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Application Type	PAS Efficacy BLA
STN	125736/218
CBER Received Date	February 15, 2023
PDUFA Goal Date	December 16, 2023
Division / Office	DB/OBPV
Committee Chair	Poornima Sharma
Clinical Reviewer(s)	Poornima Sharma
Project Manager	Hawa Camara
Priority Review	No
Reviewer Name(s)	Xue Lin
Review Completion Date / Stamped Date	
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Lead, FDA/CBER/OBPV/DB/TEB1
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBPV/DB/TEB1
	John Scott, Ph.D. Division Director, FDA/CBER/OBPV/DB
Applicant	Celgene Corporation, a Bristol-Myers Squibb Company
Established Name	idecabtagene vicleucel
Trade Name	ABECMA
Pharmacologic Class	BCMA-directed genetically-modified autologous T cell
Dosage Form(s) and Route(s) of Administration	Single intravenous infusion
Dosing Regimen	A single dose of ABECMA contains a cell suspension of 300 to 510 x 106 CAR-positive T cells in one or more infusion bags
Proposed Indication(s) and Intended Population(s)	adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

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GLOSSARY

ASCT	autologous stem cell transplant
BLA	Biologics Licensure Application
BOR	best overall response
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete remission
CRS	cytokine release syndrome
CSR	clinical study report
DLBCL	diffuse large B cell lymphoma
DOR	duration of remission
Data Safety Monitoring Board	DSMB
PFS	event free survival
FAS	full analysis set
HDT	high-dose therapy
HGBL	high-grade B-cell lymphoma
IPI	International Prognostic Index
IRC	independent review committee
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
LBCL	large B-cell lymphoma
ORR	overall remission rate
OS	overall survival
PAS	Prior Approval Supplement
PD	progressive disease
PFS	Progression-free survival
PR	partial response
QoL	quality of life
r/r	relapsed/refractory
SAE	serious adverse event
SCT	stem-cell transplantation
SD	stable disease
SOC	standard of care
TBI	total body irradiation
NHL	non-Hodgkin lymphoma

1. EXECUTIVE SUMMARY

Idecabtagene vicleucel (Abecma) is an autologous BCMA CAR T cell immunotherapy. Idecabtagene vicleucel received the FDA Biological Licensure Approval (BLA) approval in March 2021 for the indication of "Treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more lines of systemic therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD 38 monoclonal antibody." In this Prior Approval Supplement (PAS), the applicant seeks to expand indication to earlier lines of treatment. Proposing to remove "after 4 or more lines of systemic therapy," the new proposed indication is "Adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor (PI) and an anti-CD 38 monoclonal antibody."

The primary source of evidence to support the efficacy and the safety of the product in the proposed expanded indication comes from study BB2121-MM-003, which was a multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of ide-cel versus standard of care (SOC) regimens in subjects with relapsed or refractory multiple myeloma (RRMM) who have received 2 to 4 prior myeloma regimens including daratumumab (DARA), an immunomodulatory compound (IMiD), and a protease inhibitor (PI) and must have documented disease progression during or within 60 days after the last therapy. In BB2121-MM-003, 386 subjects were randomized in a 2:1 ratio to receive ide-cel or SOC regimens. The primary endpoint was progression-free survival (PFS) determined by independent review committee (IRC). The two key secondary endpoints were overall response rate (ORR) and overall survival (OS).

At the pre-specified second interim analysis for PFS, based on 242 PFS events (cut-off date of April 18th, 2022), subjects randomized to receive ide-cel had statistically significant improvement in PFS compared with subjects randomized to receive SOC. The median PFS was 13.3 months (95% CI: 11.8 to 16.1) for the ide-cel arm and 4.4 months (95% CI: 3.4 to 5.9) for the SOC arm, with a stratified hazard ratio of 0.493 (95% CI: 0.377 to 0.645), and a stratified log-rank test p-value<0.0001. Subjects in the ide-cel arm also had statistically significantly higher ORR compared with subjects in the SOC arm. The ORR was 71.3% (95% CI: 65.3%, 76.7%) for the ide-cel arm and 41.7% (95% CI: 33.2%, 50.6%) for the SOC arm, with a difference of 29.6% (95% CI: 18.9, 40.3), and with a p-value < 0.0001 based on the Cochran-Mantel-Haenszel (CMH) test. The CR/sCR (compete response or stringent compete response) rate in the ide-cel arm and the SOC arms were 38.6% (95% CI: 32.6%, 44.9%) and 5.3% (95% CI: 2.2%, 10.6%), respectively.

Despite the statistically significant improvement in PFS and ORR, the ide-cel arm did not show improvement over SOC in OS. Based on the most recent updated OS analysis with a cutoff date of April 28, 2023, the two Kaplan-Meier OS curves crossed at around 15 months after randomization, with the ide-cel arm having lower survival probability compared with SOC in the first 15 months. There was heavy censoring after the OS

crossing point. The OS results were confounded by the treatment crossover from the SOC to ide-cel upon disease progression.

The Applicant argued, at the Oncologic Drug Advisory Committee (ODAC) meeting held on March 15, 2024, that the early OS detriment is driven by patients who did not receive ide-cel likely due to inadequate bridging in the ide-cel arm and the numerically worse overall survival could be due to random variation. At the meeting, the Applicant also argued the overall survival was confounded by treatment cross-over, and after crossover adjusted analysis, the average hazard ratio was less than 1. However, these adjusted analyses were sensitivity analyses, some pre-specified and some conducted on a post-hoc basis. Additionally, such analyses rely on untestable assumptions and cannot be used to ascertain that ide-cel treatment has OS benefit when the ITT analysis, the pre-specified primary analysis, clearly indicates potential early OS detriment. In addition, in the presence of crossing hazards or a delayed effect, the average hazard ratio is not an adequate population-level summary of the treatment effect. Hence, an average hazard ratio less than 1 cannot be used in such cases as convincing evidence to weigh against the observed early detrimental effect of ide-cel on survival. Eight ODAC committee members voted "Yes" and three voted "No" to the voting question "Is the risk-benefit assessment for idecabtagene vicleucel for the proposed indication, favorable?"

In summary, ide-cel met the primary endpoint of PFS with statistical significance but demonstrated a potential early OS detriment. The interpretation of the OS results for the trial as a whole is confounded by treatment crossover. Based on the collective statistical evidence, I recommend against approval until an additional trial with properly chosen eligibility criteria is conducted to further evaluate the benefits and risk profile of ide-cel in the context of earlier line RRMM.

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)

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.

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

Table 1 summarizes the major regulatory milestone associated with this sBLA.

Table 1. Major regulatory milestones

Milestone	Date
Orphan drug designation granted	May 11, 2016
Breakthrough Therapy Designation granted	Nov 14, 2017
Original BLA submission	July 27, 2020
Pre-sBLA meeting	December 1, 2022
sBLA DCC Receipt Date	February 15, 2023
Filling Letter issued	April 14, 2023
Mid-Cycle Meeting	July 17, 2023
PUDUFA Action Due Date	December 16, 2023
ODAC	March 15, 2024

(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 BB2121-MM-003, which is the focus of this review memo.

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

The basis of this statistical memo is clinical study reports (CSR) and data sets submitted in module 5 of the BLA submission.

5.3 Table of Studies/Clinical Trials

Table 2 summarizes the major studies included in the sBLA submission.

Table 2. Major studies supporting the proposed indication in the sBLA submission

Type of Study	Description of Study	Role in the Application
BB2121-MM-003	Phase 3, multicenter, randomized, open-label study comparing the efficacy and safety of ide-cel vs standard regimen	Primary source of evidence for efficacy and safety
BB2121- MM-001	Phase 2 multicenter, open-label, single-arm study to evaluate the efficacy and safety of ide-cel	Supporting safety
BB2121-MM-002	Phase 2 multicohort, open-label, multicenter study to determine the preliminary efficacy and safety of ide-cel	Supporting safety

(Source: Abbreviated Table 1.5-1 Section 2.5 clinical overview sBLA 125736/218)

5.4 Consultations

5.4.1 Advisory Committee Meeting

This sBLA was discussed at the afternoon session of the Oncologic Drug Advisory Committee (ODAC) meeting on March 15, 2024. The following voting question was posed to the committee:

Is the risk-benefit assessment for idecabtagene vicleucel for the proposed indication, favorable?

Eight committee members voted “Yes”, three voted “No”.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 (Study BB2121-MM-003)

6.1.1 Objectives

Primary Objective:

To compare the efficacy of ide-cel to standard regimens in subjects with RRMM as measured by progression-free survival (PFS)

Secondary Objectives:

- Evaluate the safety of ide-cel compared to standard regimens in subjects with RRMM

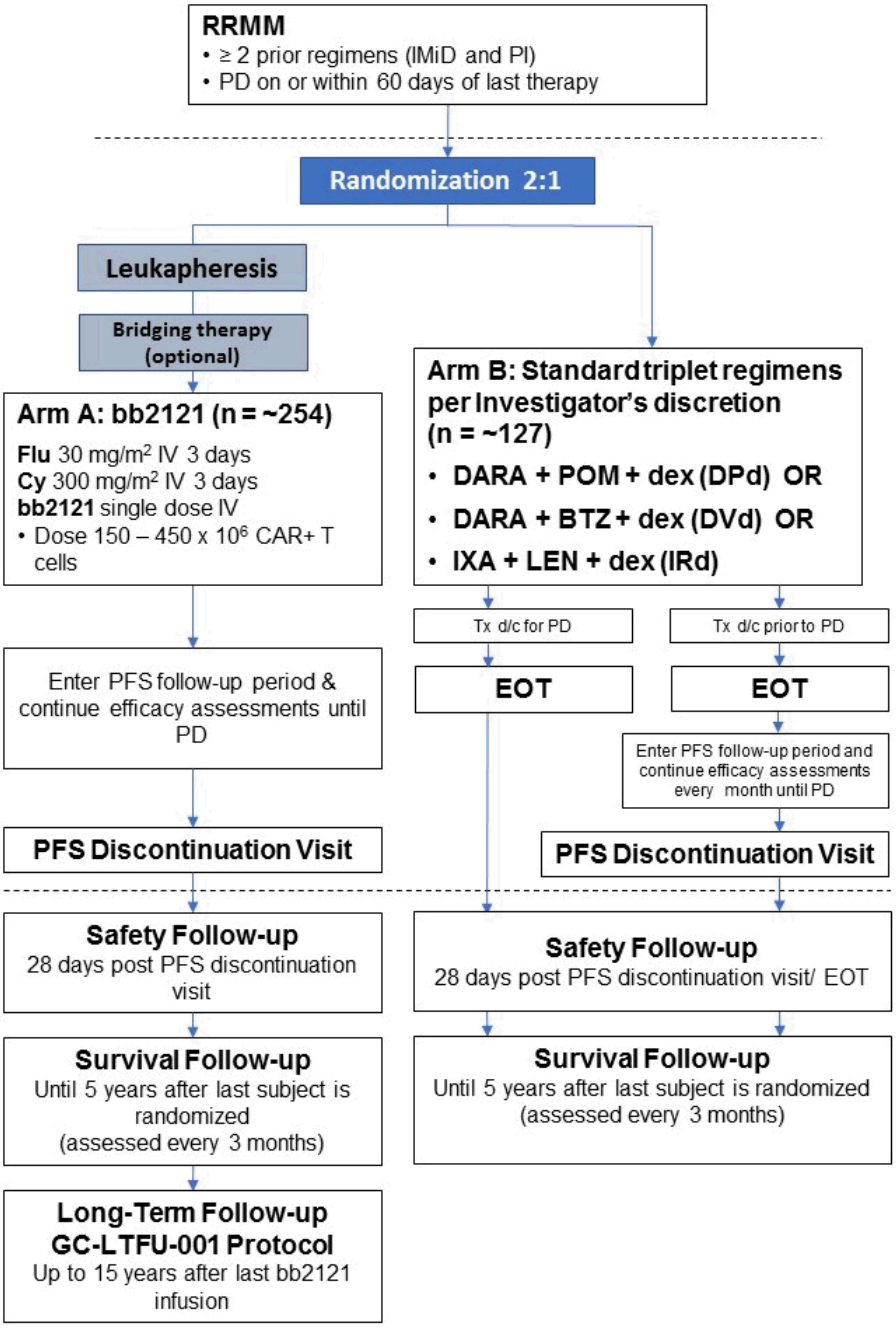
- Evaluate additional efficacy parameters of ide-cel compared to standard regimens in subjects with RRMM including overall response rate (ORR) and overall survival (OS)
- Characterize the expansion and persistence of chimeric antigen receptor (CAR) + T cells, in the peripheral blood (cellular kinetics-pharmacokinetics [PK])
- Evaluate the percentage of subjects who attain minimal residual disease (MRD) negative status by next-generation sequencing (NGS)
- Evaluate the impact of ide-cel compared to standard regimens on the changes in health-related quality of life (HRQoL)
- Evaluate the impact of ide-cel on health utility values compared with standard regimens

6.1.2 Design Overview

Figure 1 shows the study schema of BB2121-MM-003. Study BB2121-MM-003 was a multicenter, randomized, open-label, Phase 3 study, comparing the efficacy and safety of ide-cel versus standard regimens in subjects with RRMM who have received 2 to 4 prior myeloma regimens including daratumumab (DARA), an immunomodulatory compound (IMiD), and a protease inhibitor (PI) and must have documented disease progression during or within 60 days after the last therapy.

Randomization ratio was 2:1 (ide-cel vs. standard regimens) and randomization was stratified by age (< 65 years, ≥ 65 years), number of prior anti-myeloma regimens (2 vs. 3 or 4), and high risk cytogenetic abnormalities (t[4;14] or t[14;16) or del 17p: presence of known high risk cytogenetic abnormalities versus absence or unknown presence of high risk cytogenetic abnormalities).

Figure 1. Study Schema



BTZ = bortezomib; Cy = cyclophosphamide; DARA = daratumumab; d/c = discontinuation; dex = dexamethasone; EOT = End of Treatment; Flu = fludarabine; IMiD = Immunomodulatory compound; IV = intravenous; IXA = ixazomib; LEN = lenalidomide; PD = progressive disease; PFS = progression-free survival; PI = proteasome inhibitor; POM = pomalidomide; RRMM = relapsed and refractory multiple myeloma; Tx = treatment

(Source: original figure 3.1-1 Section 3.1 CSR sBLA 125736/218)

6.1.3 Population

The study population consisted of subjects ⩾ 18 years of age with RRMM who had received 2 to 4 prior myeloma regimens, including DARA, an immunomodulatory agent and a PI and had documented disease progression during or within 60 days after the last therapy. Detailed inclusion and exclusion criteria are in Section 4.2 and 4.3 of the study protocol.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects randomized to the ide-cel arm underwent leukapheresis to enable ide-cel generation. Per Investigator's discretion, subjects may receive 1 cycle or less of DPd or DVd or IRd as bridging MM therapy following leukapheresis as long as the last dose was administered ≥ 14 days prior to initiation of lymphodepleting (LD) chemotherapy. After ide-cel drug product had been successfully manufactured, additional baseline evaluation was performed to assess continued eligibility and safety at least 3 days prior to initiation of LD chemotherapy (including disease staging assessments for those subjects who received bridging MM therapy). Subjects eligible for treatment received 3 consecutive days of LD chemotherapy with fludarabine and cyclophosphamide, followed by 2 days of rest and subsequently ide-cel infusion on Day 1.

Subjects would be followed for safety and efficacy until documented progressive disease (PD) or withdrawal of consent. All subjects who received ide-cel would continue to be monitored for long term safety after exposure to gene-modified T cells under a separate Long-term Follow-up product (LTFU) study protocol for up to 15 years after ide-cel infusion, as per competent authority guidelines.

Subjects randomized to standard regimens received one of the following study treatments per Investigator's discretion:

- Daratumumab (DARA) in combination with pomalidomide (POM) and low-dose dexamethasone (dex) (DPd)
- DARA in combination with bortezomib (BTZ) and low-dose dex (DVd)
- Ixazomib (IXA) in combination with lenalidomide (LEN) and low-dose dex (IRd)
- Carfilzomib (CFZ) in combination with low-dose dexamethasone (Kd)
- Elotuzumab (ELO) in combination with POM and low-dose dexamethasone (EPd)

6.1.6 Sites and Centers

This study was conducted at 49 sites in North America, Europe, and Japan.

6.1.7 Surveillance/Monitoring

As part of the Data Review Plan, Medical Monitors reviewed individual subject data on an ongoing basis, including, but not limited to, the following: subject eligibility, SAEs for expedited SUSAR reporting, AEs for any potential safety signals or safety concerns, dose delay, dose resumption, dose interruption, and dose discontinuation. In addition, efficacy

and safety were periodically reviewed by the DSMB for risk assessment and management.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: Progression Free Survival (PFS), defined as the time from randomization to first documented progression or death due to any cause on study, whichever occurs first

Key secondary endpoints:

- Overall Response Rate (ORR), defined as the percentage of subjects who achieved partial response (PR) or better
- Overall survival (OS), defined as time from randomization to death due to any cause

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study hypotheses:
Primary hypothesis: ide-cel will prolong PFS compared to standard regimens in adult subjects with RRMM.
Key secondary hypothesis:

- ide-cel will increase ORR compared to standard regimens in adult subjects with RRMM.
- ide-cel will prolong OS compared to standard regimens in adult subjects with RRMM.

To preserve the overall significance level, statistical testing of the primary and key secondary hypotheses would follow a hierarchical order from PFS to ORR and then to OS. In addition, OS analysis would be conducted at the second PFS interim analysis and the PFS final analysis for safety and efficacy considerations regardless of whether PFS and ORR are tested.

Analysis populations

- Intent-to-treat (ITT) population: all randomized subjects
- The Treated population: all subjects in the ITT population who received leukapheresis, bridging therapy, lymphodepleting chemotherapy or bb2121 infusion in ide-cel arm, or who received any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dexamethasone in standard regimens arm.
- Safety population: all subjects in the treated population who received any study treatment, including bb2121 infusion in ide-cel arm and any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dexamethasone in standard regimens arm.
- Efficacy Evaluable (EE) Population: all subjects in the ITT population who have received any study treatment and had a baseline and at least one postbaseline efficacy assessment.

Statistical methods

Primary endpoint

- A stratified (by randomization stratification factors) log-rank test was used for the primary comparison of PFS.
- Stratified (by randomization stratification factors) Cox regression model was used to provide the estimated hazard ratio and 2-sided 95% confidence intervals for ide-cel relative to SOC.
- Kaplan-Meier (KM) curves were presented, and KM estimates and 2-sided 95% confidence intervals were calculated.

Key secondary endpoints

a. ORR
   Cochran – Mantel – Haenszel (CMH) test stratified by stratification factors was used to compare ORR. The percentage together with 95% CIs was provided.
b. OS

The same analyses methods used for PFS.

Sample size

Median PFS was assumed to be 14 months in ide-cel Arm and 9 months in standard regimens Arm. With 2:1 randomization and two PFS interim analyses (one for futility and one for superiority), approximately 289 events were required for the PFS final analysis at approximately 94% overall power and one-sided significance level of 0.025. Assuming approximately 76% event rate, 381 subjects were randomized.

For the hypothesis testing on overall survival (OS), assuming a median OS of approximately 27 months in ide-cel Arm and 20 months in standard regimens Arm, with two OS interim analyses (one conducted at the second PFS interim analysis and the other conducted at the PFS final analysis), and the final OS analysis conducted at the time when approximately 222 OS events are reached, at least 50% power can be achieved at one-sided significance level of 0.025.

Interim analyses

Two interim analyses to evaluate efficacy were planned for PFS, one at approximately 33% information of PFS (or approximately 96 PFS events) for futility only, and the other at approximately 80% information of PFS (or approximately 232 PFS events) for superiority only. O'Brien-Fleming type alpha spending and beta spending were used for superiority and futility boundaries, respectively, at the interim analyses for PFS. Futility boundary was nonbinding.

The primary endpoint PFS and key secondary endpoints ORR and OS were tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate at the second PFS interim analysis and the PFS final analysis as shown in Table 3.

Table 3: Analysis Timing and Boundaries for Primary and Key Secondary Endpoints

Timing for Analysis	PFS	ORR	OS
	Superiority Boundary (Cum. α Spent)	**Superiority Boundary (Cum. α Spent)**	**Superiority Boundary (Cum. α Spent)**
PFS Interim #1 at 33% IF	N/A (N/A)	N/A (N/A)	N/A (N/A)
PFS Interim #2 at 80% IF	0.012 (0.012)	0.012 (0.012)	0.001 (0.001)
PFS Final	0.021 (0.025)	TBD[a] (0.025)	0.01 (TBD[a])
OS Final			TBD[a] (0.025)

Cum. = Cumulative; IF = Information fraction; N/A = not applicable;

a.To be determined following the Haybittle-Peto boundary based on the actual alpha spent and actual information fraction used at the interim analysis to retain the overall alpha of 0.025 one-sided.

Subgroup analysis

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

Missing data

Censoring rule for PFS is in Appendix I.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographics of subjects enrolled in BB2121-MM-003 are summarized in Table 4. The median age was 63 years (range: 30 to 83 years), 61% were male, 65% were white. Demographics were balanced between the two treatment arms, except for distribution of Black or African American subjects (7.1% vs13.6%).

Table 4. Subject Demographics (Full Analysis Set)

Parameters	Ide-cel Arm (N = 254)	Standard Regimens Arm (N = 132)	Total (N = 386)
Age (years)			
Median (Min, Max)	63.0 (30.0, 81.0)	63.0 (42.0, 83.0)	63.0 (30.0, 83.0)
Age Categories (years), n (%)			
<65	150 (59.1)	78 (59.1)	228 (59.1)
>=65	104 (40.9)	54 (40.9)	158 (40.9)
65-74	92 (36.2)	45 (34.1)	137 (35.5)
75-84	12 (4.7)	9 (6.8)	21 (5.4)
Sex, n (%)			
Male	156 (61.4)	79 (59.8)	235 (60.9)
Female	98 (38.6)	53 (40.2)	151 (39.1)
Race, n (%)			
American Indian or Alaska Native	1 (0.4)	0	1 (0.3)
Asian	7 (2.8)	5 (3.8)	12 (3.1)
Black or African American	18 (7.1)	18 (13.6)	36 (9.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.8)	1 (0.3)
White	172 (67.7)	78 (59.1)	250 (64.8)
Other	2 (0.8)	3 (2.3)	5 (1.3)
Not Collected or Reported	54 (21.3)	27 (20.5)	81 (21.0)
Ethnicity, n (%)			
Hispanic or Latino	11 (4.3)	8 (6.1)	19 (4.9)
Not Hispanic or Latino	188 (74.0)	98 (74.2)	286 (74.1)
Not Reported	54 (21.3)	26 (19.7)	80 (20.7)
Unknown / Missing	1 (0.4)	0	1 (0.3)
Weight (kg)			
Median (Min, Max)	82.0 (41.1, 144.1)	85.5 (45.1, 177.8)	82.6 (41.1, 177.8)

(Source: original Table 5.3.1-1 CSR report body sBLA 125736/218)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline disease characteristics of subjects enrolled in BB2121-MM-003 are summarized in Table 5. Baseline disease characteristics were balanced between the two treatment arms.

Table 5. Subject Baseline Characteristics (Full Analysis Set)

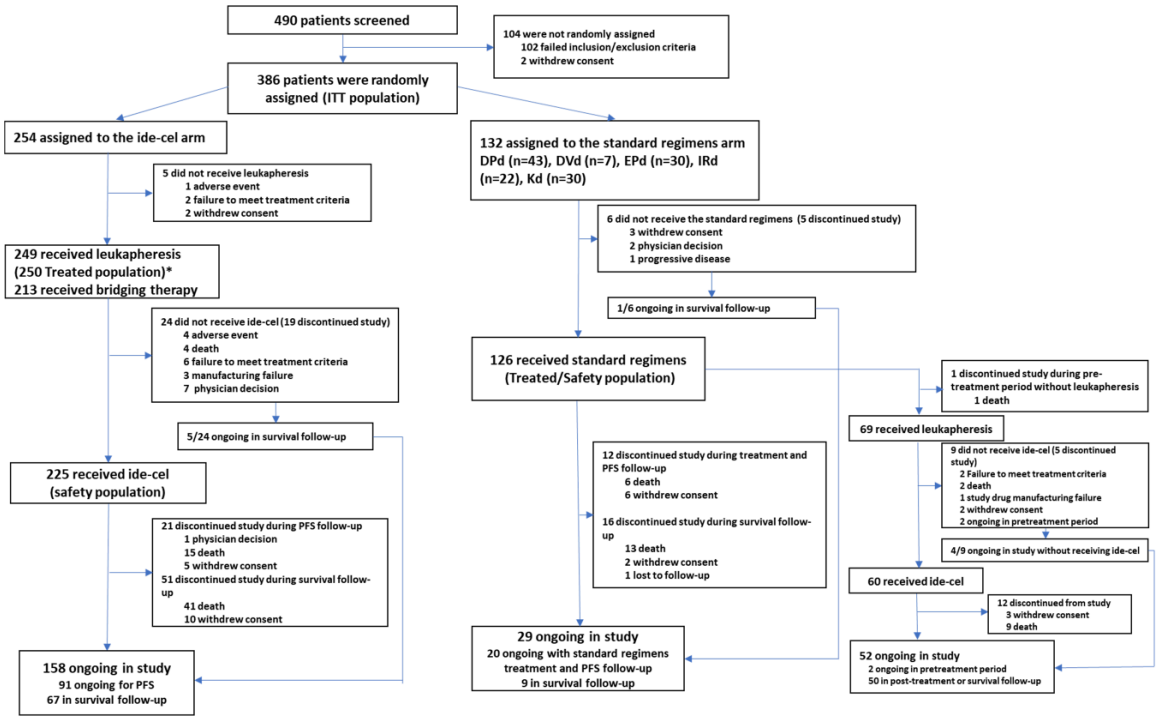
Parameters	Ide-cel Arm (N=254)	Standard Regimens Arm (N=132)	Total (N=386)
ECOG Performance Status, n (%)			
0	120 (47.2)	66 (50.0)	186 (48.2)
1	133 (52.4)	62 (47.0)	195 (50.5)
2	0	3 (2.3)	3 (0.8)
3	1 (0.4)	1 (0.8)	2 (0.5)
R-ISS at Baseline (Derived), n (%)			
Stage I	50 (19.7)	26 (19.7)	76 (19.7)
Stage II	150 (59.1)	82 (62.1)	232 (60.1)
Stage III	31 (12.2)	14 (10.6)	45 (11.7)
Missing/Unknown	23 (9.1)	10 (7.6)	33 (8.5)
Baseline Cytogenetic Abnormality, n (%)			
High Risk	107 (42.1)	61 (46.2)	168 (43.5)
Non-High Risk	114 (44.9)	55 (41.7)	169 (43.8)
Not Evaluable/Missing	33 (13.0)	16 (12.1)	49 (12.7)
Presence of Bone Lesions, n (%)			
Yes	194 (76.4)	104 (78.8)	298 (77.2)
No	59 (23.2)	28 (21.2)	87 (22.5)
Missing/Unknown	1 (0.4)	0	1 (0.3)
Tumor Burden, n (%)			
Low	172 (67.7)	90 (68.2)	262 (67.9)
High	71 (28.0)	34 (25.8)	105 (27.2)
Missing/Unknown	11 (4.3)	8 (6.1)	19 (4.9)
Prior Radiation Therapies for Multiple Myeloma, n (%)			
Yes	90 (35.4)	46 (34.8)	136 (35.2)
No	164 (64.6)	86 (65.2)	250 (64.8)
Prior Autologous Stem Cell Transplant for Multiple Myeloma, n (%)			
Yes	214 (84.3)	114 (86.4)	328 (85.0)
1 transplant	167 (65.7)	87 (65.9)	254 (65.8)
>1 transplant	47 (18.5)	27 (20.5)	74 (19.2)
No	40 (15.7)	18 (13.6)	58 (15.0)
Number of Prior Antimyeloma Regimens			
Median (Min, Max)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Distribution of Prior Antimyeloma Regimens, n (%)			
2	78 (30.7)	39 (29.5)	117 (30.3)
3	95 (37.4)	49 (37.1)	144 (37.3)
4	81 (31.9)	44 (33.3)	125 (32.4)
Refractory Status to Prior Therapies, n (%)			
IMiD	224 (88.2)	124 (93.9)	348 (90.2)
PI	189 (74.4)	95 (72.0)	284 (73.6)
Anti-CD38 Antibodies	242 (95.3)	124 (93.9)	366 (94.8)
Double-class Refractory, n (%)			
Yes	169 (66.5)	91 (68.9)	260 (67.4)
No	85 (33.5)	41 (31.1)	126 (32.6)
Triple-class Refractory, n (%)			
Yes	164 (64.6)	89 (67.4)	253 (65.5)
No	90 (35.4)	43 (32.6)	133 (34.5)

(Source: abbreviated Table 5.3.2-1 CSR report body sBLA 125736/218)

6.1.10.1.3 Subject Disposition

Figure 2 shows the subject disposition for BB2121-MM-003. Of the 254 patients randomized to receive ide-cel, 249 underwent leukapheresis, and 225 were treated with ide-cel. Of the 132 patients randomized to receive standard therapy, 126 patients received standard regimens.

Figure 2. Subject disposition



*Note: One subject in the ide-cel arm, treated population, received bridging therapy, but not leukapheresis
(Source: original Figure 5.1-1 report body, CSR, sBLA 125736/218)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

As a pre-specified interim analysis, the Applicant's analysis of PFS was based on a cut-off date of April 18th, 2022. This cutoff yields 242 PFS events which was 84% information fraction, slightly above the 80% information fraction set at the design stage for the second interim analysis. Subjects randomized to receive ide-cel had statistically significant improvement in PFS compared with subjects randomized to receive SOC. The median PFS was 13.3 months (95% CI: 11.8 to 16.1) for the ide-cel arm and 4.4 months (95% CI: 3.4 to 5.9) for the SOC arm, with a stratified hazard ratio of 0.493 (95% CI: 0.377 to 0.645) in favor of ide-cel, and a stratified log-rank test p-value<0.0001. The

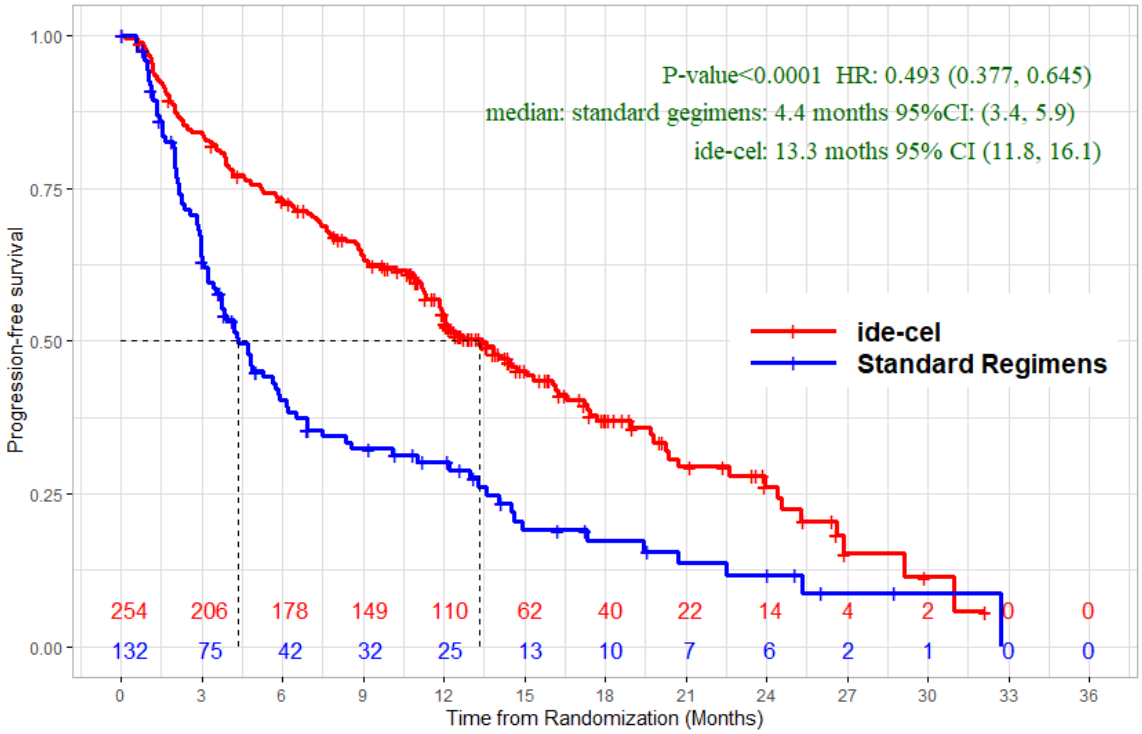
percentage of patients progression-free at 12 months was 47.2% (95% CI: 39.8, 54.3) and 17.6% (95% CI: 12.3, 23.6), respectively (Table 6, Figure 3).

Table 6. Progression-free Survival (PFS) per Central Assessment

	Ide-cel	**SOC**
Number of subjects	254	132
stratified log-rank test, two-sided p-value	<.0001	
Hazard ratio (95% CI), stratified	0.493 (0.377 to 0.645)	
KM median (95% CI) PFS time (months)	13.3 (11.8, 16.1)	4.4 (3.4, 5.9)
Events, n (%)	149 (59%)	93 (70%)
Disease progression, n (%)	129 (51%)	89 (67%)
Death from other cause, n (%)	20 (8%)	4 3%)
Censored, n (%)	105 (41%)	39 (30%)
Response ongoing, n (%)	95 (37%)	25 (19%)
No post-baseline disease assessment, n (%)	5 (2%)	6 (5%)
New anti-MM therapy	2 (1%)	6 (5%)
Extended Lost to follow up prior to event, n (%)	3 (1%)	2 (2%)
Progression-free rate, % (95% CI)		
3 month	84% (79%, 88%)	64% (55%, 72%)
6 month	73% (67%, 79%)	40% (31%, 49%)
12 month	54% (48%, 61%)	30% (22%, 39%)
24 month	26% (18%, 35%)	12% (5%, 21%)

(Source: FDA statistical reviewer)

Figure 3. Kaplan-Meier plot of PFS (Central Assessment)



(Source: FDA statistical reviewer)

Reviewer's comment #1:
The clinical team readjudicated the PFS outcome for 40 subjects and PFS data were re-analyzed as a sensitivity analysis. In this analysis, subjects randomized to receive ide-cel still had statistically significant improvement in PFS compared with subjects randomized to receive SOC. The median PFS was 12.1 months (95% CI: 11.1 to 14.7) for the ide-cel arm and 4.8 months (95% CI: 3.7 to 6.1) for the SOC arm, with a stratified hazard ratio of 0.582 (95% CI: 0.445 to 0.762) in favor of ide-cel, and a stratified log-rank test p-value<0.0001. The KM plot for this sensitivity analysis is in Appendix II Figure 1.

Reviewer comment #2:
We noticed that the two treatment arms' disease assessment schedules were not aligned, and the disease assessment of the ide-cel arm tended to be later than that of the SOC arm. SOC started right after randomization and the first disease assessment was scheduled one month from randomization(M1D1). However, the first disease assessment for the ide-cel arm (baseline assessment) was within 3 days prior to LD chemo, which was within 5 days of ide-cel infusion. Apheresis and manufacturing ide-cel took time and patients' disease needed to be under control before ide-cel infusion. Consequently, ide-cel infusion timing varied from patient to patient and considerably longer after randomization. As a result, the gap between randomization and first disease assessment also varied. The second

disease assessment was one month after ide-cel infusion (M2D1). Because time to progression could be inflated if assessments were done later, we conducted another sensitivity analysis to address bias introduced by the misalignment between the two arms' disease assessment schedules, as follows:

For subjects who received ide-cel, we changed the starting point of PFS measurement from randomization to date of ide-cel infusion. By doing this, the bias introduced by later disease assessment schedule of ide-cel arm was removed and the disease assessment became comparable between the two arms. After this realignment, the median M2D1 assessment for ide-cel arm became 29 days which was close to 34 days for the SOC arm.

For patients who were randomized to receive ide-cel but did not receive it due to various reasons, M2D1 did not apply and their PFS remained unchanged, staring from randomization.

For patients who were randomized to receive ide-cel and whose disease progressed before receiving ide-cel, PFS remained unchanged too.

For SOC patients, PFS remain the same.

We also adopted the FDA readjudication of events for this analysis.

The sensitivity analysis is very conservative. The results show clearly that ide-cel still holds a strong PFS benefit over SOC. The median PFS was 10.4 months (95% CI: 9.2 to 12.9) for the ide-cel arm and 4.8 months (95% CI: 3.7 to 6.1) for the SOC arm, with a stratified hazard ratio of 0.653 (95% CI: 0.5 to 0.854) in favor of ide-cel, and a stratified log-rank test p-value<0.0001. The KM plot for this sensitivity analysis is in Appendix II Figure 2.

These two sensitivity analyses clear indicate that the PFS benefit of ide-cel over SOC was strong and robust.

6.1.11.2 Analyses of Secondary Endpoints

ORR
Subjects in the ide-cel arm had statistically significantly higher ORR compared with subjects in the SOC arm. The ORR was 71.3% (95% CI: 65.3%, 76.7%) for the ide-cel arm and 41.7% (95% CI: 33.2%, 50.6%) for the SOC arm, with a difference in ORR of 29.6% (95% CI: 18.9, 40.3), and the Cochran-Mantel-Haenszel (CMH) test p-value < 0.0001. The CR/sCR (compete response or stringent compete response) rate in the ide-cel arm and the SOC arms were 38.6% (95% CI: 32.6%, 44.9%) and 5.3% (95% CI: 2.2%, 10.6%), respectively (Table 7).

Table 7. ORR and Best Overall Response per Central Assessment

Response Category	**Ide-cel (N = 254)**	**Standard of Care (N =**
sCR, n (%)	90 (35.4)	6 (4.5)
CR, n (%)	8 (3.1)	1 (0.8)
VGPR, n (%)	55 (21.7)	13 (9.8)
PR, n (%)	28 (11.0)	35 (26.5)
ORR (>=PR)	181 (71.3)	55(41.7)
95% CI for ORR	(65.3, 76.7)	(33.2, 50.6)
Difference in ORR (95% CI)	29.6 (18.9, 40.3)	
Stratified CMH test two-sided p-value	<.0001	
CR rate (>=CR) n (%)	98 (38.6)	7 (5.3)
95% CI	(32.6, 44.9)	(2.2, 10.6)
>=VGPR n (%)	153 (60.2)	20 (15.2)
95% CI	(53.9, 66.3)	(9.5, 22.4)

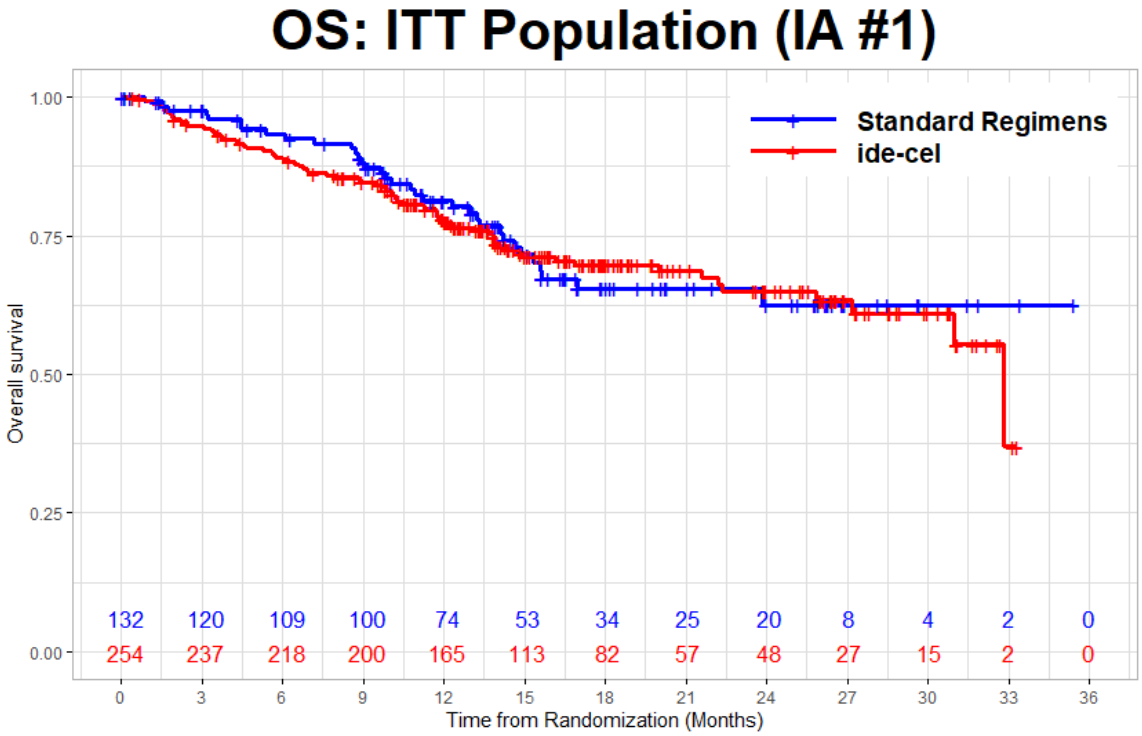
(Source: FDA statistical reviewer)

OS

The Applicant submitted three OS reports. The first two OS reports were submitted at the time of this sBLA submission.

The first interim on OS was conducted at the time of the second interim analysis of PFS. The data cutoff was April 18th, 2022, the median follow-up was 18 months and the number of events was 109, which was at 49% information fraction. The OS KM plot showed a non-proportional hazard patter (Figure 4). It appears that ide-cel tended to shorten subject's overall survival compared with SOC in the first 9 months. There was heavy censor beyond 9 months and it was not clear if there were overall survival benefit beyond 9 month.

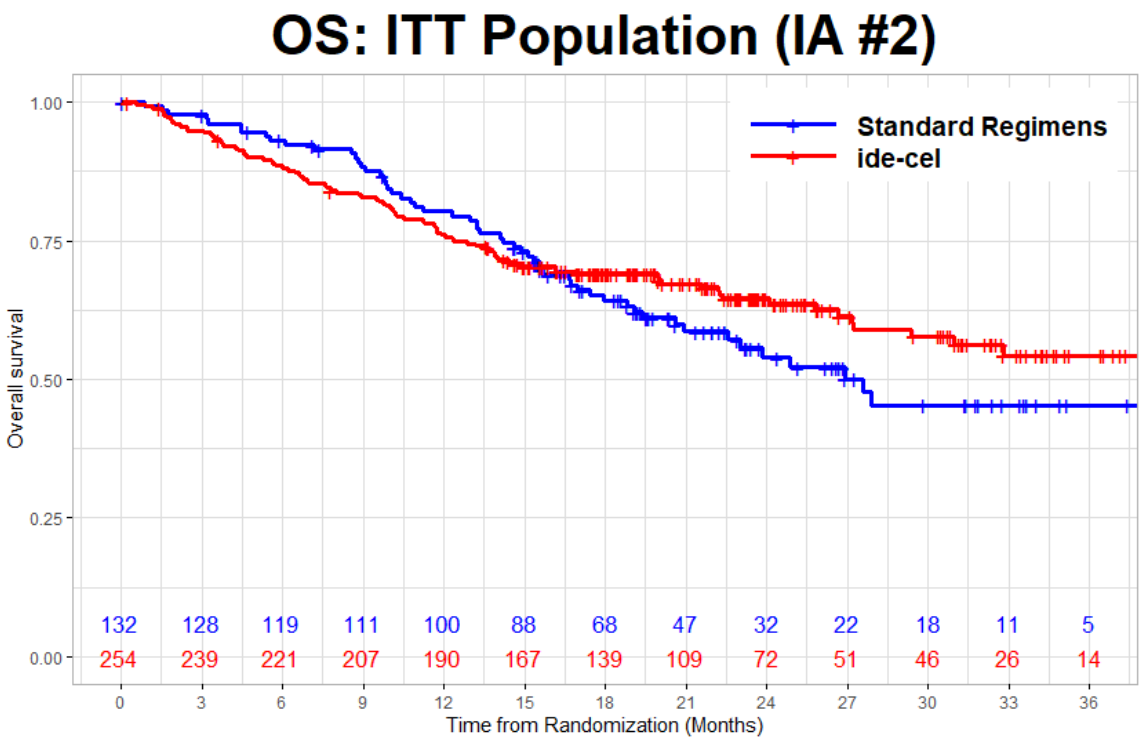
Figure 4. Kaplan-Meier Curve of Overall Survival - ITT Population (Data cutoff: 18-Apr-2022)



(Source: FDA statistical reviewer)

The second OS report was submitted at the same time of the first OS report, but with a different cutoff date (October 3, 2022). The Applicant stated that the purpose of this OS report was to address FDA's comments regarding high percentage of missing data at the pre-sBLA meeting. In this OS report, the non-proportional hazard patter persisted, and the two survival curves crossed at around month 15 with ide-cel arm had worse overall survival compared with SOC in the first 15 months (Figure 5).

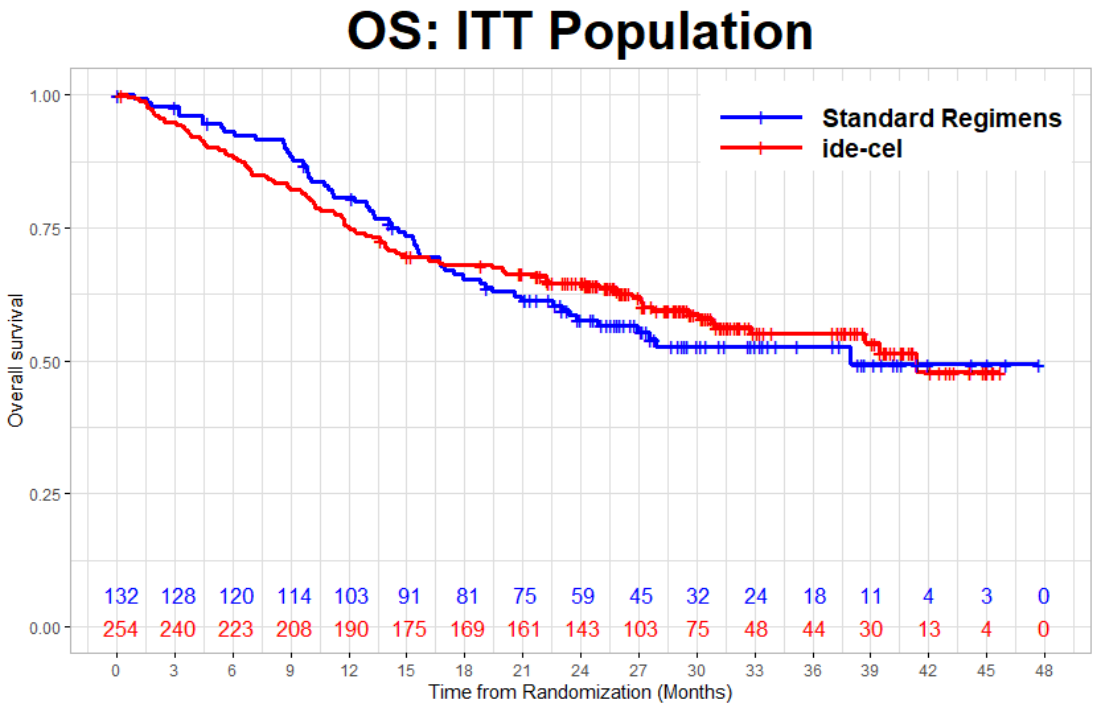
Figure 5. Kaplan-Meier Curve of Overall Survival - ITT Population (data cutoff: Oct 3, 2022)



(Source: FDA statistical reviewer)

In August 2023, the Applicant submitted a third OS analysis which was at the time of the final PFS analysis. The data cutoff was April 28, 2023. The KM curves still showed non-proportional hazard patter, and the two survival curves crossed at around month 17 with ide-cel arm had worse overall survival compared with SOC in the first 17 months (Figure 6).

Figure 6. Kaplan-Meier Curve of Overall Survival - ITT Population (data cutoff: April 28, 2023)



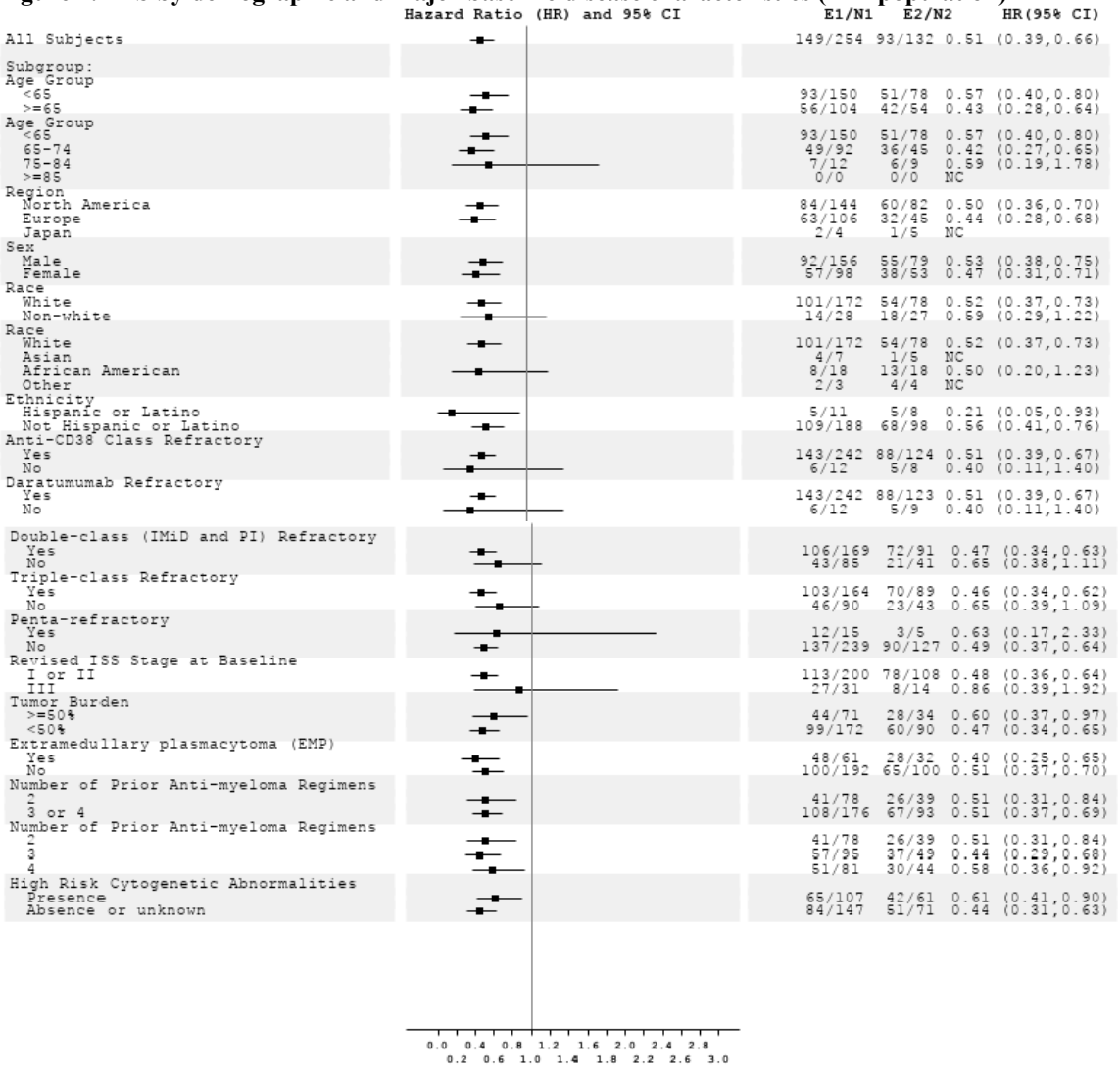
(Source: FDA statistical reviewer)

On March 15th, 2024, this sBLA was discussed at the afternoon session of the Oncologic Drug Advisory Committee (ODAC) meeting. The Applicant argued that the early OS detriment is driven by patients who did not receive ide-cel likely due to inadequate bridging in the ide-cel arm and the numerically worse overall survival could be due to random variation. At the meeting, the Applicant also argued the overall survival was confounded by treatment cross-over, and after crossover adjusted analysis, the average hazard ratio was less than 1. However, these adjusted analyses, including rank preserving structural failure time (RPSFT) method, 2-stage accelerated failure time (AFT) model, and Inverse Probability of Censoring Weighting (IPCW) method, were sensitivity analyses, some pre-specified and some conducted on a post-hoc basis. Additionally, such analyses rely on untestable assumptions and cannot be used to ascertain that ide-cel treatment has OS benefit when the ITT analysis, the pre-specified primary analysis, clearly indicates potential early OS detriment. In addition, in the presence of crossing hazards or a delayed effect, the average hazard ratio is not an adequate population-level summary of the treatment effect. Hence, an average hazard ratio less than 1 cannot be used in such cases as convincing evidence to weigh against the observed early detrimental effect of ide-cel on survival. Eight ODAC committee members voted "Yes" and three voted "No" to the voting question "Is the risk-benefit assessment for idecabtagene vicleucel for the proposed indication, favorable?"

6.1.11.3 Subpopulation Analyses

The PFS result is consistent across demographic and major baseline disease characteristics (Figure 7).

Figure 7. PFS by demographic and major baseline disease characteristics (ITT population)



(Source: Figure 7.2.1-1, BB2121-MM-003 CSR 7.2.1 sBLA 125736/218)

6.1.11.4 Dropouts and/or Discontinuations

Twenty-nine subjects (11%) in the ide-cel arm discontinued before receiving ide-cel and six subjects (5%) in the SOC arm discontinued before receiving standard regimens.

At the data cutoff (April 18th, 2022), 67 subjects in the ide-cel arm who received ide-cel and 45 subjects in the SOC arm who received at least 1 dose of standard regimen had discontinued participation in the study. For detailed discontinuation information, see section 6.1.10.1.3 Subject Disposition.

6.1.12 Safety Analyses

This section summarizes safety results of Study BB2121-MM-003.

6.1.12.1 Methods

Descriptive statistics are used to summarize safety data for study BB2121-MM-003.

6.1.12.3 Deaths

As of the 18-Apr-2022 data cutoff date, 75 (29.5%) subjects died in the ide-cel arm and 34 (25.8%) died in the standard regimens arm. Table 8 summarizes deaths for the two arms.

Table 8. Deaths reported (ITT population)

	Ide-cel (N = 254) n (%)	**Standard of Care (N = 132) n (%)**
Subjects who died	75 (29.5)	34 (25.8)
Primary cause of death		
malignant disease under study	44 (17.3)	23 (17.4)
Adverse events	15 (5.9)	8 (6.1)
Other	14 (5.5)	3 (2.3)
second primary malignant disease	2 (0.8)	0

Data cutoff date=18Apr2022
(Source: Table 8.1-1 BB2121-MM-003 CSR 7.2.1 sBLA 125736/218)

6.1.12.4 Nonfatal Serious Adverse Events

In the treated population, any Grade SAEs were reported by the applicant in 130 (52.0%) and 48 (38.1%) subjects in the ide-cel and standard regimens arms, respectively. Grade 3 or 4 SAEs were reported in 107 (42.8%) subjects in the ide-cel arm and 43 (34.1%) subjects in the standard regimens arm.

The most frequently reported SAEs in each arm were:

- Ide-cel arm: general physical health deterioration (6.8%), pneumonia (6.4%), pyrexia (4.8%), CRS and febrile neutropenia (4.0%, each)
- Standard regimens arm: pneumonia (4.8%), COVID-19 pneumonia and general physical health deterioration (3.2%, each), influenza and atrial fibrillation (2.4%, each)

6.1.12.5 Adverse Events of Special Interest (AESI)

The applicant reported that in the safety population 197 (87.6%) subjects experienced at least one event of CRS. 6 subjects (2.7%) had worst Grade 3 CRS, 3 subjects (1.3%) had worst Grade 4 CRS, and 2 subjects (0.9%) had Grade 5 CRS. One subject had ongoing CRS at time of death; the cause of death was sepsis.
The applicant reported that the most frequently reported CRS symptoms were pyrexia (194 [86.2%] subjects), hypotension (60 [26.7%] subjects), and tachycardia (53 [23.6%] subjects). The most frequently reported Grade ≥ 3 CRS symptoms were pyrexia (18 [8.0%] subjects), hypoxia (9 [4.0%] subjects), and Aspartate transaminase (AST) increased (7 [3.1%] subjects).

The applicant reported that in the ide-cel arm safety population, the majority of investigator identified neurologic toxicity (iiNT) AEs were of Grade 1 or 2 severity. The most frequently reported symptoms of iiNT were confusional state (18 [8.0%] subjects), somnolence (8 [3.6%] subjects), and depressed level of consciousness and disturbance in attention (6 [2.7%] subjects, each). A total of 7 (3.1%) subjects reported Grade 3 or 4 iiNT; the most frequently reported symptoms of which were confusional state and depressed level of consciousness (3 [1.3%] subjects, each). No Grade 5 iiNT events were reported.

The other AESIs including infections and cytopenia are presented in Table 9.

Table 9. Adverse Events of Special Interest (AESI) (Safety population)

	Adverse Event Grades			
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Safety Population	**N=225**		**N=126**	
AESIs (Number of subjects with ≥ 1 AESI/selected AE)	225 (100.0)	208 (92.4)	113 (89.7)	82 (65.1)
CRS	197 (87.6)	9 (4.0)	--	--
NT - Broad[a]	159 (70.7)	30 (13.3)	77 (61.1)	16 (12.7)
NT - Focused[b]	85 (37.8)	14 (6.2)	41 (32.5)	8 (6.3)
iiNT[c]	34 (15.1)	7 (3.1)	--	--
Infections - Overall	138 (61.3)	55 (24.4)	68 (54.0)	23 (18.3)
Cytopenia - Overall	206 (91.6)	202 (89.8)	91 (72.2)	76 (60.3)
Cytopenia - Neutropenia	193 (85.8)	189 (84.0)	57 (45.2)	51 (40.5)
Cytopenia - Thrombocytopenia	126 (56.0)	99 (44.0)	37 (29.4)	23 (18.3)
New Malignancies	15 (6.7)	--	5 (4.0)	--
SPM[d]	13 (5.8)		5 (4.0)	
MAS[e]	5 (2.2)	5 (2.2)	0	0
Autoimmune Disorders	1 (0.4)	--	0	--

a. All PTs within the primary or secondary SOCs of nervous system disorder and psychiatric disorder

b. Selected PTs of NT events as determined by Sponsor with consideration of biological/pharmacological plausibility for a drug-event relationship, known neurologic toxicities reported with this class of drug and consistent with published guidelines for CAR T encephalopathy, and clinical judgement.

c. Investigator identified NT

d. Second primary malignancies

e. Macrophage activation syndrome

(Source: modified Table 8.1-1 BB2121-MM-003 CSR 7.2.1 sBLA 125736/218)

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Idecabtagene vicleucel (Abecma) is an autologous BCMA CAR T cell immunotherapy. Idecabtagene vicleucel received FDA Biologics License Application (BLA) approval in March 2021 for the indication of "Treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more lines of systemic therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD 38 monoclonal antibody." In this Prior Approval Supplement (PAS), the applicant seeks to expand the indication to third line or later treatment. Proposing to remove "after 4 or more lines of systemic therapy," the new proposed indication is "Adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor (PI) and an anti-CD 38 monoclonal antibody."

The primary source of evidence to support the efficacy and safety of the product in the proposed expanded indication comes from study BB2121-MM-003, which was a multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of ide-cel versus standard of care (SOC) regimens in subjects with RRMM who have received 2 to 4 prior myeloma regimens including daratumumab (DARA), an immunomodulatory compound (IMiD), and a protease inhibitor (PI) and who have documented disease progression during or within 60 days after the last therapy. In BB2121-MM-003, 386 subjects were randomized in a 2:1 ratio to receive ide-cel or SOC regimens. The primary endpoint was progression-free survival (PFS) determined by independent review committee (IRC). The two key secondary endpoints were overall response rate (ORR) and overall survival (OS).

At the pre-specified second interim analysis for PFS, based on 242 PFS events (cut-off date of April 18th, 2022), subjects randomized to receive ide-cel had statistically significant improvement in PFS compared with subjects randomized to receive SOC. The median PFS was 13.3 months (95% CI: 11.8 to 16.1) for the ide-cel arm and 4.4 months (95% CI: 3.4 to 5.9) for the SOC arm, with a stratified hazard ratio of 0.493 (95% CI: 0.377 to 0.645), and a p-value<0.0001 based on the stratified log-rank test. Subjects in the ide-cel arm also had statistically significantly higher ORR compared with subjects in the SOC arm. The ORR was 71.3% (95% CI: 65.3%, 76.7%) for the ide-cel arm and 41.7% (95% CI: 33.2%, 50.6%) for the SOC arm, with a difference of 29.6% (95% CI: 18.9, 40.3), and the Cochran-Mantel-Haenszel (CMH) test p-value < 0.0001. The CR/sCR (compete response or stringent compete response) rate in the ide-cel arm and the

SOC arms were 38.6% (95% CI: 32.6%, 44.9%) and 5.3% (95% CI: 2.2%, 10.6%), respectively.

Despite the statistically significant improvement in PFS and ORR, the ide-cel arm did not show improvement over SOC in OS. Based on the most recent updated OS analysis with a cutoff date of April 28, 2023, the two Kaplan-Meier OS curves crossed at around 15 months after randomization, with the ide-cel arm having lower survival probability compared with SOC in the first 15 months. There was heavy censoring after the OS crossing point. The OS results were confounded by the treatment crossover from the SOC to ide-cel upon disease progression.

The Applicant argued at the Oncologic Drug Advisory Committee (ODAC) meeting held on March 15, 2024 that the early OS detriment is driven by patients who did not receive ide-cel likely due to inadequate bridging in the ide-cel arm and the numerically worse overall survival could be due to random variation. At the meeting, the Applicant also argued the overall survival was confounded by treatment cross-over, and after crossover adjusted analysis, the average hazard ratio was less than 1. However, these adjusted analyses were sensitivity analyses, some pre-specified and some conducted on a post-hoc basis. Additionally, such analyses rely on untestable assumptions and cannot be used to ascertain that ide-cel treatment has OS benefit when the ITT analysis, the pre-specified primary analysis, clearly indicates potential early OS detriment. In addition, in the presence of crossing hazards or a delayed effect, the average hazard ratio is not an adequate population-level summary of the treatment effect. Hence, an average hazard ratio less than 1 cannot be used in such cases as convincing evidence to weigh against the observed early detrimental effect of ide-cel on survival. Eight ODAC committee members voted “Yes” and three voted “No” to the voting question “Is the risk-benefit assessment for idecabtagene vicleucel for the proposed indication, favorable?”

10.2 Conclusions and Recommendations

In summary, ide-cel met the primary endpoint of PFS with statistical significance but demonstrated a potential early OS detriment. The interpretation of the OS results for the trial as a whole is confounded by treatment crossover. Based on the collective statistical evidence, I recommend against approval until an additional trial with properly chosen eligibility criteria is conducted to further evaluate the benefits and risk profile of ide-cel in the context of earlier line RRMM.

Appendix I. Censoring rule for PFS

Scenario	FDA Censoring Rule	
	Censor/Event	**Date**
No post baseline assessment and alive	Censor	Randomization date
Death within the first 2 scheduled assessments	Event	Death date
PD or death right after missing 2 (or more) consecutive scheduled assessments	Censor	Last adequate efficacy assessment date with no evidence of PD; if missing the first 2 assessments, then randomization date
Otherwise	Event	Documented PD or Death date whichever is earlier
PD or death after the start of new anti-myeloma drug in both arms	Censor	Last adequate assessment date with evidence of no progression before starting new drug/treatment
Start of new anti-myeloma drug without a PD before new anti-myeloma drug or PD/death after the new anti-myeloma drug	Censor	Last adequate assessment date on/before starting new drug/treatment
No documented PD and No Death	Censor	Last adequate assessment date with evidence of no progression

Appendix II

Figure 1 Kaplan-Meier plot of PFS (FDA re-judication)

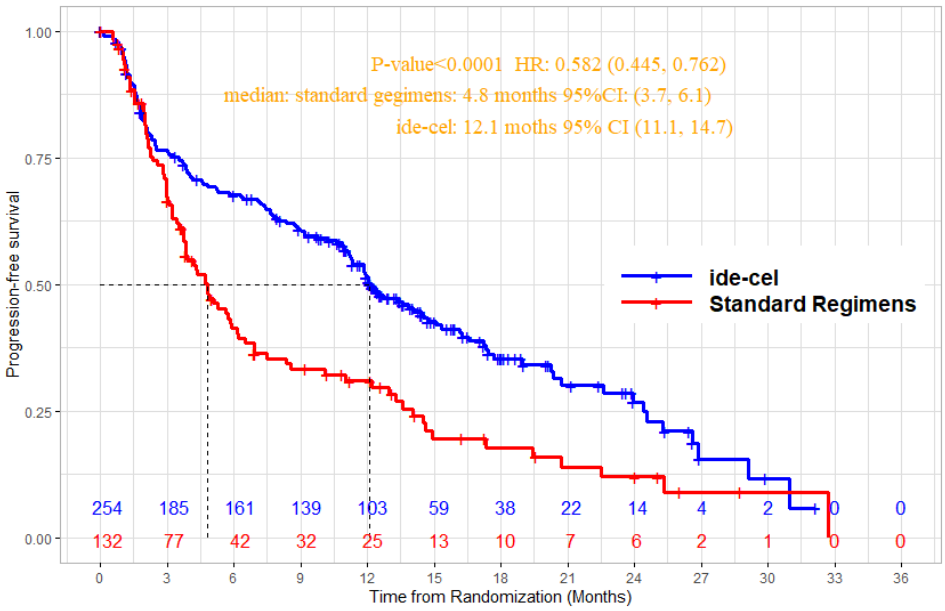


Figure 2. Kaplan-Meier plot of PFS (FDA re-judication plus realignment of disease assessment schedule)