FDA Briefing Document

BLA 125746/Supplement 74

Drug name: CARVYKTI (ciltacabtagene autoleucel)

Applicant: Janssen Biotech, Inc.

Oncologic Drug Advisory Committee Meeting

March 15, 2024

Center for Biologics Evaluation and Research/ Office of Therapeutic Products

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Glossary

AE	adverse event
AESI	adverse event of special interest
BCMA	B-cell maturation antigen
CAR	chimeric antigen receptor
CAR T	chimeric antigen receptor engineered T cell
CARVYKTI	ciltacabtagene autoleucel
CD38	cluster of differentiation 38
CI	confidence interval
CR	complete response
CRS	cytokine release syndrome
DPd	daratumumab, pomalidomide, and dexamethasone
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HLH	hemophagocytic lymphohistiocytic syndrome
HR	hazard ratio
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
ide-cel	idecabtagene vicleucel
IF	information fraction
IRd	ixazomib, lenalidomide, dexamethasone
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
ISS	International Staging Systemt
ITT	intent-to-treat
Kd	carfilzomib, dexamethasone
KM	Kaplan-Meier
LDC	lymphodepleting chemotherapy
MAS	macrophage activation syndrome
MDS	myelodysplastic syndromes
MM	multiple myeloma
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PI	proteasome inhibitor
PVd	pomalidomide, bortezomib, and dexamethasone
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
sCR	stringent complete response
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. Executive Summary

On June 6, 2023, Janssen Biotech, Inc. (Janssen), the Applicant, submitted a supplemental Biologics Licensing Application (sBLA) for CARVYKTI (ciltacabtagene autoleucel), an autologous, anti-B-cell maturation antigen (BCMA), chimeric antigen receptor engineered T cell (CAR T) therapy. The Applicant is seeking approval for the following proposed indication and recommended dosage:

- Indication: CARVYKTI is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated 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.

- Dosage: Dose range is 0.5-1.0×10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T cells per single-dose infusion

FDA is convening this meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss the results of the randomized controlled trial, CARTITUDE-4, which provides the primary evidence of CARVYKTI'S safety and effectiveness for the proposed indication. Specifically, FDA is interested in the Committee's opinion regarding the higher rate of early deaths associated with ciltacabtagene-autoleucel treatment trial, in the context of a statistically significant progression-free survival benefit in the CARTITUDE-4 trial. The sBLA submission contains the results of a single, randomized controlled trial (CARTITUDE-4) evaluating the safety and efficacy of ciltacabtagene autoleucel (trade name: CARVYKTI; hereafter referred to as cilta-cel). CARTITUDE-4 enrolled 419 patients who were randomized (1:1) to receive cilta-cel or one of two standard-of-care regimens, either pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd). The primary endpoint of CARTITUDE-4 is progression-free survival (PFS) as determined by a blinded independent review committee (IRC) using the International Myeloma Working (IMWG) 2016 criteria. Overall survival (OS) is a key secondary endpoint in CARTITUDE-4.

CARTITUDE-4 met its primary endpoint, demonstrating a statistically significant improvement in PFS in patients randomized to the cilta-cel arm compared to patients randomized to the control arm (hazard ratio [HR] was 0.41 [95% Confidence Interval {CI}: 0.30, 0.56] based on a stratified log-rank test; p-value <0.0001. The median PFS was not reached in the cilta-cel arm (95% CI: 22.8, not evaluable), and was 12 months (95% CI: 9.8, 14) in the standard therapy arm. At the time of the sBLA submission, the Applicant provided the results of an interim analysis of OS based on a data cut-off date of November 1, 2022. At the interim OS analysis, which was conducted with 34% information fraction, the OS Kaplan-Meier curves demonstrate a crossing hazards pattern at ~11 months, with lower OS in the cilta-cel arm compared to the standard of care arm prior to 11 months. The median OS in the cilta-cel arm was not achieved and was 26.7 months (95% CI: 22.5, NE) for standard therapy arm (HR 0.78 (0.51, 1.20).

The primary analysis of safety was conducted in patients who received conformal cilta-cel in the investigational arm (n=188), and patients randomized to the standard therapy (n=208). Almost all patients experienced an adverse event (AE) (cilta-cel arm: 100%; standard therapy arm: 100%). The most common (≥5 %) Grade 3-4 treatment emergent adverse events (TEAEs) in the cilta-cel arm were hypogammaglobulinemia (9%), bacterial infection (6 %), and viral infection (11 %), pneumonia (6%), in the standard therapy arm. The Grade 3-4 toxicity rate was slightly higher in the standard therapy arm

(cilta-cel arm: 84%; standard therapy:91%). Serious adverse events (SAEs) occurred in 36% and 37% of patients in the cilta-cel and standard therapy arms, respectively.

Deaths due to AEs were higher in the cilta-cel arm (11%, n=20) compared to the deaths in the standard therapy arm (8%, n=16).

The rate of death in the first 10 months post randomization was higher in the cilta-cel arm (29 of 208; 14%) than in the standard therapy arm (25 of 211; 12%) based on an analysis of the ITT population (N=419). In the safety analysis population, death events that occurred within 90 days from starting treatment were also higher in the cilta-cel arm compared to the standard therapy arm (5% versus 0%).

The main topic for discussion at the ODAC is:

- Increased number of early deaths in the cilta-cel arm:

  Overall, there is a higher rate of early deaths in the cilta-cel arm compared to the standard therapy arm. The adequacy of exploratory analyses of the CARTITUDE-4 trial to support the identification of strategies to mitigate this risk, warrants further discussion. FDA has granted approval to drugs that demonstrate a statistically significant and clinically meaningful effect on progression-free survival in the context of an acceptable risk profile. Because of the higher rate of early deaths in the cita-cel arm, it is unclear whether the overall benefit-risk assessment is favorable; specifically, whether additional data is needed to support such an assessment.

2. Background

Multiple Myeloma

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal expansion of plasma cells in bone marrow and overproduction of monoclonal immunoglobulins, leading to impaired hematopoiesis, bone destruction, and renal dysfunction. MM is the second most common hematologic malignancy, accounting for nearly 2% of all new cancer cases and deaths. In the United States, there were an estimated 35,730 new cases of MM diagnosed and 12,590 deaths from MM in 2023 (American Cancer Society 2023). The median age at diagnosis is 69 years, and the 5-year survival rate is approximately 50% (National Cancer Institute 2023). MM is considered incurable; most patients who experience an initial remission following treatment, eventually relapse and are likely to develop refractory disease. In general, the duration of remission shortens with each subsequent line of therapy.

Treatments for Relapsed/Refractory MM

Current standard therapy for MM consists of combination regimens that include proteosome inhibitors (PI)s (e.g., bortezomib, ixazomib, and carfilzomib), immunomodulatory (IMiD) agents (e.g., thalidomide, lenalidomide, and pomalidomide), and monoclonal antibodies directed against myeloma cell surface antigens (e.g., daratumumab, elotuzumab, and isatuximab). Additional treatment options include the use of autologous hematopoietic stem cell transplantation. Upon disease relapse, considerations impacting the choice of subsequent therapy include whether the patient is on maintenance therapy at the time of relapse and whether their disease is refractory to maintenance therapies such as lenalidomide or bortezomib. Treatment for relapsed disease typically consists of triplet regimens,

including at least two active drug classes other than steroids and at least one drug from a class to which the patient has not been exposed.

Due to the extensive use of lenalidomide as a frontline treatment, lenalidomide refractoriness early in the disease course is increasingly common (de Arriba de la Fuente et al. 2022). Patients with Lenalidomide-refractory MM are a population that has the benefit of a variety of contemporary regimens with established benefit. Doublet and triplet regimens containing monoclonal antibodies such as the anti-CD38 monoclonal antibodies daratumumab and isatuximab, combined with a steroid and either an IMiD or a PI, can be highly effective and demonstrate benefit, including increased OS, in randomized controlled studies (Cowan et al. 2022).

FDA-approved therapies for the treatment of RRMM are summarized in Table 19 in the Appendix. These include ABEMCA (ide-cel) and CARVYKTI (cilta-cel), approved in 2021 and 2022, respectively. Both products are indicated for treatment of adults with RRMM after four or more prior lines of therapy, including a PI, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Single arm trials evaluating overall response rate (ORR) were the basis for approval. The KarMMA study which supported the approval of ABEMCA enrolled adults who had received at least three regimens, including a PI, an immunomodulatory agent, and an anti-CD38 antibody (USPI 2021). The ORR was 72% (95% CI: 62, 81) and the rate of sCR was 28% (95% CI: 19, 38). Duration of response with a median follow up of 10.7 months was 11 months (95% CI: 10.3, 11.4). The CARTITUDE-1 study supported the approval of CARVYTI for patients who had received at least three prior lines of therapy including a PI or an IMiD, an anti-CD38 antibody. The ORR was 97.9% (95% CI: 92.7 99.7) and the rate of sCR was 78.4%. Duration of response was 21.8 months (95% CI 21.8, NE) (USPI 2022).

There are substantial safety risks with CAR T cell therapies including CRS, neurologic toxicity, HLH/MAS, and prolonged cytopenia with risk of serious infections and bleeding. These safety concerns are included in a boxed warning in the United States Prescribing Information. CAR T cell therapies are available through a restricted program under a Risk Evaluation and Mitigation Strategy. Due to the safety concerns with CAR T cell therapies, FDA issued a postmarketing requirement study under Section 505(0)(3) of the Federal Food, Drug, and Cosmetic Act, which requires registry study of patients treated with CAR T cell therapies to be conducted with 15 years of follow-up. This study will assess the long-term toxicities of CARVKTI, including risk of secondary malignancies, incidence and severity of CRS, HLH/MAS, prolonged cytopenia, and neurotoxicity.

3. Product and Regulatory History

Product Description

CARVYKTI is a BCMA-directed CAR T cell therapy composed of human autologous T cells that are genetically modified by a lentiviral vector to express a BCMA-targeting CAR. The CAR is comprised of two complementary llama-derived single domain antibodies that bind to human BCMA, a human CD8α hinge and transmembrane domain, the 4-1BB intracellular signaling domain, and the CD3ζ cytoplasmic signaling domain. Binding of the CAR to BCMA-expressing target cells leads to T cell signaling through the 4-1BB and CD3ζ domains and subsequent activation of CAR-positive T cells. Antigen-induced activation results in CAR T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

To manufacture CARVYKTI drug product, T cells are enriched from patient apheresis material. The enriched T cells are activated and transduced with the nonreplicating lentiviral vector encoding the CAR. The lentiviral-vector-transduced cells are expanded, formulated into a suspension, and cryopreserved in an infusion bag.

CARVYKTI is currently approved for the treatment of adult patients with relapsed refractory multiple myeloma (RRMM) after four or more lines of systemic therapy (traditional approval, February 28, 2022). This initial approval was based on the results of CARTITUDE-1 (NCT03548207), a multicenter, single-arm study evaluating overall response rate (ORR) and complete response (CR) rate assessed by an IRC using IMWG criteria; duration of response was a key secondary endpoint. The efficacy population consisted of 97 patients who had received three or more previous lines of therapy including a PI, an IMiD, and anti-CD38 monoclonal antibody. The ORR was 97.9% (95% CI: 92.7, 99.7) and the rate of sCR was 78.4%. Median duration of response was 21.8 months (95% CI: 21.8, NE).

In the current sBLA, the Applicant seeks approval of cilta-cel for the proposed indication, based on the results of CARTITUDE-4. A summary of pre-and post-submission interactions is shown below.

Date	Purpose and/or Key FDA Comments
Sep 11, 2019	Type B EOP2 meeting to obtain the FDA's agreement on the Phase 3 registration study (CARTITUDE-4).
Mar 29, 2021	Type C meeting to discuss PRO and the Psychometric Analysis Plan
June 24, 2022	Type B Meeting to Discuss the Proposed Format and Content for the Planned Ciltacabtagene Autoleucel Supplemental Biologic License Application.
Mar 28, 2023	Type B pre-sBLA meeting to obtain the Agency's review of the topline results from Study CARTITUDE-4 and guidance on sBLA submission plans. FDA reiterated that computerized algorithm remains unvalidated from regulatory perspective and, given the open-label nature of the study, IRC assessment of the primary and secondary endpoints should be conducted and submitted for the initial BLA submission. The efficacy analysis for PFS using the standard, "unweighted," stratified log-rank test will be considered as the primary efficacy analysis for regulatory purposes.
Jun 6, 2023	The Sponsor submitted efficacy supplement based on PFS results from the second interim analysis of CARTITUDE-4, with a cutoff date of November 1, 2022.
Aug 5, 2023	A filing notification was sent to the Applicant of a standard review. The filing letter identified the early potential OS detriment observed in the cilta-cel arm compared to the standard therapy arm in the CARTITUDE-4 as a potential review issue
Oct 3, 2023	The Applicant submitted a 120-day Safety Updated, with a clinical cutoff of April 17, 2023
Dec 8, 2023	T-con in which FDA communicated its decision to convene an oncology drug advisory committee to obtain committee's input regarding the benefit-risk of ide-cel for the indicated population given the observed early OS detriment with the cilta-cel
Jan 7, 2024	Applicant submitted an exploratory analysis conducted looking the early mortality with cilta-cel

Source: Modified from Applicant clinical study report page 32
Abbreviations: EOP2, End-of-Phase 2.

4. Clinical Study Supporting the Application

4.1 Study Design

CARTITUDE-4 (**NCT04181827**) is a randomized (1:1), open-label, multicenter trial comparing cilta-cel with standard therapy in adults with relapsed and lenalidomide-refractory MM following treatment with one to three prior lines of standard therapy including a PI and an IMiD; patients were not required to

have previously received an anti-CD38 monoclonal antibody. Patients were randomized to receive a single infusion of cilta-cel or investigator choice of two standard therapies: PVd or DPd. Bridging therapy with PVd or DPd could be administered to patients in the cilta-cel arm at the investigator's discretion during the interval between leukapheresis and lymphodepleting chemotherapy. Study treatment continued until there was documented disease progression, unacceptable toxicity, or the patient or treating physician determined it was not in the patient's best interest to continue. Randomization was stratified by investigator's choice of PVd or DPd for the control arm, International Staging System (ISS) staging (I versus II versus III), and number of prior lines of therapy (one versus two or three).

4.2 Study Population

To have been eligible to enroll in CARTITUDE-4, patients must have:

- had a prior diagnosis of MM with documented disease progression by IMWG criteria within 6 months of their last regimen
- required further treatment at time of screening
- had an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1
- received one to three prior lines of therapy, including lenalidomide and a PI and IMiD, and be refractory to both the last line of therapy and to lenalidomide per IMWG consensus guidelines (Rajkumar et al. 2011). Subjects were defined as refractory to lenalidomide by virtue of failure to achieve a PR or better to lenalidomide-containing therapy or progression within 60 days of the last dose of lenalidomide.
- had measurable disease defined as any one of the following: 1) Serum M protein >0.5 g/dL; 2) Urine M-protein level ≥200 mg/24-hour; and 3) serum free light chain >10 mg/dL and abnormal serum kappa to lambda free light chain ratio without measurable disease in the serum or the urine. See Appendix 8.3 for complete eligibility criteria.

4.3 Study Treatment

Treatment in CARTITUDE-4 was administered as follows:

- Standard therapy arm: Subjects randomized to standard therapy arm were administered one of the following two standard therapy regimens chosen prior to randomization: PVd or DPd, as per the investigator's decision based on prior therapies. Subjects started standard therapy within 7 days after randomization and were treated until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of study. Subjects who discontinued standard therapy for any reason, other than progressive disease or withdrawal of consent, continued to be followed for response assessment until confirmed progressive disease or the start of a subsequent anti-myeloma therapy.

- Cilta-cel arm: Subjects randomized to cilta-cel B underwent leukapheresis. Following apheresis, participants received bridging therapy while product was manufactured. After cilta-cel production and product release, subjects received a lymphodepletion chemotherapy regimen of fludarabine (30mg/m^2) and cyclophosphamide (300mg/m^2) intravenously for three consecutive days. A single infusion of cilta-cel was administered 5 to 7 days after the start of the lymphodepletion at a median dose of 0.7×10^6 cells/kg.
  - Bridging therapy: Included either PVd or DPd at investigator discretion (determined prior randomization) as follows PVd in 21-day cycles (pomalidomide PO 4 mg/day, bortezomib SC

1.3 mg/m2, dexamethasone PO 20 mg/day) or DPd in 28-day cycles (daratumumab SC 1800 mg, pomalidomide PO 4 mg/day, dexamethasone PO or IV 40 mg weekly)

- Standard therapy arm: Subjects randomized to standard therapy arm were administered one of the following two standard therapy regimens: PVd or DPd, as per the investigator's decision based on prior therapies. Subjects started standard therapy within 7 days after randomization and were treated until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of study. Subjects who discontinued standard therapy for any reason, other than progressive disease or withdrawal of consent, continued to be followed for response assessment until confirmed progressive disease or the start of a subsequent anti-myeloma therapy.

4.4 Study Endpoints

The primary efficacy endpoint is PFS as determined by a blinded independent review committee (IRC) according to IMWG 2016 criteria. If progression was based only on biochemical data, two consecutive assessments were required to confirm progression. The day of progression was then considered the day of the first biochemical finding. The key secondary endpoints are:

- ORR based on independent review, defined as best response of sCR, CR, very good partial response, and partial response;
- CR/sCR rate;
- OS, defined as time from randomization to death.

4.5 Analysis Plan—Efficacy

The primary efficacy analysis is based on the intent-to-treat (ITT) population. A total of 250 PFS events were determined to provide approximately 90% power to detect a HR of 0.65 with log-rank test (2-sided alpha of 0.05). One interim analysis of PFS for efficacy was planned at 75% information fraction. The study design employed the Lan-DeMets spending function with an O'Brien-Fleming-like boundary as the alpha spending function.

Three interim analyses and one final analysis were planned for OS. The first interim analysis of OS was to be performed at the time of the planned interim analysis of PFS, and the second interim analysis for OS was to be performed at the time of the final PFS analysis when all 250 PFS events have been observed. The third interim analysis for OS was to be performed when approximately 200 OS events have occurred. The final OS analysis will take place after 250 deaths have occurred and has 80% power to detect a HR of 0.70. The standard therapy arm was assumed to have a median PFS of 13 months and a median OS of 31 months for the sample size calculations.

ORR and rate of CR/sCR were included as key secondary efficacy endpoints and tested at an overall one-sided alpha level of 0.025 based on a hierarchical testing procedure. These endpoints were tested only if PFS was declared statistically significant.

The intent-to-treat (ITT) population, including all randomized subjects, was used for the primary efficacy analysis.

4.6 Study Results

The sBLA is based on a data cutoff date for the safety and efficacy analysis of November 1, 2022. At the time of data cutoff, the trial had completed enrollment. The efficacy analysis is based on 419 randomized subjects (intent-to-treat, ITT). The safety analysis is based on 396 of 419 patients; patients who received cilta-cel not conforming to the release criteria proposed for the to-be-marketed product were excluded from the safety analysis.

4.6.1 Study Population Characteristics

Characteristics of the study population are summarized in Table 1, Table 2, and Table 3.

Table 1: Demographic Characteristics, ITT Population, CARTITUDE-4

Characteristic	Cilta-cel N=208 n (%)	Standard Therapy N=211 n (%)	Total N=419 n (%)
Age (years)	-	-	-
Median (range)	61.5 (27-78)	61(35-80)	61 (27-80)
<65	126 (61)	131 (62)	257 (61)
65-75	78 (37.5)	76 (36)	154 (37)
>75	4 (1.9)	4 (1.9)	8 (1.9)
Sex	-	-	-
Male	116 (56)	124 (59)	240 (57)
Female	92 (44)	87 (41)	179 (43)
Race	-	-	-
Asian	16 (8)	20 (10)	36 (8.6)
Black	6 (3)	7 (3)	13 (3)
White	157 (76)	157 (74)	314 (75)
Other	1 (0.5)	1 (0.5)	2 (0.50)
Not reported	28 (14)	26 (12)	54 (13)
Hispanic or Latino ethnic group	-	-	-
Yes	18 (9)	10 (5)	28 (7)
No	152 (73)	165 (78)	317(76)
Not reported	38 (18)	36 (17)	80(19)
Geographic region	-	-	-
Europe	128 (61.5)	129 (61)	257(61)
United States	32 (15.4)	32 (15)	64(15)
Asia	27 (13)	25 (12)	529(12)
Australia	21 (10)	25 (12)	46(11)

Source: FDA analysis

Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Table 2: Baseline Disease Characteristics, ITT Population, CARTITUDE-4

Characteristics	Cilta-cel N=208	Standard Therapy N=211	All N=419
ECOG performance status score %	-	-	-
0/1/2	55/44/1	57/42/1	56/43/1
International Staging System stage %	-	-	-
I/II/III	65/30/6	63/30/7	64/30/6
Time since diagnosis (years)	-	-	-
Median (range)	3.0 (0.3-18)	3.4 (0.4-22)	3.2 (0.3-22)
Extramedullary disease n (%)	-	-	-
Yes	44 (21)	35 (17)	79 (19)
No	164 (79)	176 (83)	340 (81)
Bone marrow plasma cells n (%)	-	-	-
N	206	208	414
≤30	133(65)	121 (58)	254 (61)
>30-<60	31(15)	44 (21)	75 (18)
≥60%	42(20)	43/208 (21)	85 (20)
Cytogenetic risk n (%)	-	-	-
N	207	210	417
Standard	111 (54)	122 (58)	233 (55.8)
High	82 (39)	80 (38)	162 (39)
del(17p)	49 (24)	43 (21)	92 (22)
t(4;14)	30 (15)	30 (14)	60 (14)
t(14;16)	3 (2)	7 (3)	10 (2)
Missing data	15/207 (7)	8/210 (4)	23 (5)

Source: FDA analysis

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Table 3: Prior Therapies, ITT Population, CARTITUDE-4

Characteristic	Cilta-cel N=208 n (%)	Standard Therapy N=211 n (%)	Total N=419 n (%)
Prior lines of therapy	-	-	-
1	68 (33)	68 (32)	136 (32)
2	83 (40)	87 (41)	170 (41)
3	57 (27)	56 (27)	113 (27)
Prior autologous transplant*	-	-	-
Yes	171 (82)	185 (88)	356 (85)
No	37 (18)	26 (16)	63 (15)
Refractory status-	-	-	-
Lenalidomide	208 (100)	211 (100)	419 (100)
Any IMiD	208 (100)	211 (100)	419 (100)
Any PI	103 (49.5)	96 (45.5)	199 (47)
Any anti-CD38 antibody	50 (24)	46 (22)	96 (23)
Triple-class	30 (14)	33 (16)	63 (15)
Penta-refractory	2 (1)	1 (0.5)	3 (1)

Source: FDA analysis

* Four subjects in the study (three subjects in cilta-cel arm) had prior allogeneic transplant.

Abbreviations: IMiD, immunomodulatory drug; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; PI, proteasome inhibitor

Bridging Therapies

In the cilta-cel arm (n=208), 100 % of the subjects in the ITT population started at least one cycle of bridging therapy during cilta-cel manufacture. The median time from randomization to initiation of bridging therapy was 7 days (range 2-19 days). The most common bridging used was DPd (87.5 %) followed by PVd (12.5 %). The median number of bridging cycles started was 2.0 (range: 1 to 6 cycles); 162 participants (77.9%) started at least 2 cycles of bridging therapy. Most of the subjects (59%) received two cycles of bridging, 22% received 1 cycle, 16% received 3 cycles, 2.5% received 4 cycles.

4.6.2 Subject Disposition

At the cutoff date of November 1, 2022, a total of 419 subjects were randomized, 208 in the cilta-cel arm and 211 in the standard therapy arm**.** Thirty-two subjects randomized to the cilta-cel arm (15% of the total number randomized to cilta-cel) had discontinued the study and 51 subjects randomized to the standard therapy arm (24% of the subjects randomized to SOC) had discontinued in the arm. There were 39 (19%) deaths in the cilta-cel arm and 47 (22%) deaths in the standard therapy arm. Three subjects, all of whom had been randomized to the SOC arm, were not treated (0.7% of all subjects randomized to both arms combined). Table 4 shows reasons for treatment and study discontinuation in the ITT population.

Table 4: Reasons for Treatment and Study Discontinuation, ITT Population

Reasons for Discontinuation	Cilta-cel N=208 n (%)	Standard Therapy N=211 n (%)	Total N=419 n (%)
Treatment discontinuation	**32 (15)^**	**131 (63)**	**163 (39)**
Adverse event	0	3 (1.4)	3 (0.7)
Death	2 (1)	5 (2.4)	7 (1.7)
Progressive disease	30 (14)	117 (56)	147 (35)
Physician decision	0	1 (0.5)	1(0.2)
Withdrawal by patient	0	5 (2.4)	5 (1.2)
Study discontinuation	**39 (19)**	**51 (24)**	**90 (22)**
Death	39 (19)	47 (22)	86 (21)
Withdrawal by subject	0	4 (2)	4 (1)

Source: FDA analysis, data cutoff date November 1, 2022

^ Twenty subjects received cilta-cel after disease progression as subsequent therapy and 12 subjects did not receive cilta-cel.

Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Table 5 below summarizes subsequent anti-myeloma therapies that subjects received after disease progression. Chemotherapy is the most common subsequent anti-myeloma therapy subjects received in the cilta-cel arm, compared to other therapies in the standard therapy arm.

Table 5: Subsequent Therapy, ITT Population

Type of Subsequent Therapy	Cilta-cel (N=208) n (%)	Standard Therapy (N=211) n (%)
Subjects with 1 or more subsequent anti-myeloma therapies	43 (20.7)	112 (53.1)
Class of therapy	-	-
Chemotherapy	33 (15.9)	55 (26.1)
Other therapies	28 (13.5)	85 (39.8)
Autologous BCMA CAR T therapy (cilta-cel)	20 (9.6)	0
Proteasome inhibitors	20 (9.6)	62 (29.4)
Monoclonal antibodies	12 (5.8)	52 (24.6)
Immunomodulatory agents	9 (4.3)	19 (9.0)
HDT+ASCT	3 (1.4)	1 (0.5)
Antibody drug conjugates	2 (1.0)	16 (7.6)
Autologous BCMA (investigational)	0	5 (2.4)
Autologous BCMA CAR T therapy (ide-cel)	0	2 (0.9)
Other cellular therapies	0	7 (3.3)

Source: Applicant IR

Abbreviations: ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T-cell; HDT, high-dose therapy; cilta-cel, ciltacabtagene autoleucel; ITT, intent-to-treat; n (%), number of subjects in the specified group or with a particular characteristic, IR, information request; N, number of subjects in the specified group

4.6.3 Efficacy Results

Primary Endpoint—Progression-Free Survival

Treatment with cilta-cel in CARTITUDE-4 demonstrated a statistically significant improvement in PFS as assessed by IRC according to IMWG 2016 criteria, compared to the standard therapy; HR 0.41 (95% CI: 0.30, 0.56; p-value <0.0001) Median PFS was not reached for the cilta-cel arm compared to 12 months for the standard therapy arm.

Table 6 and Figure 1 below summarize the analysis of PFS.

Table 6: Progression-Free Survival Per IRC, ITT Population

	Cilta-cel (N=208)	Standard Therapy (N=211)
Progression-free survival	-	-
Number of events, n (%)	65 (31)	122 (58)
Progression, n (%)	48 (23)	118 (56)
Death, n (%)	17 (8)	4 (2)
Number of censored, n (%)	143 (69)	89 (42)
KM estimate: median, months (95% CI)	NE (22.8, NE)	12 (9.8, 14)
Hazard ratio (95% CI)	0.41 (0.30, 0.56)	
p-value[1]	<0.0001	

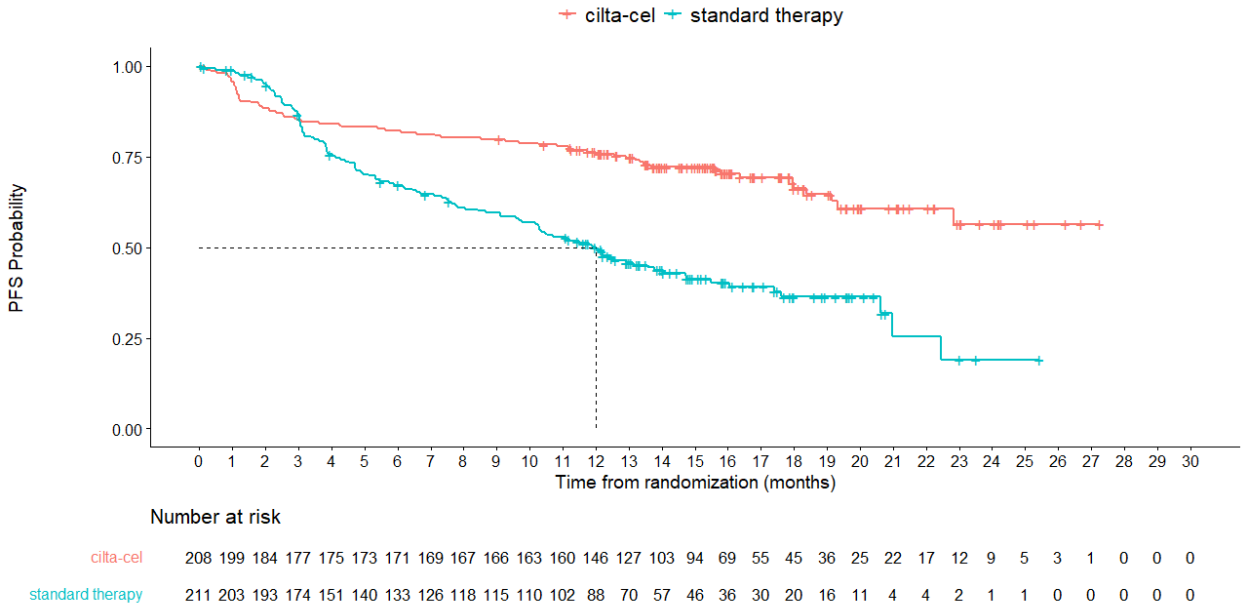
Source: FDA analysis, data cutoff November 1, 2022

1. One-sided stratified log-rank test.

Median follow-up for PFS is 15.8 (95% CI: 15.4, 16.1) months for the cilta-cel arm and 15.3 (95% CI: 14.3, 16.8) months for the standard therapy arm.

Abbreviations: CI, confidence interval; IA, interim analysis; IRC, Independent Review Committee; KM, Kaplan-Meier; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; NE, not evaluable

Figure 1: Progression-Free Survival Per IRC, ITT Population



Source: FDA analysis, data cutoff November 1, 2022
Abbreviations: IRC, Independent Review Committee; ITT, intent-to-treat; PFS, progression-free survival

The analysis of Investigator-assessed PFS demonstrates findings similar to the IRC assessment.

Interpretation of PFS Analysis Results

- Treatment with cilta-cel in CARTITUDE-4 demonstrated a statistically significant improvement in PFS as assessed by IRC, compared to the standard therapy with a HR 0.41 (95% CI: 0.30, 0.56; p-value <0.0001). Overall, the observed estimate of the treatment effect on PFS appears reliable based on balanced prognostic factors across treatment arms, and the blinded independent assessment of the PFS endpoint.

- A higher proportion of PFS events in the cilta-cel arm are attributable to deaths compared to the standard arm (cilta-cel arm: 8%, n=17; standard therapy arm 2%, n=4). Given the higher rate of deaths in the cilta-cel arm compared to the standard therapy arm, evidence of a treatment effect on survival may be needed to adequately assess whether the overall benefit-risk assessment is favorable.

Key Secondary Endpoints

Results of the analysis of the key secondary endpoints, CR/sCR and ORR by IRC are summarized in Table 7.

Table 7: Rate of CR/sCR and ORR Per IRC, ITT Population

Response Parameter	Cilta-cel (N=208)	Standard Therapy (N=211)
sCR, n (%)	137 (66)	38 (18)
CR, n (%)	17 (8)	9 (4)
VGPR, n (%)	16 (8)	49 (23)
PD, n (%)	18 (9)	6 (3)
Rate of CR/sCR	-	-
n (%)	154 (74)	47 (22)
p-value[2]	<0.0001	
Odds ratio (95% CI)	10.6 (6.6, 16.8)	
ORR (sCR+CR+VGPR+PR)	-	-
n (%)	176 (85)	143 (68)
p-value[2]	<0.0001	
Odds ratio (95% CI)	2.9 (1.8, 4.9)	

Source: FDA analysis, data cutoff January 1, 2022

1. Including MR, SD, PR, and NE.

2. One-sided Cochran-Mantel-Haenszel test controlling for pooled strata.

Abbreviations: CI, confidence interval; CR, complete response; IRC, Independent Review Committee; ITT, intent-to-treat; MR, minimal response; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Table 8 and Figure 4 below summarize the analysis of OS.

Table 8: Overall Survival, Interim Analysis, ITT Population

Category	Cilta-cel (N=208)	Standard Therapy (N=211)
Overall survival	-	-
Deaths, n (%)	39 (19)	47 (22)
Censored, n (%)	169 (81)	164 (78)
Median, months (95% CI)	NE (NE, NE)	26.7 (22.5, NE)
Hazard ratio (95% CI)	0.78 (0.51, 1.20)	
p-value[1]	0.26	

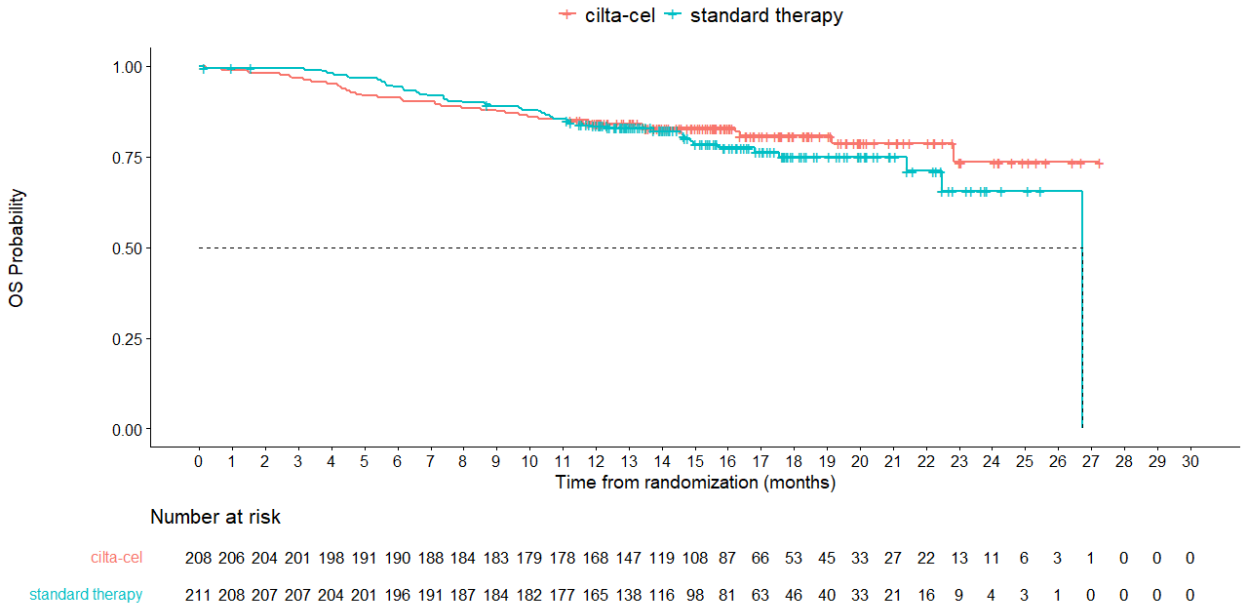
Source: FDA analysis, data cutoff November 1, 2022

1. One-sided stratified log-rank test.

Median follow-up for OS is 16.0 (95% CI: 15.6, 16.8) months for the cilta-cel arm and 15.9 (95% CI: 15.2, 16.6) months for the standard therapy arm.

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not evaluable; IA, interim analysis; ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Figure 2: Overall Survival, ITT Population



Source: FDA analysis, data cutoff November 1, 2022
Abbreviations: ITT, intent-to-treat; OS, overall survival

Interpretation of OS Analysis Results

- In the Kaplan Meier plot for OS (Figure 2), a crossing of the curves indicates that the treatment effect constancy assumption cannot be made (i.e., non-proportional hazards). In this scenario, average HR is an unreliable summary statistic to quantify the treatment effect.
- The average HR for OS at the time of the second interim analysis for PFS was reported as 0.78 (95% CI: 0.51, 1.20). The median OS estimate was 26.7 months for the standard therapy arm based on the Kaplan-Meier estimate; the median was not yet reached in the cilta-cel arm.
- The median OS estimate for the standard therapy arm should be interpreted with caution as the last subject in the at-risk set died at 26.7 months leading to an immediate OS probability drop from ~65% to 0% at that timepoint. The median OS estimates may become more reliable with longer follow-up OS data.

4.6.4 Safety Results

- Safety was assessed in all subjects who received conforming cilta-cel in the investigational arm including subjects randomized and treated under study and those randomized and treated after progression. Subjects randomized and not treated were excluded from the safety analysis (N=188).
- For the standard therapy arm, safety analysis included all subjects who received any study treatment (N=208).
- The safety review was based on the primary cutoff date of November 1, 2022, with a median follow-up of 15.6 months (Range: 2.4, 27.3 months) in the cilta-cel arm.
- For the standard therapy arm, the median follow-up for the safety population was 15.9 months (Range: 0.1, 26.7 months).
- At the time of the 120-day safety update (April 2, 2023 , data cutoff), 26 deaths were reported (6 deaths in the cilta-cel arm and 20 deaths in the standard therapy arm). Two new cases of

myelodysplastic syndrome in the cilta-cel arm were also reported, bringing the number of patients with secondary hematologic malignancies to five (2.6%) in the cilta-cel arm. No patients in the standard therapy arm developed a secondary hematologic malignancy.

- Deaths were analyzed using the primary safety data cutoff date of November 1, 2022, and were based on FDA's adjudication of deaths.

All 396 subjects (100%) had a least 1 TEAE (Table 9).

Table 9: Treatment-Emergent Adverse Events

Adverse Event	Cilta-cel N=188	Standard Therapy N=208	Total N=396
Any TEAE	188 (100)	208 (100)	396 (100)
Any Grade 3-4	158 (84)	190 (91)	348 (88)
Grade 3	39 (21)	73 (35)	112 (28)
Grade 4	119 (63)	117 (56)	236 (60)
Serious AEs	66 (35)	78 (37)	144 (36)
AEs leading to death*	20 (11)	16 (8)	36 (9)

Source: FDA analysis and Applicant's response to information request. Data cutoff November 1, 2022, * Excludes death from progressive disease.
Abbreviations: AE, adverse events; N, number of subjects in the specified group, or the total sample; SAE, serious adverse events; TEAE, treatment-emergent adverse event

TEAEs that occurred in 10% or more of subjects are summarized in Table 10.

Table 10: Treatment Emergent Adverse Events Occurring in ≥10% of Subjects, GT Safety Population, CARTITUDE-4

	Cilta-cel N=188		Standard Therapy N=208	
System Organ Class	All Grades (n/%)	Grade 3-4 (n/%)	All Grades (n/%)	Grade 3-4 (n/%)
Any TEAE	188 (100)	151 (80)	208 (100)	190 (91)
General disorders and administration site conditions	-	-	-	-
Pyrexia	148 (79)	10 (5.3)	33 (16)	2 (1)
Fatigue (GT)	53 (28)	5 (3)	104 (50)	7 (1)
Immune system disorders	-	-	-	-
Cytokine release syndrome	146 (78)	6 (3)	1 (0.5)	1 (0.5)
Hypogammaglobulinemia	92 (49)	16 (9)	13 (6)	-
Gastrointestinal disorders	-	-	-	-
Diarrhea (GT)	51 (27)	4 (2.1)	56 (27)	5 (2.4)
Infections and infestations	-	-	-	-
Viral infection (GT)	47 (25)	8 (4)	76 (36.5)	23 (11)
Bacterial infection (GT)	28 (15)	12 (6)	21 (10)	10 (4.8)
Pneumonia	29 (15)	10 (5)	38 (18)	12 (6)
COVID-19	17 (9)	4 (2)	42 (20)	4 (1.9)

	Cilta-cel N=188		Standard Therapy N=208	
System Organ Class	**All Grades (n/%)**	**Grade 3-4 (n/%)**	**All Grades (n/%)**	**Grade 3-4 (n/%)**
Nervous system disorders				
Headache	44 (23)	0	28 (13.5)	0
Encephalopathy (GT)	27 (14)	3 (1.6)	9 (4)	0
Parkinsonism (GT)	27 (14)	3 (1.6)	0	0
Dizziness (GT)	16 (9)	1 (1)	37 (18)	8 (3.8)
Neuropathy (GT)	13 (6.9)	1 (0.5)	38 (18)	1 (0.5)
Musculoskeletal and connective tissue disorders	-	-	-	-
Musculoskeletal pain (GT)	69 (37)	3 (2)	98 (47)	8 (3.8)
Respiratory, thoracic, and mediastinal disorders	-	-	-	-
Dyspnea (GT)	18 (10)	4 (2)	41 (20)	1 (0.5)
Vascular disorders	-	-	-	
Hypotension (GT)	44 (23)	7 (4)	6 (2.9)	0
Hemorrhage (GT)	17 (9)	2(1)	29 (14)	0
Psychiatric disorders	-	-	-	-
Sleep disorder	11 (6)	1 (1)	52 (25)	6 (2.9)

Source: FDA analysis. Data cutoff November 1, 2022

For listing of GT please refer to Appendix 8.4.

Abbreviations: COVID-19, Coronavirus Disease 2019; GT, grouped term; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SOC, system organ class; TEAE, treatment adverse event

The most common all-grade and Grade 3 and 4 hematologic and nonhematologic laboratory abnormalities that occurred in ≥10% of subjects are shown in Table 11.

Table 11: Laboratory Abnormalities Occurring in ≥10% of the Safety Population, CARTITUDE-4

	Cilta-cel N=188		Standard Therapy N=208	
Laboratory Abnormality	**All Grades (n/%)**	**Grade 3-4 (n/%)**	**All Grades (n/%)**	**Grade 3-4 (n/%)**
Anemia	188 (100)	61 (32.4%)	202 (97)	33 (15.9)
Lymphocyte count decreased	188 (100)	185 (98.4)	182 (87.5)	129 (62)
Neutrophil count decreased	187 (99.5)	178 (94.7)	203 (97.6)	182 (87.5)
Platelet count decreased	177 (94.1)	82 (43.6)	181 (87)	42 (20)
White blood cell decreased	188 (100)	177 (94)	207 (99.5)	143 (68.8)
ALT increased	96 (51)	6 (3.2)	57 (27.4)	7 (3.4)
ALK increased	86 (45.7)	11 (5.9)	30 (14.4)	4 (1.9)
AST increased	25 (28)	0	30 (14.4)	4 (1.9)
Potassium decreased	28 (15)	4 (2)	14 (7)	3 (1.4)
Phosphorus decreased	20 (10)	4 (1.9)	8 (3.8)	1 (0.5)

Source: FDA analysis and Applicant response to information request. Data cutoff November 1, 2022

Laboratory tested are graded according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE version 5.0). Laboratory values included in the analysis are for standard therapy arm, lab assessments on or after the study treatment start until 30 days after the last dose of study treatment or start a subsequent therapy, whichever earlier. For cilta-cel arm, lab assessment on or after cilta-cel infusion until Day 112 or start subsequent therapy, whichever earlier.

Abbreviations: ALK, alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Table 12 summarizes nonfatal SAEs that occurred in ≥2% of the safety population.

Table 12: Nonfatal Serious Treatment Emergent Adverse Events Occurring in ≥2% of the Safety Population, CARTITUDE-4

	Cilta-cel N=188		Standard Therapy N=208	
System Organ Class	**All Grades (n/%)**	**Grade 3-4(n/%)**	**All Grades (n/%)**	**Grade 3-4 (n/%)**
Any nonfatal serious TEAE	**68 (36)**	**42 (22.3)**	**78 (37.5)**	**67 (32.2)**
Infections and infestations	-	-	-	-
Pneumoniae (GT)	10 (5.3)	9 (4.8)	24 (11.5)	22(10.6)
Viral infection (GT)	12 (6.4)	5 (2.7)	12 (5.8)	12 (5.8)
Upper respiratory tract infection	3 (1.6)	2 (1)	8 (3.8)	7 (3.4)
Bacterial infection	3 (1.6)	3 (1.6)	7 (3.4)	7 (3.4)
Sepsis	5 (2.7)	5 (2.7)	2 (1)	0
Blood and lymphatic system disorders	-	-	-	-
Febrile neutropenia	0	3 (1.6)	0	5 (2.4)
Neutropenia	4 (2.1)	4 (2.1)	1 (0.5)	1 (0.5)
Nervous system disorders				
Encephalopathy	4 (2.1)	1 (0.5)	2 (1)	2 (1)
Cranial nerve palsies	10 (5.3)	2 (1)	1 (0.5)	0
Gastrointestinal disorders	-	-	-	-
Diarrhea	4 (2.1	3(1.6)	0	0
Immune system disorders	-	-	-	-
Cytokine release syndrome	12 (6.4)	4 (2.1)	0	0

Source: Applicant's IR response, data cutoff November 1, 2022
Abbreviations: GT, grouped term; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SAE, severe adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event

Adverse Events of Special Interest (AESIs) are summarized in Table 13.

Table 13: Adverse Events of Special Interest (AESI), CARTITUDE-4

	Cilta-cel N=188		Standard Therapy N=208	
AESI	**Any Grade (n/%)**	**Grade ≥3 (n/%)**	**Any Grade (n/%)**	**Grade ≥3 (n/%)**
CRS	146 (77)	6 (3)	1(1)	0
Neurotoxicity	44 (23)	8 (4)	0	0
HLH/MAS	2 (1)	1(0.5)	1 (2)	0
Infections	107 (57)	46 (24.5)	148 (71)	47 (22.6)
Secondary primary malignancy	8 (4.3)	N/A	14 (6.7)	N/A
Hematologic neoplasm	3 (1.6)	1(0.5)	0	-
Cytopenia	-	-	-	-
Neutropenia	187 (99)	178 (95)	203 (98)	182 (87)
Thrombocytopenia	177 (94)	82 (44)	181 (87)	42 (20)

Source: FDA analysis and Applicant's response to information request, data cutoff November 1, 2022
Abbreviations: CRS, cytokine release syndrome; HLH/MAS, hemophagocytic lymphohistiocytic syndrome/macrophage activation syndrome; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Prolonged and recurrent cytopenia lasting up to 60-days after cilta-cel infusion are shown in Table 14.

Table 14: Prolonged and Recurrent Cytopenia, Safety Population, CARTITUDE-4

Laboratory	Grade 3-4 After Day 1 Dosing (n/%)	Grade 3-4 Not Recovered by Day 30 (n/%)	Grade 3-4 Not Recovered by Day 60 (n/%)	Occurrence of Grade 3-4 After Day 60 (n/%)
Lymphopenia	188 (100)	6 (3.2)	20 (10.6)	33 (17.6)
Neutropenia	178 (94.7)	47 (25)	19 (10)	44 (23.4)
Thrombocytopenia	82 (43.6)	54 (28.7)	26 (13.8)	8 (4.3)
Anemia	64 (34)	5 (2.7)	5 (2.7)	8 (4.3)

Source: Applicant's response to information request, data cutoff November 1, 2022
The lab with the worst toxicity grade will be used for a calendar day. Recovery definition: must have two consecutive Grade ≤2 results from separate days if recover period ≤10 days.
Abbreviations: n (%), number of subjects with the specified characteristic

Table 15 summarizes all deaths in the safety analysis population.

Table 15: Deaths, Safety Population, CARTITUDE-4

Deaths	Cilta-cel N=188	Standard Therapy N=208	All N=396
Total deaths, n (%)	25 (13)	46 (22)	71 (18)
TEAE, n (%)	20 (11)	16 (8)	36 (9)
Progressive disease, n (%)	5 (3)	30 (14)	35 (9)
Deaths ≤90 days after treatment start, n (%)	9 (5)	0	9 (2.2)
TEAE, n (%)	8 (4)	0	8 (2)
Progressive disease, n (%)	1(0.5)	0	1(0.2)
Deaths >90 days after treatment start, n (%)	16 (8.5)	46 (22)	62 (16)
TEAE, n (%)	12 (6.4)	16 (8)	28 (7)
Progressive disease, n (%)	4 (2)	30 (14)	34 (9)

Source: FDA analysis, data cutoff November 1, 2022
Death day is from treatment start for each treatment. Only deaths that occurred after infusion of conformal cilta-cel are included in this table.
TEAE deaths include all deaths from AEs, including AEs after disease progression and after initiation of subsequent anti-myeloma therapy.
Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Table 16 lists the FDA-assessed primary cause of death due to AEs of each treatment arm.

Table 16: TEAEs as Primary Cause of Death, Safety Population, CARTITUDE-4

Category	Cilta-cel N=188 (n/%)	Standard Therapy N=208 (n/%)	Total N=396 (n/%)
Total deaths	25 (13)	46 (22)	71 (18)
Adverse events	20 (11)	16(8)	36 (9)
COVID-19 pneumonia	7 (3.7)	1 (0.5)	8 (20)
Pneumonia^	2 (1)	4 (1.9)	6 (1.5)
Sepsis	3 (1.6)	2 (0.9)	5 (1.3)
Hemorrhage*	4 (2)	2 (0.9)	6 (1.5)
CMV colitis	1 (0.5)	0	1 (0.2)

Category	Cilta-cel N=188 (n/%)	Standard Therapy N=208 (n/%)	Total N=396 (n/%)
Multiorgan failure	1 (0.5)	2 (0.9)	3 (0.7)
Acute myeloid leukemia	1 (0.5)	0	1 (0.2)
Cardiorespiratory arrest	1 (0.5)	0	1 (0.2)
Cardiogenic shock	0	1 (0.5)	1 (0.2)
JC virus	0	1 (0.5)	1 (0.2)
Progressive multifocal leukoencephalopathy	0	1 (0.5)	1 (0.2)
Pulmonary embolism	0	1 (0.5)	1 (0.2)
Respiratory distress	0	1 (0.5)	1 (0.2)

Source: FDA analysis and review of death narratives. This table represents the primary AE causing death as assessed by FDA's review of the narratives. Deaths are not grouped under SOC but grouped term. Data cutoff November 1, 2022

^ Pneumoniae includes influenza pneumoniae, respiratory infection, pneumoniae, and pneumocystis jiroveci pneumonia. * Hemorrhage includes intraparenchymal bleeding, intracranial hemorrhage, retroperitoneal bleed, and subdural hematoma.

Abbreviations: CMV, cytomegalovirus; COVID-19, Coronavirus Disease 2019; JC, John Cunningham; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; TEAE, treatment adverse event

5. FDA Major Review Issue

5.1 Increased Rate of Early Deaths in the Cilta-Cel Arm

As presented in Section 4, the OS results from the CARTITUDE-4 study demonstrated an observed early detriment in OS in subjects randomized to the cilta-cel arm compared to those randomized to standard therapy. Section 4, there is an increased rate of early deaths in the cilta-cel arm compared to the standard therapy arm, in CARTITUDE-4, in the context of a PFS benefit. This increased rate of early deaths is reflected in the Kapan-Meier curves as a crossing hazards pattern favoring the standard therapy arm up to approximately 11 months; heavy censoring limits the estimation of the treatment effect on overall survival after 11 months.

As presented in Section 4, the OS results from the CARTITUDE-4 study demonstrated an observed early detriment in OS in subjects randomized to the cilta-cel arm compared to those randomized to standard therapy. This is reflected in the Kapan-Meier curves as a crossing hazards pattern with a lower survival curve in the cilta-cel arm compared to the standard therapy arm up to approximately 11 months. While the cilta-cel arm demonstrates a benefit after 11 months, the finding is limited by heavy censoring and the pattern of early deaths attributed to adverse events in the cilta-cel arm is concerning. More 13% and 22% of deaths occurred in the cilta-cel and standard therapy arms, respectively (Table 16). However, more deaths due to AEs occurred in the cilta-cel arm (11%) compared to the standard therapy arm (8%) in the safety population. A similar trend of deaths due to AEs was observed when analyzing deaths in the ITT population (cilta-cel arm: 11%; standard therapy arm: 7%; Table 9). in the standard therapy arm). The pattern of increased early deaths in the cilta-cel arm is also observed in an analysis of PFS events which indicates that a higher proportion of subjects died before disease progression in the cilta-cel arm (8%) compared to the standard therapy arm (2%) (Table 6).

Overall survival is a gold standard endpoint in oncology because it is not subject to biased assessment, and because prolongation of life in the setting of a life-threatening and fatal disease is clinically meaningful and of clinical benefit. Overall survival is an efficacy endpoint that also captures the

treatment's effect on safety. For these reasons, FDA recommends that trials in oncology should be designed to evaluate overall survival as the primary endpoint.

When the evaluation of OS is infeasible to be used as the primary endpoint, such as when the disease has a long natural history or the availability of multiple subsequent therapies limits the interpretability of survival, FDA has granted approval to drugs that demonstrate a statistically significant and clinically meaningful effect on progression-free survival in the context of an acceptable risk profile. In these instances, FDA recommends that OS should be prioritized as a key secondary endpoint that is evaluated descriptively as part of FDA's risk assessment. This recommendation stems from experience with several oncology drugs, including anti-myeloma therapies, demonstrating a meaningful effect on tumor-based endpoints that subsequently demonstrated significant drug-related toxicity correlating with detrimental effects on survival.

FDA conducted additional descriptive analyses to characterize the risk of deaths by specific time periods, based on the ITT population; the results of these analyses are shown below in Table 17. These analyses indicate that at least until approximately 10 months, the rate of deaths attributable to AEs continues to be higher in the cilta-cel arm.

Table 17: Deaths, ITT Population, CARTITUDE-4

Deaths	Cilta-cel N=208	Standard Therapy N=211	Total N=419
Total deaths, ITT n (%)	39[1] (18.8)	47 (22.3)	86 (20)
Progressive disease	17(6.7)	30(14.7)	47 (11)
Adverse event	22 (11)	17 (7.1)	39 (9.3)
Death 0 to ≤5 months n (%)	17 (8.2)	7 (3.3)	24 (5.7)
Progressive disease	10 (5)	3 (1.4)	13 (3)
Adverse event	7 (3.4)	4(2)	11(2.6)
Death >5 to 10 months n (%)	12 (5.8)	18(8.5)	30 (7.1)
Progressive disease	3 (1.4)	13(6.2)	16 (3.8)
Adverse event	9 (4.3)	5(2.4)	14 (3.3)
Death >10 to 15 months n (%)	6 (2.8)	16 (7.6)	22 (5.2)
Progressive disease	3 (1.4)	12(5.7)	15 (3.6)
Adverse event	3 (1.4)	4 (2)	7 (1.7)
Death >15 months n (%)	4(2)	6 (2.8)	10 (5.2)
Progressive disease	1 (0.5)	3 (1.4)	7 (1.7)
Adverse event	3 (1.4)	3 (1.4)	3 (0.7)

Source: FDA analysis: November 1, 2022, data cutoff date. Death day is calculated from randomization.
1. Out of the 39 deaths in the cilta-cel arm, 11 never received the planned treatment, compared to only 3 in the standard therapy arm.
Table includes deaths in all randomized subjects including three subjects who received nonconformal cilta-cel.
Table includes all deaths after treatment from AEs including infection related AEs following disease progression and subsequent AMT.
Abbreviations: AE, adverse event; ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

A key question for this application is the duration of the period of increased risk of early death in the cilta-cel arm, compared to the standard therapy arm. Because the Kaplan Meier survival curves cross, a single average hazard ratio provides an unreliable estimate of the entire time-dependent treatment effect profile of cilta-cel on OS. There are statistical analyses such as piecewise hazard ratio assessment conducted based on selected landmark timepoints, that may provide alternative ways to estimate the treatment effect. FDA conducted such an assessment as shown in Table 18. Based on this assessment,

the increased risk of death on the cilta-cel arm appears to persist until at least 5 months and possibly up to 11 months.

Table 18: Piecewise Hazard Ratio Assessment, ITT Population

Time Interval	Piecewise HR	95% CI
Time interval of 3 months		
0-≤3	6.24	(0.75, 51.85)
3-≤6	1.07	(0.46, 2.47)
6-≤9	0.65	(0.25, 1.68)
9-≤12	0.72	(0.29, 1.78)
Time interval of 5 months		
0-≤5	2.40	(0.99, 5.85)
5-≤10	0.69	(0.33, 1.42)
10-≤15	0.35	(0.14, 0.90)
Time interval of 11 months		
0-≤11	1.04	(0.62, 1.73)

Source: FDA analysis
*> 15 months not reported due to heavy censoring
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat

While analyses like the piecewise HR assessment may provide information to support a benefit risk assessment, such analyses have limitations- for example, choosing the cutoffs for such approaches retrospectively based on observed outcomes leads to unreliable estimates that are unlikely to be replicated in future studies.

The pattern of early deaths in the context of a significant advantage in PFS, may be due to a heterogeneous patient population that includes a subgroup of patients for whom treatment with cilta-cel may be inappropriate. The CARTITUDE-4 study was not designed to evaluate risks and benefits within specific subgroups of patients enrolled in the trial. Exploratory, retrospective, data-informed analyses, in subgroups with limited sample size are hypothesis generating but may limited in providing definitive evidence to support potential risk mitigation strategies due to the inherent selection bias of post hoc analyses.

Overall, AEs were the most common cause reported for deaths that occurred in the cilta-cel arm—11% compared to 8 % in the standard therapy arm in the ITT population.

To conclude, while CARTITUDE-4 demonstrated a statistically significant effect on PFS, it is unclear whether the overall benefit-risk assessment is favorable; specifically, whether additional data is needed to support such an assessment.

6. Draft Questions

Discussion Topic:

Discuss whether the results of CARTITUDE-4 provided in the supplemental application are sufficient to support a positive risk-benefit assessment of ciltacabtagene-autoleucel for the proposed indication. Specifically, is the risk of early death associated with cilta-cel treatment acceptable in the context of the clinical benefit.

Voting Question:

Is the risk-benefit assessment for ciltacabtagene-autoleucel for the proposed indication, favorable?

7. References

American Cancer Society, 2023, Key Statistics About Multiple Myeloma, accessed December 28, 2023, 2023, https://www.cancer.org/cancer/types/multiple-myeloma/about/key-statistics.html.

Cowan, AJ, DJ Green, M Kwok, S Lee, DG Coffey, LA Holmberg, S Tuazon, AK Gopal, and EN Libby, 2022, Diagnosis and Management of Multiple Myeloma: A Review, JAMA, 327(5):464-477.

De Arriba de la Fuente, F, C Montes Gaisan, and J de la Rubia Comos, 2022, How to Manage Patients with Lenalidomide-Refractory Multiple Myeloma, Cancers (Basel), 15(1).

National Cancer Institute, 2023, Cancer Stat Facts: Multiple Myeloma, accessed December 28, 2023, 2023, https://seer.cancer.gov/statfacts/html/mulmy.html.

Rajkumar, SV, JL Harousseau, B Durie, KC Anderson, M Dimopoulos, R Kyle, J Blade, P Richardson, R Orlowski, D Siegel, S Jagannath, T Facon, H Avet-Loiseau, S Lonial, A Palumbo, J Zonder, H Ludwig, D Vesole, O Sezer, NC Munshi, J San Miguel, and P International Myeloma Workshop Consensus, 2011, Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1, Blood, 117(18):4691-4695.

USPI, 2021, Abecma Prescribing Information.

USPI, 2022, Carvykti Prescribing Information.

8. Appendix

Table 19: Approved Therapies for Relapsed/Refractory Multiple Myeloma

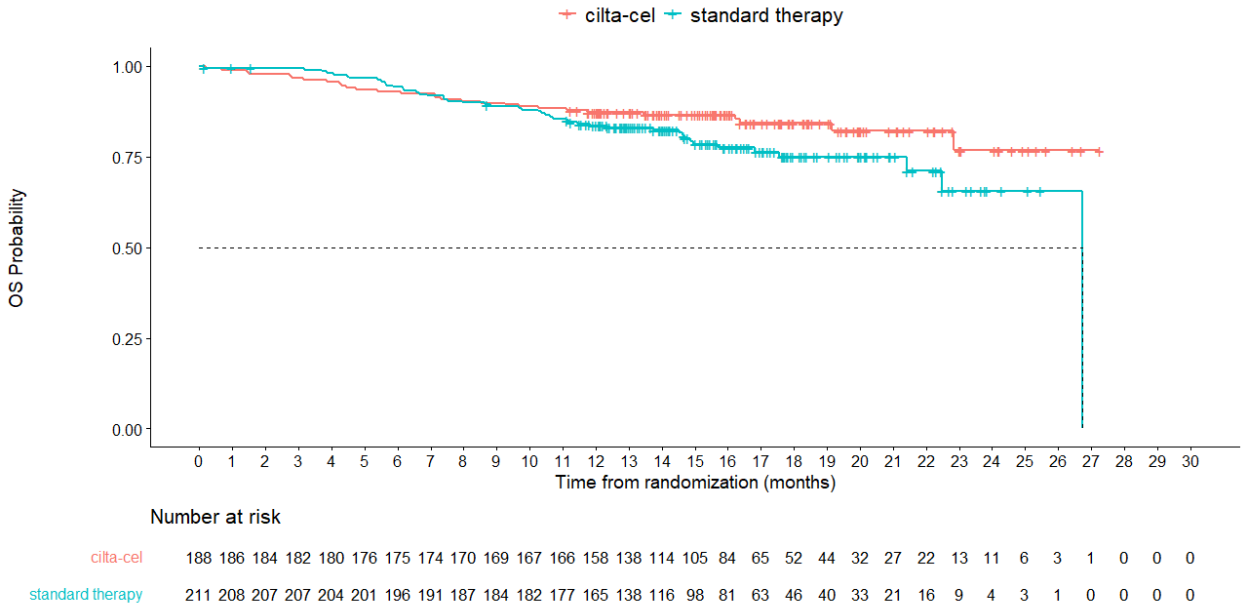
Indication	Drug/Combination
At least 1 prior line	Doxil (Liposomal doxorubicin HCl)
-	Revlimid (lenalidomide) with dexamethasone
-	Kyprolis (carfilzomib)
-	Darzalex with Rd or Vd
-	Ninlaro (ixazomib) with Rd
-	Darzalex Faspro with Rd
-	Xpovio with Vd
At least 2 prior lines, including len and PI	Pomalyst (pomalidomide) with dexamethasone
-	Velcade (bortezomib)
-	Darzalex with Pd
-	Sarclisa (isatuximab) with Pd
-	Empliciti (elotuzumab) with Pd
1-3 prior lines	Velcade
-	Kyprolis with Rd, Kyprolis with dexamethasone
-	Empliciti (elotuzumab) with Rd
-	Darzalex with Kd
-	Darzalex Faspro with Kd
≥1 prior lines including Len and PI	Darzalex Faspro with Pd
At least 3 prior lines, including PI and IMiD	Darzalex (daratumumab)
At least 3 prior lines, including PI and IMiD or PI/IMiD double refractory	Darzalex Faspro (daratumumab and hyaluronidase)
At least 4 prior lines including a PI, an IMiD, and anti-CD38 antibody	Abecma (Idecabtagene vicleucel), Carvykti (ciltacabtagene autoleucel), Teclistamab, Elranatamab, Talquetemab
At least 4 prior lines, refractory to 2 Pis, 2 ImiDs, and anti-CD38 mAb	Xpovio (selinexor) with dexamethasone

Source: FDA
Abbreviations: d, dexamethasone; IMiD, immunomodulatory drug; K, Kyprolis ; len, lenalidomide; mAb, monoclonal antibody; P, pomalidomide; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; V, Velcade

8.1 Limitations of Exploratory Post Hoc Subgroup Analyses

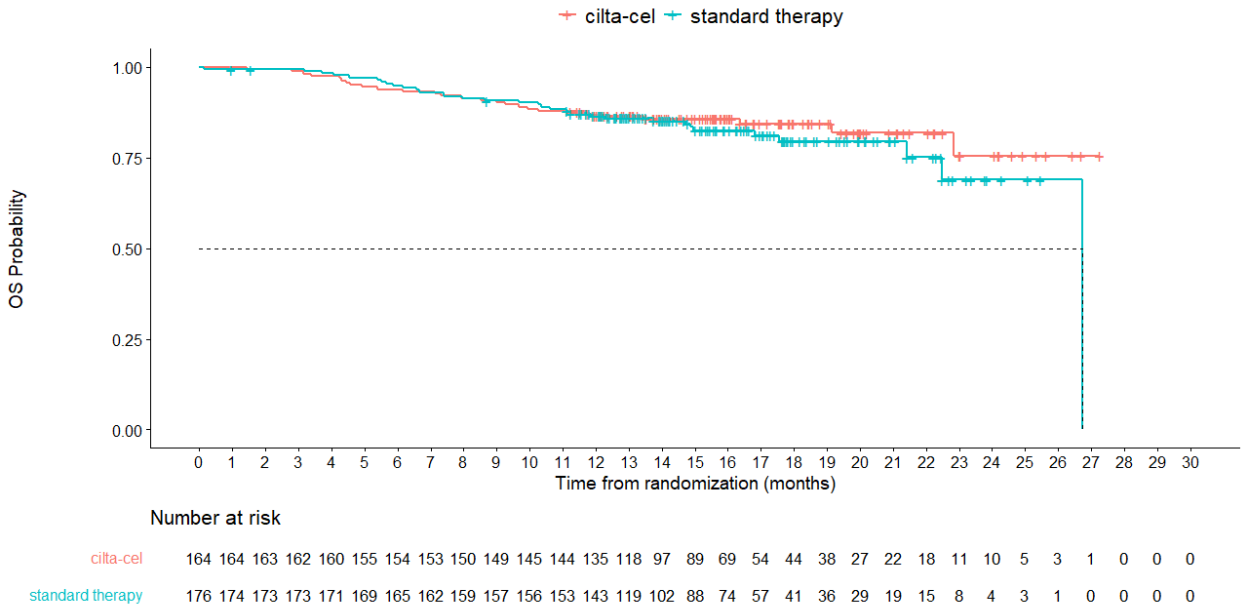
The Applicant listed five subpopulations that may have caused the crossing hazards pattern for OS with an early OS detriment. Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, and Figure 8 show the Kaplan-Meier curves for OS if each subpopulation or the combined population of subjects with any of the five factors are excluded. Figure 9 shows the Kaplan-Meier curves for OS if subjects in both arms who have progressive disease within 3 months after randomization are excluded.

Figure 3: Overall Survival, Subpopulation A Excluded



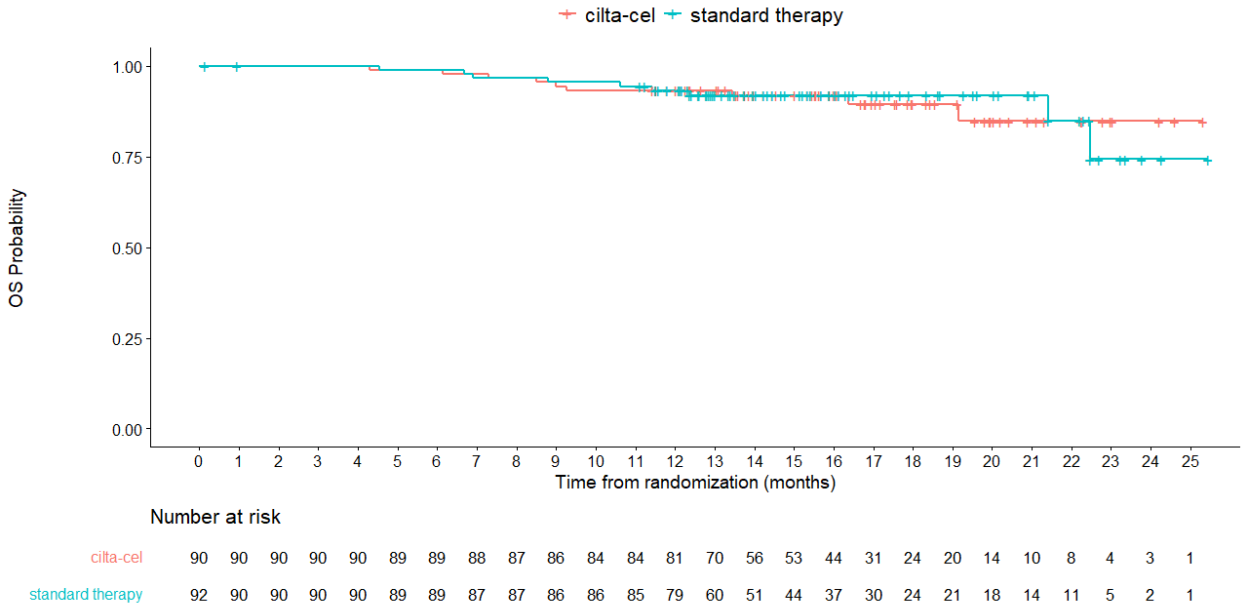
Source: FDA analysis
Abbreviations: OS, overall survival

Figure 4: Overall Survival, Subpopulation B Excluded



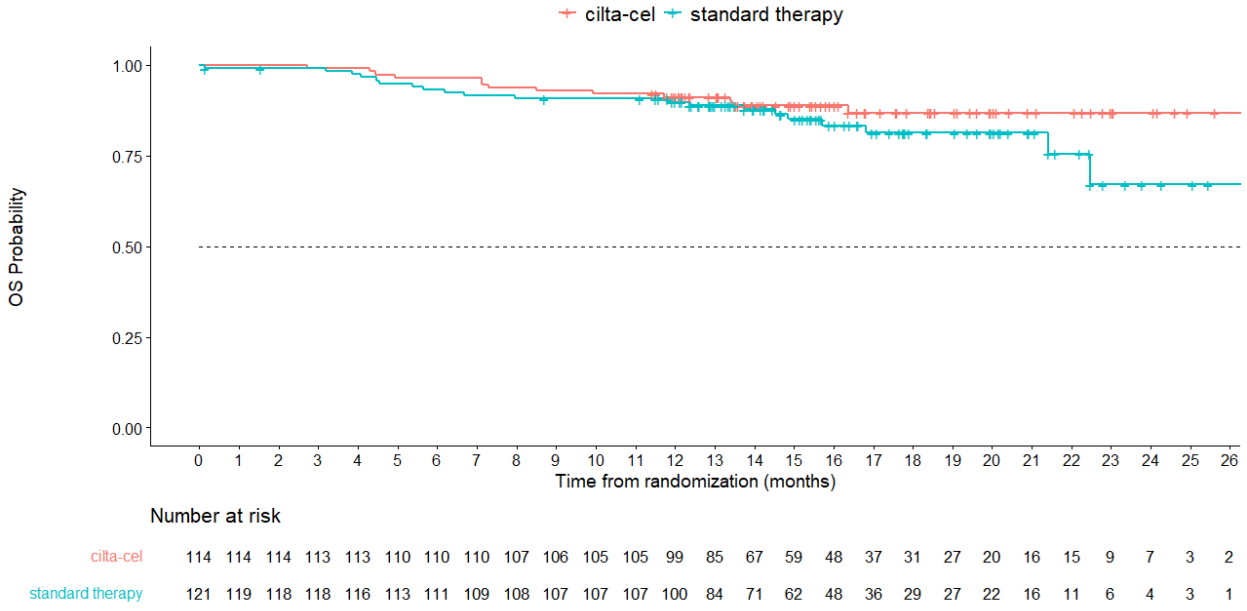
Source: FDA analysis
Abbreviations: OS, overall survival

Figure 5: Overall Survival, Subpopulation C Excluded



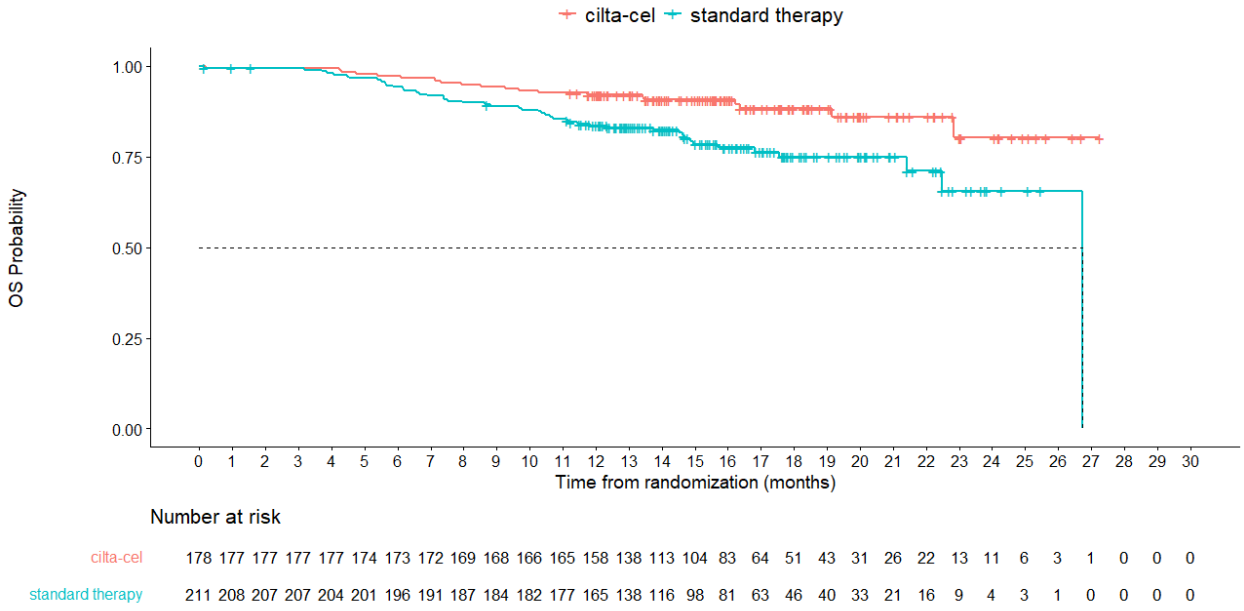
Source: FDA analysis
Abbreviations: OS, overall survival

Figure 6: Overall Survival, Subpopulation D Excluded



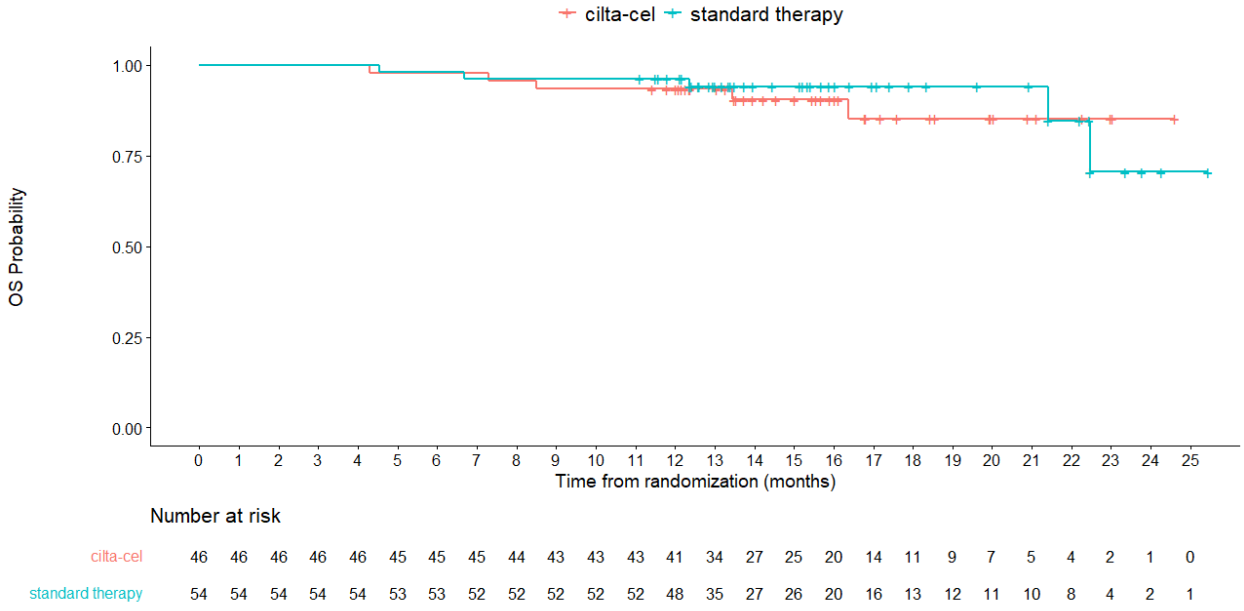
Source: FDA analysis
Abbreviations: OS, overall survival

Figure 7: Overall Survival, Subpopulation E Excluded



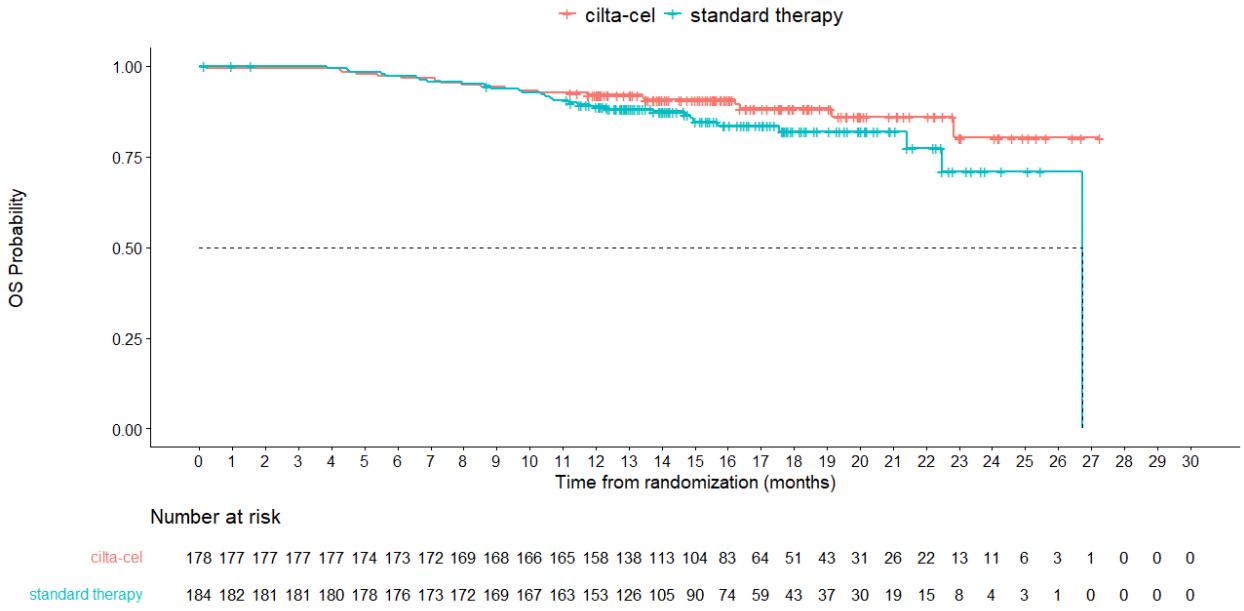
Source: FDA analysis
Abbreviations: OS, overall survival

Figure 8: Overall Survival, Combination of Five Subpopulations Excluded



Source: FDA analysis
Abbreviations: OS, overall survival

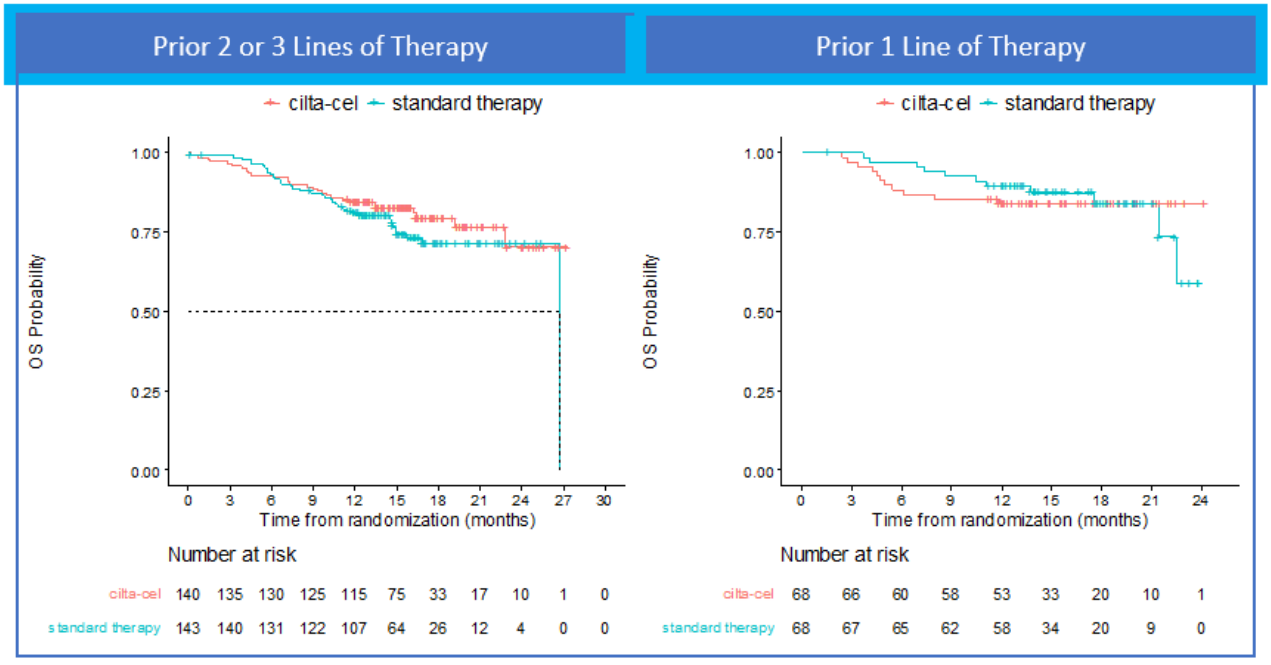
Figure 9: Overall Survival, Progressive Disease Within 3 Months After Randomization in Both Arms Excluded



Source: FDA analysis
Abbreviations: OS, overall survival; PD, progressive disease

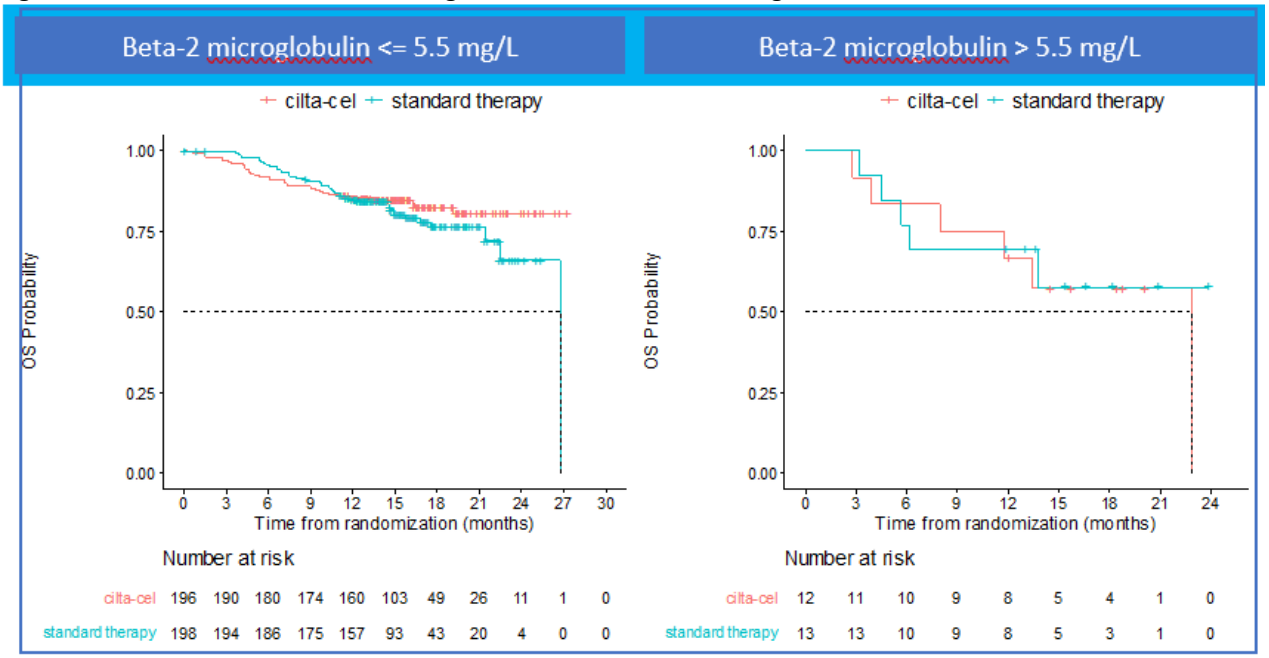
Figure 10, Figure 11, and Figure 12 show OS based on FDA's additional post hoc subgroup analyses.

Figure 10: Overall Survival, Prior 2 or 3 Lines of Therapy Vs. Prior 1 Line of Therapy



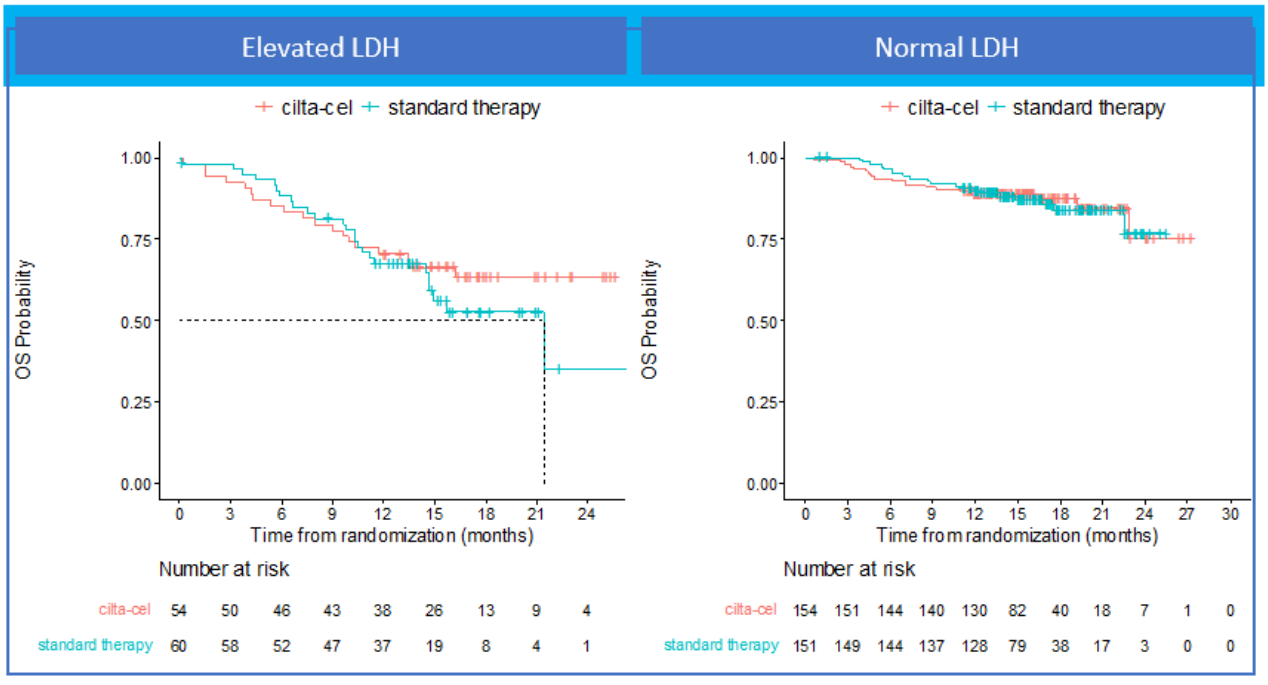
Source: FDA analysis
Abbreviations: OS, overall survival

Figure 11: Overall Survival, Beta-2 Microglobulin≤5.5 Vs. Beta-2 Microglobulin >5.5



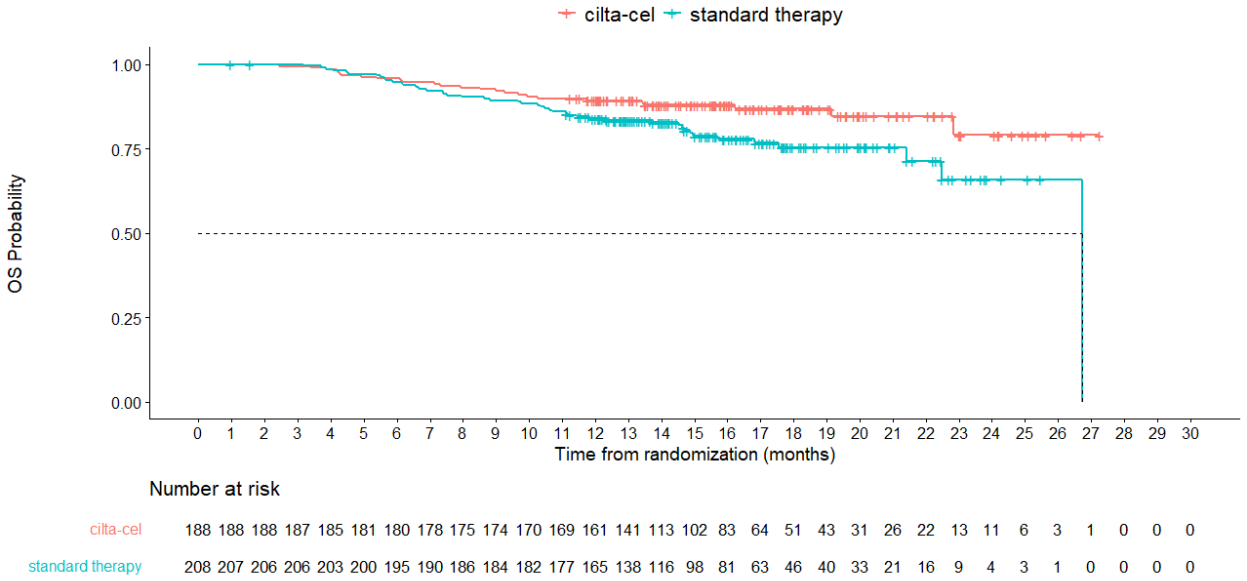
Source: FDA analysis
Abbreviations: OS, overall survival

Figure 12: Overall Survival, Elevated LDH Vs. Normal LDH



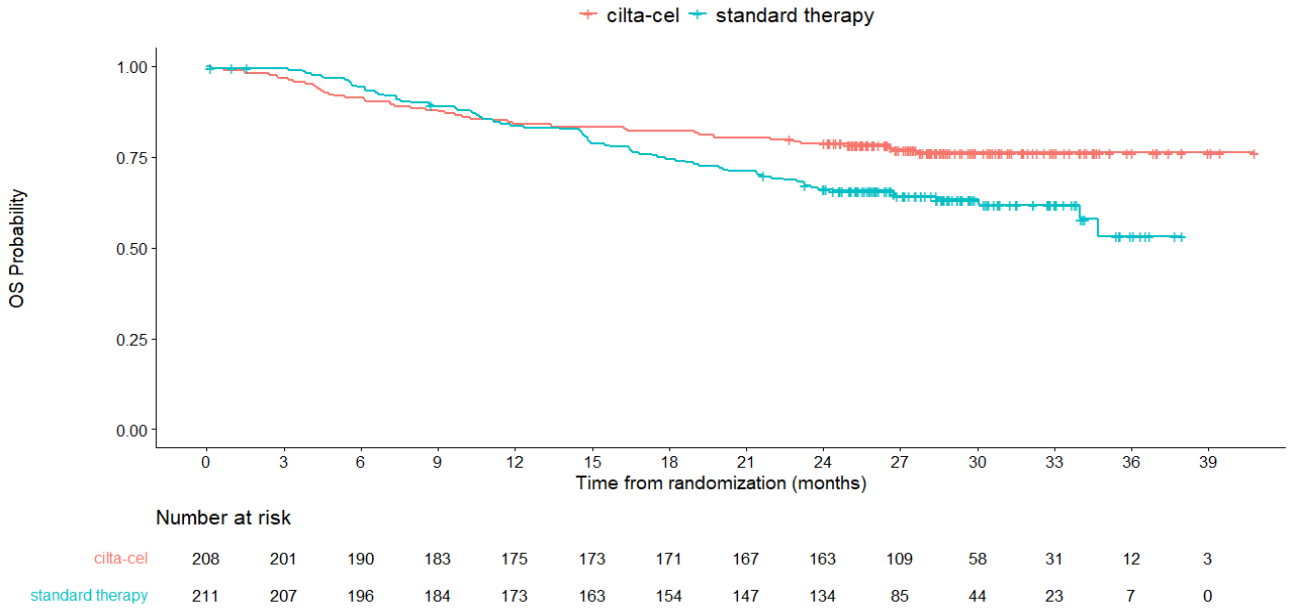
Source: FDA analysis
Abbreviations: LDH, Lactic acid dehydrogenase; OS, overall survival

Figure 13: Overall Survival, Safety Population



Source: FDA analysis, data cutoff November 1, 2022
Abbreviations: ITT, intent-to-treat; OS, overall survival

Figure 14: Overall Survival, Data Cutoff of December 13, 2023



Source: FDA analysis
Abbreviation: OS, overall survival

8.2 PFS Analysis Per Investigator

Table 20: Progression-Free Survival Per Investigator, Interim Analysis, ITT Population

Category	Cilta-cel (N=208)	Standard Therapy (N=211)
Progression-free survival	-	-
Number of events, n (%)	65 (31)	126 (60)
Progression	48 (23)	122 (58)
Death	17 (8)	4 (2)
Number of censored, n (%)	143 (69)	85 (40)
Median, months (95% CI)	NE (22.8, NE)	11.2 (9.1,13.6)
Hazard ratio (95% CI)	0.38 (0.28, 0.52)	
p-value[1]	<0.0001	

Source: FDA analysis, data cutoff November 1, 2022

1. One-sided stratified log-rank test.

Abbreviations: CI, confidence interval; IA, interim analysis; ITT, intent-to-treat; KM, Kaplan-Meier; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; NE, not evaluable; PFS, progression-free survival

8.3 Eligibility Criteria

Patient Eligibility Criteria (section 5.1, Protocol CARTITUDE-4, Version 5.0: 18 August, 2022):

Inclusion Criteria

Each potential subject must satisfy all the following criteria to be enrolled in the study:

1. Be at least 18 years of age.
2. Criterion modified per Amendment 2.
   2.1 Have documented diagnosis of multiple myeloma (MM) as defined by the criteria below:
   - Multiple myeloma diagnosis according to the International Myeloma Working Group (IMWG) diagnostic criteria (section 10.8).
   - Measurable disease at screening as defined by any of the following:
     - Serum monoclonal paraprotein (M-protein) level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
     - Light chain MM without measurable M-protein in the serum or the urine: serum free light chain ≥10 mg/dL and abnormal serum free light chain ratio.

Note: Local laboratory assessments may be used to establish measurable disease at screening, with local laboratory result ≥125% of requirements. However, subjects must have laboratory studies for diseases assessment received by central laboratory prior to randomization. If central and local laboratory studies are performed on the same day, only the central laboratory results will be considered.

3. Have received one to three prior lines of therapy including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD). Subject must have undergone at least one complete cycle of treatment for each line of therapy, unless progressive disease was the best response to the line of therapy (see section 10.9).

Note: induction with or without hematopoietic stem cell transplant, consolidation and maintenance therapy is considered a single line of therapy.

4. Have documented evidence of progressive disease by IMWG criteria based on investigator's determination on or within 6 months of their last regimen.
5. Subjects with only one prior line of therapy must have progressed within 36 months of a stem cell transplant, or if not transplanted, then within 42 months of starting initial therapy.
6. Criterion modified per Amendment 1.
   6.1. Criterion modified per Amendment 2.
   6.2. Be refractory to lenalidomide per IMWG consensus guidelines (Rajkumar et al. 2011) (failure to achieve minimal response or progression on or within 60 days of completing lenalidomide therapy). Progression on or within 60 days of the last dose of lenalidomide given as maintenance will meet this criterion. For subjects with more than one prior line of therapy, there is no requirement to be lenalidomide refractory to the most recent line of prior therapy. However, subjects must be refractory to lenalidomide in at least one prior line.
7. Have an ECOG Performance Status score of 0 or 1 (section 10.10).
8. Have clinical laboratory values meeting the following criteria during the Screening Phase (retesting is allowed but the below criteria must be met in the latest test prior to randomization):

   - Hemoglobin ≥8 g/dL (without prior red blood cell transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted).
   - Absolute neutrophil count ≥1×109/L (without recombinant human granulocyte colony-stimulating factor within 7 days and without pegylated granulocyte colony-stimulating factor within 14 days of the laboratory test).
   - Platelet count ≥75×109/L (without prior platelet transfusion within 7 days before the laboratory test) in subjects in whom <50% of bone marrow nucleated cells are plasma cells; platelet count ≥50×109/L (without prior platelet transfusion within 7 days before the laboratory test) in subjects in whom ≥50% of bone marrow nucleated cells are plasma cells.
   - Lymphocyte count ≥0.3×109/L.
   - Aspartate aminotransferase ≤3×upper limit of normal (ULN).
   - Alanine aminotransferase ≤3×ULN.
   - Total bilirubin 2.0×ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5×ULN is required).
   - Estimated glomerular filtration rate 40 mL/min per 1.73 m^2 (to be calculated using the Modification of Diet in Renal Disease formula, (section 10.11).

9. Women of childbearing potential must have two negative pregnancy tests prior to starting pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd). The first, 10 to 14 days prior to the start of PVd or DPd and prior to randomization. The second pregnancy test will need to be done within 24 hours prior to the start of PVd or DPd. The investigator must verify that the results of these tests are negative prior to starting PVd or DPd. See section 10.12 for definition of females who are not of reproductive potential.
10. When a woman is of childbearing potential, the subject must commit either to abstaining continuously from heterosexual intercourse or agree to use two methods of reliable birth control simultaneously. One of them a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly; see examples below) and one other effective method (i.e., male latex or synthetic condom, diaphragm, or cervical cap) and agree to remain on both methods from the time of signing the informed consent form (ICF) until at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of

pomalidomide, whichever is later (Arm A), or at least 1 year after receiving a cilta-cel infusion, or at least 3 months after receiving the last dose of daratumumab or bortezomib, or 28 days after the last dose of pomalidomide, whichever is later (Arm B) (section 10.12). Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Examples of highly effective contraceptives include:

- User-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner (vasectomy must be confirmed by two negative semen analyses).
- User-dependent method: progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable). Estrogen-containing hormonal contraception is contraindicated due to increased risk of thromboembolic events with pomalidomide. Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Refer to section 10.12 for further information.
- Women of childbearing potential must follow the contraception criteria outlined in the local pomalidomide pregnancy prevention program.

11. A man must commit either to abstaining continuously from heterosexual sexual intercourse or a man:

    - Who is sexually active with a woman of childbearing potential or a pregnant woman must agree to use a barrier method of contraception (e.g., latex or synthetic condom with spermicidal foam/gel/film/cream/suppository) from the time of signing the ICF until at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least 1 year after receiving a cilta-cel infusion or at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm B), even if they have undergone a successful vasectomy;
    - Should agree to practice contraception according to and for the time frame specified in the local pomalidomide pregnancy prevention program.

12. Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for at least 3 months after receiving the last dose of daratumumab or bortezomib, or 28 days after the last dose of pomalidomide, whichever is later (Arm A), or at least 1 year after receiving a cilta-cel infusion, or at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm B).
13. Must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.
14. Willing and able to adhere to the lifestyle restrictions specified in this protocol (section 5.3).

Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study. The subject will be excluded if he or she has or had:

1. Prior treatment with chimeric antigen receptor engineered T cell (CAR T) therapy directed at any target.
2. Any previous therapy that is targeted to B-cell maturation antigen (BCMA).
3. Ongoing toxicity from previous anticancer therapy that has not resolved to baseline levels or to Grade 1 or less, except for alopecia.
4. Subjects with Grade 1 peripheral neuropathy with pain or Grade 2 or higher peripheral neuropathy will not be permitted to receive PVd as standard therapy or bridging therapy; however, subject may receive DPd as standard therapy or bridging therapy.
5. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to randomization (section 10.13).
6. Criterion modified per Amendment 2.
   6.1. Was vaccinated with live attenuated vaccines within 6 weeks prior to randomization.
7. Subject received any antitumor therapy as follows, prior to randomization:
   - Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used an invasive investigational medical device within 14 days or at least five half-lives, whichever is less.
   - Investigational vaccine within 4 weeks.
   - Monoclonal antibody treatment within 21 days.
   - Cytotoxic therapy within 14 days.
   - PI therapy within 14 days.
   - Immunomodulatory agent therapy within 7 days.
   - Radiotherapy within 14 days. However, if the radiation is given for palliative purposes and the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy. Radiotherapy within 14 days on measurable extramedullary plasmacytoma(s) is not permitted even in the setting of palliation for symptomatic management**.**
8. Active malignancies (i.e., progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:
   - Nonmuscle invasive bladder cancer treated within the last 24 months that is considered completely cured.
   - Skin cancer (nonmelanoma or melanoma) treated within the last 24 months that is considered completely cured.
   - Noninvasive cervical cancer treated within the last 24 months that is considered completely cured.
   - Localized prostate cancer (N0M0):
     - With a Gleason score of ≤6, treated within the last 24 months or untreated and under surveillance,
     - With a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
   - History of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.

- Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
- Malignancy that is considered cured with minimal risk of recurrence.

9. Plasma cell leukemia at the time of screening, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary amyloidosis.
10. Criterion modified in Amendment 1.
    10.1. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to cilta-cel or its excipients, including dimethyl sulfoxide (refer to Investigator's Brochure), or to fludarabine, cyclophosphamide, tocilizumab, pomalidomide, dexamethasone.

    - Subjects with contraindications or life-threatening allergies, hypersensitivity, or intolerance to daratumumab will not be permitted to receive DPd as standard therapy or bridging therapy; however, subjects may receive PVd as standard therapy or bridging therapy. Likewise, subjects with contraindications or life-threatening allergies, hypersensitivity, or intolerance to bortezomib will not be permitted to receive PVd as standard therapy or bridging therapy; but may receive DPd as standard therapy or bridging therapy**.**

11. Pregnant or breast-feeding or planning to become pregnant while enrolled in this study or within 3 months of receiving the last dose of daratumumab or bortezomib, or within 28 days after the last dose of pomalidomide, whichever is later (Arm A), or at least within 1 year after receiving cilta-cel infusion, or at least within 3 months after receiving the last dose of daratumumab or bortezomib, or within 28 days after the last dose of pomalidomide, whichever is later (Arm B).
12. Plans to father a child while enrolled in this study or within 3 months of receiving the last dose daratumumab or bortezomib, or within 28 days after the last dose of pomalidomide, whichever is later (Arm A), or at least within 1 year after receiving cilta-cel infusion, or at least within 3 months after receiving the last dose of daratumumab or bortezomib, or within 28 days after the last dose of pomalidomide, whichever is later (Arm B).
13. Stroke or seizure within 6 months of signing ICF.
14. Received either of the following:

    - An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must have stopped all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease. Subjects with active graft-versus-host disease are excluded.
    - An autologous stem cell transplantation ≤12 weeks before apheresis.

15. Known active, or prior history of central nervous system involvement or exhibits clinical signs of meningeal involvement of MM.
16. Subject with chronic obstructive pulmonary disease with a forced expiratory volume in 1 second <50% of predicted normal will not be able to receive DPd as standard therapy or bridging therapy; however, subject may receive PVd as standard therapy or bridging therapy. Note that forced expiratory volume in 1 second testing is required for subjects who are planned to receive treatment with DPd and are suspected of having chronic obstructive pulmonary disease.

17. Criterion revised per Amendment 1.
    17.1. Any of the following:
    a) Seropositive for HIV
    b) Hepatitis B infection: In the event the infection status is unclear, quantitative viral levels are necessary to determine the infection status. Subjects who are anti-hepatitis B surface antibody positive and without history of vaccination or for subjects who are anti-hepatitis B core antibody positive with or without positive anti-hepatitis B surface antibody should have hepatitis B virus-DNA quantification test done. Please consult section 10.6 for further details.
    c) Hepatitis C infection (defined as anti-hepatitis C virus antibody positive or hepatitis C virus-RNA positive) or known to have a history of hepatitis C. For subjects with known history of hepatitis C virus infection, confirmation of sustained virologic response is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.
18. Criterion revised per Amendment 1.
    18.1. Criterion modified per Amendment 2.
    18.2. Serious underlying medical or psychiatric condition or disease, that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study, such as:

- Requirement of supplemental oxygen to maintain oxygen saturation.
- Evidence of serious active viral or bacterial infection, requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection.
- Active autoimmune disease.
- Clinical evidence of dementia or altered mental status.
- Any history of Parkinson's disease or other neurodegenerative disorder
- Clinically significant cardiac disease, such as:
- New York Heart Association Class III or IV congestive heart failure (see section 10.14).
- Myocardial infarction or coronary-artery-bypass graft 6 months prior to enrollment.
- History of clinically significant ventricular arrhythmia or unexplained
- Syncope, not believed to be vasovagal in nature or due to dehydration.
- History of severe non-ischemic cardiomyopathy.
- Impaired cardiac function (left ventricle ejection fraction <45%) as assessed by echocardiogram or multiple-gated acquisition scan performed ≤8 weeks before randomization.

19. Major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has major surgery planned during the time the subject is expected to participate in the study.

Note: Kyphoplasty or vertebroplasty are not considered major surgery. If there is a question about whether a procedure is considered a major surgery, the investigator must consult with the Applicant and resolve any issues before enrolling a subject in the study.

20. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and before randomization. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before randomization such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

Section 5.4 (Screen Failures) describes options for retesting. The required source documentation to support meeting the enrollment criteria is noted in section 10.3—Regulatory, Ethical, and Study Oversight Considerations.

8.4. FDA Grouped Terms

Table 21: FDA Grouped Terms Used for FDA Analyses of Adverse Events

FDA Grouped Term	AEDECOD/Preferred Terms
Bacterial infection	Abscess limb, cellulitis, cholecystitis, cholecystitis active, clostridium difficile infection, clostridium difficile colitis, clostridium difficile infection, enterocolitis bacterial, klebsiella infection, osteomyelitis, perirectal abscess, soft tissue infection, staphylococcal infection, and tooth infection, Superinfection bacterial, clostridial infection
Dizziness	Dizziness, dizziness exertional, dizziness postural, presyncope, syncope, vertigo
Diarrhea	Colitis, diarrhoea
Dyspnea	Acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure, tachypnoea
Encephalopathy	Amnesia, bradyphrenia, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, immune effector cell-associated neurotoxicity syndrome, lethargy, memory impairment, mental impairment, mental status changes, noninfective encephalitis, somnolence
Fatigue	Asthenia, fatigue, malaise
Hemorrhage	Conjunctival haemorrhage, contusion, ecchymosis, epistaxis, eye contusion, haemorrhage intracranial, haematochezia, haemoptysis, Lower gastrointestinal haemorrhage infusion site haematoma, oral contusion, petechiae, post procedural haemorrhage, retinal haemorrhage, Retroperitoneal haemorrhage, subdural haematoma, subarachnoid haemorrhage, hematemesis, haematoma, hematuria.
Hypotension	Hypotension, orthostatic hypotension
Musculoskeletal pain	Arthralgia, back pain, bone pain, joint pain, flank pain, muscle strain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, noncardiac chest pain, pain in extremity, pain in jaw, pelvic pain, spinal pain, sacral pain
Neuropathy	Burning sensation, hypoaesthesia, neuralgia, peripheral motor neuropathy, peripheral sensory neuropathy, paraesthesia, Polyneuropathy, sciatica
Parkinsonism	Affect lability, apathy, ataxia, balance disorder, bradykinesia, bradyphrenia, cognitive disorder, confusional state, coordination abnormal, depressed level of consciousness dysgraphia, disturbance in attention, dysmetria, extrapyramidal disorder, flat affect, gait disturbance, head titubation, memory impairment, mental disorder, micrographia, myoclonus, parkinsonism, personality change, psychomotor retardation, reduced facial expression, tremor

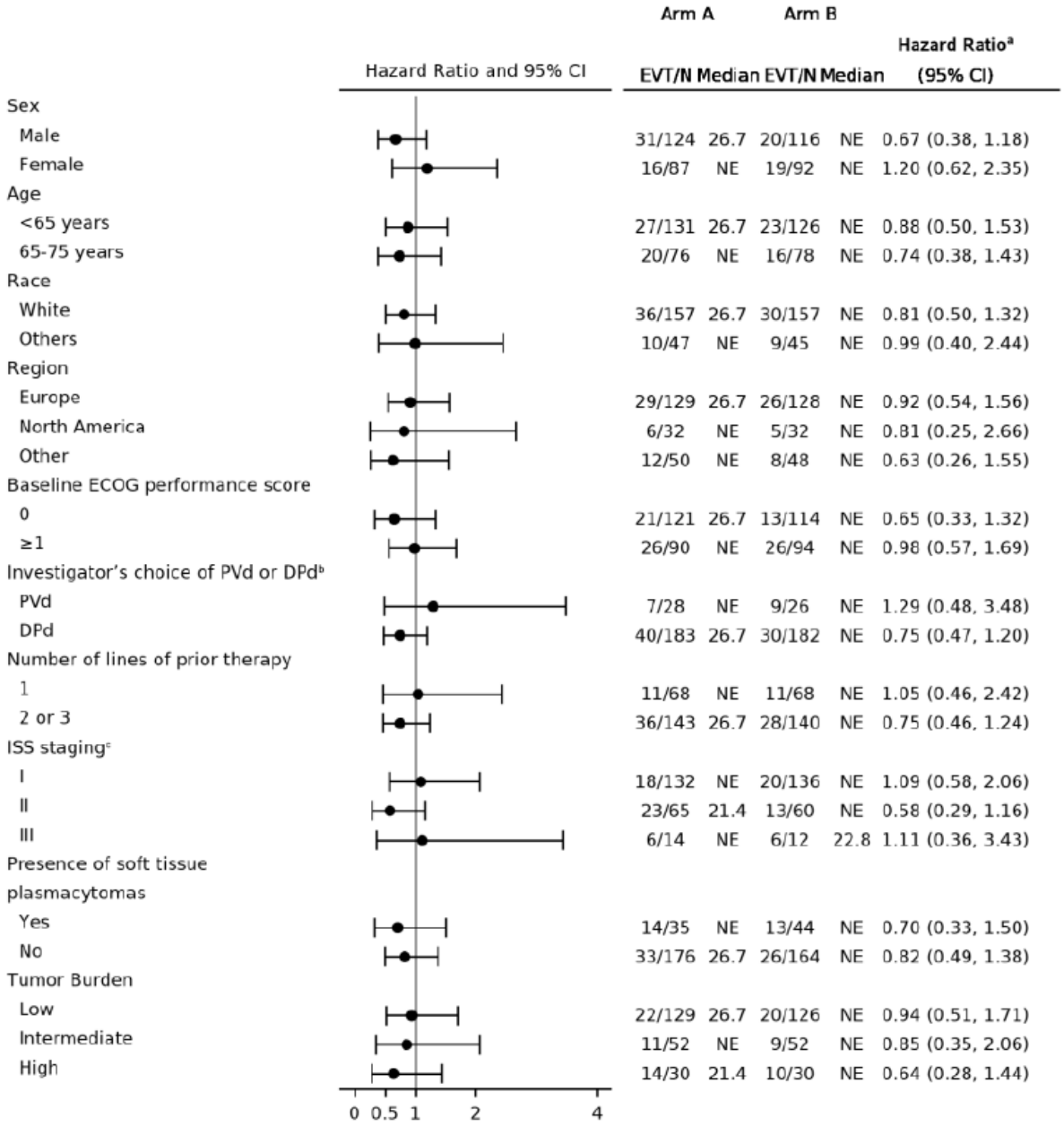
FDA Grouped Term	AEDECOD/Preferred Terms
Pneumonia	Atypical pneumonia, COVID-19 pneumoniae, lung abscess, lung opacity, metapneumovirus pneumonia, pneumocystis jirovecii pneumonia, pneumonia aspiration, pneumonia moraxella, pneumonia pseudomonal, pneumonia streptococcal
Viral infection	Adenovirus infection, coronavirus infection, cytomegalovirus infection, enterovirus infection, herpes simplex, herpes simplex hepatitis, herpes simplex reactivation, herpes simplex reactivation, herpes virus infection, herpes zoster, herpes zoster disseminated, human herpesvirus 6 infection, influenza, influenza like illness, meningitis viral, metapneumovirus infection, oral herpes, parainfluenzae virus infection, parvovirus B19 infection, parvovirus infection, Respiratory syncytial virus infection, Respiratory tract infection viral, rhinovirus infection, rotavirus infection

Source: FDA
Abbreviations: ADECOD, adverse event dictionary-derived term; COVID-19, Coronavirus Disease 2019

8.5. Forest Plot for OS

Figure 15 below shows the forest plot for OS in major subgroups conducted by the Applicant. Notably, there are limitations of their forest plot: 1) the HR estimate within each subgroup was calculated based on an unstratified log-rank test ignoring all the stratification factors; and 2) the HR reported within each subgroup was the average HR which is unreliable in the setting of non-proportional hazards.

Figure 15: Overall Survival in Major Subgroups by the Applicant



Source: Modified from clinical study report: CARTITUDE-4, page 332

Abbreviations: CI, confidence interval; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG, Eastern Cooperative Oncology Group; EVT, Event; ISS, International Staging System; NE, not evaluable; PVd, pomalidomide, bortezomib, and dexamethasone