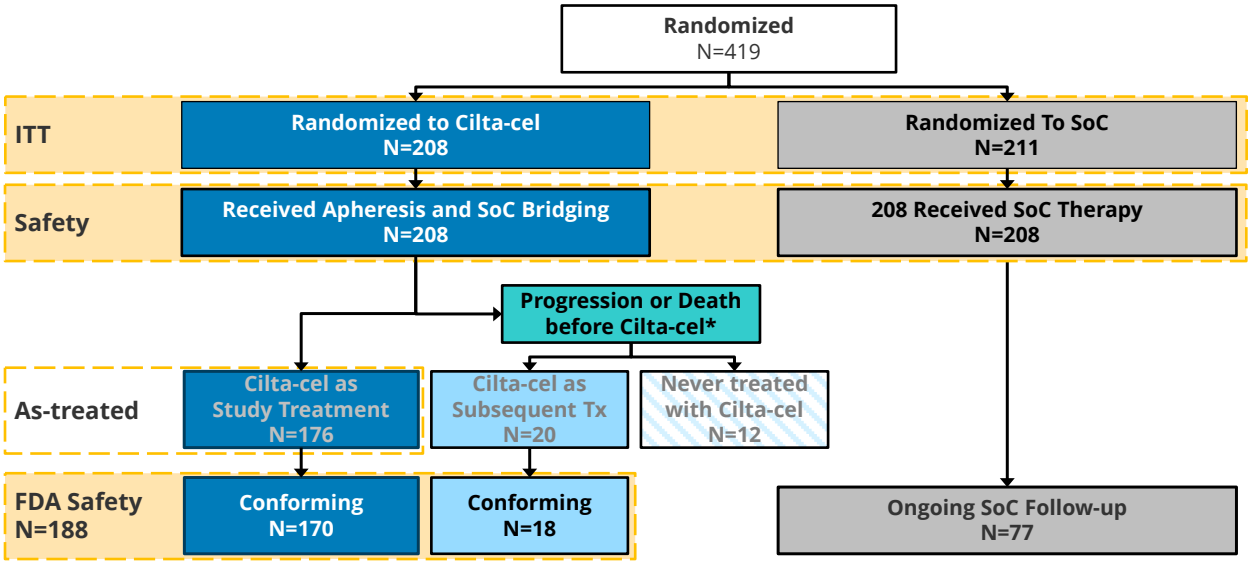
- The safety profile of cilta-cel in patients with relapsed or refractory multiple myeloma after 1 to 3 prior lines of therapy is generally consistent with the established safety profile in the approved indication and the mechanism of CAR-T therapy.
- The rate and severity of several cilta-cel specific AEs (e.g., CRS, MNT) appeared to be lower in the CARTITUDE-4 study compared with the CARTITUDE-1 study that enrolled a more heavily pretreated and refractory population.
- Disease progression during bridging therapy, prior to cilta-cel infusion, and administration of cilta-cel as subsequent therapy in the setting of uncontrolled disease, was associated with a worse safety profile.

7.1 FDA Safety Analysis Sets

Safety analysis is presented based on the FDA-proposed safety analysis set (N=188), including patients who received conforming cilta-cel as study treatment (170 out of 176 patients) and patients who received conforming cilta-cel as subsequent therapy (18 out of 20 patients; Figure 27). Conforming product is cilta-cel drug product that meets all pre-specified release criteria for clinical supply.

Per FDA's guidance, the Sponsor compared post-infusion AEs for patients who received conforming cilta-cel either as study treatment or as subsequent therapy (N=188), against patients in the SoC arm (N=208). Post-infusion AEs were defined as any AE that occurred on or after cilta-cel infusion (Day 1) until Day 112 post-cilta-cel infusion or the start of subsequent therapy, whichever occurred first, or at any time if related to cilta-cel. AEs for patients in the SoC arm (N=208) were defined as any AE from Day 1 of study treatment until 30 days after the last dose of study treatment or the start of subsequent therapy, whichever occurred first, or at any time if related to study treatment.

Figure 27: CARTITUDE-4 Study: CONSORT Diagram Describing FDA Safety Analysis Set



*31 patients progressed, and 1 patient died prior to access to cilta-cel infusion.
CONSORT=Consolidated Standards of Reporting Trials; FDA=Food and Drug Administration; ITT=Intent-to-Treat; SoC=standard of care; Tx=treatment.

The clinical cutoff date for the safety analysis was 1 November 2022 unless otherwise specified. AE summaries are presented by grouped terms as provided by the FDA as well as MedDRA preferred terms. Throughout this safety section, unless otherwise noted, all in-text references to the cilta-cel arm refer to patients who received conforming cilta-cel.

7.2 Summary of Adverse Events

A summary of AEs in the CARTITUDE-4 study is provided in Table 20. The incidence of AEs was 100% in both treatment arms. Serious AEs (SAEs) were reported for 37.8% of patients in the cilta-cel arm and 38.9% of patients in the SoC arm. Grade 3 or 4 AEs were reported for 92.0% of patients in the cilta-cel arm and 94.2% of patients in the SoC arm.

Table 20: CARTITUDE-4 Study: Overall Summary of Adverse Events by Treatment Arm (FDA Safety Analysis Set)

	Received Conforming Cilta-Cel			
Patients with	Cilta-cel as Study Treatment (n=170) n (%)	Cilta-cel as Subsequent Therapy (n=18) n (%)	Cilta-cel (N=188) n (%)	SoC (N=208) n (%)
Any AE	170 (100.0)	18 (100.0)	188 (100.0)	208 (100.0)
Grade 3/4	156 (91.8)	17 (94.4)	173 (92.0)	196 (94.2)
Any SAE	60 (35.3)	11 (61.1)	71 (37.8)	81 (38.9)

FDA=Food and Drug Administration; SAE=serious adverse event; SoC=standard of care.

7.2.1 Common Adverse Events

AEs reported in ≥30% of patients in either treatment arm are provided in Table 21. The most common AEs in the cilta-cel arm (CRS, cytopenias, and hypogammaglobulinemia) are expected events for BCMA-directed CAR-T therapy. Fatigue, musculoskeletal pain, and upper respiratory tract infection were observed with higher frequency in the SoC arm.

Table 21: CARTITUDE-4 Study: Adverse Events in ≥30% of Patients in Either Treatment Arm (FDA Safety Analysis Set)

	Received Conforming Cilta-Cel			
	Cilta-cel as Study Treatment (n=170) n (%)	Cilta-cel as Subsequent Therapy (N=18) n (%)	Cilta-cel (n=188) n (%)	SoC (N=208) n (%)
Total number of patients with AE	170 (100)	18 (100)	188 (100)	208 (100)
Neutropenia[a]	143 (84.1)	15 (83.3)	158 (84.0)	177 (85.1)
Cytokine release syndrome	130 (76.5)	16 (88.9)	146 (77.7)	1 (0.5)
Fatigue[a]	48 (28.2)	4 (22.2)	52 (27.7)	104 (50.0)
Anemia[a]	77 (45.3)	14 (77.8)	91 (48.4)	54 (26.0)
Thrombocytopenia[a]	79 (46.5)	11 (61.1)	90 (47.9)	65 (31.3)
Hypogammaglobulinemia[a]	84 (49.4)	6 (33.3)	90 (47.9)	13 (6.3)
Musculoskeletal pain[a]	58 (34.1)	6 (33.3)	64 (34.0)	98 (47.1)
Upper respiratory tract infection[a]	45 (26.5)	2 (11.1)	47 (25.0)	83 (39.9)
Viral infection[a]	41 (24.1)	3 (16.7)	44 (23.4)	64 (30.8)

a. FDA grouped term.
AE=adverse event; FDA=Food and Drug Administration; SoC=standard of care

7.2.2 Adverse Events Grade 3/4

The most common Grade 3 or 4 AEs, reported in ≥20% of patients in either treatment arm, were cytopenia events as shown in Table 22.

Table 22: CARTITUDE-4 Study: Adverse Events of Grade 3/4 in ≥20% of Patients in Either Treatment Arm (FDA Safety Analysis Set)

	Received Conforming Cilta-Cel			
	Cilta-cel as Study Treatment (n=170) n (%)	Cilta-cel as Subsequent Therapy (N=18) n (%)	Cilta-cel (n=188) n (%)	SoC (N=208) n (%)
Total number of patients with AE Grade 3/4	156 (91.8)	17 (94.4)	173 (92.0)	196 (94.2)
Neutropenia[a]	143 (84.1)	15 (83.3)	158 (84.0)	171 (82.2)
Thrombocytopenia[a]	60 (35.3)	11 (61.1)	71 (37.8)	39 (18.8)
Anemia[a]	49 (28.8)	11 (61.1)	60 (31.9)	30 (14.4)
Lymphopenia[a]	35 (20.6)	3 (16.7)	38 (20.2)	25 (12.0)

a. FDA grouped term
AE=adverse event; FDA=Food and Drug Administration; SoC=standard of care.

7.2.3 Serious Adverse Events

The most common SAEs reported in ≥3% of patients in either treatment arm are shown in Table 23. Overall, SAE incidence was similar across both arms. The most commonly reported SAEs in both arms were infections (pneumonia and viral infections).

Other SAEs in the cilta-cel arm included CRS and cranial nerve palsies, largely reflecting AEs known to be associated with cilta-cel treatment (Section 7.4).

Table 23: CARTITUDE-4 Study: Serious Adverse Events in ≥3% of Patients in Either Treatment Arm (FDA Safety Analysis Set)

	Received Conforming Cilta-Cel			
	Cilta-cel as Study Treatment (n=170) n (%)	Cilta-cel as Subsequent Therapy (N=18) n (%)	Cilta-cel (n=188) n (%)	SoC (N=208) n (%)
Total number of patients with SAE	60 (35.3)	11 (61.1)	71 (37.8)	81 (38.9)
Pneumonia[a]	15 (8.8)	2 (11.1)	17 (9.0)	25 (12.0)
Viral infection[a]	12 (7.1)	0	12 (6.4)	12 (5.8)
Cytokine release syndrome	7 (4.1)	5 (27.8)	12 (6.4)	1 (0.5)
Cranial nerve palsies[a]	10 (5.9)	0	10 (5.3)	1 (0.5)
Upper respiratory tract infection[a]	3 (1.8)	0	3 (1.6)	9 (4.3)
Sepsis[a]	5 (2.9)	2 (11.1)	7 (3.7)	3 (1.4)
Bacterial infection[a]	2 (1.2)	1 (5.6)	3 (1.6)	7 (3.4)

a. FDA grouped term
SAE=serious adverse event; FDA=Food and Drug Administration; SoC=standard of care.

7.3 Adverse Events as Primary Cause of Death

An unplanned assessment of survival status was performed using a survival sweep of 13 December 2023. This analysis showed that AEs were the primary cause of death for 23 patients (12.2%) in the cilta-cel arm and 28 patients (13.5%) in the SoC arm (Table 24).

Of note, these events include all AEs as the primary cause of death, including AEs that occurred outside of the AE reporting period (as defined in Section 7.1) or after the start of subsequent therapy.

AEs (FDA grouped terms or MedDRA preferred terms) as the primary cause of death for more than 1 patient in the cilta-cel arm included pneumonia (9 patients [4.8%], of which 7 [3.7%] were COVID-19 pneumonia), hemorrhage (4 patients [2.1%]), sepsis (3 patients [1.6%]), and hematologic malignancies (3 patients [1.6%], 2 AML, 1 MDS). AEs as the primary cause of death for more than 1 patient in the SoC arm included pneumonia (5 patients [2.4%], of which 2 [1.0%] were pneumocystis jirovecii pneumonia and 2 [1.0%] were COVID-19 pneumonia), sepsis (5 patients [2.4%], of which 2 [1.0%] were septic shock), viral infection (4 patients [1.9%], of which 2 [1.0%] were COVID-19), renal failure (3 patients [1.4%], of which 2 [1.0%] were acute kidney injury), upper respiratory tract infection (2 patients [1.0%]), hemorrhage (2 patients [1.0%]), and multiple organ dysfunction syndrome (2 patients [1.0%]).

Causes of deaths showing all FDA groupings are provided in Appendix 11.2.

Table 24: CARTITUDE-4 Study: Adverse Events as the Primary Cause of Death (FDA Safety Analysis Set; 13 December 2023 Survival Sweep)

	Received Conforming Cilta-Cel			
	Cilta-cel as Study Treatment (n=170) n (%)	Cilta-cel as Subsequent Therapy (N=18) n (%)	Cilta-cel (n=188) n (%)	SoC (N=208) n (%)
Total number of patients with AEs as primary cause of death	18 (10.6)	5 (27.8)	23 (12.2)	28 (13.5)
Pneumonia[a]	9 (5.3)	0	9 (4.8)	5 (2.4)
Sepsis[a]	1 (0.6)	2 (11.1)	3 (1.6)	5 (2.4)
Hemorrhage[a]	2 (1.2)	2 (11.1)	4 (2.1)	2 (1.0)
Viral infection[a]	1 (0.6)	0	1 (0.5)	4 (1.9)
Hematologic malignancies[b]	3 (1.8)	0	3 (1.6)	0
Renal failure[a]	0	0	0	3 (1.4)
Upper respiratory tract infection[a]	0	0	0	2 (1.0)
Multiple organ dysfunction syndrome	1 (0.6)	0	1 (0.5)	2 (1.0)
Cholecystitis[a]	0	0	0	1 (0.5)
Thrombosis[a]	0	0	0	1 (0.5)
Acute interstitial pneumonitis	0	0	0	1 (0.5)
Condition aggravated[c]	0	0	0	1 (0.5)
Cardio-respiratory arrest	0	1 (5.6)	1 (0.5)	1 (0.5)
Plasma cell myeloma[c]	1 (0.6)	0	1 (0.5)	0

a. FDA grouped term.
b. Includes one patient diagnosed with MDS/AML and Grade 5 lung infection following the 4MSU CCO.
c. Patients died after the 4MSU CCO due to disease progression, pending reconciliation of records.
4MSU=4-month safety update; AE=adverse event; AML=acute myeloid leukemia; CCO=clinical cutoff; FDA=Food and Drug Administration; MDS=myelodysplastic syndrome; SoC=standard of care.

7.4 Adverse Events of Special Interest

7.4.1 In Patients Treated with Cilta-cel

Cilta-cel specific events of CRS (Section 7.4.1.1) and CAR-T Cell Neurotoxicity (Section 7.4.1.2) are summarized below for the 188 patients who received cilta-cel (either as study treatment [N=170] or as subsequent therapy [N=18]). Key details for CRS, ICANS, and Other Neurotoxicity are provided in Table 25.

Table 25: CARTITUDE-4 Study: Summary of Adverse Events of Special Interest

	Received Conforming Cilta-Cel (N=188)				
	Any Grade	Grade 3/4	Median time to onset (days)	Median duration (days)	Resolved[a]
Cytokine release syndrome (CRS)	146 (77.7%)	6 (3.2%)	8	3	99%
Immune effector cell-associated neurotoxicity syndrome (ICANS)	14 (7.4%)	1 (0.5%)	9	2	93%
Cranial nerve palsy	16 (8.5%)	2 (1.1%)	21	77	88%
Peripheral neuropathy	14 (7.4%)	1 (0.5%)	51	168	57%
Movement and neurocognitive toxicity (MNT)	2 (1.1%)	0	60	265	Ongoing at clinical cutoff

a. Percentage resolved were calculated based on the number of patients with the events as the denominator.
AE=adverse event

7.4.1.1 Cytokine Release Syndrome

Among the 188 patients in the cilta-cel arm, 146 patients (77.7%) experienced CRS. Most patients experienced Grade 1 or 2 CRS and 2.1% experienced Grade 3 CRS. Only 2 patients (1.1%) experienced Grade 4 CRS, both of whom received cilta-cel as subsequent therapy. No patients experienced Grade 5 CRS events. The median time from cilta-cel infusion to first onset of CRS was 8.0 days (range: 1 to 23 days), and the median duration of CRS was 3.0 days (range: 1 to 17 days). CRS resolved in 99% of patients. Hemophagocytic lymphohistiocytosis (HLH) was reported in the context of CRS for 2 patients: Grade 1 HLH in a patient who received cilta-cel as study treatment and Grade 4 HLH in a patient who received cilta-cel as subsequent therapy.

7.4.1.2 CAR-T Cell Neurotoxicity

CAR-T Cell Neurotoxicity is categorized as ICANS as well as Other Neurotoxicity determined by the Investigator to be related to CAR-T therapy and occurring after recovery of CRS and/or ICANS. Among the 188 patients in the cilta-cel arm, 44 patients (23.4%) experienced CAR-T Cell Neurotoxicity, including ICANS in 14 patients (7.4%; Section 7.4.1.2.1) and Other Neurotoxicity in 35 patients (18.6%; Section 7.4.1.2.2).

7.4.1.2.1 Immune Effector Cell-associated Neurotoxicity Syndrome

Among the 188 patients in the cilta-cel arm, ICANS was reported for 14 patients (7.4%). Most patients experienced Grade 1 or 2 ICANS. The only patient who experienced Grade 3 ICANS received cilta-cel as subsequent therapy. No patient experienced Grade 4 or 5 ICANS.

The median time from cilta-cel infusion to first onset of ICANS was 9.0 days (range: 2 to 15 days), and the median duration of ICANS was 2.0 days (range: 1 to 21 days). All

events of ICANS were resolved in patients who received cilta-cel as study treatment. One event of ICANS in a patient who received cilta-cel as subsequent therapy was considered not resolved. Eleven patients (5.9%) had ICANS concurrent with CRS.

7.4.1.2.2 Other Neurotoxicity Events

Other Neurotoxicity includes AEs reported as CAR-T cell neurotoxicity that are not ICANS nor the associated symptoms of ICANS. Other Neurotoxicity was reported for 35 of 188 patients (18.6%) in the cilta-cel arm. Most patients experienced Grade 1 or Grade 2 events. Six patients (3.2%) experienced Grade 3 events; there were no Grade 4 or 5 events.

Specific categories are described below:

- Movement and Neurocognitive toxicities (i.e., Parkinsonism): 2 patients (1.1%; one patient received cilta-cel as study treatment and one patient as subsequent therapy). All events were ≤Grade 2.
- Cranial Nerve Palsy: 16 patients (8.5%). Maximum toxicity was Grade 2 for 14 patients (7.4%) and Grade 3 for 2 patients (1.1%).
- Peripheral Neuropathies: 14 patients (7.4%). Maximum toxicity was Grade 1 for 5 patients (2.7%), Grade 2 for 8 patients (4.3%), and Grade 3 for 1 patient (0.5%).
- Guillain-Barré syndrome: No events were reported.

7.4.2 Both Arms

7.4.2.1 Second Primary Malignancy

Second primary malignancies up to the 4-month safety update cutoff date of 17 April 2023 are presented here.

Seventeen (9.0%) of the 188 patients who received conforming cilta-cel and 17 (8.2%) of the 208 patients in the SoC arm had a second primary malignancy during the study (Table 26).

Five patients (2.7%) in the cilta-cel arm and no patients in the SoC arm had a hematologic second primary malignancy. Events reported in the cilta-cel arm included AML (1 patient; onset Day 301 post-infusion), MDS (3 patients; range of onset 56 to 758 days post- infusion), and peripheral T-cell lymphoma unspecified (1 patient; onset Day 159 post-infusion; CAR-positive). The case of peripheral T-cell lymphoma was considered as related to cilta-cel by the Investigator. One event each of AML and MDS in the cilta-cel arm had fatal outcomes. One patient with MDS died of intracranial hemorrhage. Of note, all five patients had previous exposure to melphalan and lenalidomide, including 4 patients with high-dose melphalan followed by stem cell transplantation.

AML/MDS was added as an adverse drug reaction and included as a boxed warning in the cilta-cel United States Prescribing Information (USPI; December 2023). Following

FDA new Safety labeling Change Notification in January 2024, across all marketed CAR-T products, the Sponsor is in the process of adding T-cell lymphoma as an adverse drug reaction and T-cell malignancies as a boxed warning in the cilta-cel USPI.

Table 26: CARTITUDE-4 Study: Second Primary Malignancies (FDA Safety Analysis Set) as of Updated Safety Cutoff Date (17 April 2023)

	Received Conforming Cilta-Cel			
	Cilta-cel as Study Treatment (n=170) n (%)	Cilta-cel as Subsequent Therapy (N=18) n (%)	Cilta-cel (n=188) n (%)	SoC (N=208) n (%)
Patients with Second Primary Malignancies	17 (10.0)	0	17 (9.0)	17 (8.2)
Cutaneous/non-invasive malignancies	9 (5.3)	0	9 (4.8)	12 (5.8)
Non-cutaneous/invasive malignancies	3 (1.8)	0	3 (1.6)	5 (2.4)
Hematologic Malignancies	5 (2.9)	0	5 (2.7)	0
Acute myeloid leukaemia	1 (0.6)	0	1 (0.5)	0
Myelodysplastic syndrome	3 (1.8)	0	3 (1.6)	0
Peripheral T-cell lymphoma unspecified	1 (0.6)	0	1 (0.5)	0

FDA=Food and Drug Administration; SoC=standard of care.

7.5 Other Significant Adverse Events

7.5.1 In Patients Treated with Cilta-cel

7.5.1.1 Cytopenias

Among the 188 patients in the cilta-cel arm, Grade 3 or 4 cytopenias (based on laboratory values) following cilta-cel infusion were reported as follows:

- lymphopenia, 188 patients (100.0%),
- neutropenia, 178 patients (94.7%),
- thrombocytopenia, 82 patients (43.6%), and
- anemia, 64 patients (34.0%).

Prolonged cytopenia events defined as Grade 3 or 4 cytopenias that have not recovered to ≤Grade 2 by Day 60 were observed in 11% of patients for lymphopenia, 10% for neutropenia, 14% for thrombocytopenia, and 3% for anemia.

7.5.1.2 Hypogammaglobulinemia

Among the 188 patients in the cilta-cel arm, 177 patients (94.1%) had either a post-infusion hypogammaglobulinemia AE or post-cilta-cel IgG level <500 mg/dL:

- 90 patients (47.9%) had a post-infusion hypogammaglobulinemia AE,
- 176 patients (93.6%) had a post-cilta-cel laboratory finding of IgG level <500 mg/dL, and
- 132 patients (70.2%) received intravenous immunoglobulin (IVIG) following cilta-cel infusion.

7.5.2 Both Arms

7.5.2.1 Infections

Grade 3 or 4 infections were reported for 35 of 188 patients (18.6%) in the cilta-cel arm and for 47 of 208 patients (22.6%) who received SoC. The most common (≥5%) Grade 3 or 4 infections in the cilta-cel arm were the FDA grouped terms of bacterial infection (12 patients [6.4%]) and sepsis (10 patients [5.3%]). The most common Grade 3 or 4 infections in the SoC arm were the FDA grouped terms of pneumonia (22 patients [10.6%]) and viral infection (11 patients [5.3%]).

As of 13 December 2023, infections were the primary cause of death for 13 patients (6.9%) in the cilta-cel arm including 9 patients (4.8%) with pneumonia, of which 7 (3.7%) were COVID-19 pneumonia, 3 patients (1.6%) with sepsis, and 1 patient (0.5%) with viral infection. In the SoC arm, infections were the primary cause of death for 17 patients (8.2%) including 5 patients (2.4%) with pneumonia, of which 2 (1.0%) were pneumocystis jirovecii pneumonia and 2 (1.0%) were COVID-19 pneumonia, 5 patients (2.4%) with sepsis, of which 2 (1.0%) were septic shock, 4 patients (1.9%) with viral infections, of which 2 (1.0%) were COVID-19, 2 patients (1.0%) with upper respiratory tract infection, and 1 patient (0.5%) with cholecystitis.

The first study patient was screened on 30 June 2020. All patients in this study received cilta-cel during the COVID-19 pandemic. Due to the observed imbalance of fatal COVID-19 infection between treatment arms, additional safety measures were implemented during the study (June 2022). Mitigations included awareness of the importance of (re)vaccination post-cilta-cel after immune reconstitution, the use of prophylaxis (e.g., Evusheld, where available), the early use of antiviral therapy (e.g., Paxlovid, where available) including for asymptomatic COVID-19 infection, and the importance of continued adherence to strict preventative measures. In addition, protocol guidance reinforced the use of prophylactic immunoglobulins, monoclonal antibodies, and antimicrobials. No fatal COVID-19 infections were reported in the cilta-cel arm after mitigation measures were implemented.

7.6 Pharmacovigilance

Overall, no new significant safety information has been identified for CARVYKTI in the post-marketing setting. Ongoing periodic review of post-marketing data is consistent with the known safety profile for cilta-cel. The Sponsor will continue to monitor post-marketing data via routine and additional pharmacovigilance activities.

7.7 CAR-T-Specific Adverse Events in CARTITUDE-4 Versus CARTITUDE-1

Safety data from CARTITUDE-4 suggest improvement in the rate, and reduction in the severity, of several cilta-cel specific AEs in an earlier disease setting compared with the heavily pretreated, relapsed and refractory setting from CARTITUDE-1 (Table 27).

Table 27: Adverse Events of Special Interest in Cilta-cel Treated Patients Across CARTITUDE-4 and CARTITUDE-1

	Received Cilta-cel					
	CARTITUDE-4 (Conforming N=188)			CARTITUDE-1 (N=97)		
	Any Grade	Grade 3–4	Grade 5	Any Grade	Grade 3–4	Grade 5
CRS	78%	3%	0	95%	5%	1%
ICANS	7%	1%	0	23%	3%	2%
Cranial Nerve Palsy	9%	1%	0	3%	1%	0
Peripheral Neuropathy	7%	1%	0	7%	2%	0
Movement and Neurocognitive Toxicity (MNT)	1%	0	0	6%	4%	1%

CRS=cytokine release syndrome; ICANS=Immune Effector Cell-associated Neurotoxicity Syndrome.

7.8 Safety Conclusions

Safety findings from the pivotal CARTITUDE-4 study were consistent with previous cilta-cel experience and the current understanding of the mechanism of CAR-T therapies. Further, the data suggest improvement in the rate, and reduction in severity, of several cilta-cel specific AEs in an earlier disease setting compared with cilta-cel specific AEs in the heavily pretreated, relapsed and refractory setting.

Collectively, the safety data support a favorable benefit-risk profile for cilta-cel in lenalidomide-refractory multiple myeloma patients who have received 1 to 3 prior lines of therapy, including a PI and an IMiD.

8 OVERVIEW OF FINDINGS FOR PATIENTS RECEIVING CILTA-CEL AS SUBSEQUENT THERAPY

Twenty patients randomized to the cilta-cel arm progressed on bridging therapy (considered a PFS event for the primary analysis) and received cilta-cel as subsequent therapy at the Investigator's request. These 20 patients represent a distinct and higher-risk population compared with patients who received cilta-cel as study treatment. Therefore, data from these patients are reviewed in this section.

At study enrollment, 70% of these 20 patients had at least one high-risk abnormality (including del17p in 45%, gain/amp(1q) in 45%, and t(4;14) in 25%) and soft-tissue plasmacytomas were noted in 35%. Additionally, 60% of these patients were refractory to daratumumab and 35% were triple-class refractory. These 20 patients progressed rapidly through Investigator's choice of DPd (n=14) or PVd (n=6) with a median time from randomization to progression on bridging therapy (prior to cilta-cel) of 1.4 months. As 8 patients received additional subsequent therapy after bridging therapy and prior to receiving cilta-cel as subsequent therapy, the median number of prior lines for these 20 patients was 3 (range: 2 to 5 prior lines). Nine of the 20 patients had received 4 or more prior lines of therapy by the time of lymphodepletion and infusion of cilta-cel. Importantly, as a result these patients would not have been eligible for the CARTITUDE-4 study by protocol specified inclusion criteria.

For these 20 patients, median PFS from cilta-cel infusion was 7.4 months, CR or better rate was 40% (95% CI: 19.1–63.9) and the ORR was 65% (95% CI: 40.8–84.6). Overall, 6 patients died of an AE, 6 patients progressed, and 8 patients were progression free at the data cutoff with a median follow-up of 13.8 months (range: 11.5 to 20.4 months) since randomization. Median OS from randomization for these 20 patients was 13.4 months.

Of these 20 patients, 18 received conforming cilta-cel and are part of the FDA safety analysis set. All 18 patients (100.0%) experienced at least one post-infusion AE, i.e., any AE that occurred on or after cilta-cel infusion (Day 1) as subsequent therapy, until Day 112 or start of subsequent therapy, whichever is earlier, or any AE that is considered related to cilta-cel infusion as subsequent therapy, regardless of event onset. Serious post-infusion AEs were reported for 11 patients (61.1%). Grade 3 or 4 post-infusion AEs were reported for 17 patients (94.4%). Five patients (27.8%) experienced a post-infusion AE with outcome of death, of which 2 occurred in the period Day 1–30 and 3 occurred in the period Day 31–90 after cilta-cel infusion.

Only 2 patients experienced Grade 4 CRS in the study, both of whom received cilta-cel as subsequent therapy. No patients experienced Grade 5 CRS events. CRS did not recover fully in 2 patients who received cilta-cel as subsequent therapy. Grade 4 HLH was reported in a patient who received cilta-cel as subsequent therapy. The only patient who experienced Grade 3 ICANS in the study received cilta-cel as subsequent therapy. No patient experienced Grade 4 or 5 ICANS. Grade 3 or 4 events of Other Neurotoxicity included encephalopathy (1 patient [6%]) and myelitis (1 patient [6%]). A summary of

AEs of special interest information is provided in Table 28 for patients who received cilta-cel as study treatment or as subsequent therapy.

In summary, compared with patients who did not progress prior to receiving cilta-cel, patients who received cilta-cel as subsequent therapy had more high-risk disease and rapid PD despite bridging therapy. As a group, these patients had poorer outcomes, both in terms of efficacy and safety compared to patients whose disease was controlled with bridging therapy and who received cilta-cel as study treatment. However, a subset of those who received cilta-cel as subsequent therapy clearly benefited with deep and durable responses. This observation suggests the importance of disease control prior to cilta-cel infusion.

Table 28: CARTITUDE-4 Study: Events of Special Interest in Cilta-cel Treated Patients (FDA Safety Analysis Set)

	Received Conforming Cilta-cel			
	As Study Treatment N=170		As Subsequent Therapy N=18	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
CRS	76%	1%	89%	22%
ICANS	5%	0	33%	6%
Cranial Nerve Palsy	9%	1%	0	0
Peripheral Neuropathy	7%	1%	11%	0
Movement and Neurocognitive Toxicity (MNT)	1%	0	6%	0

AE=adverse event; FDA=Food and Drug Administration; CRS=cytokine release syndrome; ICANS=Immune Effector Cell-associated Neurotoxicity Syndrome.

9 BENEFIT-RISK ASSESSMENT

Lenalidomide-refractory multiple myeloma is a progressive and incurable disease that leads to significant morbidity and mortality (Orlowski 2013). These patients have worse outcomes than their lenalidomide-sensitive or lenalidomide- naïve counterparts. Moreover, there is a high attrition rate (85%) for this patient population beyond the fourth line setting (Dhakal et al 2023), highlighting the importance of making effective interventions available earlier in the disease course.

CAR-T cell-based therapies offer potential advantages over SoC and other T-cell redirection therapeutic strategies. While other therapies require prolonged exposure, generally until progression of disease, CAR-T cell therapy is complete after a single infusion due to its in vivo expansion and potential for long-term disease response.

One-time infusion of cilta-cel demonstrated clinical meaningful and statistically significant improvement in PFS. The median PFS in the cilta-cel arm was not reached compared with a median PFS of 11.8 months for the standard therapy arm. The HR for this comparison (0.40; 95% CI: 0.29–0.55; p<0.0001) indicates a 60% reduction in the risk of disease progression or death for cilta-cel compared with SoC. The treatment effect was consistent across all clinically relevant subgroups. Key secondary endpoints of CR or better rate, ORR, and overall MRD negativity rate also demonstrate a consistent, highly significant treatment effect favoring cilta-cel. OS data indicate a trend favoring cilta-cel. The most recent descriptive update of OS was based on the 13 December 2023 survival sweep at the request of the EMA with a HR of 0.57 (95% CI: 0.40–0.83).

A comprehensive analysis of potential factors that may have resulted in an imbalance of early PFS events did not identify a definite underlying cause. No subpopulations have been identified where cilta-cel should be avoided. The imbalance of relative lower dose intensity of pomalidomide and bortezomib may have contributed to the imbalance of early PFS events although the extent is unknown.

Typically, HRQoL is maintained at baseline level despite clinical benefits associated with highly effective myeloma therapies (Hungria et al 2021; Richardson et al 2018; Terpos et al 2022; Weisel et al 2018). By contrast, improvement in HRQoL was observed after cilta-cel in the CARTITUDE-4 study.

Safety findings from CARTITUDE-4 were consistent with previous cilta-cel experience and the current understanding of the mechanism of CAR-T therapies.

CRS and ICANS were generally low grade. Two patients had MNTs (i.e., Parkinsonism); all events were Grade ≤2. Most Grade 3 or 4 cytopenias recovered by Day 60. No fatal COVID-19 infections were reported in the cilta-cel arm after mitigation measures were implemented. The product label has been updated regarding the risk of AML/MDS, and an update regarding the risk of T-cell malignancy is being implemented across the class of CAR-T agents.

In patients who had rapid disease progression on bridging therapy and received cilta-cel as subsequent therapy, poorer outcomes were observed in terms of efficacy and safety compared to patients whose disease was controlled at the time of cilta-cel infusion. This suggests that effective disease control prior to treating with cilta-cel may be important.

As a regulatory requirement, all patients who are treated with cilta-cel as study treatment are followed and monitored for long-term safety for at least 15 years.

9.1 Benefit-Risk Conclusion

The CARTITUDE-4 study demonstrated a positive benefit-risk profile of one-time infusion of cilta-cel for the treatment of patients with relapsed and refractory multiple myeloma who have received at least one prior therapy and are refractory to lenalidomide.

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11 APPENDICES

11.1 CARTITUDE-4 Study: Summary of All Primary Causes of Death (ITT Analysis Set)

	0-≤3 Months				>3 - ≤6 Months				>6 Months			
	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)
Total Deaths	**6**	**1**	**-**	**1**	**3**	**4**	**4**	**11**	2	7	21	65
Progressive disease	**4**	**-**	**-**	**1**	**3**	**-**	**1**	**5**	1	6	5	43
AEs	**2**	**1**	**-**	**-**	**-**	**4**	**3**	**6**	1	1	16	22
FDA Grouped term or Preferred term												
Preferred term												
Dyspnea	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Respiratory failure	1	-	-	-	-	-	-	-	-	-	-	-
Hemorrhage	**1**	**1**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**2**	**2**
Gastrointestinal haemorrhage	1	-	-	-	-	-	-	-	-	-	-	-
Cerebral haemorrhage	-	-	-	-	-	1	-	-	-	-	-	1
Traumatic intracranial haemorrhage	-	-	-	-	-	-	-	-	-	-	-	1
Haemorrhage intracranial	-	-	-	-	-	-	-	-	-	-	1	-

	0-≤3 Months				>3 - ≤6 Months				>6 Months			
	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)
Retroperitoneal haemorrhage	-	1	-	-	-	-	-	-	-	-	-	-
Subdural haematoma	-	-	-	-	-	-	-	-	-	-	1	-
Pneumonia	**-**	**-**	**-**	**-**	**-**	**1**	**3**	**3**	**1**	**-**	**6**	**2**
COVID-19 Pneumonia	-	-	-	-	-	-	3	1	-	-	4	1
Bronchopulmonary aspergillosis	-	-	-	-	-	1	-	-	-	-	-	-
Pneumocystis jirovecii pneumonia	-	-	-	-	-	-	-	1	-	-	1	1
Pneumonia influenza	-	-	-	-	-	-	-	1	-	-	-	-
Pneumonia	-	-	-	-	-	-	-	-	1	-	1	-
Sepsis	**-**	**-**	**-**	**-**	**-**	**2**	**-**	**-**	**-**	**-**	**1**	**5**
Sepsis	-	-	-	-	-	1	-	-	-	-	-	1
Pseudomonal sepsis	-	-	-	-	-	1	-	-	--	-	-	-
Septic Shock	-	-	-	-	-	-	-	-	-	-	-	2
Enterococcal sepsis	-	-	-	-	-	-	-	-	-	-	-	1
Neutropenic sepsis	-	-	-	-	-	-	-		-	-	1	1

	0-≤3 Months				>3 - ≤6 Months				>6 Months			
	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)
Viral infection	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1**	**-**	**-**	**1**	**3**
COVID-19	-	-	-	-	-	-	-	-	-	-	-	2
JC virus infection	-	-	-	-	-	-		-	-	-	-	1
Progressive multifocal leukoencephalopathy	-	-	-	-	-	-		1	-	-	-	-
Cytomegalovirus colitis	-	-	-	-	-	-	-	-	-	-	1	-
Upper respiratory tract infection	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**1**
Respiratory tract infection	-	-	-	-	-	-	-	1	-	-	-	1
Acute interstitial pneumonitis	-	-	--	-	-	-	-	-	-	-	-	1
Renal failure	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**3**
Acute kidney injury	-	-	-	-	-	-	-	-	-	-	-	2
Renal failure	-	-	-	-	-	-	-	-	-	-	-	1
Multiple organ dysfunction syndrome	-	-	-	-	-	-	-	1	-	-	1	1

	0-≤3 Months				>3 - ≤6 Months				>6 Months			
	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)
Cardio-respiratory arrest	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1**	**-**	**1**
Cardiac arrest	-	-	-	-	-	-	-	-	-	-	-	1
Cardio-respiratory arrest	-	-	-	-	-	-	-	-	-	1	-	-
Cholecystitis	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1**
Cholecystitis acute	-	-	-	-	-	-	-	-	-	-	-	1
Thrombosis	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1**
Pulmonary embolism	-	-	-	-	-	-	-	-	-	-	-	1
Acute interstitial pneumonitis	-	-	-	-	-	-	-	-	-	-	-	1
Hematologic Malignancies	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**3**	**-**
Acute myeloid leukaemia[a]	-	-	-	-	-	-	-	-	-	-	2	-
Myelodysplastic syndrome	-	-	-	-	-	-	-	-	-	-	1	-
Non-cutaneous / invasive Malignancies	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1**	**-**
Angiosarcoma	-	-	-	-	-	-	-	-	-	-	1	-

	0-≤3 Months				>3 - ≤6 Months				>6 Months			
	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)	Never treated with Cilta-cel (n=12)	Cilta-cel as Subsequent Therapy (n=20)	Cilta-cel as Study Treatment (n=176)	SoC (N=211)
Plasma cell myeloma[b]	-	-	-	-	-	-	-	-	-	-	1	-
Condition aggravated[b]	-	-	-	-	-	-	-	-	-	-	-	1

a. Includes one patient diagnosed with MDS/AML and Grade 5 lung infection following the 4MSU CCO.
b. Patients died after the 4MSU CCO due to disease progression, pending reconciliation of records.
Note: For each time interval, the events occurred after this interval are censored, the patients who had the event or censored before this interval are excluded.
Note: Intent-to-treat analysis set consists of patients who were randomized in the study.
4MSU=4-month Safety Update; AE=adverse event; AML=acute myeloid leukemia; CCO=clinical cutoff; ITT=Intent-to-Treat; MDS=myelodysplastic syndrome; SoC=standard of care.

11.2 CARTITUDE-4 Study: Adverse Events as Primary Cause of Death (FDA Safety Analysis Set)

	Received Conforming Cilta-Cel			
	Cilta-cel as Study Treatment (n=170) n (%)	Cilta-cel as Subsequent Therapy (N=18) n (%)	Cilta-cel (n=188) n (%)	SoC (N=208) n (%)
Total number of patients with AEs as primary cause of death	18 (10.6)	5 (27.8)	23 (12.2)	28 (13.5)
FDA Grouped term or Preferred term				
Preferred term				
Pneumonia	9 (5.3)	0	9 (4.8)	5 (2.4)
COVID-19 Pneumonia	7 (4.1)	0	7 (3.7)	2 (1.0)
Pneumocystis jirovecii pneumonia	1 (0.6)	0	1 (0.5)	2 (1.0)
Pneumonia influenza	0	0	0	1 (0.5)
Pneumonia	1 (0.6)	0	1 (0.5)	0
Sepsis	1 (0.6)	2 (11.1)	3 (1.6)	5 (2.4)
Septic Shock	0	0	0	2 (1.0)
Enterococcal sepsis	0	0	0	1 (0.5)
Neutropenic sepsis	1 (0.6)	0	1 (0.5)	1 (0.5)
Sepsis	0	1 (5.6)	1 (0.5)	1 (0.5)
Pseudomonal sepsis	0	1 (5.6)	1 (0.5)	0
Viral infection	1 (0.6)	0	1 (0.5)	4 (1.9)
COVID-19	0	0	0	2 (1.0)
JC virus infection	0	0	0	1 (0.5)
Progressive multifocal leukoencephalopathy	0	0	0	1 (0.5)
Cytomegalovirus colitis	1 (0.6)	0	1 (0.5)	0
Renal failure	0	0	0	3 (1.4)
Acute kidney injury	0	0	0	2 (1.0)
Renal failure	0	0	0	1 (0.5)
Hemorrhage	2 (1.2)	2 (11.1)	4 (2.1)	2 (1.0)
Cerebral haemorrhage	0	1 (5.6)	1 (0.5)	1 (0.5)
Traumatic intracranial haemorrhage	0	0	0	1 (0.5)
Haemorrhage intracranial	1 (0.6)	0	1 (0.5)	0
Retroperitoneal haemorrhage	0	1 (5.6)	1 (0.5)	0
Subdural haematoma	1 (0.6)	0	1 (0.5)	0

	Received Conforming Cilta-Cel			
	Cilta-cel as Study Treatment (n=170) n (%)	Cilta-cel as Subsequent Therapy (N=18) n (%)	Cilta-cel (n=188) n (%)	SoC (N=208) n (%)
Upper respiratory tract infection	0	0	0	2 (1.0)
Respiratory tract infection	0	0	0	2 (1.0)
Multiple organ dysfunction syndrome	1 (0.6)	0	1 (0.5)	2 (1.0)
Cardio-respiratory arrest	0	1 (5.6)	1 (0.5)	1 (0.5)
Cardiac arrest	0	0	0	1 (0.5)
Cardio-respiratory arrest	0	1 (5.6)	1 (0.5)	0
Cholecystitis	0	0	0	1 (0.5)
Cholecystitis acute	0	0	0	1 (0.5)
Thrombosis	0	0	0	1 (0.5)
Pulmonary embolism	0	0	0	1 (0.5)
Acute interstitial pneumonitis	0	0	0	1 (0.5)
Condition aggravated[a]	0	0	0	1 (0.5)
Hematologic Malignancies	3 (1.8)	0	3 (1.6)	0
Acute myeloid leukaemia[b]	2 (1.2)	0	2 (1.1)	0
Myelodysplastic syndrome	1 (0.6)	0	1 (0.5)	0
Plasma cell myeloma[a]	1 (0.6)	0	1 (0.5)	0

a. Patients died after the 4MSU CCO due to disease progression, pending reconciliation of records.
b. Includes one patient diagnosed with MDS/AML and Grade 5 lung infection following the 4MSU CCO.
Note: Adverse events are reported using MedDRA version 25.0.
Note: Percentages calculated with the number of patients in each treatment group as denominator.
Note: FDA Safety analysis set consists of patients who received any part of study treatment for the SoC arm and patients who received conforming cilta-cel for the cilta-cel arm.
4MSU=4-month Safety Update; AE=adverse event; AML=acute myeloid leukemia; CCO=clinical cutoff; FDA=Food and Drug Administration; MDS=myelodysplastic syndrome; MedDRA=Medical Dictionary for Regulatory Activities; SoC=standard of care.
Clinical cutoff date: 13 December 2023 Survival Sweep.