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Division / Office	DCGT/OTAT
Committee Chair	Zhaohui Ye
Clinical Reviewer(s)	Kavita Natrajan (Safety) Megha Kaushal (Efficacy)
Project Manager	Nadia Whitt, Rachel Blasdell
Priority Review	Yes
Reviewer Name(s)	Tianjiao Dai
Review Completion Date / Stamped Date	October 25, 2021
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Lead, FDA/CBER/OBE/DB/TEB
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBE/DB/TEB
	John Scott, Ph.D. Director, FDA/CBER/OBE/DB
Applicant	Janssen Biotech, Inc.
Established Name	ciltacabtagene autoleucel
(Proposed) Trade Name	CARVYKTI™
Pharmacologic Class	B cell maturation antigen (BCMA)-directed genetically modified autologous T-cell
Formulation(s), including Adjuvants, etc.	A single dose of CARVYKTI contains a cell suspension of 0.5-1.0×10 ⁶ CAR-positive viable T- cells per kg body weight up to a maximum of 1×10 ⁸ CAR-positive viable T-cells suspended in either a 30 mL or 70 mL patient-specific infusion bag
Dosage Form(s) and Route(s) of Administration	cell suspension for infusion.
Dosing Regimen	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
Proposed Indication(s) and Intended Population(s)	Treatment of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody.

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Glossary

Abbreviation	Definition
ADA	Anti-drug (cilta-cel) antibodies
ALL	Acute lymphocytic leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
CAR-T	Chimeric antigen receptor T (cells)
CBR	Clinical benefit rate
CI	Confidence interval
CR	Complete response
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CV	Coefficient of variation
DOR	Duration of response
DLT	Dose limiting toxicities
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FDA	Food and Drug Administration
FL	Follicular lymphoma
HGL	High-grade lymphoma
IND	Investigational new drug
ICANS	Immune effector cell-associated neurotoxicity syndrome
iNHL	Indolent non-Hodgkin lymphoma
KM	Kaplan-Meier
MZL	Marginal zone lymphoma
MRD	Minimal residual disease
NE	Not evaluable
NHL	Non-Hodgkin lymphoma
NR	Not reached
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
R/R	Relapsed or refractory
SAE	Serious adverse event
SD	Stable Disease
STD	Standard deviation
US	United States

1. EXECUTIVE SUMMARY

Ciltacabtagene autoleucel (cilta-cel, JNJ-68284528) is a chimeric antigen receptor T-cell (CAR-T) therapy that targets B-cell maturation antigen (BCMA). The purpose of this biological license application (BLA) was to apply the product to the indication of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 antibody.

The primary source of evidence to support this BLA is the Phase 1b/2 single-arm, open-label, multicenter study 68284528MMY2001/ CARTITUDE-1 (hereafter referred to as MMY2001). In this cohort, a total of 113 subjects underwent apheresis. Of these 113 subjects, 97 received cilta-cel using a data cutoff date of February 11, 2021. The results for these 97 treated subjects constitute the primary evidence of efficacy and safety for the product's indication. The pre-specified primary efficacy endpoint was overall response rate (ORR), defined as the incidence of partial response (PR) or better according to the IMWG response criteria, as assessed by Independent Review Committee (IRC). Efficacy results summarized in this memo are based on a data cut-off date of February 11, 2021; safety results are based on a data cut-off date of September 01, 2020.

The ORR was 97.9% (95% exact confidence interval [CI]: 92.7% to 99.7%) and the lower limit of the 95% confidence interval was well above the pre-specified null hypothesis rate of 30%. Among the 95 subjects with overall response, the median duration of response (DOR) was 21.8 months. Among all treated subjects, the median PFS was 22.8 months. The median overall survival (OS) was not reached. The median duration of follow-up is 18.0 months for all treated subjects.

Deaths occurred in 14 of 97 treated subjects (14.4%). Serious fatal treatment emergent adverse events (TEAEs) were reported in 53 subjects (54.6%). The most common adverse event of special interest (AESI) was cytokine release syndrome (CRS), which occurred in 92 treated subjects (94.8%).

The statistical analysis results for this BLA provide substantial evidence of effectiveness to support the approval of cilta-cel for the applicant's proposed indication of adult patients with relapsed or refractory multiple myeloma.

2. CLINICAL AND REGULATORY BACKGROUND

The applicant requested rolling submission (request dated November 16, 2020) in three units. The first unit submission of this BLA was submitted on December 18, 2020, the second unit was submitted on February 02, 2021 and the last unit was submitted on March 31, 2021. The initial clinical study report was based on a data cut-off date of September 1, 2020. The updated efficacy data and analysis results for Study 68284528MMY2001 (Study MMY2001), with a data cutoff date of February 11, 2021, was submitted on April 30, 2021. This provides a median efficacy follow-up of

approximately 18-months, per agreement between FDA and the applicant on December 8, 2020 Type B Pre-BLA meeting.

2.1 Disease or Health-Related Condition(s) Studied

Multiple myeloma is a malignant disorder of the plasma cells characterized by uncontrolled and progressive proliferation of a plasma cell clone. It accounts for approximately 10% of hematological malignancies[1, 2]. The proliferation of the malignant clonal plasma cells leads to subsequent replacement of normal bone marrow hematopoietic precursors and overproduction of monoclonal paraproteins (M-proteins). Characteristic hallmarks of multiple myeloma include osteolytic lesions, anemia, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurological complications [3]. Profound intra-tumoral heterogeneity is observed throughout the disease course but is especially problematic after multiple lines of treatment. The coexistence of different tumor subclones displaying different drug sensitivities contributes to both progression of disease and development of drug resistance[4].

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), histone deacetylase inhibitors (panobinostat), immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), and monoclonal antibodies (daratumumab [anti-CD38] and elotuzumab [anti-CS1/SLAMF7]) have provided many therapeutic avenues for patients with multiple myeloma. A newer class of medications including XPO1 inhibitors (selinexor) and antibody drug conjugates targeting BCMA (belantamab mafodotin-blmf) have been approved by the FDA recently.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1 summarizes the major pre- and post-submission regulatory activities associated with this BLA.

Table 1. Summary of major regulatory activities

Date	Milestone
12/08/2020	Meeting for the BLA submission plans; request of rolling review
12/31/2020	Unit 1 submission of the BLA
03/31/2021	Original BLA submission complete (all three units are submitted)
04/21/2021	First Committee Meeting
04/30/2021	Efficacy data update
05/25/2021	Filing letter issued to the Applicant
07/29/2021	Mid-cycle meeting with Applicant
09/14/2021	Late-cycle meeting with Applicant
11/29/2021	PDUFA action due date

(Source: FDA statistical reviewer's summary)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the product for the indication comes from Study MMY2001, which is the focus of this review memo. The review of the efficacy is based on the data with a cutoff date 02/11/2021. The safety results are based on a cutoff date of 09/01/2020.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical memo is the review on clinical study reports (and efficacy update) and datasets submitted in modules 2 and 5 (and efficacy data update) of the BLA supplement.

5.3 Table of Studies/Clinical Trials

In addition to Study MMY2001, supportive safety data of cilta-cel in subjects with relapsed or refractory (R/R) multiple myeloma were also analyzed from Japan cohort of Study MMY2001 and Study 68284528MMY2003. Table 2 summarizes the 3 studies included in the BLA submission. Results from Study MMY2001 formed the primary evidence of safety and efficacy of cilta-cel for this BLA. The efficacy data cutoff is February 11, 2021.

Table 2. Studies in the BLA application

Study code	Study population	Study design	# of subjects treated
68284528MMY2001 (pivotal)	Adult R/R multiple myeloma	Phase 1b/2, open-label, single-arm, multicenter	97
68284528MMY2001-Japan Cohort	Adult R/R multiple myeloma	Phase 2, open-label, single-arm, multicenter	9
68284528MMY2003	Adult R/R multiple myeloma	Multicohort, open-label, multicenter study	18

(Source: Clinical Overview, Synopses of individual studies in module 2; FDA statistical reviewer's summary)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study MMY2001

Study MMY2001 was a Phase 1b/2 single-arm, open-label, multicenter study that constitutes the primary evidence of safety and efficacy of cilta-cel (JNJ-68284528) in the new indication of subjects with heavily pre-treated relapsed or refractory multiple myeloma who have exhausted other effective treatment options.

6.1.1 Objectives

Primary objective of the Phase 2 portion was to evaluate the efficacy of JNJ-68284528, as measured by ORR, in subjects with advanced relapsed or refractory multiple myeloma.

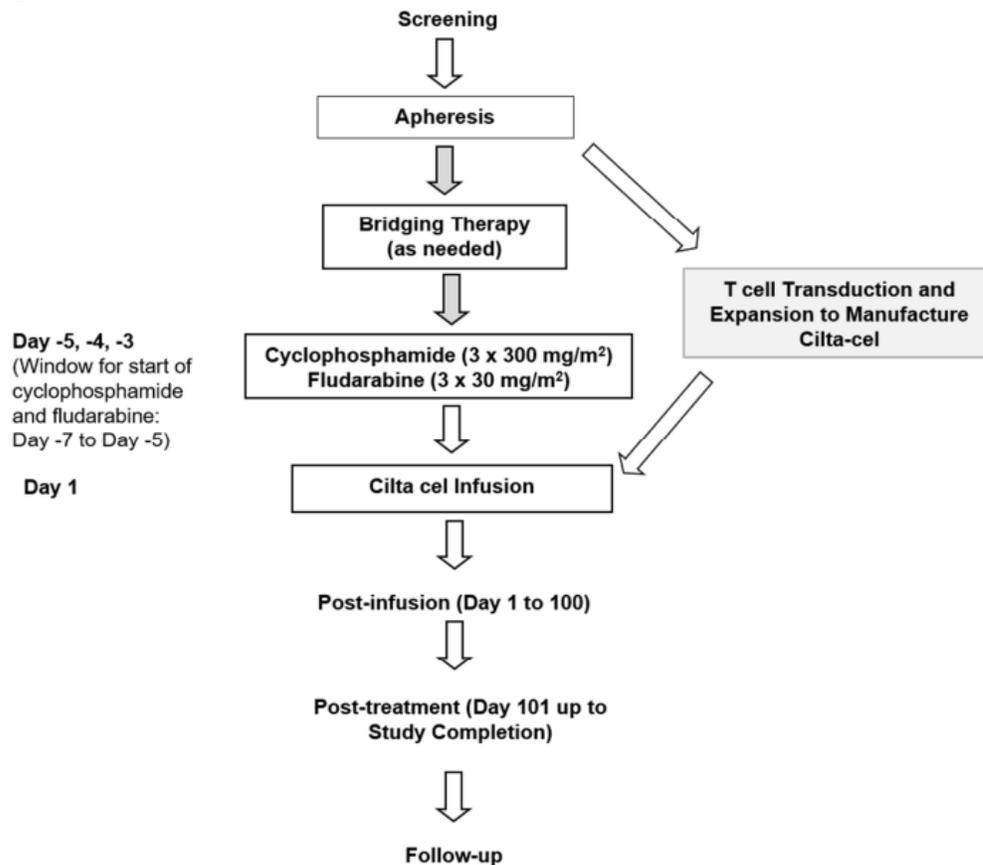
Key secondary objectives were to characterize the pharmacokinetics, pharmacodynamics and safety profile, and determine VGPR or better rate, MRD negativity rate, CBR, DOR, TTR, PFS, OS.

6.1.2 Design Overview

Study MMY2001 was a Phase 1b-2, single arm, open-label, multicenter study to evaluate the safety and efficacy of JNJ-68284528 in adult subjects with relapsed or refractory multiple myeloma.

At least 24 and up to approximately 50 subjects were planned to be enrolled in the Phase 1b portion and an approximately 60 subjects in the Phase 2 portion of the study. Enrolled subjects were treated with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 0.75×10^6 CAR-positive viable T cells/kg. Figure 1 below gives the overview of study flow chart.

Figure 1. Study flow chart



(Source: BLA 125746/0 Module 5 Clinical study report Figure 1, p.27)

6.1.3 Population

Key elements of eligibility criteria for Study MMY2001 are listed below:

- ≥ 18 years of age with a documented diagnosis of multiple myeloma according to IMWG diagnostic criteria, and have an ECOG Performance Status score of 0 or 1.
- Measurable disease at screening as defined by any of the following: Serum M-protein level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours; or light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥ 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.
- Received at least 3 prior lines of therapy or were double refractory to a PI and an IMiD (induction with or without hematopoietic stem cell transplant and with or without maintenance therapy was considered a single regimen), subjects were to have undergone at least 1 complete cycle of treatment for each regimen (unless progressive disease [PD] was the best response).
- Received a PI, an IMiD, and anti-CD38 antibody (prior exposure could have been from different monotherapy or combination regimens).

- Documented disease progression during, or within 12 months, of the most recent anti-myeloma therapy.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Cilta-cel was administered as a single infusion with a total targeted dose of 0.75×10^6 CAR-positive viable T cells/kg (range: $0.5-1.0 \times 10^6$ CAR-positive viable T cells/kg) five to 7 days after the start of a conditioning regimen of intravenous (IV) cyclophosphamide 300 mg/m² and fludarabine 30 mg/m² in 3 daily doses.

6.1.6 Sites and Centers

Seventeen (17) study sites in US.

6.1.7 Surveillance/Monitoring

A Safety Evaluation Team (SET) was established to ensure safety monitoring. An Independent Review Committee (IRC) assessed response status according to International Myeloma Working Group (IMWG) criteria for the primary efficacy analysis.

6.1.8 Endpoints and Criteria for Study Success

In Study MMY2001, the primary endpoint is ORR, defined as the proportion of subjects who achieve a partial response (PR) or better according to the IMWG response criteria, as assessed by IRC, where the responders are defined as subjects with a PR or better response.

The study protocol also included the following secondary efficacy endpoints:

- a. Very good partial response (VGPR) or better rate defined as the proportion of subjects who achieve a VGPR or better response according to the IMWG criteria
- b. Duration of response (DOR), defined as the time from first response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria.
- c. Minimum residual disease (MRD) negativity rate
- d. Clinical benefit rate (CBR; $CBR = ORR (sCR + CR + VGPR + PR) + MR$ (minimal response))
- e. Time to response (TTR), defined as the time between date of the initial infusion of JNJ-68284528 and the first efficacy evaluation that the subject has met all criteria for PR or better.
- f. Progression-free survival (PFS), the time from the date of the initial infusion of JNJ-68284528 to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurs first.
- g. Overall survival (OS), defined as the time from the date of the initial infusion of JNJ-68284528 to the date of the subject's death.

Among the secondary endpoints above, the major secondary endpoints are VGPR or better rate, DOR, MRD negativity rate, TTR, PFS and OS.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical hypothesis:

H_0 : $ORR \leq 30\%$ vs. H_a : $ORR > 30\%$.

The threshold of 30% in the hypothesis is established based on a reference overall response rate of 30% based on results of daratumumab monotherapy in r/r MM. This threshold was agreed to by clinical review team (clinical review memo for IND 18080/0 dated 25-MAY-2018)

Analysis populations:

- *Modified Intent-To-Treat (mITT) Analysis Set*: This set consists of subjects who received a JNJ-68284528 infusion at the targeted dose [0.75×10^6 CAR-positive viable T cells/kg (range: $0.5-1.0 \times 10^6$ CAR-positive viable T cells/kg)] and will be considered as the primary analysis set for all efficacy summaries.
- *All Treated Analysis Set*: This set consists of subjects who received JNJ-68284528 infusion and will be considered as the primary analysis set for safety summaries.
Note: The mITT population is the same set as *All Treated Analysis Set*, since all subjects treated received the targeted dose.
- *Pharmacokinetic Analysis Set*: This set consists of all subjects who received JNJ-68284528 infusion and have at least 1 post-dose pharmacokinetic sample.
- *Immunogenicity Analysis Set*: This set consists of all subjects who received JNJ-68284528 infusion and have at least 1 post-dose immunogenicity sample.

Statistical methods:

Efficacy analyses were conducted on the mITT population. For efficacy, assessment by the IRC will be used as primary.

Primary endpoint

The primary efficacy endpoint, ORR, was calculated along with the 2-sided 95% exact Clopper-Pearson confidence interval (CI). The p-value from a 1-sided exact binomial test with significant level of 0.025 for the null hypothesis of $ORR \leq 30\%$ was to be provided.

Secondary endpoints

- a. VGPR or better rate: the rate and its 2-sided 95% Clopper-Pearson exact CI were estimated.
- b. DOR: The Kaplan-Meier (KM) method was used to estimate the median DOR along with the 95% CI. The reverse KM method was used to estimate the median follow-up time for DOR with the 95% CI.
- c. MRD (Minimum residual disease) negativity rate: the rate and its 2-sided 95% Clopper-Pearson exact CI were estimated.
- d. TTR (Time to Response): summary statistics of time to first response (PR or better), best response and CR or better were calculated.
- e. PFS: The analysis of PFS was conducted similarly to the analysis of DOR.

- f. OS: The OS analysis included all available survival information with long-term follow-up data. Data from surviving subjects were censored at the last time that the subject was known to be alive. The distribution function of OS would be estimated using KM method and the median OS along with 95% CI would be presented.

Interim analyses:

None.

Sample size and power calculation:

With 60 subjects treated with cilta-cel in the Phase 2 portion of the study, the study achieves 90% power to test the null hypothesis that the ORR is 30% vs. the alternative hypothesis that the ORR is 50% at a 1-sided alpha level of 0.025.

Sensitivity analyses:

Sensitivity analyses of the primary efficacy endpoints ORR were performed based on mITT set using:

- disease response assessed by the computerized algorithm
- investigator assessment according to the IMWG response criteria
- only subjects receiving study drug which met all pre-specified release criteria.

Subgroup analyses:

- In the inferential analysis set, subgroup analyses were performed on the following baseline characteristics: Age: < 65, 65-75 and \geq 65 years at the time of the first infusion
- Sex: male vs. female
- Race: White, African American and other races
- Total CAR-T positive cells infused: < median value
- Baseline ECOG performance score: 0, 1 or 2
- Baseline ISS staging: I, II or III
- Lines of prior therapy: \leq 4 lines or > 4 lines
- Prior autologous stem cell transplant: Yes or No
- Prior allogenic stem cell transplant: Yes or No
- Type of myeloma: IgG or Non-IgG
- Penta-exposed: Yes or No
- Refractory status: PI+IMiD, PI+IMiD+anti-CD38 antibody, at least 2 PIs + at least 2 IMiDs + 1, anti-CD38 antibody, Carfilzomib, Pomalidomide, Daratumumab or Last line of prior therapy
- Cytogenetic risk groups: high risk or standard risk
- Baseline bone marrow plasma cells: \leq 30, > 30 to < 60 and \geq 60
- Baseline BCMA expression: \geq median value
- Study site

Missing data:

All subjects who did not meet the criteria for an objective response by the analysis cut-off date were considered as non-responders. For assessment of DOR, PFS and OS, loss to follow-up subjects would be censored at the date of the last evaluable disease assessment prior to the data cutoff date or new anti-cancer therapy start date, whichever was earlier.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

For analyses of efficacy and safety in Study MMY2001, Table 3 summarizes the sizes of study analysis sets. There were 113 total enrolled subjects. Of those subjects, the 97 (85.8%) subjects who received the product constituted the primary efficacy and safety analysis set. This is also the modified intent-to-treat (mITT) set.

Table 3. Analysis sets

Analysis Set	Phase 1b	Phase 2	Phase 1b + Phase 2, N (%)
All Enrolled (=ITT)	35	78	113
All Treated (=mITT)	29	68	97 (85.8%)

(Source: reviewer's summary)

6.1.10.1.1 Demographics

Table 4 shows the demographic information for phase 1b and phase 2 and combined respectively in the *All Treated* (mITT) subset.

Table 4. Demographics for All Treated analysis sets

	Phase 1b	Phase 2	Phase 1b + Phase 2, N (%)
N	29	68	97
Age (years)			
<65	21 (72.4%)	41 (60.3%)	62 (63.9%)
65-75	8 (27.6%)	19 (27.9%)	27 (27.8%)
>75	0	8 (11.8%)	(8.2%)
Mean (STD)	60.9 (6.42)	62.5 (9.09)	62.0 (8.38)
Median (min, max)	60 (50, 75)	62 (43, 78)	61 (43, 78)
Sex n (%)			
Female	15 (51.7%)	25 (36.8%)	40 (41.2%)
Male	14 (48.3%)	43 (63.2%)	57 (58.8%)
Race n (%)			
American Indian or Alaska native	1 (3.4%)	0	1 (1.0%)
Asian	1 (3.4%)	0	1 (1.0%)
Black or African American	5 (17.2%)	12 (17.6%)	17 (17.5%)
Native Hawaiian or Other Pacific Islander	0	1	1
White	20 (69.0%)	49 (72.1%)	69 (71.1%)
Multiple	0	0	0

	Phase 1b	Phase 2	Phase 1b + Phase 2, N (%)
Not reported	2 (6.9%)	6 (8.8%)	8 (8.2%)
Ethnicity n (%)			
Hispanic or Latino	2 (6.9%)	4 (5.9%)	6 (6.2%)
Not Hispanic or Latino	25 (86.2%)	60 (88.2%)	85 (88.7%)
Not reported	2 (6.9%)	4 (5.9%)	6 (6.2%)

(Source: Table 6 in section 4.2.1 of CSR)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 5 shows the baseline characteristics for subjects in All Treated analysis set. There were no outstanding differences in the rates among phase 1b and phase 2, as well as Phase 1b and Phase 2 combined with respect to subject baseline characteristics.

Table 5. Baseline characteristics for All Treated analysis sets

	Phase 1b	Phase 2	Phase 1b + Phase 2
All Treated (N)	29	68	97
Type of myeloma by immunofixation, n (%)			
N	29	68	97
IgG	16 (55.2%)	41 (60.3%)	57 (58.8%)
IgA	2 (6.9%)	6 (8.8%)	8 (8.2%)
IgM	1 (3.4%)	1 (1.5%)	2 (2.1%)
IgD	1 (3.4%)	1 (1.5%)	2 (2.1%)
IgE	0	0	0
Light chain	8 (27.6%)	16 (23.5%)	24 (24.7%)
Biclonal	1 (3.4%)	3 (4.4%)	4 (4.1%)
Negative immunofixation	0	0	0
Type of measurable disease, n (%)			
N	29	68	97
Serum only	14 (48.3%)	35 (51.5%)	49 (50.5%)
Serum and urine	2 (6.9%)	4 (5.9%)	6 (6.2%)
Urine only	2 (6.9%)	9 (13.2%)	11 (11.3%)
Serum FLC only	11 (37.9%)	19 (27.9%)	30 (30.9%)
Not evaluable	0	1 (1.5%)	1 (1.0%)
ISS staging at study baseline, n (%)			
N	29	68	97
I	20 (69.0%)	41 (60.3%)	61 (62.9%)
II	9 (31.0%)	13 (19.1%)	22 (22.7%)
III	0	14 (20.6%)	14 (14.4%)
Time since initial MM diagnosis to enrollment, years			
N	29	68	97
Mean (SD)	6.16 (3.525)	7.11(3.644)	6.82 (3.617)
Median	5.05	6.65	5.94
Range	(1.6, 16.3)	(1.6, 18.2)	(1.6; 18.2)
Number of lytic bone lesions			
N	29	68	97
None	12 (41.4%)	16 (23.5%)	28 (28.9%)
1-3	5 (17.2%)	13 (19.1%)	18 (18.6%)
4-10	4 (13.8%)	11 (16.2%)	15 (15.5%)
More than 10	8 (27.6%)	28 (41.2%)	36 (37.1%)
Presence of extramedullary plasmacytomas, n (%)			

	Phase 1b	Phase 2	Phase 1b + Phase 2
N	29	68	97
Yes	4 (13.8%)	9 (13.2%)	13 (13.4%)
No	25 (86.2%)	59 (86.8%)	84 (86.6%)
Presence of evaluable bone marrow assessment			
N	29	68	97
Yes	29 (100%)	67 (98.5%)	96 (99.0%)
No	0	1 (1.5%)	1 (1.0%)
% Plasma cells, bone marrow biopsy/aspirate			
N	29	67	96
≤ 30	17 (58.6%)	41 (61.2%)	58 (60.4%)
>30~ <60	5 (17.2%)	12 (17.9%)	17 (17.7%)
≥ 60	7 (24.1%)	14 (20.9%)	21 (21.9%)
% Plasma cells, bone marrow biopsy			
N	24	59	83
≤ 30	14 (58.3%)	36 (61.0%)	50 (60.2%)
>30~ <60	3 (12.5%)	12 (20.3%)	15 (18.1%)
≥ 60	7 (29.2%)	11 (18.6%)	18 (21.7%)
% Plasma cells, bone marrow aspirate			
N	28	62	90
≤ 30	19 (67.9%)	49 (79.0%)	68 (75.6%)
>30~ <60	6 (21.4%)	6 (9.7%)	12 (13.3%)
≥ 60	3 (10.7%)	7 (11.3%)	10 (11.1%)
Bone marrow cellularity by biopsy			
N	24	61	85
Hypercellular	9 (37.5%)	16 (26.2%)	25 (29.4%)
Normocellular	12 (50.0%)	23 (37.7%)	35 (41.3%)
Hypocellular	1 (4.2%)	15 (24.6%)	16 (18.8%)
Indeterminate	2 (8.3%)	7 (11.5%)	9 (10.6%)
Cytogenetic risk at study baseline			
N	29	68	97
Standard risk	22 (75.9%)	46 (67.6%)	68 (70.1%)
High risk	7 (24.1%)	16 (23.5%)	23 (23.7%)
unknown	0	6 (8.8%)	6 (6.2%)
Tumor BCMA expression (%)			
N	20	42	62
Mean (SD)	73.7 (20.3)	77.6 (14.4)	76.3 (16.4)
Median	81.4	79.0	79.9
Range	(19.8; 98.4)	(38.5; 98.4)	(19.8; 98.4)
≥ 50%	18 (90.0%)	39 (92.9%)	57 (91.9%)

FLC = free light chain; ISS = International Staging System; MM = multiple myeloma.

(Source: Table 4 in CSR efficacy Update, section 3.2.1)

6.1.10.1.3 Subject Disposition

At the time of the data cutoff date 02/11/2021, 37 out of the 113 enrolled subjects have died or otherwise discontinued from the study while 76 were still on study in the follow-up portion of the study. Among the 37 subjects who discontinued, the most common reason for discontinuation was death (N =30).

6.1.11 Efficacy Analyses

6.1.11.1 Primary efficacy

Table 6 shows the best response per IRC assessment for subjects in *All Treated Analysis Set*. The primary endpoint ORR (PR or better) as assessed by the IRC is 97.9% (95% CI: 92.7% to 99.7%) for *All Treated Analysis Set* (n=97).

Table 6. Best response Based on Independent Review Committee (IRC) Assessment for All Treated Analysis Set.

	Phase 1b	Phase 2	Phase 1b + Phase 2, N (%)
	29	68	97
ORR (sCR + CR + VGPR + PR), n (%)	29 (100.0%)	66 (97.1%)	95 (97.9%)
95% CI	(88.1%, 100.0%)	(89.8%, 99.6%)	(92.7%, 99.7%)
sCR rate, n (%)	27 (93.1%)	49 (72.1%)	76 (78.4%)
95% CI	(82.2%, 99.9%)	(61.4%, 83.5%)	(71.1%, 87.8%)
CR rate, n (%)	0	0	0
95% CI	(NE, NE)	(NE, NE)	(NE, NE)
MRD-negative CR/sCR rate	16 (55.2%)	26 (38.2%)	42 (43.3%)
95% CI	(35.7%, 73.6%)	(26.7%, 50.8%)	(33.3%, 53.7%)
CBR (overall response + MR)	29 (100.0%)	66 (97.1%)	95 (97.9%)
95% CI	(88.1%, 100.0%)	(89.8%, 99.6%)	(92.7%, 99.7%)
VGPR rate, n (%)	1 (3.4%)	15 (22.1%)	16 (16.5%)
95% CI	(NE, NE)	(11.7%, 32.1%)	(8.1%, 23.0%)
PR rate, n (%)	1 (3.4%)	2 (2.9%)	3 (3.1%)
95% CI	(0.1%, 17.8%)	(0.4%, 10.2%)	(0.6%, 8.8%)
Stable disease, n (%)	0	0	0
Progressive disease, n (%)	0	1 (1.5%)	1 (1.0%)
Not evaluable, n (%)	0	1 (1.5%)	1 (1.0%)

(Source: Table 8, Efficacy Update section 4.2, page 17)

Among the 97 subjects in *All Treated Analysis Set*, 95 subjects (97.9%) achieved response of PR or better based on IRC assessment. The lower limit of the 95% exact Clopper-Pearson confidence interval for ORR was 92.7% which is well above the pre-specified null hypothesis rate of 30%. Among the 95 responders, 76 (78.4%) subjects had a best response of sCR, 16 (16.5%) subjects had a best response of VGPR, and 3 (3.1%) subjects had a best response of PR.

The VGPR and sCR rates in table 6 and 7 are different from that in sponsor's CSR due to the FDA clinical review team's re-evaluation of the response status. Two subjects (Subject (b) (6) and Subj (b) (6)) were downgraded to VGPR from sCR based on this re-evaluation.

Table 7 shows the best response based on IRC for *All Enrolled Analysis Set*. The ORR for this set (n=113) is 84.1% (95% CI: 76.0%, 90.3%)

Table 7. Best response per IRC for *All Enrolled Analysis Set*.

	Phase 1b	Phase 2	Phase 1b + Phase 2, N (%)
	35	78	113
ORR (sCR + CR + VGPR + PR), n (%)	29 (82.9%)	66 (84.6%)	95 (84.1%)
95% CI	(66.4%, 93.4%)	(74.7%, 91.8%)	(76.0%, 90.3%)
sCR rate, n (%)	27 (77.1%)	49 (62.8%)	76 (67.3%)
95% CI	(63.1%, 91.6%)	(52.4%, 74.7%)	(59.6%, 77.4%)
CR rate, n (%)	0	0	0
95% CI	(NE, NE)	(NE, NE)	(NE, NE)
MRD-negative CR/sCR rate	16 (45.7%)	26 (33.3%)	42 (37.2%)
95% CI	(28.8%, 63.4%)	(23.1%, 44.9%)	(28.3%, 46.8%)
VGPR rate, n (%)	1 (2.9%)	15 (19.2%)	16 (14.2%)
95% CI	(NE, NE)	(10.2%, 28.3%)	(6.9%, 19.9%)
PR rate, n (%)	1 (2.9%)	2 (2.6%)	3 (2.7%)
95% CI	(0.1%, 14.9%)	(0.3%, 9.0%)	(0.6%, 7.6%)
Stable disease (SD), n (%)	0	0	0
95% CI	(NE, NE)	(NE, NE)	(NE, NE)
Progressive disease, n (%)	0	1 (1.3%)	1 (0.9%)
95% CI	(NE, NE)	(0.0%, 6.9%)	(0.0%, 4.8%)
Not evaluable, n (%)	6 (17.1%)	11 (14.1%)	17 (15.0%)
95% CI	(6.6%, 33.6%)	(7.3%, 23.8%)	(9.0%, 23.0%)

(Source: Table 9, Efficacy Update section 4.2, page 18)

6.1.11.2 Analyses of Major Secondary Endpoints

The results of these major secondary endpoints based on my independent analyses are consistent with that in CSR.

VGPR or Better Rate

Overall response of VGPR or better per IRC assessment for subjects in *All Treated Analysis Set* (n=97) is 94.8% (95% CI: 88.4% to 98.3%) as shown in Table 8 below.

Table 8. VGPR or better per IRC for All Treated analysis set.

	Phase 1b	Phase 2	Phase 1b + Phase 2, N (%)
	29	68	97
VGPR or better, n (%)	28 (96.6%)	64 (94.1%)	92 (94.8%)
95% CI	(82.2%, 99.9%)	(85.6%, 98.4%)	(88.4%, 98.3%)

(Source: FDA statistical reviewer's analysis)

In the all-enrolled analysis set (n=113), the VGPR or better rate is 81.4% (95% CI: 73.0% to 88.1%) as shown in Table 9.

Table 9. VGPR or better per IRC for all enrolled analysis set.

	Phase 1b	Phase 2	Phase 1b + Phase 2, N (%)
	35	78	113
VGPR or better, n (%)	28 (80.0%)	64 (82.1%)	92 (81.4%)
95% CI	(63.1%, 91.6%)	(71.7%, 89.8%)	(73.0%, 88.1%)

(Source: FDA statistical reviewer's analysis)

Duration of response (DOR)

Table 10 summarizes the DOR results for responders in *All Treated Analysis Set* based on IRC assessment.

Table 10. DOR results of responders in *All Treated Analysis Set*

	Phase 1b	Phase 2	Phase 1b + Phase 2, N (%)
Number of subjects achieved PR or better, n	29	66	95
Number of events, n (%)	10 (34.5%)	21 (31.8%)	31 (32.6%)
Progression	8 (27.6%)	14 (21.2%)	22 (23.2%)
Death	2 (6.9%)	7 (10.6%)	9 (9.5%)
Censored, n (%)	19 (65.5%)	45 (68.2%)	64 (67.4%)
DOR (months)			
median	21.8	NE	21.8
95% CI	(15.9, NE)	(NE, NE)	not reported
Follow-up (months)			
median	24.0	19.8	23.6
95% CI	(22.8, NE)	(17.9, NE)	(22.8, 26.2)
Percentage of subjects with response duration (%) (95% CI)*			
≥6 months	93.1% (75.1%, 98.2%)	81.6% (69.9%, 89.1%)	85.2% (76.2%, 90.9%)
≥9 months	86.2% (67.3%, 94.6%)	76.7% (64.4%, 85.3%)	79.7% (70.0%, 86.5%)
≥12 months	72.1% (51.8%, 85.0%)	73.5% (60.8%, 82.6%)	72.9% (62.6%, 80.9%)

*The estimated percentage of subjects with response duration $\geq 6, 9,$ and 12 months was presented with 95% CIs using the KM method.

(Source: Table 10, Efficacy Update section 4.3.2, page 24)

Reviewer's comment:

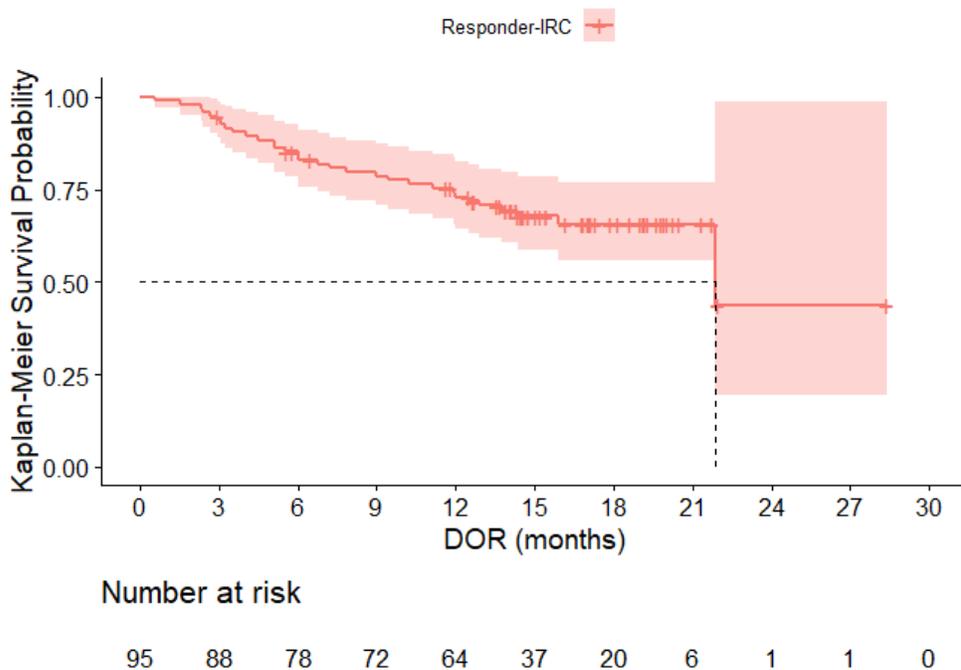
For the analysis of DOR per IRC, the overall median was 21.8 months. Its 95% CI is not reported in the table because the upper limit cannot be estimated and the lower limit estimate is the same as the median, 21.8 months, which is not a useful or believable CI estimate. The reason why the median estimate and its 95% CI lower limit are the same is as follows. The last two events happened at 15.9 and 21.8 months, leading the survival probabilities to 0.656 and 0.437, respectively, which are right above and below 0.5. This makes the median DOR and its lower limit both at 21.8 months. In other words, due to the lack of long-term follow-up data, the observed event time of 21.8 months is the only time point whose survival probability falls within the 95% CI of 0.5. This phenomenon is

also demonstrated in the Kaplan-Meier plot of DOR (Figure 2). The sharp drop towards the end of Kaplan-Meier curve causes the median estimate to coincide with its lower limit of 95% CI. With more long-term follow-up data to be collected, a more accurate estimate of median DOR time and its associated CI can be obtained.

The probabilities of the responders in *All Treated Analysis Set* remaining in response at 9 months and 12 months were 79.7% (95% CI: 70.0% to 86.5%) and 72.9% (95% CI: 62.6% to 80.9%), respectively.

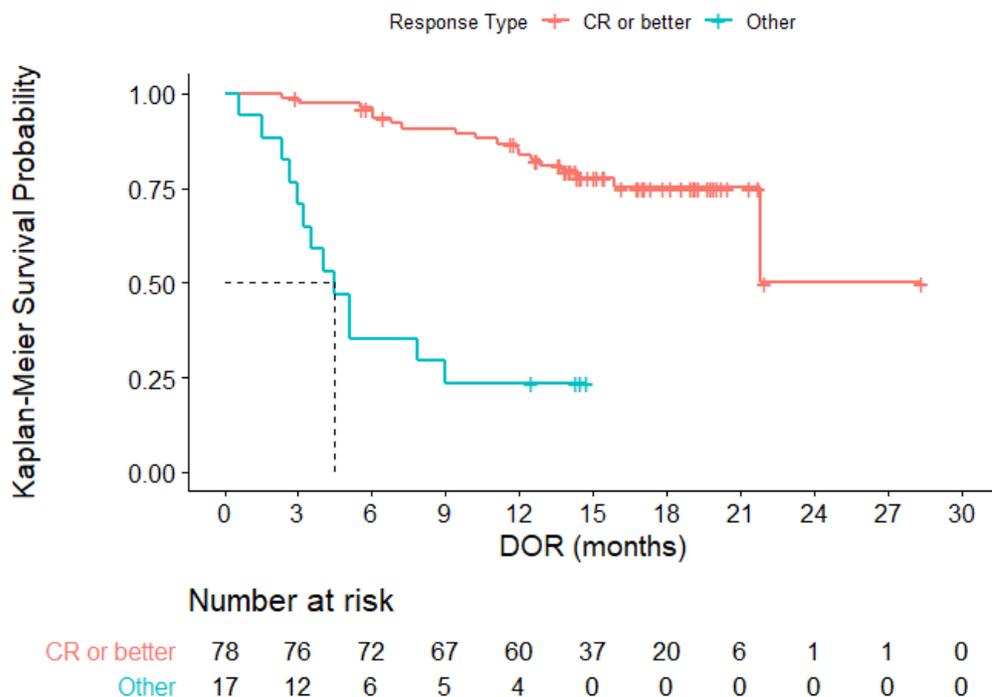
Assessment of DOR based on IRC assessment of best response achieved is presented graphically in Figure 3. Duration of response for subjects with best response of CR or better appears to be longer compared to that for other responders. The group of CR or better did not reach its median DOR at the time of clinical cut off.

Figure 2. Kaplan-Meier curves of DOR for responders per IRC in *All Treated Analysis Set*.



(Source: FDA statistical reviewer’s analysis; Figure 3 on page 24 of Efficacy Update)

Figure 3. Kaplan-Meier curves of DOR for responders achieving CR versus Other responders per IRC in *All Treated Analysis Set*.



(Source: FDA statistical reviewer’s analysis; Figure 4 of Efficacy update, page 25)

MRD Negativity Rate

The results of MRD negativity rate for *All Treated Analysis Set* are shown in Table 11 below. In such set, 56 subjects (57.7%) achieved MRD negativity at the 10^{-5} threshold of sensitivity. Among the 61 evaluable samples at sensitivity level of 10^{-5} , 42 subjects (68.9%) achieved CR/sCR (Table 12).

Table 11. MRD negativity rate for *All Treated Analysis Set*

	Phase 1b, N (%)	Phase 2, N (%)	Phase 1b + Phase 2, N (%)
All-treated	29	68	97
MRD negativity rate 10^{-4}	23 (79.3%)	42 (61.8%)	65 (67.0%)
95% CI	(60.3%, 92.0%)	(49.2%, 73.3%)	(56.7%, 76.2%)
MRD negativity rate 10^{-5}	19 (65.5%)	37 (54.4%)	56 (57.7%)
95% CI	(45.7%, 82.1%)	(41.9%, 66.5%)	(47.3%, 67.7%)
MRD negativity rate 10^{-6}	17 (58.6%)	21 (30.9%)	38 (39.2%)
95% CI	(38.9%, 76.5%)	(20.2%, 43.3%)	(29.4%, 49.6%)

(Source: reviewer’s analysis results)

Table 12. MRD Negativity Rate for Subjects with Evaluable Sample at 10^{-5} in *All Treated Analysis Set*

	Phase 1b, N (%)	Phase 2, N (%)	Phase 1b + Phase 2, N (%)
Evaluable sample at 10^{-5} MRD	19	42	61
MRD negativity and CR or sCR	16 (84.2%)	26(61.9%)	42 (68.9%)
95% CI	(60.4%, 96.6%)	(45.6%, 76.4%)	(55.7%, 80.1%)
MRD negativity and \geq VGPR	17 (89.5%)	34 (81.0%)	51 (83.6%)
95% CI	(66.9%, 98.7%)	(65.9%, 91.4%)	(71.9%, 91.8%)
Overall MRD negativity	19 (100%)	37 (88.1%)	56 (91.8%)
95% CI	(82.4%, 100.0%)	(74.4%, 96.0%)	(81.9%, 97.3%)

(Source: table 11 on page 29 of CSR Efficacy Update)

Time to Response

Time to first response (PR or better), best response, and CR or better are shown in table 13 for *All Treated Analysis Set*.

Table 13. Time to response per IRC for responders in *All Treated Analysis Set*

	Phase 1b, N (%)	Phase 2, N (%)	Phase 1b + Phase 2, N (%)
All-treated	29	66	95
Time to first response (months)			
	29	66	95
Mean (SD)	1.14 (0.46)	1.53 (1.82)	1.41 (1.54)
median	0.95	0.95	0.95
range	(0.89, 2.83)	(0.85, 10.68)	(0.85, 10.68)
Time to best response (months)			
	29	66	95
mean	5.13 (4.94)	4.74 (4.06)	4.86 (4.32)
median	2.60	2.61	2.60
range	(0.92, 15.21)	(0.85, 12.68)	(0.85, 15.21)
Time to CR or better (months)			
N	28	50	78
Mean (SD)	5.24 (4.99)	5.27 (4.38)	5.36 (4.58)
median	2.61	2.89	2.63
range	(0.92, 15.21)	(0.85, 12.68)	(0.85, 15.21)

(Source: Table 12 on page 30, section 4.3.4 of Efficacy Update)

Progression-free Survival (PFS)

Table 14 summarizes the PFS results for *All Treated Analysis Set*. The 12-month PFS rates for the 11 February 2021 clinical cutoff is 76.3% (95% CI: 66.5% to 83.6%).

Table 14. PFS results in *All Treated Analysis Set*

	Phase 1b, N (%)	Phase 2, N (%)	Phase 1b + Phase 2, N (%)
All-treated	29	68	97
Number of events, n (%)	10 (34.5%)	22 (32.4%)	32 (33.0%)
Progression	8 (27.6%)	15 (22.1%)	23 (23.7%)
Death	2 (6.9%)	7 (10.3%)	9 (9.3%)
Number of Censored, n (%)	19 (65.5%)	46 (67.6%)	65 (67.0%)
Study cut-off	19 (65.5%)	45 (66.2%)	64 (66.0%)
Start subsequent anti-myeloma therapy	0	1 (1.5%)	1 (1.0%)
PFS (months)			
median	22.8	NE	22.8
95% CI	(16.8, NE)	(NE, NE)	not reported
Percentage of subjects with PFS at			
6 months	93.1 (75.1, 98.2)	85.3 (74.4, 91.8)	87.6 (79.2, 92.8)
9 months	86.2 (67.3, 94.6)	76.5 (64.5, 84.9)	79.4 (69.9, 86.2)
12 months	82.8 (63.4, 92.4)	73.5 (61.3, 82.4)	76.3 (66.5, 83.6)
18 months	69.0 (48.8, 82.5)	65.9 (52.5, 76.3)	66.0 (54.9, 75.0)

(Source: Table 13 on page 31, section 4.3.5 of Efficacy Update)

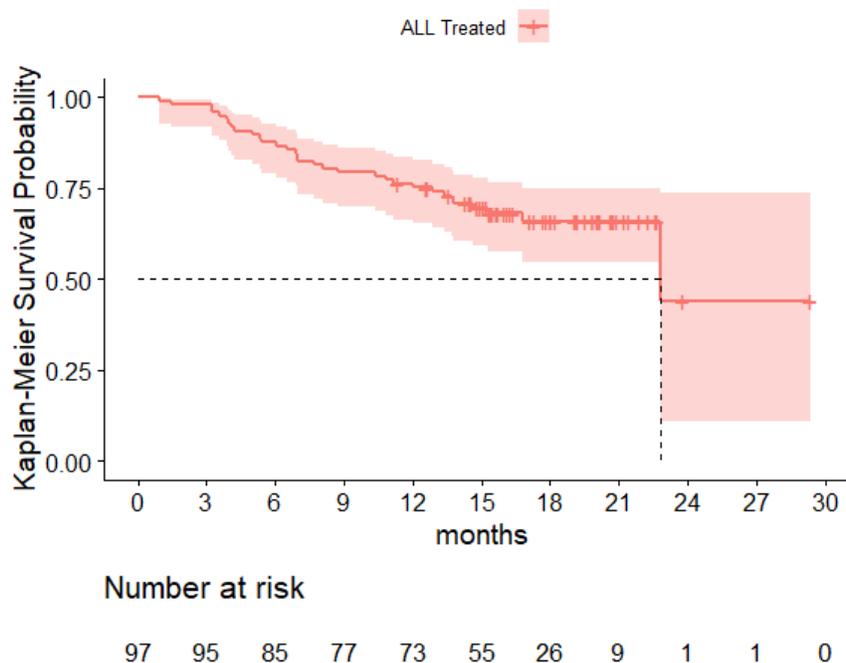
Reviewer's comment:

The overall median PFS based on the IRC response assessment was 22.8 months. The corresponding 95% confidence interval is not useful and thus not reported in the table. The estimated lower limit is 22.8 months, the same as the median, and the upper limit is not estimable. The reason why the median estimate and its 95% CI lower limit are the same is as follows. The last two events happened at 16.8 and 22.8 months, leading the survival probabilities to 0.660 and 0.440, respectively, which are right above and below 0.5. This makes the median PFS and its lower limit both at 22.8 months. In other words, due to the lack of long-term follow-up data, the observed event time of 22.8 months is the only time point whose survival probability falls within the 95% CI of 0.5. This phenomenon is also demonstrated in the Kaplan-Meier plot of PFS (Figure 4a). The sharp drop towards the end of Kaplan-Meier curve causes the median estimate to coincide with its lower limit of 95% CI. With more long-term follow-up data to be collected, a more accurate estimate of median PFS time and its associated CI can be obtained.

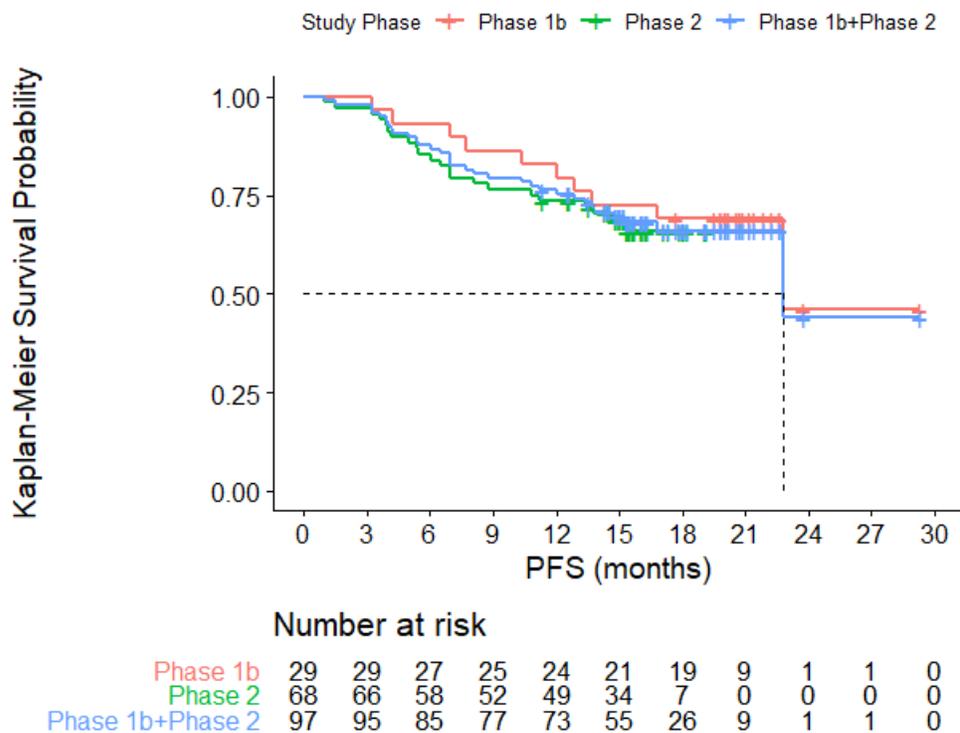
Figure 4b below shows Kaplan-Meier curves of PFS per IRC assessment by study phase for *All Treated Analysis Set*. The median PFS was not reached for either Phase 1b or Phase 2 studies. Figure 5 suggests a possible positive association between depth of response and PFS. Subjects achieving CR or better had a higher 12-month PFS rate than other responders.

Figure 4. Kaplan-Meier Curves of PFS per IRC

a. Kaplan-Meier Curves of PFS per IRC for *All Treated Analysis Set*.

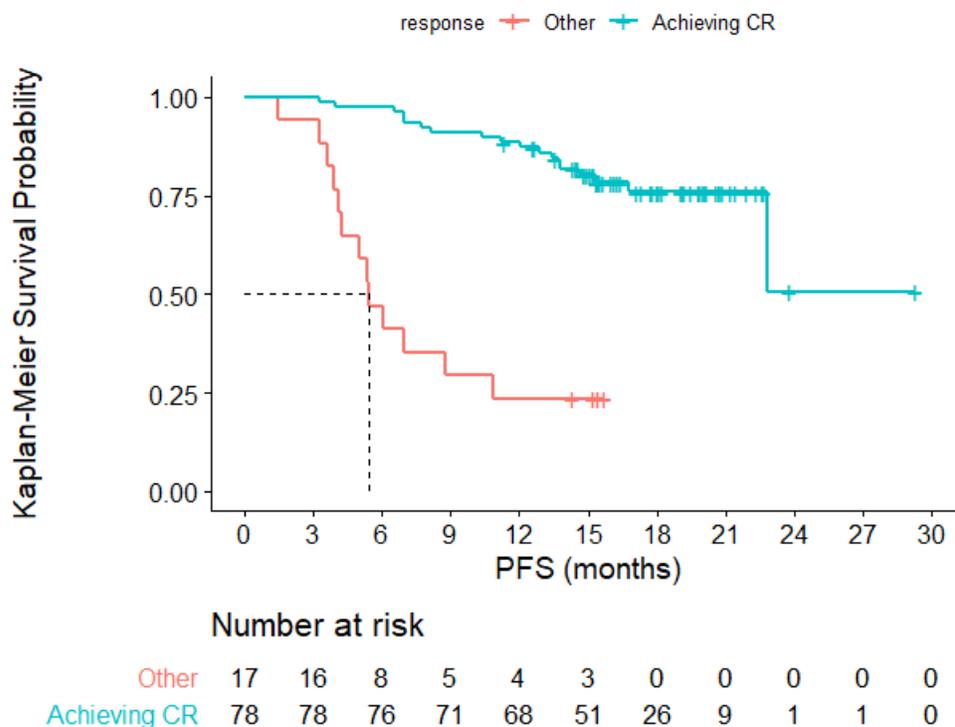


b. Kaplan-Meier Curves of PFS per IRC by Study Phase for *All Treated Analysis Set*.



(Source: FDA statistical reviewer's analysis)

Figure 5. Kaplan-Meier curves of PFS for responders achieving CR versus Other responders per IRC in *All Treated Analysis Set*



The limited PFS data suggests that there may exist a positive association between depth of response and PF, as subjects achieving CR or better had a 12-month PFS rate of 88.5% (95% CI: 79.0% to 93.8%), whereas other responders achieved the 12-month PFS rate of 23.5% (95% CI: 7.3% to 44.9%).

Overall Survival (OS)

A total of 21 subjects (21.6%) died and 76 subjects (78.4%) had their OS data censored in *All Treated Analysis Set* (n=97) as of the February 11, 2021 clinical cutoff. The median OS was not reached (95% CI: 23.6, NE), with a median follow up of 18.0 months. The 12-month OS rate for the 11 February 2021 clinical cutoff is 87.6% (95% CI: 79.2% to 92.8%).

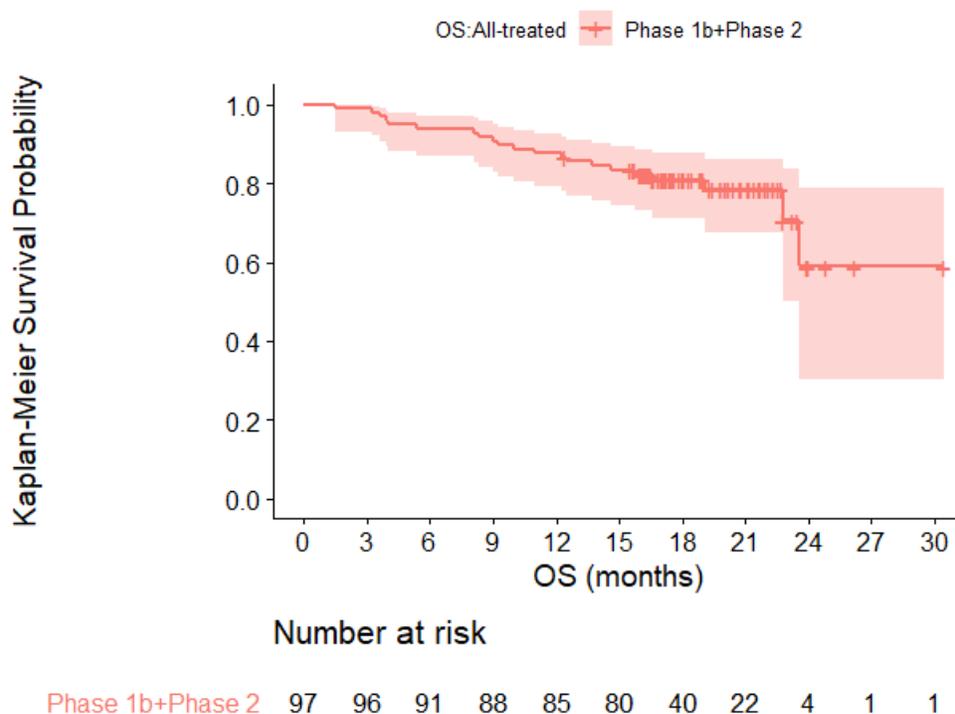
The OS results are shown in table 15 and the overall K-M curves are shown in Figure 6.

Table 15. OS results in *All Treated Analysis Set*

	Phase 1b, N (%)	Phase 2, N (%)	Phase 1b + Phase 2, N (%)
All-treated	29	68	97
Overall Survival, n (%)			
Events, n (%)	6 (20.7%)	15 (22.1%)	21 (21.6%)
Censored, n (%)	23 (79.3%)	53 (77.9%)	76 (78.4%)
K-M estimate (months)			
median	NE	NE	NE
95% CI	(23.6, NE)	(NE, NE)	(23.6, NE)
Percentage of subjects with PFS at			
6 months	96.6 (77.9, 99.5)	92.6 (83.2, 96.9)	93.8 (86.7, 97.2)
9 months	93.1 (75.1, 98.2)	89.7 (79.6, 95.0)	90.7 (82.9, 95.1)
12 months	93.1 (75.1, 98.2)	85.3 (74.4, 91.8)	87.6 (79.2, 92.8)
18 months	89.7 (71.3, 96.5)	76.7 (63.9, 85.4)	80.9 (71.4, 87.6)

(Source: Table 14 on page 33, section 4.3.6 of Updated Efficacy)

Figure 6. Kaplan-Meier Curves for Overall Survival for All Treated Analysis Set

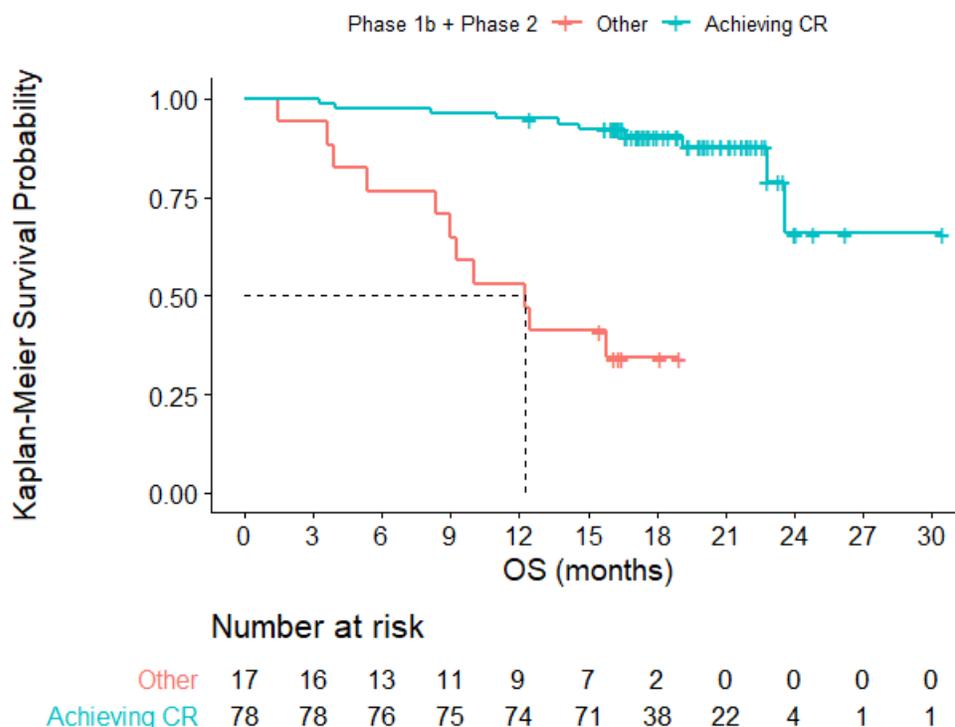


(Source: FDA statistical reviewer's analysis)

Figure 7 shows the KM estimate for responders achieving CR versus the others. The limited OS data suggests that a positive association between depth of response and OS may exist, as subjects achieving CR or better had a 12-month OS rate of 94.9% (95% CI:

86.9% to 98.0%), whereas for other responders achieved a 12-month OS rate of 52.9% (95% CI: 27.6% to 73.0%).

Figure 7. Kaplan-Meier Curves for Overall Survival for responders achieving CR versus the others in All Treated Analysis Set.

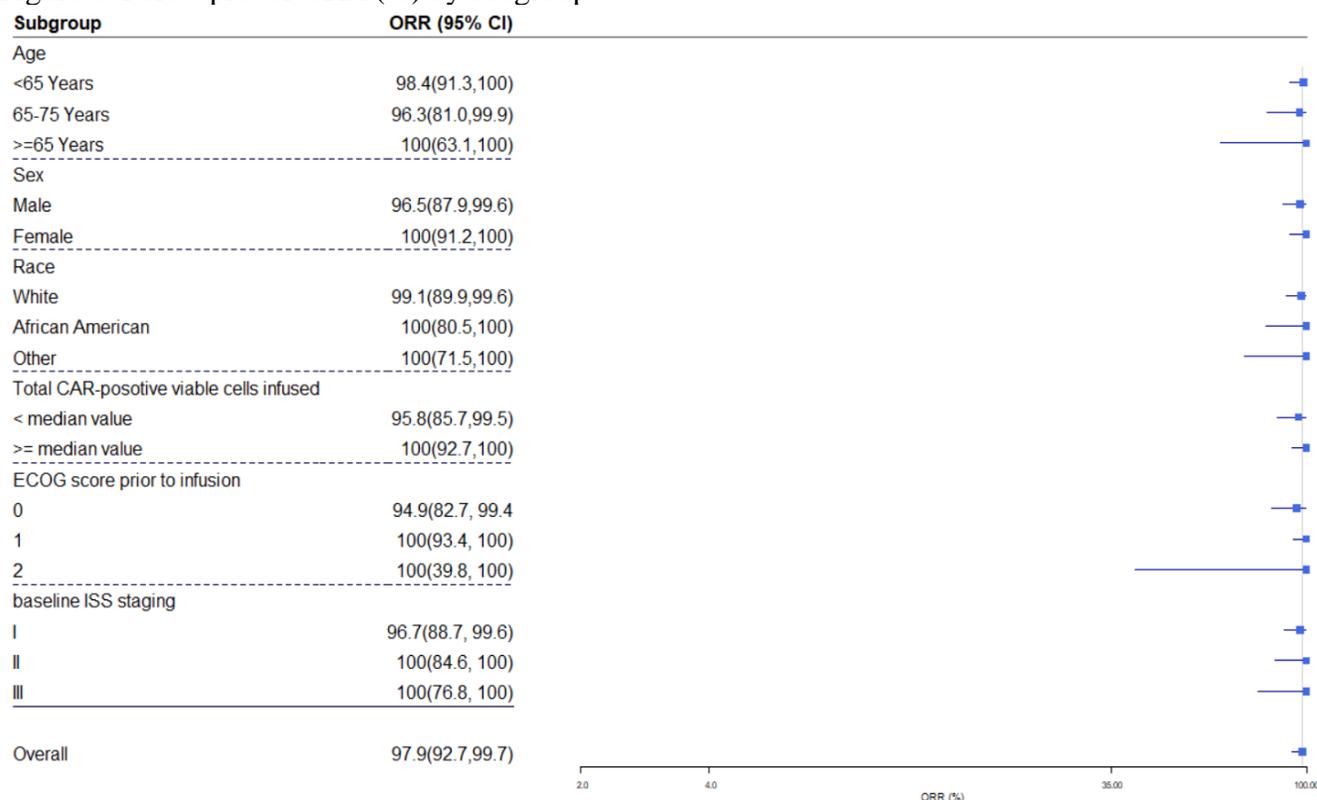


(Source: FDA statistical reviewer’s analysis)

6.1.11.3 Subpopulation Analyses

Figure 8 shows the forest plot of ORR in *All Treated Analysis Set* across baseline characteristic subgroups by age, sex, race, and other baseline factors. Results of ORR appear to be consistent across subgroups. The lower limit of 95% exact Clopper-Pearson confidence interval for ORR is above the null hypothesis rate of 30% for each subgroup. There’s no evidence of meaningful site-to-site heterogeneity in ORR based on subgroup analysis.

Figure 8. Forest plot of ORR (%) by subgroup



(Source: FDA statistical reviewer’s analysis; results in Figure 2 on page 20-22 of Efficacy Update has been verified)

6.1.11.4 Discontinuations

Table 16 summarizes the study discontinuation status of subjects in the All Treated population with cut-off date of February 11, 2021 for efficacy. The only reason for discontinuation is death. Among the 97 treated subjects, 21 subjects had discontinued the study due to death and 76 subjects had ongoing follow-up.

Table 16. Subjects’ discontinuations (cut-off date of February 11, 2021)

treatment received	97 (100%)
Follow-up ongoing	76 (78.4%)
Death	21 (21.6%)

(Source: FDA statistical reviewer’s summary)

6.1.12 Safety Analyses

This section summarizes safety results of Study MMY2001 based on the safety data with cutoff date of September 01, 2020.

6.1.12.1 Methods

Descriptive statistics were used to summarize safety data for Study MMY2001. For data summary, the primary analysis population for all safety analyses was the All Treated population which included all 97 subjects who received a cilta-cel infusion (i.e., the safety analysis set is the same as *All Treated Analysis Set*.)

6.1.12.3 Deaths

Deaths reported in the safety analysis set are listed in Table 17. Among the 97 all treated subjects, 14 (14.4%) subjects died anytime post the first infusion.

Table 17. Deaths reported in the safety analysis set (i.e., All Treated analysis set)

	Phase 1b, N (%)	Phase 2, N (%)	Phase 1b + Phase 2, N (%)
All treated	29	68	97
Total number of subjects who died during study	5 (17.2%)	9 (13.2%)	14 (14.4%)
Primary cause of death			
Adverse event	3 (10.3%)	6 (8.8%)	9 (9.3%)
Progressive Disease	2 (6.9%)	3 (4.4%)	5 (5.2%)
Total number of subjects who died within 30 days of the initial JNJ-68284528 infusion			
	0	0	0
Total number of subjects who died within 100 days of the initial JNJ-68284528 infusion			
	1 (3.4%)	1 (1.5%)	2 (2.1%)
Primary cause of death			
	1 (3.4%)	1 (1.5%)	2 (2.1%)

(Source: CSR p.106 Table 38)

6.1.12.4 Nonfatal Serious Adverse Events

Serious adverse events were reported for 53 subjects (54.6%) in *All Treated Analysis Set*. The most frequently reported ($\geq 5\%$ subjects) SAEs were CRS (n=20, 20.6%), Pneumonia (n=5, 5.2%), Sepsis (n=5, 5.2%), and ICANS (n=5, 5.2%).

Table 18 summarizes the treatment emergent nonfatal SAEs reported in at least 5% of subjects by system organ class, preferred term, and worst event grade of 3 or higher in All Treated analysis set.

Table 18. Treatment-emergent nonfatal SAEs reported in $\geq 5\%$ of All Treated subjects

Analysis set: all treated	Total 29	Phase 1b		Total 68	Phase 2		Total 97	Phase 1b + Phase 2	
		Grade 3 or 4	Grade 5		Grade 3 or 4	Grade 5		Grade 3 or 4	Grade 5
Total number of subjects with serious TEAE	11 (37.9%)	7 (24.1%)	1 (3.4%)	42 (61.8%)	22 (32.4%)	5 (7.4%)	53 (54.6%)	29 (29.9%)	6 (6.2%)
MedDRA system organ class/preferred term									
Infections and infestations	4 (13.8%)	3 (10.3%)	0	17 (25.0%)	12 (17.6%)	3 (4.4%)	21 (21.6%)	15 (15.5%)	3 (3.1%)
Pneumonia	1 (3.4%)	1 (3.4%)	0	4 (5.9%)	4 (5.9%)	0	5 (5.2%)	5 (5.2%)	0
Sepsis	1 (3.4%)	1 (3.4%)	0	4 (5.9%)	3 (4.4%)	1 (1.5%)	5 (5.2%)	4 (4.1%)	1 (1.0%)
Immune system disorders	5 (17.2%)	2 (6.9%)	1 (3.4%)	15 (22.1%)	2 (2.9%)	0	20 (20.6%)	4 (4.1%)	1 (1.0%)
Cytokine release syndrome	5 (17.2%)	2 (6.9%)	1 (3.4%)	15 (22.1%)	2 (2.9%)	0	20 (20.6%)	4 (4.1%)	1 (1.0%)
Nervous system disorders	3 (10.3%)	2 (6.9%)	0	13 (19.1%)	8 (11.8%)	1 (1.5%)	16 (16.5%)	10 (10.3%)	1 (1.0%)
Immune effector cell-associated neurotoxicity syndrome	1 (3.4%)	1 (3.4%)	0	4 (5.9%)	1 (1.5%)	0	5 (5.2%)	2 (2.1%)	0

Keys: TEAE = treatment-emergent adverse event.

Note: The output includes the diagnosis of CRS and ICANS along with other AEs and the symptoms of CRS or ICANS are excluded.

Note: Adverse events are reported using MedDRA version 23.0.

Note: For 1 subject in Phase 1b with serious TEAE of Immune Effector Cell-Associated Neurotoxicity (ICANS), the reported term was CAR-T cell Related Encephalopathy Syndrome (CRES). The event was reported prior to publication of the ASTCT consensus grading system and graded according to NCI-CTCAE version 5.0 by investigator. For this subject, the maximum toxicity grade was Grade 3 according to NCI-CTCAE version 5.0.

Note: Adverse events are graded according to the NCI-CTCAE Version 5.0, with the exception of immune effector cell-associated neurotoxicity (ICANS) and cytokine release syndrome (CRS), which were evaluated according to the ASTCT consensus grading system, and adverse events associated with changes in handwriting, which were graded according to the protocol criteria.

Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.

(Source: Clinical study report p.108, Table 4)

6.1.12.5 Adverse Events of Special Interest (AESI)

Table 19 summarizes the AESI post first infusion. CRS occurred most frequently in 94.8% (=92/97) of All Treated subjects.

Table 19. Adverse events of special interest (AESI) reported in All Treated analysis set

Term	N (%)
Cytokine release syndrome	92 (94.8%)
CAR-T Cell Neurotoxicity	20 (20.6%)
ICANS	16 (16.5%)
Other Neurotoxicity of any grade	12 (12.4%)
Other Neurologic Adverse Events	63 (64.9%)
Tumor Lysis Syndrome	1 (1.0%)
Second Primary Malignancy	7 (7.2%)
Cytopenias	97 (100%)

(Source: Clinical study report, page 110, section 7.2.2.4; FDA statistical reviewer's summary)

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Cilta-cel (JNJ-68284528) is a genetically modified autologous T cell immunotherapy. The primary source of evidence to support this BLA is the Phase 1b-2, open-label study 68284528MMY2001. Of the 113 enrolled subjects in this study, 97 subjects received JNJ-68284528 infusion at the targeted dose. These 97 subjects constituted *All Treated Analysis Set*, which was the basis for all efficacy and safety analyses.

The pre-specified primary efficacy endpoint is overall response rate (ORR), defined as the incidence of PR or better based on IRC assessment. Efficacy results summarized in this memo are based on a data cut-off date of February 11, 2021.

The ORR as assessed per IRC was 97.9% (95/97; 95% CI: 92.7%, 99.7%) and the lower limit of the 95% exact Clopper-Pearson confidence interval of 92.7% was well above the pre-specified null hypothesis rate of 30%. Median duration of response (DOR) was 21.8 months; the probabilities of the responders remaining in response at 9 months and 12 months were 79.7% (95% CI: 70.0% to 86.5%) and 72.9% (95% CI: 62.6% to 80.9%), respectively. 78 subjects (80.4%) achieved complete response (CR) or better. 92 subjects (94.8%) achieved VGPR or better. Clinical benefit rate (CBR) was 97.9% which is the same as ORR. Of 61 subjects with evaluable samples, 91.8% (56 subjects) achieved MRD negativity in bone marrow at a sensitivity level of 10^{-5} .

The median time to first response (PR or better) and to best response were 0.95 and 2.60 months, respectively. With a median duration of follow-up of 18.0 months, median progression-free survival (PFS) was 22.80 months. The 12-month PFS rate (95% CI) was 76.3% (66.5%, 83.6%).

The safety results of the study are summarized with cutoff date of September 1, 2020. Deaths occurred in 14.4% (= 14/97) of treated subjects who received cilta-cel. SAEs were

reported in 54.6% (= 53/97) of treated subjects. CRS occurred in 92 (94.8%) subjects, of which the majority (n=87, 95%) were Grade 1/2 assessed using ASTCT consensus grading system. CAR-T neurotoxicity was observed in 20 (20.6%) subjects which included 16 (16.5%) subjects who experienced ICANS (2.1% grades 3 and 4, 0% fatal), and 12 (12.4%) subjects who experienced Other Neurotoxicity (8.2% grades 3 and 4, 1% fatal).

10.2 Conclusions and Recommendations

The statistical analysis results provide sufficient evidence of effectiveness to support the approval of cilta-cel for the proposed indication of adult patients with relapsed or refractory multiple myeloma.

11. REFERENCES

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