Application Type	BLA
STN	125736
CBER Received Date	July 27, 2020
PDUFA Goal Date	March 26, 2021
Division / Office	OBE/DB
Committee Chair	Anna Kwilas
Clinical Reviewer(s)	Poornima Sharma
Project Manager	Colleen Caldwell and Juliane Carvalho
Priority Review	Yes
Reviewer Name(s)	Xue Lin
Review Completion Date / Stamped Date	
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Leader, 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	Celgene Corporation
Established Name	idecabtagene vicleucel
(Proposed) Trade Name	ABECMA
Pharmacologic Class	BCMA directed genetically-modified autologous T cell
Proposed Formulation(s), including Adjuvants, etc	(b) (4) x 10^6 chimeric antigen receptor (CAR)-positive T cells 50% Plasma-Lyte A and 50% CryoStor® CS10
Dosage Form(s) and Route(s) of Administration	intravenous infusion
Proposed Dosing Regimen	The target dose is 450 x 106 CAR-positive T cells within a range of (b) (4) × 106 CAR-positive T cells
Indication(s) and Intended Population(s)	adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody

Table of Contents

GLOSSARY

AE adverse event
AMT Antimyeloma therapy
ASCT autologous stem cell transplant
BCMA B-cell maturation antigen
BLA Biologics Licensure Application
BOR best overall response
CI confidence interval
CR complete remission
CRS cytokine release syndrome
CSR clinical study report
DOR duration of remission
FAS full analysis set
IMWG International Myeloma Working Group
IRC independent review committee
IV intravenous
LD lymphodepleting chemotherapy
MM multiple myeloma
ORR overall remission rate
OS overall survival
PFS Progression-free survival
PI Proteasome inhibitor
RP2D recommended phase 2 dose
r/r relapsed/refractory
rrmm relapsed/refractory multiple myeloma
SCT stem-cell transplantation

1. EXECUTIVE SUMMARY

This Biologics License Application (BLA) seeks licensure of idecabtagene vicleucel (ide-cel) for the treatment of adult patients with relapsed/refractory multiple myeloma (r/r mm). Ide-cel is an engineered autologous T cell immunotherapy.

The primary source of evidence to support this application is a Phase II, single-arm, multicenter study (MM-001). The primary efficacy endpoint was overall remission rate (ORR), which is defined as the proportion of subjects who achieved partial response (PR) or better (i.e. stringent complete response, complete response, very good partial response, partial response) as assessed by an independent review committee (IRC).

Study MM-001 enrolled 140 subjects and 127 were infused with conformal ide-cel. Subjects were treated at 3 target dose levels: 150 x 10^6 (N=4), 300 x 10^6 (N=70) and 450 x 10^6 (N=53) chimeric antigen receptor (CAR)-positive T cells. The FDA clinical review team re-adjudicated the response assessments, based on which the ORR was 50% (95% CI: 6.8%, 93.2%) for the 150 x 10^6 dose level, 64.3% (95% CI: 51.9%, 75.4%) for the 300 x 10^6 dose level and 79.3% (95% CI: 65.9%, 89.2%) for the 450 x 10^6 dose level, respectively. For both 300 x 10^6 dose level and 450 x 10^6 dose level, the lower limit of

the 95% confidence interval was above the pre-set null hypothesis rate of 50%. And the CR rates for these two dose levels were 22.9% (95% CI: 13.7%, 34.5%) and 39.2% (95% CI: 18.3%, 44.3%), respectively. The lower limits of the 95% confidence intervals for both dose levels were above the pre-set null hypothesis rate of 10%. Follow-up time for Duration of Response (DOR) ranged from 1 day to 20 months with a median of 10.5 months. The estimated median DOR was 10.0 months (95% CI: 5.4, 11.0) for the 300 x 10^6 dose level, and 11.3 months (95% CI: 10.3, 11.4) for the 450 x 10^6 dose level.

These results are also supported by Study CRB-401, a first-in-human, dose escalation and expansion, Phase 1 trial. A total of 62 subjects were enrolled in four different dosage groups, 50 x 10^6, 150 x 10^6, 450 x 10^6, and 800 x 10^6. The ORRs for the 150 × 10^6 dosage group with 18 subjects and 450 × 10^6 dosage group with 38 subjects are generally consistent with those of study MM-001.

The two dose levels, 300 x 10^6 and 450 x 10^6, in Study MM-001 met the primary efficacy endpoint: The pre-specified null hypothesis of 50% ORR was rejected. The statistical analysis results support the product's effectiveness in the proposed indication.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Multiple myeloma (MM) is a cancer of plasma cells characterized by the proliferation of malignant plasma cells both within the bone marrow and at the plasmacytomas. Based on information submitted by the applicant, MM accounts for approximately 18% of hematologic malignancies in the United States (U.S.). In the U.S. in 2020, there were an estimated 32,270 new cases of MM and 12,830 estimated deaths due to MM. MM primarily affects older individuals, and the median age at onset is 69 years in the U.S.

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

Based on information submitted by the applicant, the course of MM is characterized by a period of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapy. Since the beginning of 2015, the U.S. FDA has approved nine products in 13 relapsed/refractory (r/r) MM indications, including carfilzomib, pomalidomide, panobinostat, daratumumab, ixazomib, elotuzumab, selinexor, isatuximab-ifrc, and Dara SC. Despite the available treatment options for relapsed/refractory MM, no standard of care exists for patients with MM who have been exposed to an immunomodulatory agent, a proteasome inhibitor (PI), and an anti-CD38 antibody, and only 1 drug (selinexor in combination with dexamethasone) has been granted accelerated approval for patients previously exposed to all three antimyeloma therapy (AMT) classes, but in a more refractory population.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

N.A.

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. The major pre and post-submission regulatory activities

Date	Milestone
9/30/2015	IND submission
5/11/2016	Orphan Drug Designation granted
11/15 2017	Breakthrough Therapy Designation granted
12/12/2019	Pre-BLA Meeting
3/30/2020	BLA (b) (4) submission
5/11/2020	BLA (b) (4) refuse to file letter issued
7/27/2020	BLA 125736 submission
9/21/2020	Filing notification letter sent
10/23/2020	3-Month Safety Update Report

(Source: FDA Statistical Reviewer)

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 proposed product comes from study MM-001, which is the focus of this review memo. In addition, study CRB-401 provides supportive evidence and is reviewed briefly in this memo.

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

The basis of this statistical memo includes review of

- Clinical study reports and data sets submitted in SN0001

- 3 Month Safety update submitted in SN0012

5.3 Table of Studies/Clinical Trials

Table 2 summarizes the studies included in the BLA submission.

Table 2. Studies supporting the proposed indication in the BLA submission

Study ID	Study Design	Status
CRB-401	First-in-human, Phase 1 dose escalation and dose expansion	Enrollment complete, follow-up on-going, 62 treated
MM-001	Pivotal Phase 2, single-arm, multinational	Enrollment complete, follow-up on-going, 128 treated
MM-001 JAP	Single arm, multicenter in Japan	Enrollment on-going, 3 treated *
MM-002	Single arm, multinational	Enrollment on-going, 31 treated*
MM-003	Phase 3 randomized, open-label	Enrollment ongoing, 22 treated*

*cutoff date=16 October 2019
(source: abbreviated Table 1 Clinical Overview BLA 125736/0.0)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (Study MM-001)

6.1.1 Objectives

The primary objective of the study is to evaluate the efficacy, in terms of overall response rate (ORR), of ide-cel in subjects with r/r multiple myeloma (RRMM)

The secondary objectives included assessing the safety of ide-cel and additional efficacy endpoints.

6.1.2 Design Overview

Study MM-001 was an open-label, single-arm, multicenter, multinational, Phase 2 study to evaluate the efficacy and safety of ide-cel in subjects with RRMM. Up to 140 subjects were to be enrolled in the study. The study consisted of 3 periods:

- pre-treatment: screening and leukapheresis
- treatment: lymphodepleting chemotherapy and ide-cel infusion
- post-treatment: for a minimum of 24 months post-ide-cel infusion or until documented disease progression, whichever is longer

6.1.3 Population

Eligible subjects received at least 3 prior antimyeloma treatment regimens, were refractory to the last regimen received, and had been previously treated with an immunomodulatory agent, a PI, and an anti-CD38 antibody. Detailed inclusion and exclusion criteria are in Section 9.3 of the clinical study report.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects underwent leukapheresis, bridging therapy (as needed), and lymphodepleting chemotherapy before they received ide-cel infusion

6.1.6 Sites and Centers

Twenty centers participated in the trial; 10 in north America and 10 in Europe.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was ORR (partial response [PR] or better) according to International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma, as assessed by an independent response committee (IRC).

The key secondary efficacy endpoint was complete response (CR) rate, which was defined as percentage of subjects who achieved stringent CR (sCR) or CR according to IMWG Uniform Response Criteria for Multiple Myeloma, as assessed by IRC.

Additional secondary efficacy endpoints included:

- Time to response (TTR)
- Duration of response (DOR)
- Progression free survival (PFS)
- Time to progression (TTP)
- Overall survival (OS)
- Minimal Residual Disease (MRD) status using next generation sequencing (NGS)

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study hypotheses:

Primary hypothesis: H_0: $ORR \leqslant 0.5$ vs. H*a*: $ORR > 0.5$

Key secondary hypothesis: H_0: $CR \leqslant 0.1$ vs. H*a*: $CR > 0.1$.

Key secondary hypothesis was tested only if the test for the primary hypothesis was statistically significant at the one-sided 0.025 significance level.

Reviewer's comment: I consulted with the clinical reviewer, Dr. Sharma. She stated that clinical team agreed with 50% and 10%. The sponsor provided justification for 50% in the protocol. The sponsor stated that the selection of a null hypothesis of 50% ORR was based on the observed clinical activity of the best available single agent therapy in a heavily pretreated RRMM patient population.

Analysis populations

- Screened population: all subjects who signed informed consent
- Enrolled population: all subjects in the Screened population who underwent leukapheresis
- ide-cel-treated population: all subjects in the Enrolled population who received ide-cel infusion

The ide-cel-treated population was used for the primary analysis for efficacy and safety.

Statistical methods

Primary endpoint

To select the best response, the following order of response was used:
stringent complete response (sCR) > complete response (CR) > very good partial response (VGPR) > partial response (PR) > minimal (MR) response > stable disease (SD) > progressive disease (PD).
The ORR was percentage of subjects who achieved PR or better according to IMWG Uniform Response Criteria for Multiple Myeloma as assessed by an IRC. The ORR was calculated together with the 2-sided 95% CI.

Key secondary endpoint

The CR rate, percentage of subjects who achieved CR or sCR according to IMWG Uniform Response Criteria for Multiple Myeloma as assessed by an IRC. The CR rate was calculated together with the 2-sided 95% CI.

Other secondary endpoints

a. Duration of response (DOR)

DOR was defined only for subjects who experience an objective response (PR or better) and was the time from the first objective response to the first documented disease progression or death. Responders who did not progress or die were censored at the last adequate assessment date. Duration of response was analyzed using the KM method. Median DOR and the corresponding 95% CI were provided.

For subjects who initiated new anti-cancer therapy, DOR was censored at last evaluable disease assessment date prior to the initiation of new therapy in the primary analysis.

PD or death after missing 2 (or more) consecutive scheduled assessments was censored at last adequate efficacy assessment date with no evidence of PD. Similarly, PD or death after missing the first 2 assessments was censored at the ide-cel infusion date.

b. Time to Response (TTR)

TTR was defined as the time from ide-cel infusion date to the first date of documented response (PR or better). Time to response was summarized using descriptive statistics.

c. Progression free survival (PFS)

PFS was defined as the time from the ide-cel infusion date to the date of disease progression or death from any cause.
Kaplan-Meier plots, survival probability estimates, and 2-sided 95% confidence intervals were generated for PFS. The same censoring rule for DOR was applied to PFS.

d. Time to Progression (TTP)
TTP was defined as time from ide-cel infusion to the first documented progression. Censoring rules for TTP were similar as those for PFS, except that death was not considered as an event but censored at the last response assessment date. TTP was summarized for the ide-cel-Treated population using Kaplan-Meier (KM) statistics. The median TTP along with the two-sided 95% CI for the median were estimated.

e. Overall survival (OS)
OS was defined as the time from ide-cel infusion to the date of death from any cause. Subjects who had not died by the analysis data cutoff date were censored at the last date known to be alive or the data cutoff date, whichever was earlier.
The distribution function of OS was estimated using Kaplan-Meier method. The median OS along with 95% confidence intervals were presented.

f. MRD status
The primary analysis on MRD status was MRD negative rate defined as the proportion of subjects who achieved $\geqslant$ VGPR and MRD negative status at a sensitivity of 10^{-5} at any time point within 3 months prior to achieving at least VGPR until the time of PD/death (exclusive) based on the ide-cel treated population. The MRD negative rate with 95% confidence intervals were provided.

Sample size
With a null ORR rate of 50% and a target ORR rate of 70%, a sample size of 119 subjects would provide > 99% power at a one-sided 0.025 alpha level. Assuming a dropout rate of 15% between the time of study enrollment and ide-cel infusion, a total number of up to 140 subjects were to be enrolled.

Interim analyses
No interim analysis was planned.

Subgroup analysis
Subgroup analyses were planned based on age, sex, race, and a variety of baseline clinical characteristics.

Missing data
The method for handling missing data was described in the definition for each efficacy endpoint.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographics for the ide-cel-treated population and enrolled population are summarized in Table 3. The median age for the ide-cel-treated population was 60.5 years, and 35% were above 65 years. Seventy-six (59.4%) subjects were male. The majority of ide-cel treated subjects were white (80.5%). The demographics are similar across the three target dose groups. The enrolled population had similar demographics to the Ide-cel treated population.

Table 3. Subject Demographics (Treated population and enrolled population)

	Treated population Target dose				**Enrolled population (N = 140)**
	[150 x 10^6] (N = 4)	**[300 x 10^6] (N = 70)**	**[450 x 10^6] (N = 54)**	**Total [150 to 450 x 10^6] (N = 128)**	
Age (years)					
Median	54.0	60.5	62.0	60.5	60.5
Min, max	49, 69	33, 76	43, 78	33, 78	33, 78
Age category, n (%)					
< 65 years	3 (75.0)	47 (67.1)	33 (61.1)	83 (64.8)	92 (65.7)
≥ 65 years	1 (25.0)	23 (32.9)	21 (38.9)	45 (35.2)	48 (34.3)
Sex, n (%)					
Male	4 (100.0)	38 (54.3)	34 (63.0)	76 (59.4)	82 (58.6)
Female	0	32 (45.7)	20 (37.0)	52 (40.6)	58 (41.4)
Race, n (%)					
Asian	0	3 (4.3)	0	3 (2.3)	3 (2.1)
Black or African American	0	3 (4.3)	3 (5.6)	6 (4.7)	8 (5.7)
White	4 (100.0)	58 (82.9)	41 (75.9)	103 (80.5)	113 (80.7)
Unknown	0	2 (2.9)	8 (14.8)	10 (7.8)	10 (7.1)
Other	0	4 (5.7)	2 (3.7)	6 (4.7)	6 (4.3)
Ethnicity, n (%)					
Hispanic or Latino	0	7 (10.0)	4 (7.4)	11 (8.6)	13 (9.3)
Not Hispanic or Latino	4 (100.0)	58 (82.9)	41 (75.9)	103 (80.5)	112 (80.0)
Not reported	0	1 (1.4)	8 (14.8)	9 (7.0)	9 (6.4)
Unknown	0	4 (5.7)	1 (1.9)	5 (3.9)	6 (4.3)

Data cutoff=16 Oct 2019

(source: Abbreviated Table 9 MM-001 Clinical Study Report BLA 125736/0.0)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline disease characteristics for the ide-cel-treated population and enrolled population are summarized in Table 4. The median number of prior antimyeloma regimens for the ide-cel-treated population was 6.0 (range: 3, 16), with 38.3% of subjects receiving $\geqslant 7$ prior regimens and 93.8% of subjects receiving at least one prior stem-cell transplant (34.4% received at least 2 prior stem cell transplants). 89.1% of subjects were double refractory (ie, refractory to an immunomodulatory agent and a Proteasome inhibitor), 84.4% of subjects were triple refractory (ie, refractory to an immunomodulatory agent, Proteasome inhibitor [PI] , and CD38 antibody), and 25.8% of subjects were penta-refractory (defined as refractory to two immunomodulatory agents [ie, lenalidomide, pomalidomide], two Proteasome inhibitor [ie, bortezomib, carfilzomib], and one anti-CD38 [ie, daratumumab]). The enrolled population had similar baseline disease characteristics to the ide-cel treated population.

Table 4. Subject Baseline Disease Characteristics (Treated population and enrolled population)

Characteristic	**Ide-cel-treated population Ide-cel (CAR+ T cells) target dose**				**Enrolled population (N = 140)**
	[150 x 10^6] (N = 4)	**[300 x 10^6] (N = 70)**	**[450 x 10^6] (N = 54)**	**Total [150 to 450 x 10^6] (N = 128)**	
ECOG performance status, n (%)					
0	3 (75.0)	31 (44.3)	23 (42.6)	57 (44.5)	60 (42.9)
1	1 (25.0)	38 (54.3)	29 (53.7)	68 (53.1)	77 (55.0)
2[a]	0	1 (1.4)	2 (3.7)	3 (2.3)	3 (2.1)
Tumor BCMA expression, n(%)					
< 50% BCMA+	0	1 (1.4)	2 (3.7)	3 (2.3)	3 (2.1)
≥ 50% BCMA+	4 (100.0)	60 (85.7)	45 (83.3)	109 (85.2)	109 (77.9)
Unknown	0	9 (12.9)	7 (13.0)	16 (12.5)	28 (20.0)
Time since initial diagnosis (years)					
Median	9.5	6.6	5.8	6.0	6.0
Min, max	6.0, 12.3	1.7, 17.9	1.0, 16.8	1.0, 17.9	1.0, 17.9
Number of prior antimyeloma regimens					
Median (min, max)	8.5 (4, 12)	6.0 (3, 16)	5.0 (3, 13)	6.0 (3, 16)	6.0 (3, 17)
Distribution of prior antimyeloma regimens, n (%)					
3	0	8 (11.4)	7 (13.0)	15 (11.7)	16 (11.4)
4	1 (25.0)	8 (11.4)	10 (18.5)	19 (14.8)	20 (14.3)
5	0	11 (15.7)	11 (20.4)	22 (17.2)	23 (16.4)
6	1 (25.0)	12 (17.1)	10 (18.5)	23 (18.0)	25 (17.9)

≥ 7	2 (50.0)	31 (44.3)	16 (29.6)	49 (38.3)	56 (40.0)
Prior stem-cell transplant for MM, n (%)					
Yes	4 (100.0)	67 (95.7)	49 (90.7)	120 (93.8)	131 (93.6)
1 prior transplant	1 (25.0)	44 (62.9)	31 (57.4)	76 (59.4)	82 (58.6)
> 1 prior transplant	3 (75.0)	23 (32.9)	18 (33.3)	44 (34.4)	49 (35.0)
No	0	3 (4.3)	5 (9.3)	8 (6.3)	9 (6.4)
Prior radiation therapies for MM, n (%)					
Yes	2 (50.0)	45 (64.3)	24 (44.4)	71 (55.5)	75 (53.6)
No	2 (50.0)	25 (35.7)	30 (55.6)	57 (44.5)	65 (46.4)
Prior refractory status, n (%)					
Immunomodulatory agent	4 (100.0)	70 (100.0)	52 (96.3)	126 (98.4)	138 (98.6)
Proteasome inhibitor (PI)	4 (100.0)	63 (90.0)	49 (90.7)	116 (90.6)	126 (90.0)
Anti-CD38 antibodies	4 (100.0)	66 (94.3)	50 (92.6)	120 (93.8)	131 (93.6)
Daratumumab	3 (75.0)	61 (87.1)	45 (83.3)	109 (85.2)	120 (85.7)
Immunomodulatory agent and PI (double refractory)	4 (100.0)	63 (90.0)	47 (87.0)	114 (89.1)	124 (88.6)
Immunomodulatory agent, PI, and anti-CD38 antibodies (triple refractory)	4 (100.0)	60 (85.7)	44 (81.5)	108 (84.4)	117 (83.6)
Penta-refractory	1 (25.0)	24 (34.3)	8 (14.8)	33 (25.8)	37 (26.4)

a. These subjects had ECOG PS scores of < 2 at screening for eligibility but subsequently deteriorated to ECOG PS scores of 2 at baseline prior to start of LDC.

(Source: Abbreviated Table 10 MM-001 Clinical Study Report BLA 125736/0.0)

6.1.10.1.3 Subject Disposition

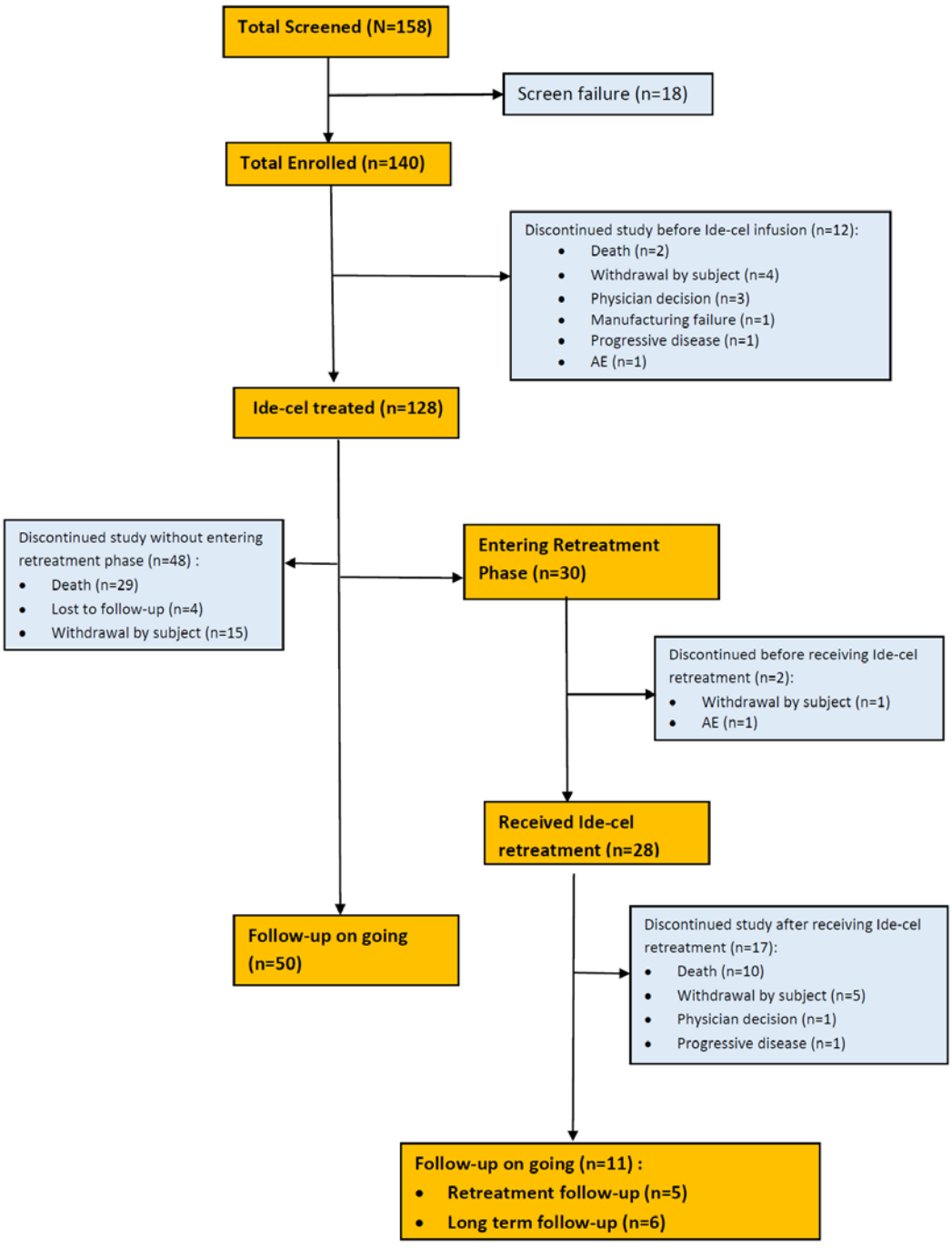
Subject disposition is summarized in Figure 1. The data cutoff was January 14th, 2020. One hundred and fifty-eight (158) subjects were screened and 18 (11.4%) were screen failure. One hundred and forty (140) subjects were enrolled into the study (ie, underwent leukapheresis). Twelve (12) (8.6%) discontinued prior to receiving ide-cel infusion.

128 subjects received ide-cel infusion. Of the 128 ide-cel-treated subjects, 61 (47.7%) subjects were still followed-up as of the data cutoff date, including 50 (39.1%) ongoing after initial ide-cel infusion without entering the retreatment period and 11 (8.6%) ongoing after entering the retreatment period.

Sixty-seven (52.3%) of the 128 ide-cel-treated subjects discontinued, with 39 (30.5%) subjects discontinuing due to death, 21 (16.4%) subjects discontinuing due to withdrawal by subject, 4 (3.1%) subject discontinuing due to lost to follow-up, 1 (0.8%) subject

discontinuing due to physician decision, and 1 (0.8%) subject discontinuing due to progressive disease.

Figure 1. Subject disposition



Data cutoff = January 14, 2020
(source: FDA statistical reviewer)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint and key secondary endpoint

The FDA clinical review team considered Subject (b) (6) not evaluable for efficacy analyses, because this subject was treated with a non-conformal product. In addition, the FDA clinical review team considered Subject (b) (6) in the 300 x 10^6 dose cohort for efficacy analyses though this subject was enrolled in the 450 x 10^6 target dose cohort. A full dose could not be manufactured, and this subject was actually treated with 339 million CAR+ T cells, which falls within the 300 million +/- 20% dose range.

The FDA clinical review team re-adjudicated the response assessments, based on which the ORR was 50% (95% CI: 6.8%, 93.2%) for the 150 x 10^6 dose level, 64.3% (95% CI: 51.9%, 75.4%) for the 300 x 10^6 dose level and 79.3% (95% CI: 65.9%, 89.2%) for the 450 x 10^6 dose level. For both the 300 x 10^6 dose level and 450 x 10^6 dose level, the lower limit of the 95% confidence interval was above the pre-set null hypothesis rate of 50%. And the CR rate for these two dose levels were 22.9% (95% CI: 13.7%, 34.5%) and 39.2% (95% CI: 18.3%, 44.3%), respectively. The lower limits of the 95% confidence intervals for both dose levels were above the pre-set null hypothesis rate of 10%. Note that the analyses by dose were post hoc analyses for this trial and there is no adjustment for multiple testing.

Table 5: Overview of Efficacy – Study MM-001 (Ide-cel-treated and Enrolled Populations)

	Ide-cel-treated Population Ide-cel (CAR+ T cells) Target Dose				**Enrolled Population (N = 140)**
	150 × 10^6 (N = 4)	**300 × 10^6 (N = 70)**	**450 × 10^6 (N = 53)**	**150 to 450 × 10^6 (N = 127)**	
ORR (≥ PR)					
n (%)	2 (50.0)	45 (64.3)	42 (79.3)	89 (70.1)	89 (63.6)
95% CI*	6.8, 93.2	51.9, 75.4	65.9, 89.2	61.3, 77.9	55.0, 71.5
sCR, n (%)	1 (25.0)	16 (22.9)	16 (30.2)	33 (26.0)	33 (23.6)
CR, n (%)	0	0	0	0	0
VGPR, n (%)	1 (25.0)	11 (15.7)	17 (32.1)	29 (22.8)	29 (20.7)
PR, n (%)	0	18 (25.7)	9 (17.0)	27 (21.3)	27 (19.3)
CR rate (≥ CR)					
n (%)	1 (25.0)	16 (22.9)	16 (30.2)	33 (26.0)	33 (23.6)
95% CI*	0.6, 80.6	13.7, 34.5	18.3, 44.3	18.6, 34.5	16.8, 31.5
≥ VGPR rate					
n (%)	2 (50.0)	27 (38.6)	33 (62.3)	62 (48.8)	62 (44.3)
95% CI*	6.8, 93.2	27.2, 51.0	47.9, 75.2	39.9, 57.8	35.9, 52.9

Data cutoff=January 14, 2020

*Clopper-Pearson exact CI

(Source: FDA statistical reviewer)

6.1.11.2 Analyses of Other Secondary Endpoints

Duration of response (DOR)
Table 6 summarizes the DOR results based on FDA re-adjudication. The follow-up time ranged from 0.03 to 20 months with a median of 10.5 months. The estimated median DOR was 10.0 months (95% CI: 5.4, 11.0) for the 300 x 10^6 dose level, and 11.3 months (95% CI: 10.3, 11.4) for the 450 x 10^6 dose level. The 150 x 10^6 dose level had only 2 responders, and the median DOR was not estimable.

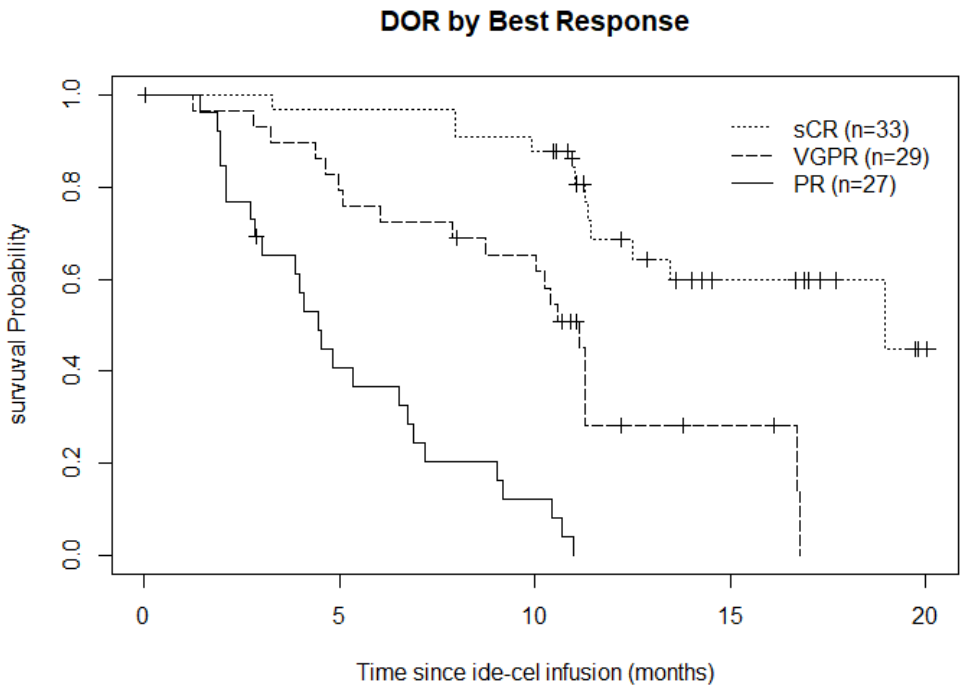
The duration of response was strongly associated with the BOR: subjects whose BOR was sCR had the longest DOR, subjects whose BOR was PR had the shortest DOR of the three (Figure 2). The estimated median DOR and 95% CIs were 19.0 months (11.4, N.E.), 11.1 months (7.9, 11.3), and 4.5 months (2.9, 6.7) for the three BOR subgroups, respectively. This reviewer also examined the association between DOR and dosage, and the result was inconclusive, due to small sample size in the 150 x 10^6 dose group, and high percentage of censoring in the 450 x 10^6 dose group (Figure 3).

Table 6. Duration of Response – Study MM-001 (BOR≥ PR)

	Ide-cel-treated Population Ide-cel (CAR+ T cells) Target Dose			
	150 × 10^6 (N = 2)	**300 × 10^6 (N = 45)**	**450 × 10^6 (N = 42)**	**150 to 450 × 10^6 (N = 89)**
DOR (months)				
Median	N.E.	10.0	11.3	11.0
95% CI[b]	(2.8, N.E.)	(5.4, 11.0)	(10.3, 11.4)	(9.0, 11 3)
Follow-up duration (months)				
Median (min, max)	11.3 (2.8, 19.8+)	9.0 (0.03+, 20.0+)	10.8 (1 2, 14 5+)	10.5 (0.03+, 20+)
Percentage censored	1 (50%)	12 (26.7%)	19 (45 2%)	32 (36.0%)
On-going without event	1 (50%)	9 (20%)		29 (32.6%)
Discontinued study without progression /death	0	1 (2.2%)	19 (45 2%)	1 (1.1%)
New anti-mm therapy	0	1 (2.2%)	0	1 (1.1%)
Progression after two or more missed assessments	0	1 (2.2%)	0	1 (1.1%)
DOR by BOR				
BOR is CR or sCR				
Median (95% CI)	N.A.	19.0 (10.9, N.E.)	N.E. (11.3, N.E.)	19.0 (11.4, N.E.)
Percentage censored	100%	50%	75%	62.5%
BOR is VGPR				
Median (95% CI)	N.A.	10.0 (5.0, 16.7)	11.3 (8.7, 11.3)	11.1 (7.9, 11.3)
Percentage censored	0%	18.2%	41.2%	32%
BOR is PR				
Median (95% CI)	N.A.	4.5 (2.1, 7.2)	4.5 (1.9, 6.9)	4.5 (2.9, 6.7)
Percentage censored	N.A.	11.1%	0	7.4%

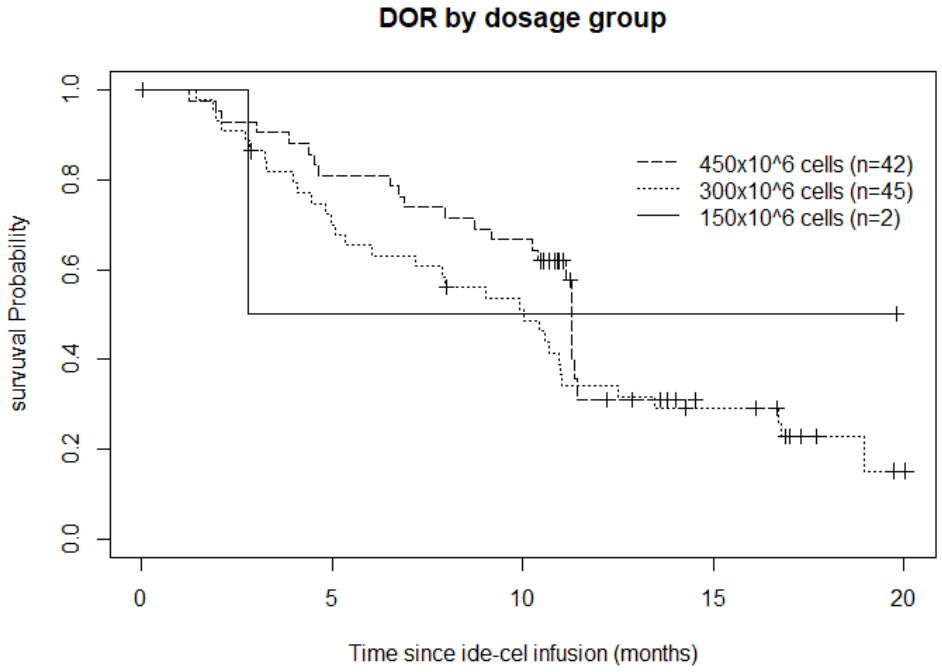
Data cutoff=January 14, 2020 b. +: censored (Source: FDA statistical reviewer)

Figure 2. DOR by BOR



(Source: FDA statistical reviewer)

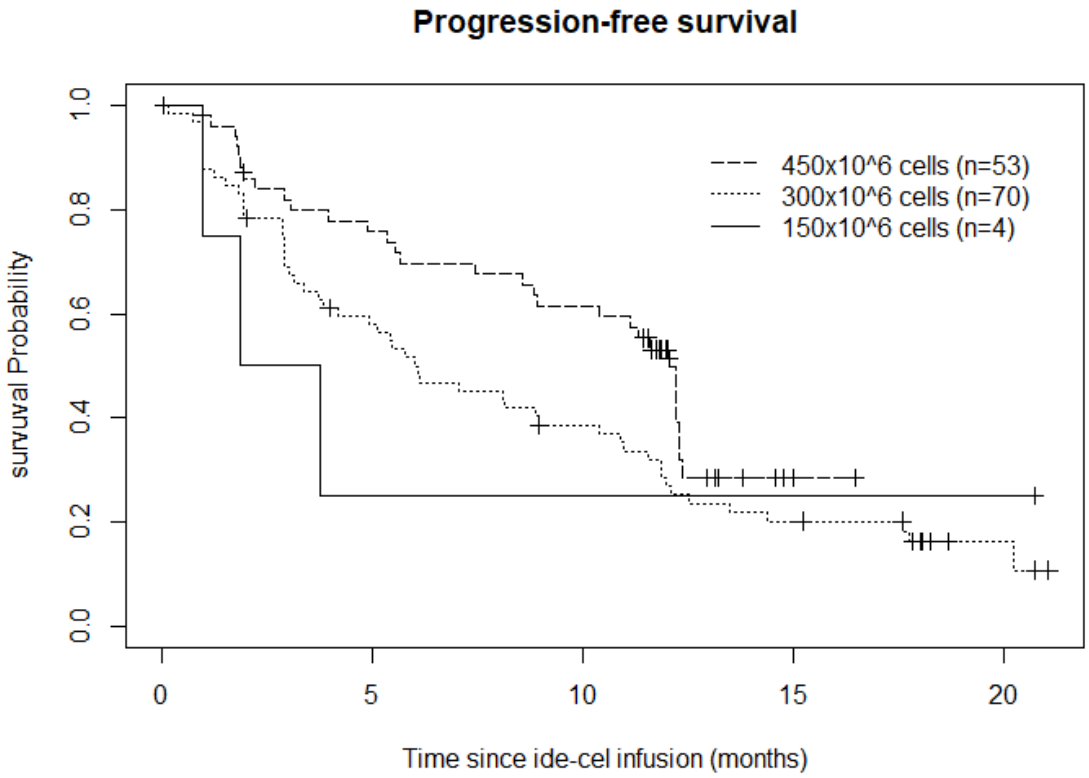
Figure 3. DOR by dosage group



(Source: FDA statistical reviewer)

a. Progression-free survival
Figure 4 shows the Kaplan-Meier curves of PFS by dosage group. It appears that the lowest dosage group had shorter PFS than the other dosage groups, but the sample size in the lowest dosage group is too small to make any meaningful conclusion.

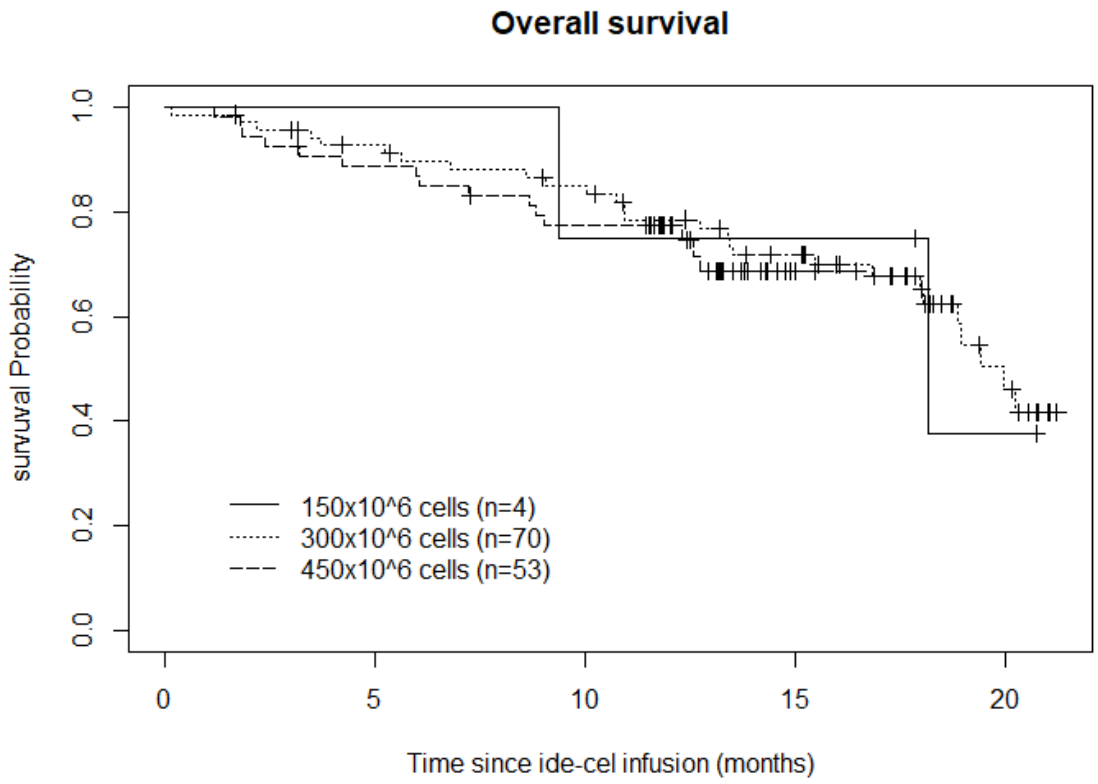
Figure 4. PFS by dosage group



(Source: FDA statistical reviewer)

b. Overall survival
Figure 5 shows the Kaplan-Meier curves of OS by dosage group. The censoring is too heavy to draw any meaningful conclusions.

Figure 5. OS by dosage group



(Source: FDA statistical reviewer)

6.1.11.3 Subpopulation Analyses

ORR appears to be consistent across race, ethnicity, age category and sex (Table 7).

Table 7. ORR by age group, ethnicity, race and sex

Subgroup		# of subjects treated (N=127) n (%)	ORR # of responders (%)	95% CI[a] (%)
Age	<=65 years	82 (65%)	51 (62.2%)	(50.8, 72.7)
	>65 years	45 (35%)	38 (84.4%)	(70.5, 93.5)
Sex	Female	51 (40%)	39 (76.5%)	(62.5, 87.2)
	Male	76 (60%)	50 (65.8%)	(54, 76.3)
Race	White	102 (80%)	71 (69.6%)	(59.7, 78.3)
	Asian	3 (2%)	3 (100%)	(29.2, 100)
	Black or African American	6 (5%)	3 (50%)	(11.8, 88.2)
	Other	6 (5%)	4 (66.7%)	(22.3, 95.7)
	Unknown	10 (8%)	8 (80%)	(44.4, 97.5)
Ethnicity	HISPANIC OR LATINO	10 (8%)	7 (70%)	(34.8, 93.3)
	NOT HISPANIC OR LATINO	103 (81%)	72 (69.9%)	(60.0, 78.6)
	Not reported	9 (7%)	7 (77.8%)	(40.0, 97.2)
	Unknown	5 (4%)	3 (60%)	(14.7, 94.7)
Overall	127 (100%)	127 (100%)	89 (70.1%)	(61.3, 77.9)

a. Clopper-Pearson exact confidence interval

(Source: FDA statistical reviewer)

Table 8 shows subgroup analysis of ORR by study site. ORR is generally consistent across study sites. Though some sites had lower ORR than others, the number of subjects treated at these sites was too small to make any meaningful conclusion.

Table 8. Subgroup analysis of ORR by study site

Study Site	# of subjects treated (total=127) n (%)	ORR # of responders (%)
101	10 (7.9%)	5 (50%)
102	8 (6.3%)	7 (87.5%)
103	11 (8.7%)	7 (63.6%)
104	16 (12.6%)	12 (75%)
105	9 (7.1%)	6 (66.7%)
106	7 (5.5%)	5 (71.4%)
107	7 (5.5%)	3 (42.9%)
108	14 (11%)	10 (71.4%)
109	11 (8.7%)	7 (63.6%)
201	3 (2.4%)	3 (100%)
301	1 (0.8%)	1 (100%)
401	4 (3.2%)	3 (75%)
402	4 (3.2%)	3 (75%)
501	2 (1.6%)	1 (50%)
502	2 (1.6%)	2 (100%)
503	2 (1.6%)	2 (100%)
601	2 (1.6%)	2 (100%)
602	1 (0.8%)	1 (100%)
701	8 (6.3%)	6 (75%)
702	5 (3.9%)	3 (60%)
Overall	127 (100%)	89 (70.1%)

(Source: FDA statistical reviewer)

6.1.11.4 Dropouts and/or Discontinuations

One hundred and forty (140) subjects were enrolled, 12 (8.6%) discontinued before receiving ide-cel. Sixty-seven (52.3%) of the 128 ide-cel-treated were no longer in the follow-up. The details of the dropouts/discontinuations are provided in 6.1.10.1.3 Subject Disposition.

6.1.12 Safety Analyses

This section summarizes safety results of Study MM-001.

6.1.12.1 Methods

Descriptive statistics are used to summarize safety data for study MM-001. For data summary, the safety analysis set in this section includes a total of 128 subjects who received at least one dose of ide-cel. The data cutoff was April 07th, 2020, as in the 3-Month Safety Update submitted by the application in amendment SN0012.

6.1.12.3 Deaths

The applicant reported that 47 subjects (36.7%) had died as of the data cutoff of April 7th, 2020. Twenty-nine subjects (29) died due to multiple myeloma or complication due to multiple myeloma. Fourteen subjects (14) died within 6 months of ide-cel infusion, and 33 subjects died > 6 months after the ide-cel infusion. Ten subjects died due to AEs. Deaths are summarized in Table 9.

Table 9. Deaths in the safety analysis set

	<=8 weeks	>8weeks to <=6 months	>6 months to <=24 months	>24 moths	Total (n=128)
Total number of deaths, n (%)	5 (3.9)	9 (7.0)	33 (25.8)	0	47 (36.7)
Primary cause of death, n (%)					
Death from multiple myeloma, or complication due to multiple myeloma	2 (1.6)	8 (6.3)	19 (14.8)	0	29 (22.7)
Adverse event	3 (2.3)	1 (0.8)	6 (4.7)	0	10 (7.8)
Other	0	0	8 (6.3)	0	8 (6.3)

Data cutoff date=07APR2020
(Source: abbreviated Table 14.3.2.10.2 3-Month Safety Update Report 12703/0.11)

6.1.12.4 Nonfatal Serious Adverse Events

The applicant reported 87 (68%) subjects in the safety analysis set had at least one Serious Adverse Events on or after ide-cel infusion, 57(44.5%) subjects had at least one SAE within 8 weeks of ide-cel infusion. The most common SAEs were Cytokine Release Syndrome (22 subjects, 17.2%).

6.2 Trial #2 (CRB-401)

This section briefly reviews the supportive study CRB-401.

6.2.2 Design Overview

Study CRB-401 is a first-in-human (FIH), dose escalation and expansion, Phase 1 study in subjects with relapsed or refractory multiple myeloma. The dose escalation part used the 3+3 design. In the expansion part, subjects were to be treated at the recommended phase 2 dose (RP2D)(s) selected based on results from the dose escalation part.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

6.2.10.1.1 Demographics

Demographic characteristics were well-balanced across the target dose levels. The median age of subjects in the ide-cel-treated population (N = 62) was 61.0 years (range: 37, 75) and more than half (62.9%) of these subjects were < 65 years of age. The majority were male (62.9%) and 88.7% were white.

Table 10. Subject Demographics – Study CRB-401

	Ide-cel-treated Population						**Enrolled Population (N = 67)**
	Parts A and B Combined by Ide-cel (CAR+ T Cells) Target Dose				**RP2D (N = 56)**	**Total Study (N = 62)**	
	50×10^6 (N = 3)	**150×10^6 (N = 18)**	**450×10^6 (N = 38)**	**800×10^6 (N = 3)**			
Age (years)							
Median	60.0	63.5	61.0	57.0	61.5	61.0	61.0
Min, max	58, 68	44, 75	37, 74	41, 67	37, 75	37, 75	37, 80
Age group (years), n (%)							
< 65	2 (66.7)	10 (55.6)	25 (65.8)	2 (66.7)	35 (62.5)	39 (62.9)	43 (64.2)
≥ 65	1 (33.3)	8 (44.4)	13 (34.2)	1 (33.3)	21 (37.5)	23 (37.1)	24 (35.8)
< 75	3 (100.0)	17 (94.4)	38 (100.0)	3 (100.0)	55 (98.2)	61 (98.4)	65 (97.0)
≥ 75	0	1 (5.6)	0	0	1 (1.8)	1 (1.6)	2 (3.0)
Sex, n (%)							
Female	1 (33.3)	5 (27.8)	15 (39.5)	2 (66.7)	20 (35.7)	23 (37.1)	24 (35.8)
Male	2 (66.7)	13 (72.2)	23 (60.5)	1 (33.3)	36 (64.3)	39 (62.9)	43 (64.2)
Ethnicity, n (%)							
Hispanic or Latino	0	0	1 (2.6)	0	1 (1.8)	1 (1.6)	1 (1.5)
Not Hispanic or Latino	1 (33.3)	16 (88.9)	37 (97.4)	2 (66.7)	53 (94.6)	56 (90.3)	60 (89.6)
Not reported	2 (66.7)	2 (11.1)	0	1 (33.3)	2 (3.6)	5 (8.1)	6 (9.0)
Race, n (%)							
White	2 (66.7)	15 (83.3)	35 (92.1)	3 (100.0)	50 (89.3)	55 (88.7)	59 (88.1)
Black or African American	0	2 (11.1)	2 (5.3)	0	4 (7.1)	4 (6.5)	4 (6.0)
Asian	1 (33.3)	0	1 (2.6)	0	1 (1.8)	2 (3.2)	2 (3.0)
Other	0	1 (5.6)	0	0	1 (1.8)	1 (1.6)	2 (3.0)

Data cutoff=22 Jul 2019

(source: Abbreviated Table 21 CRB-401 Clinical Study Report BLA 125736/0.0)

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline disease characteristics of Study CRB-401 are summarized in Table 11. The median number of prior antimyeloma regimens for the ide-cel-treated population was 6.0 (range: 3, 18), with 54.8% of subjects receiving ⩾ 6 prior regimens and 91.9% of subjects receiving at least one prior stem-cell transplant (25.8% received at least 2 prior

stem cell transplants). 80.6% of subjects were double refractory and 69.4% of subjects were triple refractory.

Table 11. Subject Baseline Disease Characteristics – CRB401

	Ide-cel-treated Population						Enrolled Population (N = 67)
	Parts A and B Combined by Ide-cel (CAR+ T Cells) Target Dose				RP2D (N = 56)	Total Study (N = 62)	
	50×10^6 (N = 3)	150×10^6 (N = 18)	450×10^6 (N = 38)	800×10^6 (N = 3)			
ECOG performance status category, n (%)							
0	1 (33.3)	5 (27.8)	9 (23.7)	1 (33.3)	14 (25.0)	16 (25.8)	17 (25.4)
1	1 (33.3)	13 (72.2)	28 (73.7)	2 (66.7)	41 (73.2)	44 (71.0)	47 (70.1)
≥ 2	1 (33.3)	0	1 (2.6)	0	1 (1.8)	2 (3.2)	3 (4.5)
Tumor BCMA level, n (%)							
Low (< 50%)	1 (33.3)	8 (44.4)	11 (28.9)	0	19 (33.9)	20 (32.3)	21 (31.3)
High (≥ 50%)	2 (66.7)	10 (55.6)	20 (52.6)	3 (100.0)	30 (53.6)	35 (56.5)	37 (55.2)
Missing	0	0	7 (18.4)	0	7 (12.5)	7 (11.3)	9 (13.4)
Median number of prior antimyeloma regimens (min, max)	4.0 (3, 11)	8.0 (4, 15)	6.0 (3, 18)	6.0 (5, 7)	6.0 (3, 18)	6.0 (3, 18)	NA
Prior antimyeloma regimens, n (%)							
≤ 6	2 (66.7)	8 (44.4)	22 (57.9)	2 (66.7)	30 (53.6)	34 (54.8)	36 (53.7)
> 6	1 (33.3)	10 (55.6)	16 (42.1)	1 (33.3)	26 (46.4)	28 (45.2)	31 (46.3)
Prior ASCT, n (%)	3 (100.0)	16 (88.9)	35 (92.1)	3 (100.0)	51 (91.1)	57 (91.9)	NA
1 prior transplant	2 (66.7)	11 (61.1)	26 (68.4)	2 (66.7)	37 (66.1)	41 (66.1)	NA
> 1 prior transplant	1 (33.3)	5 (27.8)	9 (23.7)	1 (33.3)	14 (25.0)	16 (25.8)	NA
Refractory to last prior therapy, n (%)[j]	1 (33.3)	11 (61.1)	34 (89.5)	1 (33.3)	45 (80.4)	47 (75.8)	NA
Prior refractory status, n (%)							
Immunomodulatory agent	1 (33.3)	16 (88.9)	36 (94.7)	2 (66.7)	52 (92.9)	55 (88.7)	NA
Proteasome inhibitor	1 (33.3)	15 (83.3)	33 (86.8)	3 (100.0)	48 (85.7)	52 (83.9)	NA
Anti-CD38 antibody	0	14 (77.8)	35 (92.1)	1 (33.3)	49 (87.5)	50 (80.6)	NA
Immunomodulatory agent and PI (double-refractory)	1 (33.3)	15 (83.3)	32 (84.2)	2 (66.7)	47 (83.9)	50 (80.6)	NA
Immunomodulatory agent, PI, and anti-CD38 antibody (triple-refractory)	0	13 (72.2)	29 (76.3)	1 (33.3)	42 (75.0)	43 (69.4)	NA

Data cutoff=22 Jul 2019

(source: Abbreviated Table 22 CRB-401 Clinical Study Report BLA 125736/0.0)

6.2.10.1.3 Subject Disposition

A total of 67 subjects were enrolled into Study CRB-401, including 24 subjects in Part A (dose escalation) and 43 subjects in Part B (dose expansion). Of the 67 enrolled subjects, 5 discontinued prior to ide-cel administration and a total of 62 (92.5%) enrolled subjects received ide-cel infusion. As of the data cutoff (22 July 2019), of the 62 ide-cel-treated subjects, 45 (72.6%) discontinued from Study CRB-401 after receiving ide-cel, with the most common reasons being due to progressive disease (32 subjects; 51.6%) and death (6 subjects; 9.7%). A total of 17 (27.4%) subjects underwent retreatment with a second dose of ide-cel following disease progression.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The results for the ORR are presented in Table 12. The ORR for the **150×10^6** dosage group and **450×10^6** dosage group seem to be consistent with that of study MM-001.

Table 12. Response Rate for Study CRB-401

	Ide-cel-treated Population						**Enrolled Population (N = 67)**
	Parts A and B Combined by Ide-cel (CAR+ T Cells) Target Dose				**RP2D (N = 56)**	**Total Study (N = 62)**	
	50×10^6 (N = 3)	**150×10^6 (N = 18)**	**450×10^6 (N = 38)**	**800×10^6 (N = 3)**			
ORR, n (%)[b]	1 (33.3)	10 (55.6)	32 (84.2)	3 (100.0)	42 (75.0)	46 (74.2)	46 (68.7)
95% CI[c]	0.8, 90.6	30.8, 78.5	68.7, 94.0	29.2, 100.0	61.6, 85.6	61.5, 84.5	56.2, 79.4
VGPR rate, n (%)[b]	0	7 (38.9)	27 (71.1)	3 (100.0)	34 (60.7)	37 (59.7)	37 (55.2)
95% CI[c]	0.0, 70.8	17.3, 64.3	54.1, 84.6	29.2, 100.0	46.8, 73.5	46.4, 71.9	42.6, 67.4
CR rate, n (%)[b]	0	6 (33.3)	14 (36.8)	2 (66.7)	20 (35.7)	22 (35.5)	22 (32.8)
95% CI[c]	0.0, 70.8	13.3, 59.0	21.8, 54.0	9.4, 99.2	23.4, 49.6	23.7, 48.7	21.8, 45.4

Data cutoff=22 Jul 2019

(source: Original Table 27 CRB-401 Clinical Study Report BLA 125736/0.0)

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary source of evidence to support this application is a Phase II, single-arm, multicenter study (MM-001). The primary efficacy endpoint was overall remission rate (ORR), which is defined as the proportion of subjects who achieved partial response (PR)

or better (i.e. stringent complete response, complete response, very good partial response, partial response) as assessed by an independent review committee (IRC).

Study MM-001 enrolled 140 subjects, of whom 127 were infused with conformal ide-cel. Subjects were treated at 3 target dose levels: 150 x 10^6 (N=4), 300 x 10^6 (N=70) and 450 x 10^6 (N=53) chimeric antigen receptor (CAR)-positive T cells. The FDA clinical review team re-adjudicated the response assessments, based on which the ORR was 50% (95% CI: 6.8%, 93.2%) for the 150 x 10^6 dose level, 64.3% (95% CI: 51.9%, 75.4%) for the 300 x 10^6 dose level and 79.3% (95% CI: 65.9%, 89.2%) for the 450 x 10^6 dose level, respectively.

For both the 300 x 10^6 dose level and 450 x 10^6 dose level, the lower limits of the 95% confidence intervals for ORR were above the pre-set null hypothesis rate of 50%. The CR rate for these two dose levels were 22.9% (95% CI: 13.7%, 34.5%) and 39.2% (95% CI: 18.3%, 44.3%), respectively. The lower limits of the 95% confidence intervals for CR for both dose levels were above the pre-set null hypothesis rate of 10%.

Follow-up time for Duration of Response (DOR) ranged from 1 day to 20 months with a median of 10.5 months. The estimated median DOR was 10.0 months (95% CI: 5.4, 11.0) for the 300 x 10^6 dose level, and 11.3 months (95% CI: 10.3, 11.4) for the 450 x 10^6 dose level.

These results are also supported by Study CRB-401, a first-in-human, dose escalation and expansion, Phase 1 trial. A total of 62 subjects were enrolled in four different dosage groups, 50 x 10^6, 150 x 10^6, 450 x 10^6, and 800 x 10^6. The ORRs for the 150 × 10^6 dosage group with 18 subjects and 450 × 10^6 dosage group with 38 subjects are generally consistent with those of study MM-001.

10.2 Conclusions and Recommendations

The two dose levels, 300 x 10^6 and 450 x 10^6, in Study MM-001 met the primary efficacy endpoint: The pre-specified null hypothesis of 50% ORR was rejected. The statistical analysis results support the product's effectiveness in the proposed indication.