FDA Briefing Document

BLA 125736/Supplement 218

Drug name: Abecma (idecabtagene vicleucel)

Applicant: Celgene Corporation, a Bristol-Myers Squibb Company

Oncologic Drugs Advisory Committee Meeting

March 15, 2024

Center for Biologics Evaluation and Research

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office or Center. We have brought Abecma (idecabtagene vicleucel) [BLA 125736/S218] to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AE	adverse event
AST	aspartate aminotransferase
BCMA	B -cell maturation antigen
CAR	chimeric antigen receptor
CD38	cluster of differentiation 38
CNS	central nervous system
CRS	cytokine release syndrome
DPd	daratumumab, pomalidomide, dexamethasone
DVd	daratumumab, bortezomib, dexamethasone
EPd	elotuzumab, pomalidomide, and dexamethasone
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 sec
HLH	macrophage activation syndrome
HR	hazard ratio
HSCT	hematopoietic stem cell transplant
ide-cel	idecabtagene vicleucel
IF	information fraction
IMiD	immunomodulatory drug
IRC	independent review committee
IRd	ixazomib, lenalidomide, dexamethasone
ISS	International Staging System
ITT	intent-to-treat
Kd	carfilzomib, dexamethasone
KM	Kaplan-Meier
LDC	lymphodepleting chemotherapy
MAS	macrophage activation syndrome
MDS	myelodysplastic syndromes
MM	multiple myeloma
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PI	proteasome inhibitor
R-ISS	Revised International Staging System
RPSFT	rank preserving structural failure time
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Prescribing Information

1. Executive Summary

On February 15, 2023, Celgene Corporation, a Bristol-Myers Squibb Company (Celgene), submitted a supplemental Biologics Licensing Application (sBLA) for ABEMCA (idecabtagene vicleucel), an autologous, anti-B-cell maturation antigen (BCMA), chimeric antigen receptor engineered T cell (CAR T) therapy. The Applicant is seeking approval for the following proposed indication and recommended dosage:

- Indication: *Treatment of adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody.*

- Dosage: *Dose range is 300-510 x 10^6 CAR-positive T cells* per single-dose infusion

FDA is convening this meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss the results of the randomized controlled trial, KarMMa-3, which provides the primary evidence of ABEMCA's safety and effectiveness for the proposed indication. FDA seeks the Committee's discussion of the benefits and risks of treatment with ABEMCA in the indicated population. In particular, FDA is interested in the Committee's opinion regarding the higher rate of early deaths in the ide-cell arm, in the context of a statistically significant progression-free survival benefit in the KarMMa-3 trial.

This sBLA contains the results of a single, randomized controlled trial (KarMMa 3) of idecabtagene vicleucel (trade name: ABECMA; hereby referred to as ide-cel), an autologous, anti-B-cell maturation antigen (BCMA), chimeric antigen receptor engineered T cell (CAR T) therapy. KarMMa-3 enrolled 386 patients who were randomized (2:1) to receive ide-cel or standard of care therapy, including five FDA-approved doublet and triplet regimens (daratumumab, pomalidomide and dexamethasone [DPd], daratumumab, bortezomib, dexamethasone [DVd], elotuzumab, pomalidomide and dexamethasone [EPd], ixazomib, lenalidomide, dexamethasone [IRD], and carfilzomib and dexamethasone [Kd]).

The primary endpoint of KarMMa-3 is progression-free survival (PFS) as determined by a blinded independent review committee (IRC) according to the International Myeloma Working Group (IMWG) 2016 criteria; overall response rate (ORR) and overall survival (OS) were key secondary endpoints.

KarMMa-3 met its primary endpoint, demonstrating a statistically significant improvement in PFS in patients randomized to the ide-cel arm compared to patients randomized to the control arm (hazard ratio [HR] was 0.49 [95% Confidence Interval CI: 0.379, 0.647] based on a stratified log-rank test; p value <0.0001. The median PFS was 13.3 months in the ide-cel arm (95% CI: 11.8, 16.1), and 4.4 months (95% CI: 3.4, 5.9) in the standard of care (SOC) arm. At the time of the sBLA submission, the Applicant provided the results of an interim analysis of OS which was conducted at the time of the primary PFS analysis, based on 49% information fraction. The median OS in the ide-cel arm was 32.8 months (95% CI: 30.9, NE) and was not reached (95% CI: NE, NE) in the SOC arm (HR 1.093 (95% CI: 0.727, 1.645).

At the primary data cutoff of April 18, 2022, all patients in the ide-cell arm and 98% of patients in the SOC arm experienced at least one treatment emergent adverse event (TEAE). The rate of Grade 3 and Grade 4 AEs was 18% and 64% in the ide-cel arm compared to 28% and 51% in the SOC arm. The most common (≥5%) Grade 3-4 treatment emergent adverse events (TEAEs) in the ide-cel arm were febrile neutropenia (51%), infection (16%), fever (9%), hypertension (7%), hypoxia (6%), and renal failure (5%). The rate of serious AEs was 43% in the ide-cel arm compared to 56% in the SOC arm. The rate of death from AEs was 9% 20in the ide-cel arm compared to 8% in the SOC arm. The rate of Grade 3-4

hematological toxicity was higher in the ide-cel arm (neutropenia:96%, thrombocytopenia: 59%, anemia:52%) compared to the SOC arm (neutropenia: 72%, thrombocytopenia: 46%, anemia: 45%).

The rate of deaths in the first 9 months post randomization was higher in the ide-cel arm (45/254; 18%) compared to the SOC arm (15/132; 11%) in the ITT population (N=386). In the safety analysis population, the rate of deaths from adverse events that occurred within 90 days from starting treatment was 2.7% in the ide-cel arm and 1.6 % in the SOC arm.

Main topics for discussion at the ODAC:

- Issue #1: Increased number of early deaths in the ide-cel arm

  Overall, there is a higher rate of early deaths in the ide-cel arm compared to the SOC arm. The adequacy of exploratory analyses of the KarMMa-3 trial to support the identification of strategies to mitigate this risk, warrants further discussion.

- Issue #2: Clinical benefit of treatment with ide-cel

  Ide-cel demonstrated a statistically significant effect on PFS, but a higher rate of early deaths compared to the standard of care arm. FDA has granted approval to drugs that demonstrate a statistically significant and clinically meaningful effect on progression-free survival in the context of an acceptable risk profile. Because of the higher rate of early deaths in the ide-cel arm, it is unclear whether the overall benefit-risk assessment is favorable.

2. Background

Multiple Myeloma

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

Treatment for Relapsed/Refractory Multiple Myeloma

Patients who are exposed to the three major classes of myeloma therapy have an unmet medical need (Gandhi et al. 2019). While most patients in the United States with relapsed disease will have been exposed to an IMiD, a PI, corticosteroids, and an anti-CD38 monoclonal antibody (triple-class exposed), retreatment with previously used agents or agents in the same class of drug can be effective, provided that the patient is not refractory to that agent or not exposed to that agent in the last line of therapy. The choice of treatment regimen is generally guided by both efficacy and tolerability considerations. In KarMMa 3, all subjects were triple class exposed. All SOC arm subjects received at least one drug that was different from the drugs in the last prior regimen to limit cross resistance. DPd was the most frequently selected regimen (33%), with 81% of subjects assigned to receive DPd being daratumumab refractory and 9% being pomalidomide refractory in the most recent prior regimen. The other therapeutic class available to the triple-class-exposed subjects is the anti-SLAMF7 agent, elotuzumab,

used, in combination with an IMiD and steroids. Twenty-three percent of the subjects in the SOC arm of KarMMa-3 were assigned to elotuzumab in combination with pomalidomide and dexamethasone (EPd). None of these subjects were refractory to elotuzumab, and 20% were refractory to pomalidomide in the most recent prior line of therapy.

Selinexor, a selective inhibitor of nuclear export in combination with bortezomib and dexamethasone, is another treatment option for triple-class-exposed patients with MM. Autologous HSCT is considered in eligible patients who have not received HSCT or had a prolonged response to initial HSCT. In addition, several alkylator-based chemotherapy regimens such as bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide, VTd-PACE), cyclophosphamide, and bendamustine-containing regimens are off-label treatment options for the triple-class-exposed population.

FDA-approved therapies for the treatment of RRMM are summarized in Table 22 in the Appendix. These include ABEMCA (ide-cel) and CARVYKTI (cilta-cel), approved in 2021 and 2022, respectively. Both products are indicated for treatment of adults with RRMM after four or more prior lines of therapy, including a PI, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Single arm trials evaluating overall response rate (ORR) were the basis for approval. The KarMMA study, which supported the approval of ABEMCA, enrolled adults who had received at least three regimens, including a PI, an immunomodulatory agent, and an anti-CD38 antibody. The ORR was 72% (95% CI: 62, 81) and the rate of sCR was 28% (95% CI: 19, 38). Duration of response with a median follow up of 10.7 months was 11 months (95% CI: 10.3, 11.4) (USPI 2021). The CARTITUDE-1 study supported the approval of CARVYTI. CARTITUDE-1 enrolled adults who had received at least three prior lines of therapy including a PI, an IMiD and an anti-CD38 monoclonal antibody. The ORR was 97.9% (95% CI: 92.7, 99.7) and sCR was 78.4% (95% CI: 68.8, 86.1). Median duration of response was 21.8 months (95% CI: 21.8, NE) at a median duration of follow up of 18 months (USPI 2022).

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

3. Product and Regulatory History

Product Description

Ide-cel is a CAR-positive T cell therapy targeting BCMA, which is expressed on the surface of normal and malignant plasma cells. The CAR construct includes an anti-BCMA single-chain variable fragment-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of ide-cel results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Ide-cel drug product (DP) is manufactured using patient derived T cells that are modified with the anti-BCMA02 CAR lentiviral vector and expanded ex vivo with IL-2. Following expansion, the modified cells are harvested, formulated, and cryopreserved in a bag for intravenous administration.

Key Regulatory Interactions

In the current sBLA, the Applicant seeks traditional approval of ide-cel for the proposed indication, based on the results of KarMMa 3. A summary of key pre- and post-submission interactions is provided below.

Table 1. Regulatory History

Date	Purpose and/or Key Comments Provided
July 19, 2018	KarMMa-3 original protocol submitted to IND 16664
August 21, 2020	Protocol amendment to update CRS, neurotoxicity, and infection management guidelines to mitigate the risk of treatment related mortality of 2.7% (9/326) observed with ide-cel across the clinical development program. Four out of the nine deaths which prompted revisions in the treatment guidelines had occurred in KarMMa 3.
March 26, 2021	Ide-cel granted traditional approval
October 12, 2021	FDA advised that: • The second interim PFS analysis for superiority should be performed at approximately 80% information fraction (IF) rather than the sponsor's proposed analysis at 67% IF. • The study should continue until the final PFS and OS analyses are complete, even after the primary efficacy endpoint is met, to evaluate that the long-term efficacy and safety of the investigational regimen. • Sponsor should propose statistical analyses to address the effect of crossover on OS. • Sponsor should perform OS analyses at the interim and final PFS analyses regardless of the outcomes of PFS and ORR analyses, since OS is an indicator of safety and efficacy.
November 29, 2022	FDA issued preliminary meeting responses for Type B pre-BLA meeting for KarMMa-3 in which FDA stated that PFS benefit alone is insufficient to assess the risk and benefit of ide-cel in the proposed population and that OS data will be required for a regulatory submission.
December 22, 2022	At pre-BLA meeting, Applicant stated their plan to submit an OS report with the planned s BLA. KarMMa-3 study team to remain blinded to OS data per the SAP.
January 4, 2023	Sponsor informed FDA that it plans to perform a post hoc interim OS analysis based on October 3, 2022, data cutoff, which aligns with 90-day safety update.
January 12, 2023	FDA advised in written correspondence that a post hoc interim OS analysis cannot be used to support efficacy labeling claims and the additional OS analysis should be submitted at the time of the submission.
January 13, 2023	Applicant submitted an addendum to the SAP which outlined the plan to spend an administrative alpha of 0.001 for the additional post hoc interim OS analysis.
February 15, 2023	The Applicant submitted an efficacy supplement which included the results of both the first and the unplanned (post hoc) interim OS analyses.
April 13, 2023	A filing notification was sent informing the Applicant of a standard review. The filing letter identified the early potential OS detriment observed in the ide-cel arm compared to the standard of care arm in KarMMa 3 KarMMa-3as a potential review issue.
August 18, 2023	The Applicant submitted the results of the second prespecified interim OS analysis performed at the time of the final PFS analysis with a data cutoff date of April 28, 2023.

Date	Purpose and/or Key Comments Provided
September 27, 2023	FDA notified that the timeline for the final OS analysis is projected for November 2024.
October 13, 2023	Teleconference with Applicant to discuss the updated OS analysis.
October 30, 2023	Teleconference meeting held to discuss the results of the following Applicant exploratory analyses: • Early mortality in the ide-cel arm in subjects with respect to high-risk features • OS analyses with and without any high-risk features • OS analyses with and without 17 p deletion
November 17, 2023	Teleconference meeting held to inform the Applicant of FDA's plan to convene an oncology drug advisory committee meeting to discuss the benefit-risk of ide-cel for the indicated population given the potential OS detriment with ide-cel.

Source: FDA Reviewer Summary

4. Clinical Study Supporting Application

4.1 Study Design

Trial Design

KarMMa 3 (NCT03651128) is a randomized (2:1), open-label, multicenter trial comparing ide-cel with standard of care (SOC) in adults with relapsed refractory multiple myeloma after two to four prior lines of therapy including a PI, an IMiD, and daratumumab. All patients were refractory to the last line of therapy. Patients were randomized to receive a single infusion of ide-cel or investigator choice of five standard therapies: DPd, DVd, EPd, IRd or Kd. Bridging therapy could be administered to patients in the ide-cel arm at investigator's discretion during the interval between leukapheresis and lymphodepleting chemotherapy. Study treatment continued until there was documented disease progression or unacceptable toxicity. Crossover from the SOC arm to ide-cel was permitted upon IRC-confirmed disease progression at investigator request if subjects met the eligibility criteria to receive ide-cel. Randomization was stratified according to age (<65 years versus >/=65 years), prior regimens (2 versus 3 or 4), and cytogenetics (high-risk versus absence or unknown).

4.2 Study Population

Patients must have met the following key criteria at screening and prior to apheresis, to be eligible for the trial:

- Diagnosis of MM with measurable disease defined as M-protein serum protein electrophoresis ≥0.5gm/dl or M-protein urine protein electrophoresis ≥200 mg/24 hours or serum-free light chain ≥10 mg/dl and abnormal kappa lambda light chain ratio.
- A minimum of two and maximum of four prior lines of therapy including treatment with a PI, an IMiD and daratumumab.
    - Refractory to the last treatment regimen prior to study enrollment per International Myeloma Working Group consensus guidelines (Rajkumar et al. 2011).
    - Eastern Cooperative Oncology Group performance status of 0 to 1

4.3 Study Treatment

Treatment in KarMMa 3 was administered as follows:

- Standard of Care Arm: Included DPd, DVd, IRd, EPd or KD selected prior to randomization and administered according to dosage described in the US Prescribing Information. Treatment was continued until progressive disease, toxicity, or consent withdrawal.

- Ide-cel Arm: Subjects underwent leukapheresis followed by one cycle of optional bridging therapy administered at investigator discretion while product was manufactured. A 14-day wash-out period was required between bridging and lymphodepleting chemotherapy. This was followed by lymphodepleting chemotherapy: fludarabine 30 mg/m2 and cyclophosphamide 300 mg/m2 intravenous for 3 consecutive days followed by a single infusion of ide-cel at a dose of 150 to 450 million (+20%) CAR+ T cells.
    - Bridging therapy: Included DPd, DVd, IRd, EPd or KD administered according to dosage described in the US Prescribing Information.

4.4 Study Endpoints

The primary endpoint is PFS, defined as the time from randomization to the first documentation of progressive disease, or death due to any cause, as assessed by an independent review committee (IRC) according to the International Myeloma Working Group (IMWG) 2016 Criteria (Kumar et al. 2016).

Key secondary endpoints were:

- Overall response rate defined as best response of stringent complete response, complete response, very good partial response, and partial response, as assessed by IRC.
- Overall survival.

4.5 Analysis Plan—Efficacy

The primary efficacy analysis plan is based on the Intent-to-Treat (ITT) population. A total of 289 PFS events were determined to provide approximately 94% power to detect a HR of 0.64 using a one-sided log rank test with an overall significance level of 2.5%. The first interim analysis (futility) was planned at 33% information fraction (IF), for futility. A second interim efficacy analysis was to be conducted at 80% IF.

ORR was tested at an overall one-sided alpha level of 0.025, if PFS was declared statistically significant.

Two interim analyses and one final analysis were planned for OS. The first OS interim analysis was to be performed at the time of the planned PFS interim analysis and the second OS interim analysis was to be performed at the time of the final PFS analysis after 289 PFS events have occurred. The final OS analysis will take place after 222 deaths have occurred.

Assuming a median OS of approximately 27 months in the ide-cel Arm and 20 months in the standard regimens Arm, KarMMa-3 has 50% power at a one-sided significance level of 0.025 to detect an OS HR of 0.74.

The statistical assumptions for the SOC arm were as follows: median PFS by IRC of 9 months, ORR by IRC of 50% and median OS of 20 months.

4.6 Study Results

The efficacy analysis is based on 386 randomized patients (i.e., ITT). The data cutoff date for the primary efficacy and first interim OS analysis was April 18, 2022. At the time of data cut off, KarMMa-3 had completed enrollment. The data cutoff for the second interim OS analysis was April 28, 2023.

The data cutoff date for the primary safety analysis was April 18, 2022; the data cutoff for the safety update was October 3, 2022. The safety analysis population consists of all patients who received conforming ide-cel in the investigational arm (n=222), and all patients who received any study treatment in the SOC arm (n=126).

4.6.1. Study Population Characteristics

Table 2 and Table 3 summarize characteristics of the study population.

Table 2. Demographic Characteristics, ITT Population

Category	Ide-cel N=254	SOC N=132	Total N=386
Age (years)			
Median (min, max)	63 (30, 81)	63 (42, 83)	63 (30, 83)
Age categories (years), n (%)			
<65	150 (59)	78 (59)	228 (59)
>/=65	104 (41)	54 (41)	158 (41)
>/=75	12 (5)	9 (7)	21 (5)
Sex, n (%)			
Male	156 (61)	79 (60)	235 (61)
Female	98 (39)	53 (40)	151 (39)
Race, n (%)			
White	172 (68)	78 (59)	250 (65)
Black or African American	18 (7)	18 (14)	36 (9)
Asian	7 (3)	5 (4)	12 (3)
American Indian or Alaska Native	1 (0.4)	0	1 (0.3)
Native Hawaiian or other Pacific Islander	0	1 (0.8)	1 (0.3)
Not collected or reported	54 (21)	27 (21)	81 (21)
Other	2 (0.8)	3 (2.3)	5 (1.3)
Ethnicity, n (%)			
Not Hispanic or Latino	188 (74)	98 (74)	286 (74)
Hispanic or Latino	11 (4)	8 (6)	19 (5)
Not reported	54 (21)	26 (20)	80 (21)
Unknown/missing	1 (0.4)	0	1 (0.3)
Geographical Region			
United States	134 (53)	73 (55)	207 (54)
Europe	106 (42)	45 (34)	151 (39)
Canada	10 (4)	9 (7)	19 (5)
Asia (Japan)	4 (1.6)	5 (3.8)	9 (2.3)

Source: FDA analysis

Table 3. Baseline Disease Characteristics and Prior Treatment, ITT Population,

Parameters	Ide-cel N=254	SOC N=132	Total N=386
R-ISS at baseline, n (%)			
Stage I	50 (20)	26 (20)	76 (20)
Stage II	150 (59)	82 (62)	232 (60)
Stage III	31 (12)	14 (11)	45 (12)
Missing/unknown	23 (9)	10 (8)	33 (9)
Baseline cytogenetic abnormalities, n (%)			
High risk	103 (41)	58 (44)	161 (42)
Non high risk	114 (45)	55 (42)	169 (44)
Not evaluable/missing	37 (15)	19 (14)	56 (15)
Presence of extramedullary plasmacytoma, n (%)			
Yes	61 (24)	32 (24)	93 (24)
No	192 (76)	100 (76)	292 (76)
Tumor burden, n (%)			
Low	172 (68)	90 (68)	262 (68)
High	71 (28)	34 (26)	105 (27)
Missing/unknown	11 (4)	8 (6)	19 (5)
Prior autologous stem cell transplant, n (%)			
Yes	214 (84)	114 (86)	328 (85)
No	40 (16)	18 (14)	58 (15)
Prior antimyeloma regimens, median (range)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Prior antimyeloma regimens, n (%)			
2	78 (31)	39 (30)	117 (30)
3	95 (37)	49 (37)	144 (37)
4	81 (32)	44 (33)	125 (32)
Refractory status to prior therapies, n (%)			
IMiD	224 (88)	124 (94)	348 (90)
PI	189 (74)	95 (72)	284 (74)
Anti-CD38 antibodies	242 (95)	124 (94)	366 (95)
Triple-class refractory	164 (65)	89 (67)	253 (66)
Penta-refractory	15 (6)	5 (4)	20 (5)
Time to progression on last prior therapy (months)			
Median (min, max)	7.1 (0.7, 68)	6.9 (0.4, 66)	6.9 (0.4, 68)

Source: FDA analysis

High-risk cytogenetic is defined as presence of any of the following abnormality: del17p13, t(14;16) or t (4;14). Tumor burden is based on CD138+ plasma cells in bone marrow: low tumor burden: <50%, high tumor burden: ≥50%. Triple-class refractory: refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody. Penta-refractory: refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and one anti-CD38 monoclonal antibody.

One subject enrolled in KarMMa-3was considered refractory due to lack of response to the last line of therapy. The remaining subject had PD on or within 60 days of the last regimen. Refractory to a drug was based on the most recent line of therapy including the respective agent.

Table 4 below shows the treatment regimens used in the SOC arm and for bridging therapy in the ide-cel arm.

Table 4. Regimens in SOC Arm and Bridging Therapy for Ide-cel Arm

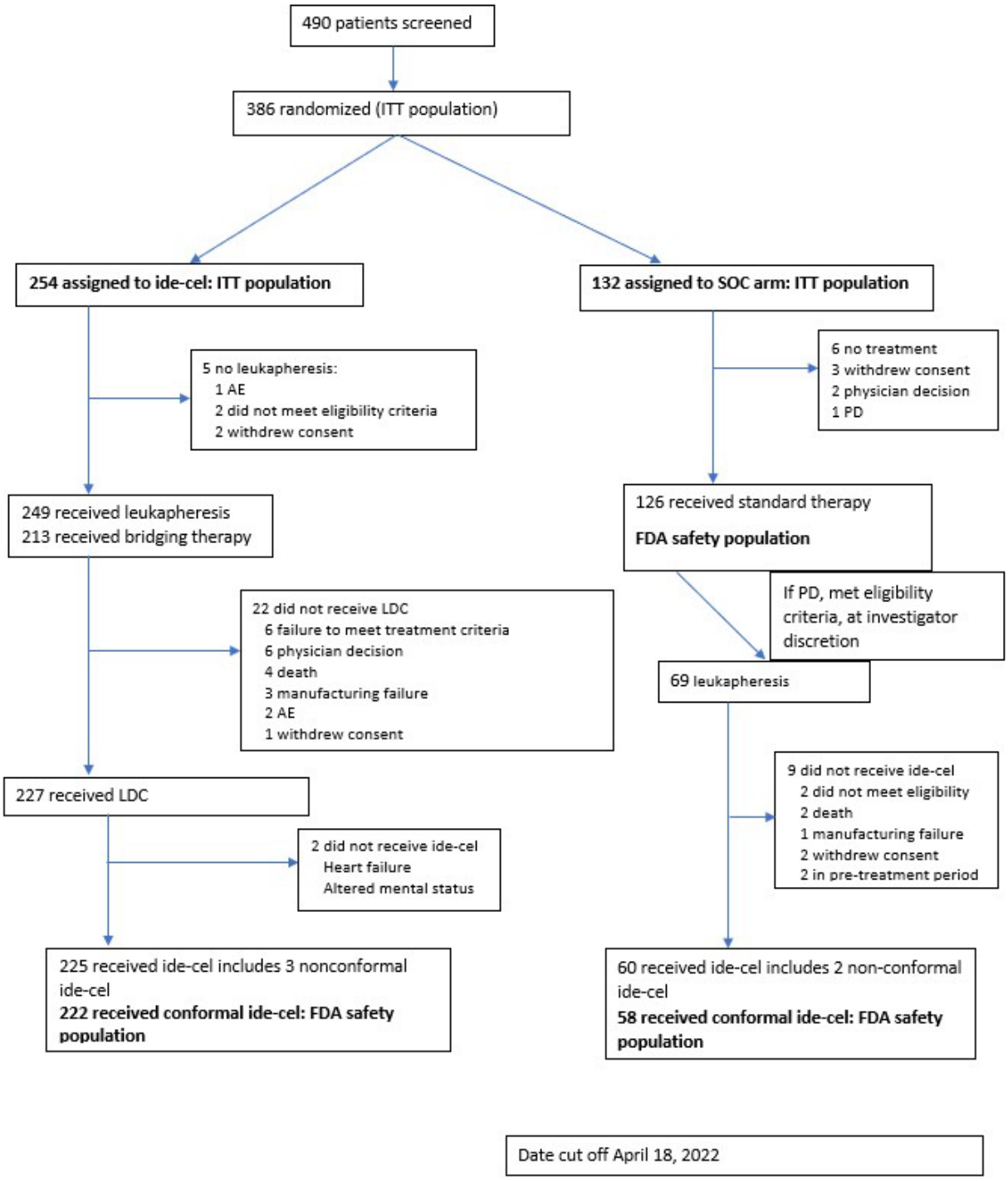
Regimens	SOC (N=132) n (%)	Ide-cel (N=254) n (%)
EPd	30 (23)	61 (24)
DPd	41 (31)	50 (20)
Kd	28 (21)	29 (11)
IRd	20 (15)	26 (10)
DVd	7 (5)	21 (8)
Other bridging therapies*	N/A	26 (10)
Received SOC or bridging	126 (95)	213 (84)
No SOC/bridging	6 (4.5)	41 (16)

Source: FDA analysis and Applicant IR.
*Non-protocol specified bridging therapy

4.6.2 Subject Disposition

The figure below summarizes patient disposition from randomization until study treatment.

Figure 1. Study Disposition, KarMMa 3



Source: Adapted from the clinical study report: KarMMa 3
Abbreviations: AE, adverse events; ide-cel, idecabtagene vicleucel; ITT, intent-to-treat; LDC, lymphodepleting chemotherapy; PD, progressive disease; SOC, standard of care

Reasons for study discontinuation and treatment discontinuation are summarized in the tables below.

Table 5. Reasons for Study Discontinuation

Reason for Study Discontinuation	Ide-cel N=254 n (%)	SOC N=132 n (%)
Death	75 (30%)	33 (25%)
Withdrawal by subject	19 (7%)	16 (12%)
Physician decision	2 (0.8%)	1 (0.8%)
Lost to follow-up	0	1 (0.8%)
Total	96 (38%)	51 (39%)

Source: FDA analysis, April 18, 2022, data cutoff.

Table 6. Reasons for Treatment Discontinuation, Standard of Care Arm

Reason for Treatment Discontinuation	SOC, N=126
Progressive disease	87 (69%)
Withdrawal by subject	7 (6%)
Death	5 (4%)
Adverse Events	1 (0.8%)
Total	100 (79%)

Source: FDA analysis and Applicant IR. April 18, 2022, data cutoff.

4.6.3 Efficacy Results

Treatment with ide-cel is associated with a statistically significant improvement in PFS per IRC compared to SOC (HR of 0.49 [95% CI: 0.379, 0.647];one-sided p-value <0.0001). The median PFS was 13.3 months (95% CI: 11.8, 16.1) for ide-cel and 4.4 months (95% CI: 3.4, 5.9) for the SOC arm. The treatment effect on PFS generally appears consistent across subgroups. Table 7 and Figure 2 summarize PFS per IRC analysis.

Table 7. PFS per IRC, ITT Population, KarMMa-3

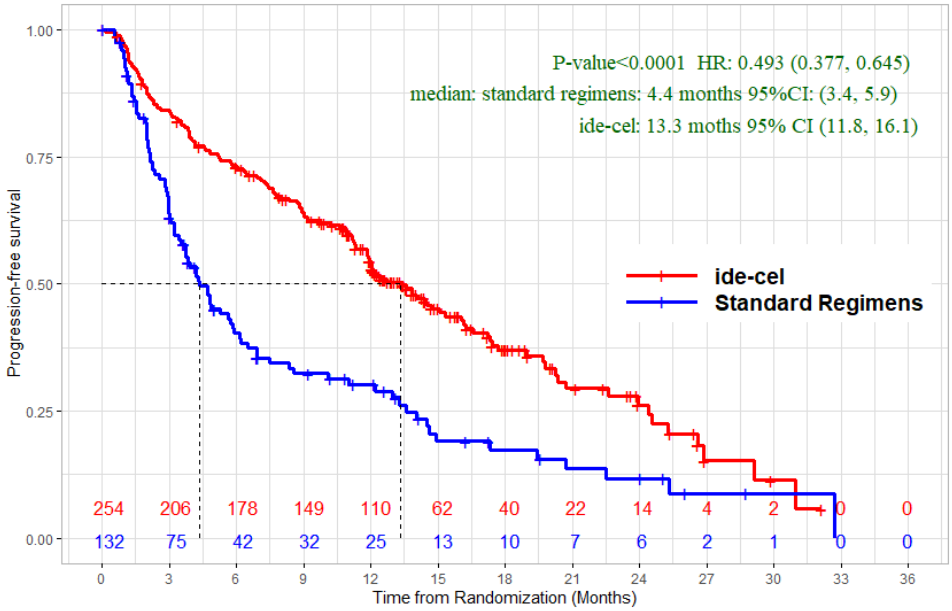
Variable	Ide-cel N=254	SOC N=132
Subjects with PFS event, n (%)	149 (59%)	93 (70%)
Progression	129 (51%)	89 (67%)
Death	20 (8%)	4 (3%)
Subjects censored, n (%)	105 (41%)	39 (30%)
Median PFS (95% CI)	13.3 (11.8, 16.1)	4.4 (3.4, 5.9)
Hazard ratio[1] (95% CI)	0.495 (0.379 to 0.647)	
p-value [2]	<.0001	

Source: FDA analysis. Data cutoff April 18, 2022

[1]Stratified Cox proportional hazards model

[2] One-sided stratified log-rank test

Figure 2. Primary Progression-Free Survival Analysis Per IRC, ITT Population



Source: FDA analysis. Data cutoff April 18, 2022

Interpretation of the PFS Analysis

a. While the absolute magnitude of median PFS (mPFS) difference between the arms is considered clinically meaningful in the RRMM setting, the mPFS in the SOC arm (4.4 months) is lower than the statistical assumption (9 months). Analyses indicate heterogeneity in the mPFS across regimens used in the SOC arm, ranging from 2.8 months to 10.1 months (DPd: n=43, mPFS is 8.5 months [95% CI: 3.7, 14.6]; Kd: n=30, mPFS is 10.1 months [95% CI: 3.2, 14.9]; EPd: n=30, mPFS is 2.8 months [95% CI: 2.0, 4.7]; IRD: n=22, mPFS is 3.7 months [95% CI: 1.1, 6.9]. Because the trial was not designed to evaluate treatment effects within subgroups defined by the SOC used, definitive conclusions cannot be made based on these observed differences. Additionally, many factors, including patient selection may account for differences across subgroups. Overall, the observed estimate of the treatment effect on PFS appears reliable based on balanced prognostic factors across treatment arms, the blinded independent assessment of the PFS endpoint, and comparable absolute difference in the medians between the investigator and the independently assessed PFS.

b. A higher proportion of PFS events in the ide-cel arm are attributable to deaths compared to the SOC arm (ide-cel arm: 8%, n=20; SOC arm: 3%, n=4). In the ide-cel arm, 8 out of 20 deaths occurred in subjects who did not receive ide-cel; the remaining 12 deaths were attributable to TEAEs. In the SOC arm, three out of the four deaths were attributable to TEAEs. Given the higher rate of deaths in the ide-cel arm compared to the SOC arm, evidence of a treatment effect on survival is needed to adequately assess whether the overall benefit-risk assessment is favorable.

Key Secondary Efficacy Endpoints

Overall Response Rate (ORR)

The ORR by IRC was statistically significant as shown in Table 8.

Table 8. Overall Response Rate, Ide-cel Versus SOC, IRC Assessment, KarMMa 3

Overall Response Rate (ORR)*	Ide-cel (N=254) N (%)	SOC Arm (N=132) N (%)
Overall Response Rate[1]	181 (71)	55 (42)
sCR	90 (35)	6 (4.5)
CR	8 (3.1)	1 (0.8)
VGPR	55 (22)	13 (10)
PR	28 (11)	35 (27)
Common Rate difference (95% CI)	29.3 (19.3, 39.3)	
p-value	<.0001	
Median Duration of Response[1] (months) 95% CI	14.8 (12, 18.6)	9.7 (5.4, 16.3)

Source: FDA analysis. Data cutoff April 18, 2022

*ORR assessment according to IMWG 2016 criteria. [1]Median is based on Kaplan-Meier estimation.

Abbreviations: CR, complete response; [1] ORR, overall response rate includes partial response or better; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Overall Survival

Results of overall survival analyses are summarized in Table 9. The first interim analysis of OS was prespecified and conducted at the time of primary PFS analysis. A second interim analysis of OS was prespecified to occur at the time of the final analysis of PFS. The Applicant conducted and submitted to the BLA at the time of the 90-day safety update, the results of an unplanned, post-hoc analysis of OS. The Kaplan Meier plots for these OS analyses are shown in Figure 3, and Figure 4.

Table 9. Analyses of Overall Survival, ITT, KarMMa 3

	Pre-specified		Post-Hoc		Pre-Specified	
	First Interim Analysis		Interim Analysis		Second Interim Analysis	
Variable	Ide-cel N=254	SOC N=132	Ide-cel N=254	SOC N=132	Ide-cel N=254	SOC N=132
OS analysis	Planned at Interim PFS analysis		*Unplanned at Safety Update		Planned at Final PFS analysis	
IF	49%		67%		74%	
Deaths, n(%)	75 (29.5)	34 (25.8)	92 (36.2)	57 (43.2)	106 (41.7)	58 (43.9)
Censored, n(%)	179 (70.5)	98 (74.2)	162 (63.8)	75 (56.8)	148 (58.3)	74 (56.1)
Median OS (95% CI)	32.8 (30.9, NA)	NA	NA (29.4, NA)	27.6 (20.9, NA)	41.4 (30.9, NA)	37.9 (23.4, NA)
Median follow-up (95% CI)	17.6 (15.9, 18.4)	16.4 (14.3, 17.8)	23.5 (22.1, 24.3)	23.2 (20.6, 26.5)	30.3 (28.9, 31.3)	29.2 (26.8, 31.2)
Hazard ratio (95% CI)	1.093 (0.727, 1.645)		0.891 (0.637,1.246)		1.012 (0.731, 1.400)	

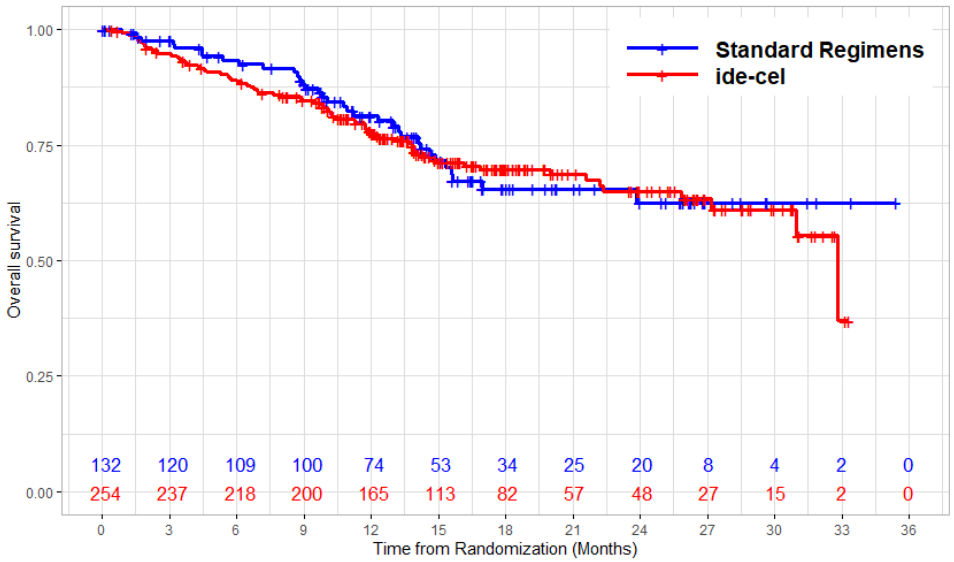
Source: FDA analysis

Data cut off for first interim analysis, April 18, 2022. Data cut off for post-hoc interim analysis, October 3, 2022. Data cut off for second interim analysis April 28, 2023.

IF: Information Fraction * Unplanned and post-hoc OS analysis done at the time of Safety update.

The first interim OS analysis (Figure 3) was performed at the time of the primary PFS analysis (i.e., data cutoff of April 18, 2022) with a median follow up of 16.9 months (95% CI:15.9, 17.9) and 49% IF. Visual inspection of the Kaplan Meier plot indicates OS detriment up to 15 months; heavy censoring from Month 9 onward indicates that data are immature.

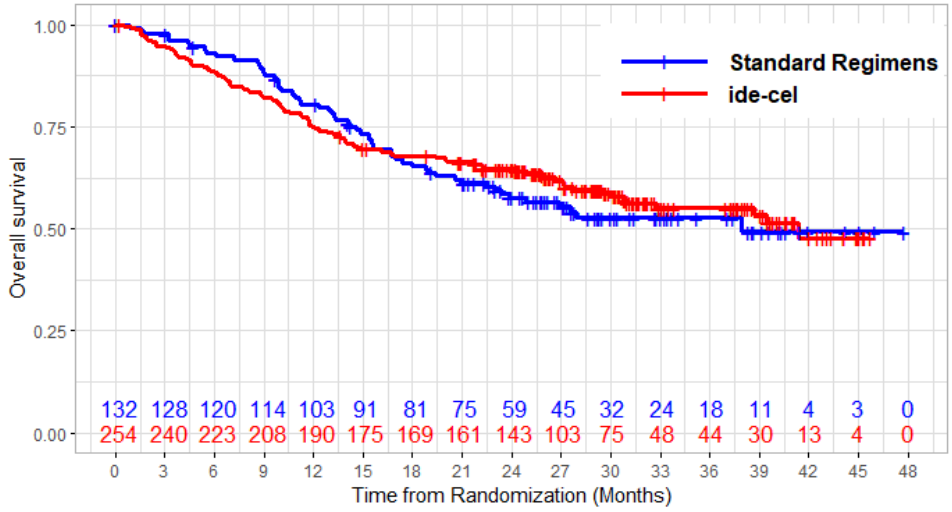
Figure 3. Overall Survival, ITT Population, Interim Analysis #1



Source: FDA analysis; Data cutoff=April 18, 2022

The second prespecified interim OS analysis (Figure 4) was performed at the time of the final PFS analysis with a data cutoff of April 28, 2023. With an estimated median follow-up of 29.7 months (95% CI: 28.7, 30.9) and 74 % IF, the OS data are shown in below. At this time, 42% of the subjects in the ide-cel arm and 44 % of the subjects in the SOC arm have died. The median OS in the ide-cel arm is 41.4 months (95 % CI: 30.9, NA) and 37.9 months in the SOC arm (95% CI: 23.4, NA). Fifty-six percent of the subjects in the SOC arm crossed over and received ide-cel.

Figure 4. Overall Survival, ITT Population, Interim Analysis #2



Source: FDA analysis Data cutoff=April 28, 2023

Interpretation of OS Analyses

- Early deaths in the ide-cel arm: The first interim analysis of OS which occurred at the time of the primary PFS analysis (see Figure 3), suggests a higher rate of deaths in the ide-cel arm compared to the SOC arm for up to 15 months. However, significant censoring from Month 9 onward reflects the immaturity of the OS analysis and warrants additional follow-up.

- In the second interim analysis for OS (see Figure 4) which provides more mature OS data reflecting an additional year of follow-up for OS, 42% of the subjects randomized to the ide-cel arm and 44% of the subjects randomized to the SOC arm, had died. The median OS in the ide-cel arm is 41.4 months (95 % CI: 30.9, NA) and 37.9 months in the SOC arm (95% CI: 23.4, NA). At the time of this analysis, 56% (74/132) of subjects in the SOC arm had crossed over and received ide-cel. Out of these 74 subjects, 69 had progressed prior to cross over.

- Visual inspection of the Kaplan Meier plot for OS represents a crossing of the curves which indicates that the treatment effect constancy assumption cannot be made (i.e., there is non proportional hazards). In this scenario, average HR is an unreliable summary statistic to quantify the treatment effect.

4.6.4 Safety Analysis Approach and Results

- The primary safety analysis was performed on all subjects who received study treatment (i.e., conformal ide-cel) in the investigational arm (n=222) or standard therapy on the SOC arm (n=126). All safety events and deaths that occurred after patients had crossed over to receive ide-cel were analyzed according to randomization (n=58). Therefore, deaths observed in the SOC arm include deaths that occurred after cross-over and ide-cel infusion.
- The primary safety review is based on the primary data cutoff of April 18, 2022, with a median follow-up of 12.9 months (range: 0.2, 31.8 months) in the ide-cel arm.
- Deaths were analyzed using the primary safety data cutoff date of April 18, 2022, and the most updated April 28, 2023, data cutoff.
- Safety analysis includes FDA's adjudication of CRS, neurotoxicity, infections and deaths.

- At the time of the safety update (October 3, 2022, data cutoff), two additional cases of MDS were reported in the ide-cel arm. In total, five cases of myeloid neoplasms: one case of acute myelogenous leukemia and four cases of MDS (2.2%) have occurred in the ide-cel arm at a median follow-up of 18.2 months. At the safety update, one subject in the SOC arm developed metastatic carcinoma of unknown primary after ide-cel infusion.

Results

Table 10 provides an overview of the safety analysis results.

Table 10. Treatment-Emergent Adverse Events Occurring On and After Treatment, KarMMa-3

TEAE	Ide-cel N=222 n (%)	SOC N=126 n (%)	Ide-cel in the SOC arm N=58 n (%)
Any TEAE	222 (100)	124 (98)	57 (98)
Serious AE	95 (43)	71 (56)	18 (31)
Max Grade 3-5 TEAE	210 (95)	114 (90)	53 (91)
Max Grade 3-4 TEAE	183 (82)	99 (79)	48 (83)
Max Grade 3 TEAE	41 (18)	35 (28)	5 (9)
Max Grade 4 TEAE	142 (64)	64 (51)	43 (74)
Deaths from AE	21 (9)	10 (8)	3 (5)

Source: FDA analysis. Data cutoff date April 18, 2022
Ide-cel columns in the table above represent subjects who received conformal ide-cel

Table 11 summarizes any grade TEAEs that occurred in ≥20% of subjects and/or Grade 3 or 4 TEAEs that occurred in ≥5 % of subjects after start of investigational therapy in both arms.

Table 11. Any-Grade TEAEs Occurring in ≥20% of Subjects and/or Grade 3 or 4 TEAEs Occurring in ≥5% of Subjects, KarMMa 3

Variable	Ide-cel N=222 n (%)		SOC Arm N=126 n (%)	
-	All Grades	Grade 3-4	All Grades	Grade 3-4
Blood and lymphatic system disorders				
Febrile neutropenia	113 (51)	113 (51)	35 (28)	35 (28)
Cardiac disorders				
Cardiac arrhythmia (GT	15 (7)	6 (2.7)	12 (10)	7 (6)
Tachycardia (GT)	71 (32)	0	27 (21)	0
General disorders and administration site conditions				
Pyrexia	203 (91)	20 (9)	67 (53)	7 (6)
Fatigue (GT)	74 (33)	3 (1.4)	61 (48)	5 (3.9)
Edema (GT)	44 (20)	1 (0.5)	35 (28)	3 (2.4)
Immune system disorders				
Cytokine release syndrome	202 (91)	9 (4.1)	51 (40)	1 (0.8)
Hypogammaglobulinemia	185 (83)	2 (0.9)	79 (63)	0

Variable	Ide-cel N=222 n (%)		SOC Arm N=126 n (%)	
Gastrointestinal disorders				
Nausea	60 (27)	2 (0.9)	61 (48)	0
Diarrhea (GT)	68 (31)	5 (2.3)	44 (35)	4 (3.2)
Infections and infestations				
Any infection	124 (56)	35 (16)	81 (64)	23 (18)
Infections pathogens unspecified	78 (35)	20 (9)	50 (40)	14 (11)
Viral infections	40 (18)	12 (5)	35 (28)	8 (6)
Bacterial infections	33 (15)	10 (4.5)	24 (19)	10 (8)
Pneumonia (GT)	29 (13)	17 (8)	17 (13)	14 (11)
Sepsis (GT)	14 (6)	7 (3.2)	13 (10)	7 (6)
Nervous system disorders				
Headache (GT)	54 (24)	0	37 (29)	2 (1.6)
Neuropathy (GT)	23 (10)	0	27 (21)	1 (0.8)
Encephalopathy (GT)	49 (22)	8 (3.6)	26 (21)	6 (4.8)
Motor dysfunction (GT)	19 (9)	2 (0.9)	36 (29)	4 (3.2)
Metabolism and nutrition disorders				
Decreased appetite	37 (17)	4 (1.8)	26 (21)	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain (GT)	81 (36)	4 (1.8)	62 (49)	10 (8)
Renal disorders				
Renal failure (GT)	29 (13)	11 (5)	19 (15)	5 (4)
Respiratory, thoracic and mediastinal disorders				
Dyspnea (GT)	46 (21)	4 (1.8)	39 (31)	3 (2.4)
Cough	32 (14)	0	26 (21)	0
Hypoxia (GT)	41 (18)	13 (6)	10 (8)	2 (1.6)
Vascular disorders				
Hypotension (GT)	79 (36)	5 (2.3)	24 (19)	2 (1.6)
Hypertension	31 (14)	16 (7)	26 (21)	14 (11)
Sleep disorder				
Sleep disorder	24 (11)	0	28 (22)	3 (2.)

Source: FDA analysis. Data cutoff April 18, 2022
Grouped term, see Appendix 8.2, Table 22.
For hypogammaglobulinemia: rates are calculated using either laboratory or adverse events. Grade 3 and higher rates of hypogammaglobulinemia are based on adverse event only.
For febrile neutropenia: rates are calculated using fever overlapping with Grade 3 or higher neutropenia excluded documented infection; this AE could be overlapping with CRS.
Abbreviations: GT, grouped term; TEAE, treatment-emergent adverse event.
AE under Pneumonia and sepsis may also be included under pathogen categories.

All Grade 3 and 4 laboratory abnormalities were observed in a higher proportion of subjects in the ide-cel arm compared to the SOC arm. Notably, the rate of Grade 3 or 4 hematological toxicity was higher in the ide-cel arm compared to the SOC arm.

Table 12. Grade ≥3 Laboratory Abnormalities Worsening From Baseline in at Least 10% of Subjects, KarMMa 3

Laboratory Abnormality	Ide-cel N=222 n (%)	SOC Arm N=126 n (%)
Lymphopenia	218 (98)	98 (78)
Leukopenia	214 (96)	81 (64)
Neutropenia	213 (96)	91 (72)
Thrombocytopenia	130 (59)	58 (46)
Anemia	116 (52)	57 (45)
ALT increase	29 (13)	10 (8)
GGT increased	23 (10)	7 (6)
Hypophosphatemia	100 (45)	38 (30)
Hyponatremia	24 (11)	9 (7)
Hypertriglyceridemia	47 (21)	13 (10)

Source: FDA analysis AND Applicant's response to Information Request. Data cutoff April 18, 2022
Lab tests are graded according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 4.03. Baseline value is defined as the last non missing value before or on the date of leukapheresis for Ide-cel Arm and before or on Month 1 Day 1 for SOC arm. Worsening is defined as a postbaseline abnormality that is at least 1 grade higher than baseline.

Adverse Events of Special Interest (AESI) are presented in Table 13 below. A list of all second primary malignancies in KarMMa-3 is included in Appendix 8.4.

Table 13. Adverse Events of Special Interest, KarMMa 3

	Ide-cel N=222 n (%)		SOC N=126 n (%)	
AESI	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS	202 (91)	11 (5)	51 (40)	1 (0.8)
Neurotoxicity	103 (46)	11 (5)	26 (21)	1 (0.8)
HLH/MAS	5 (2)	5 (2)	1 (0.8)	0
Infections	124 (56)	45 (20)	81 (64)	31 (25)
Secondary primary malignancy	13 (6)	6 (2.7)	5 (4)	3 (2.4)
Myeloid neoplasm	3 (1.4)	2 (0.9)	0	0
Cytopenia				
Neutropenia	221 (100)	213 (96)	111 (88)	91 (72)
Thrombocytopenia	204 (92)	130 (59)	113 (90)	58 (46)

Source: FDA analysis. Data cutoff April 18, 2022
CRS is graded by Lee's criteria 2014 (Lee et al. 2014). All other AEs are graded per NCI-CTCAE v4.03
Cytopenia: Analysis is based on ADLB (laboratory dataset).

Table 14. Prolonged Cytopenia After Treatment in the Ide-cel Arm (N=222)

Laboratory		Grade 3-4 cytopenia	Grade 3-4 not recovered by Day 30 (n/%)	Recovered to <Grade 3 after Day 30 (n/%)	Median time to recovery in months (Range)
Neutropenia		214 (96)	87 (39)	80 (36)	1.6 (1.1, 5.6)
Thrombocytopenia		119 (54)	83 (37)	70 (32)	1.7 (1.1, 9.3)

Cytopenia and Prolonged cytopenia: Analysis is based on ADLB (laboratory dataset).
Prolonged cytopenia is defined as Grade 3 or 4 neutropenia or thrombocytopenia that is persistent for more than 1 month after receiving ide-cel.
Recovery from neutropenia is achieved when ANC is ≥1000 cells/mm3. Recovery from thrombocytopenia is achieved when platelet count is ≥50,000 cells/mm3.

Deaths in the Safety Population

Deaths in the Safety Population at the Primary PFS Analysis

At the time of the primary PFS analysis, 69 subjects (52%) in the SOC arm have crossed over and undergone leukapheresis. Sixty subjects (45%) have received ide-cel infusion (including 2 subjects who received nonconformal ide-cel).

The percentage of deaths in the safety population was 24% for the ide-cel arm versus 26% for the SOC arm. The most common cause of death in both arms was disease progression. The overall deaths from TEAE were 9% in the ide-cel arm compared to 8% in the SOC arm. Out of 10 deaths from TEAE that occurred in the SOC arm, 3 deaths occurred after ide-cel infusion. The TEAE death rate within the first 90 days of treatment was 2.3% in the ide-cel arm compared to 1.6% in the SOC arm.

Table 15**. Deaths in the Safety Population at Primary PFS Analysis**

Parameter	**Ide-cel N=222 n (%) (All Deaths)**	**SOC N=126 n (%) (All Deaths)**	**SOC (Ide-cel Subgroup) n (%) N=58**
Total deaths	54 (24)	33 (26)	10 (17)
TEAE[1]	21 (9)	10 (8)	3 (5)
Progressive disease	27 (12)	22 (17)	7 (12)
Unknown	6 (2.7)	1 (0.8)	0 (0)
Deaths ≤90 days after treatment start	8 (3.6)	4 (3.2)	2 (3.4)
TEAE	5 (2.3)	2 (1.6)	1 (1.7)
Progressive disease	3 (1.4)	2 (1.6)	1 (1.7)
Unknown	0	0	0
Deaths >90 days after treatment start	46 (21)	29 (23)	8 (14)
TEAE	16 (7)	8 (6)	2 (3.4)
Progressive disease	24 (11)	20 (16)	6 (10)
Unknown	6 (2.7)	1 (0.8)	0 (0)

Source: FDA analysis. Data cutoff date April 18, 2022

Ide-cel columns in the table above represent subjects who received conformal ide-cel

TEAE deaths Includes all deaths from AE including AEs after disease progression and after initiation of subsequent anti-myeloma therapy.

SOC arm includes deaths post leukapheresis and ide-cel. Received upon crossover. 58 subjects in the SOC arm received conformal ide-cel at April 18, 2022, data cutoff.

*Three out of the 8 deaths from TEAE >90 days after treatment start in the SOC arm occurred in subjects who received ide-cel. Causes of three deaths include neurotoxicity (n=1), sepsis (n=2).

Deaths in the Safety Population

At the time of the final PFS analysis, 82 subjects (62%) in the SOC arm have crossed over and undergone leukapheresis. Seventy-four (56%) have received ide-cel infusion (including 2 subjects who received nonconformal ide-cel).

The percentage of deaths in the safety population was 36% for the ide-cel arm versus 43% for the SOC arm. The most common cause of death in both arms was disease progression. The overall deaths from TEAE were 11% in the ide-cel arm compared to 10% in the SOC arm. Out of 12 deaths from TEAE that occurred in the SOC arm, 4 deaths occurred after ide-cel infusion. The TEAE death rate within the first 90 days of treatment start was 2.7% in the ide-cel arm compared to 1.6% in the SOC arm.

Table 16. Deaths in the Safety Population at the Final PFS Analysis

Parameter	Ide-cel Arm N=222 n (%) (All Deaths)	SOC Includes Ide-cel in SOC Arm N=126 n (%) (All Deaths)	SOC Ide-cel in SOC Arm (Subgroup of SOC Arm) n (%) N=72
Total deaths	79 (36)	54 (43)	21 (29)
TEAE[1]	24 (11)	12 (10)	4 (6)
Progressive disease	42 (19)	36 (29)	15 (21%)
Unknown	13 (6)	6 (4.8)	2 (2.8)
Deaths ≤90 days after treatment start	9 (4.1)	4 (3.2)	2 (2.8)
TEAE	6 (2.7)	2 (1.6)	1 (1.4)
Progressive disease	3 (1.4)	2 (1.6)	1 (1.4)
Unknown	0	0	0
Deaths >90 days after treatment start	70 (32)	50 (40)	19 (26)
TEAE	18 (8)	10* (8)	3 (4.2)
Progressive disease	39 (18)	34 (27)	14 (19)
Unknown	13 (6)	6 (4.8)	2 (2.8)

Source: FDA analysis; Data cutoff: April 28, 2023
Death day is from treatment start for each arm. Treatment start is after ide-cel infusion for Column 1 and 3. After start of any SOC treatment for Column 2.
Only deaths that occurred after infusion of conformal ide-cel are included in this Table.
TEAE deaths Includes all deaths from AE including AEs after disease progression and after initiation of subsequent anti-myeloma therapy.
SOC arm includes deaths post leukapheresis and ide-cel. Received upon crossover. Seventy-two subjects in the SOC arm received conformal ide-cel at April 2023 data cutoff.
*Four out of the 10 deaths from TEAE >90 days after treatment start in the SOC arm occurred in subjects who received ide-cel. Causes of four deaths include neurotoxicity (n=1), sepsis (n=2) and carcinoma of unknown primary (n=1).

In the safety population, the primary cause of death due to an AE was infection in both the arms as shown in Table 17.

Table 17. Deaths Due to Adverse Events

Characteristic	Ide-cel N=222 n (%)	SOC N=126[1] n (%)	Ide-cel in SOC (Subgroup of SOC) N=72 n (%)
Total deaths	79 (36)	54 (43)	21 (29)
Adverse events	24 (11)	12 (10)	4 (6)
CRS and/or HLH/MAS	2 (0.9)	0	0
Neurotoxicity	1 (0.5)	1 (0.8)	1 (1.4)
Infection	14 (6)	8 (6)	2 (2.8)
Second primary malignancy	3 (1.4)	1** (0.8)	1** (1.4)
Hemorrhage	2 (0.9)	0	0
Respiratory failure	0	2 (1.6)	0
Cardiac (coronary artery dissection)	1 (0.5)	0	0
Sudden death	1 (0.5)	0	0
Stroke from atrial fibrillation*	1 (0.5)	0	0

Source: FDA analysis. April 28, 2023
All deaths included in Table are in subjects who received conformal ide-cel.
[1] Includes deaths that have occurred after leukapheresis and ide-cel infusion in SOC arm.
Death due to CRS, HLH/MAS, and invasive candidiasis in one subject in the ide-cel arm is included under both CRS/HLH and infection.
*Atrial fibrillation was sequela of CRS
** Carcinoma of unknown primary

5. Main Topics for Discussion

5.1 Increased Rate of Early Deaths in the Ide-cel Arm

Overall, there is a higher rate of early deaths in the ide-cel arm compared to the SOC arm. The adequacy of exploratory analyses of the KarMMa-3 trial to support the identification of strategies to mitigate this risk warrants further discussion. Retrospective subgroup analyses, which are not pre-specified at the initiation of the study and not supported by an adequate sample size, cannot adequately characterize a heterogeneous patient population. Instead, due to the inherent selection bias of post hoc analyses, they can only serve as hypothesis-generating explorations.

Visual inspection of the Kaplan Meier plot for OS indicates that at the time of the primary PFS analysis and in subsequent analyses of OS reflecting extended follow-up, there were more early deaths occurring in the ide-cel arm compared to the SOC arm. OS in the Kapan-Meier (KM) curve in the first 15 months after randomization was lower in the ide-cel arm with crossing of the OS curves at approximately 15 months. The crossing pattern of the Kaplan-Meier curves for OS renders the estimated HR an unreliable measure of the estimated treatment effect because the proportional hazards assumption does not hold. For this reason, FDA does not consider the OS HR 1.012 (0.731, 1.400) at the time of the most recent analysis of OS, to represent the treatment effect on OS or to support the assessment of potential OS detriment. Instead, FDA based its assessment a review of deaths as shown in Table 18.

Table 18. Deaths, ITT Population

Variable	Ide-cel N=254 n (%)	SOC N=132 n (%)
Total deaths in ITT population (treated and untreated)	106[1] (42)	58[1] (44)
Death from PD	60 (24)	36 (27)
Deaths from AE	29 (11)	14 (11)
Unknown	17 (7)	8 (6)
All deaths in the first 9 months (treated and untreated)	45 (18)	15 (11)
Death from PD	25 (10)	9 (7)
Death from AE	14 (6)	6[2] (4.5)
Unknown	6 (2.4)	0
All deaths from 9-18 months	36 (14)	29 (22)
Death from PD	20 (8)	19 (14)
Death from AE	10 (3.9)	7[3] (5)
Unknown	6 (2.4)	3 (2.3)
All deaths after 18 months	25 (10)	14 (11)
Death from PD	15 (6)	8 (6)
Death from AE	5[4](2)	1 (0.8)
Unknown	5 (2)	5 (3.8)

Source: FDA analysis: April 28, 2023, data cutoff date. Death day is calculated from randomization. Table includes deaths in all randomized subjects including two subjects who received nonconformal ide-cel

Table includes all deaths after treatment from AEs including infection related AEs following disease progression and subsequent AMT.

[1]Out of the 106 deaths in the ide-cel arm, 25 never received the intended treatment; (20 of these deaths were in the first 9 months) compared to 4 deaths in the SOC arm.

[2] Includes one death from ide-cel neurotoxicity after crossover

[3] Includes three deaths from AE post ide-cel: two deaths from sepsis, one death from carcinoma of unknown primary

[4] Includes death in recipient of nonconformal ide-cel from amyotrophic lateral sclerosis in the setting of renal cell carcinoma.

The cause of death in 25 subjects who did not receive ide-cel treatment include: infection, respiratory failure, disease progression and unknown. The cause of death in four subjects who did not receive SOC treatment include: Grade 5 CRS on another clinical trial, ventricular tachycardia and unknown.

In the Safety Population analysis, the overall rate of fatal TEAEs was 11% in the ide-cel arm compared to 10% in the SOC arm. In the first 90 days from treatment start, 2.7% of subjects in the ide-cel group died from TEAEs compared to 1.6% in the SOC arm Table 15. This includes six deaths that occurred in the ide-cel arm from CRS, CRS/HLH and candidiasis (in one subject), neurotoxicity, sepsis, stroke in the setting of atrial fibrillation (sequela of CRS) and pneumonia. A higher proportion of subjects died before disease progression in the ide-cel arm (8%) compared to the standard of care arm (3%) (Table 7). Of the 45 subjects in the ide-cel arm that died in the first 9 months from randomization, 20 subjects died without receiving ide-cel infusion and 25 subjects died after ide-cel infusion. FDA considers the risks associated with administration of the treatment to be integral to the benefit-risk assessment of a drug. None of the subjects in the SOC arm died without receiving the intended treatment in the first 9 months from randomization.

An analysis of the reasons for death in the patients randomized to the ide-cel arm who experienced early mortality but did not receive the intended therapy are shown in in the Appendix. The reasons varied and included inability to proceed with the first treatment step, leukapheresis, manufacturing failure, need for repeat leukapheresis with delayed product availability, physician decision, subject withdrawal, disease progression and adverse events. Early mortality in subjects who did not receive ide-cel may highlight uncertainties including patient selection, what constitutes adequate disease control while awaiting CAR T product, and product manufacturing issues.

A key question for this application is the duration of the period of increased risk of early death in the ide-cel arm, compared to the SOC arm. Piecewise Hazard ratio assessment can aid in estimating treatment effect at set time intervals in the setting of non-proportional hazards. Based on this assessment (see Table 19) and on a numeric assessment death rate by time 3-month intervals (see Table 20), there appears to be an increased risk of death extending to at least 9 months in KarMMa 3.

Table 19. Piecewise Hazard Ratio Assessment, ITT Population

Time Interval	**0-9 Months**		**9-18 Months**		
HR (95% CI)	1.65 (0.92, 2.97)		0.71 (0.43, 1.15)		
Time Interval	**0-3 Months**	**3-6 Months**	**6-9 Months**	**9-12 Months**	**12-15 Months**
HR (95% CI)	2.41 (0.68, 8.46)	1.58 (0.62, 4.01)	1.35 (0.52, 3.49)	1.05 (0.48, 2.28)	0.88 (0.38, 2.04)

Source: FDA analysis
*> 18 months not reported due to heavy censoring

Table 20. Deaths by Time Intervals From Randomization, ITT Population

Time Interval (Months)	**Arm A (Ide-cel) (N=254) Deaths/# of Sub at Risk**	**SOC (N=132) Deaths/# of Sub at Risk**
0-6	30/254 (11.8%)	9/132 (6.8%)
6-9	15/223 (6.7%)	6/120 (5.0%)
9-12	18/208 (8.7%)	10/114 (8.8%)
12-15	14/190 (7.4%)	9/103 (8.7%)

Source: FDA analysis

5.2 Clinical Benefit of Treatment with Ide-cel

KarMMa-3 demonstrated a statistically significant improvement in PFS per IRC compared to SOC (HR of 0.49 [95% CI: 0.379, 0.647]; one-sided p-value <0.0001). The median PFS was 13.3 months (95% CI: 11.8, 16.1) for ide-cel and 4.4 months (95% CI: 3.4, 5.9) for the SOC arm. This effect is consistent across important subgroups, by assessor (i.e., by IRC and by Investigator). The effect on overall response rate (ORR) was also statistically significant (71% vs 42% with a common rate difference of 29.3% (95% CI: (19.3, 39.3); p value <.0001. The median duration of response by Kaplan Meier estimate was 14.8 months (95% CI: 12, 18.6) in the ide-cel arm and 9.7 months (95% CI: 5.4, 16.3) in the SOC arm.

KarMMa-3 was powered to detect a HR of 0.74 with 50% power, which would translate into a 7-month difference between the two arms. At the time of the first interim analysis of OS which occurred at the time of the primary analysis of PFS, the boundary for statistical significance was not crossed. At the second interim analysis for OS which occurred when 74% of the events required for the final analysis had occurred (i.e., 164 of 222 OS events), statistical significance was not met; unstratified HR 1.012 (95% CI: (0.731, 1.400), p value 0.5287. The median OS was 41.4 months (95% CI: 30.9, NA) in the ide-cel arm and 37.9 months (95% CI: 23.4, NA) in the SOC arm.

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

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

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

While KarMMa-3 demonstrated a statistically significant effect on PFS, an increased rate of early deaths was observed as described above leading to uncertainties regarding whether the overall benefit-risk assessment for ide-cel in the indicated population, is favorable. While a final analysis of OS was pre-specified, the results from a fairly mature OS analysis are included in the BLA, which shows that early OS detriment persisted. Furthermore, additional follow-up of overall survival even if statistically significant, is unlikely to overcome the increased risk of early deaths.

The Applicant provided the results of exploratory analyses to identify factors that potentially account for the differential rate of early deaths, as described above. Some of these analyses included assessing OS in the Safety Population, with the resulting Kaplan Meier plot for OS showing overlapping curves until approximately 15 months with separation afterwards (Refer to in Appendix 6; for this analysis, the average HR of 0.83 (95% CI: 0.58, 1.18). However, this analysis is difficult to interpret because the comparison is no longer between two randomized and comparable groups; more subjects with poor prognosis may be excluded from the ide-cel arm than the SOC arm in the Safety Population and the comparison may be biased in favor of the ide-cel arm. Additionally, the Applicant conducted analyses based on the rank preserving structural failure time (RPSFT) model, the two-stage accelerated failure time model, and the Inverse Probability of Censoring Weighting (IPCW) method. These analyses are aimed to support the position that crossover of patients from the SOC arm to ide-cel may have blunted the treatment effect on OS. These analyses, which resulted in estimated HR below 1, rely on unverifiable and questionable model assumptions, limiting their interpretability. For example, a key assumption of the RPSFT model is a "common treatment effect," meaning that it is assumed that ide-cel has the same treatment effect on OS regardless of when it is administered. This raises a critical question regarding the impact of the treatment on OS when administered after disease progression on SOC arm versus upfront after randomization. Patients who crossed over and received ide-cel cannot be assumed to be similar to the "as randomized" population. They likely are a selected subgroup of patients who retained the eligibility criteria to receive ide-cel after disease progression on the SOC arm. Because potential differences in underlying patient and disease characteristics could influence the prognosis of these patients, the "common treatment effect" assumption may not hold, thus limiting the reliability of RPSFT analysis results. In all, the Applicant's analyses do not provide convincing evidence that ide-cel treatment provides OS benefit. In conclusion, residual uncertainty remains regarding the benefit of PFS given the risks of treatment and the lack of demonstrated OS benefit to date.

6. Draft Questions

Discussion Topic:

Discuss whether the results of KarMMa-3 provided in the supplemental application are sufficient to support a positive risk-benefit assessment of idecabtagene vicleucel for the proposed indication. Specifically, is the risk of early death associated with ide-cel treatment acceptable in the context of the clinical benefit.

Voting Question:

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

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8. Appendix

Table 21 below outlines the treatment options for patients with relapsed/refractory MM, including those who are triple-class exposed.

Table 21. Approved Therapies for Relapsed/Refractory Multiple Myeloma

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

Source: FDA
Bolded text indicates SOC arm regimens in KarMMa 3.
Abbreviations: dex, dexamethasone; Kd, carfilzomib and dexamethasone; Pd, pomalidomide and dexamethasone; Rd, lenalidomide (Len) and dexamethasone; Vd, bortezomib and dexamethasone

8.1 Eligibility Criteria

Inclusion Criteria

1. Subject has documented diagnosis of multiple myeloma (MM) and measurable disease, defined as:
    - Serum protein electrophoresis or urine protein electrophoresis: serum protein electrophoresis ≥0.5 g/dL or urine protein electrophoresis ≥200 mg/24 hours and/or
    - Light chain MM without measurable disease in the serum or urine: Serum immunoglobulin free light chain ≥10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free light chain ratio

2. Subject has received at least two but no greater than four prior MM regimens. *Note: Induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered as one regimen.*
3. Subject has received prior treatment with daratumumab, a proteasome inhibitor and an immunomodulatory compound-containing regimen for at least two consecutive cycles.
4. Subject must be refractory to the last treatment regimen. Refractory is defined as documented progressive disease during or within 60 days (measured from the last dose of any drug within the regimen) of completing treatment with the last anti-myeloma regimen before study entry.
5. Subject achieved a response (minimal response or better) to at least one prior treatment regimen.
6. Subject has an Eastern Cooperative Oncology Group performance status of 0 or 1.
7. Recovery to Grade 1 or baseline of any nonhematologic toxicities due to prior treatments, excluding alopecia and Grade 2 peripheral neuropathy.

Key Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has non-secretory MM.
2. Subject has any of the following laboratory abnormalities:
    - Absolute neutrophil count <1,000/µL
    - Platelet count: <75,000/µL in subjects in whom <50 % of bone marrow nucleated cells are plasma cells and platelet count <50,000/µL in subjects in whom ≥50 % of bone marrow nucleated cells are plasma cells (it is not permissible to transfuse a subject to reach this level)
    - Hemoglobin <8 g/dL (<4.9 mmol/L) (it is not permissible to transfuse a subject to reach this level)
    - Serum creatinine clearance <45 mL/min
    - Corrected serum calcium >13.5 mg/dL (>3.4 mmol/L)
    - Serum aspartate aminotransferase (AST) or alanine aminotransferase >2.5 × upper limit of normal (ULN)
    - Serum total bilirubin >1.5 × ULN or >3.0 mg/dL for subjects with documented Gilbert's syndrome
3. Subject has inadequate pulmonary function defined as oxygen saturation (SaO_2) <92 % of predicted normal. *Note that forced expiratory testing (FEV1) is required for subjects suspected of having chronic obstructive pulmonary disease and subjects must be excluded if FEV1 is <50 % of predicted normal.*
4. Subject has a history or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, subarachnoid hemorrhage or other CNS bleed, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
5. Previous history of an allogeneic hematopoietic stem cell transplantation, treatment with any gene therapy-based therapeutic for cancer, investigational cellular therapy for cancer or BCMA targeted therapy.
6. Subject has received autologous stem cell transplantation within 12 weeks prior to randomization.
7. Subject has received any of the following within the last 14 days prior to randomization:
    - Plasmapheresis
    - Major surgery (as defined by the Investigator)
    - Radiation therapy other than local therapy for myeloma-associated bone lesions
    - Use of any investigational agents and systemic anti-myeloma drug therapy
8. Echocardiogram or multigated acquisition with left ventricular ejection fraction <45 %.
9. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine or systemic steroids at any dose). Intermittent topical, inhaled or intranasal corticosteroids are allowed.

10. Subject is positive for human immunodeficiency virus (HIV-1 and HIV-2), chronic or active hepatitis B or active hepatitis A or C.
11. Subject has uncontrolled systemic fungal, bacterial, viral or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antimicrobial treatment) or requiring intravenous antimicrobials for management.
12. Subject has a history of class III or IV congestive heart failure or severe nonischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months prior to randomization.

Eligibility Criteria for LDC (Treatment Arm A and Cross-over for SOC arm Only)

1. No bridging anti-myeloma therapy within 14 days prior to start of LDC.
2. Adequate hepatic function defined by AST and/or alanine aminotransferase ≤2.5 x ULN and total bilirubin ≤1.5 x ULN (unless due to Gilbert's syndrome and direct bilirubin is ≤1.5 x ULN).
3. Adequate renal function defined by serum clearance creatinine ≥30 mL/min.
4. Adequate bone marrow function defined by absolute neutrophil count ≥500/µL and platelet count ≥50,000/µL (unless inadequate bone marrow function is thought to be related to bone marrow myeloma involvement, this should be discussed with the Medical Monitor).
5. Lack of active infection.

Eligibility Criteria for Ide-cel Infusion (Treatment Arm A and Cross-over for SOC arm Only)

1. Suspected or active systemic infection
2. Onset of fever ≥38°C/100.4°F, not related to underlying disease
3. Requirement for supplemental oxygen to keep saturation greater than 91 %, or presence of progressive radiographic abnormalities on chest x-ray
4. Cardiac arrhythmia not controlled with medical management
5. Hypotension requiring vasopressor support
6. New-onset or worsening of other nonhematologic organ dysfunction ≥ Grade 3

8.2 FDA Grouped Terms

Table 22. FDA Grouped Preferred Terms

FDA Grouped Term	AEDECOD Preferred Term
Cardiac arrhythmia	arrhythmia, atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block first degree, conduction disorder, electrocardiogram qt prolonged, sinus arrest, supraventricular tachycardia, tachyarrhythmia, ventricular extrasystoles, ventricular tachycardia
Diarrhea	colitis, colitis microscopic, enterocolitis, diarrhea
Dizziness	dizziness, presyncope, syncope, vertigo, vertigo positional, vestibular disorder
Dyspnea	dyspnea, dyspnea exertional, dyspnea paroxysmal nocturnal, tachypnoea
Edema	eyelid oedema, face oedema, fluid retention, generalized oedema, hypervolemia, localized oedema, mouth swelling, oedema, oedema peripheral, periorbital oedema, periorbital swelling, peripheral swelling, swelling, swelling face
Encephalopathy	amnesia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dysgraphia, encephalopathy, immune effector cell-associated neurotoxicity syndrome,

FDA Grouped Term	AEDECOD Preferred Term
	incoherent, lethargy, memory impairment, mental status changes, metabolic encephalopathy, somnolence, stupor, toxic encephalopathy
Fatigue	asthenia, fatigue, malaise, muscle fatigue
Headache	head discomfort, headache
Hypotension	hemodynamic instability, hypotension, orthostatic hypotension
Hypoxia	hypoxia, oxygen saturation decreased
Motor dysfunction	akathisia, dyskinesia, dysphonia, hypertonia, muscle spasms, muscle twitching, muscular weakness, restless legs syndrome
Musculoskeletal pain	arthralgia, back pain, bone pain, joint stiffness, muscle strain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, noncardiac chest pain
Neuropathy	carpal tunnel syndrome, dysaesthesia, hyperaesthesia, hypoaesthesia, hypoaesthesia oral, mononeuropathy, neuralgia, neuritis, neuropathy peripheral, paraesthesia, paraesthesia oral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, radicular pain, radiculopathy, sacral radiculopathy, sciatica, sensory loss, toxic neuropathy
Pneumonia	bronchopulmonary aspergillosis, coronavirus pneumonia, covid-19 pneumonia, organizing pneumonia, pneumonia, pneumonia escherichia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia fungal, pneumonia influenzas, pneumonia legionella, pneumonia parainfluenza viral, pneumonia pseudomonal, pneumonia streptococcal, pneumonia viral, pulmonary nocardiosis
Renal failure	acute kidney injury, blood creatinine increased, chronic kidney disease, creatinine renal clearance decreased, glomerular filtration rate decreased, nephropathy toxic, oliguria, renal failure, renal impairment, urine output decreased
Sepsis	bacteremia, bacterial sepsis, candida sepsis, escherichia bacteremia, clostridial sepsis, device related bacteremia, enterococcal sepsis, , escherichia sepsis, klebsiella bacteremia, klebsiella sepsis, multiple organ dysfunction syndrome, neutropenic sepsis, pulmonary sepsis, sepsis, septic shock, staphylococcal bacteremia, streptococcal bacteremia, streptococcal sepsis
Sleep disorder	hypersomnia, insomnia, sleep disorder
Tachycardia	heart rate increased, sinus tachycardia, tachycardia

Source: FDA
Abbreviations: AEDECOD, AE dictionary-derived term

8.3 Summary of Subsequent Therapy, ITT Population

Table 23. Subsequent Therapy, ITT Population

Type of Subsequent Therapy	Arm A (Ide-cel) (N=254) n (%)	Arm B (Standard Regimens) (N=132) n (%)
Number of subjects received subsequent therapy	146 (57.5)	104 (78.8)
Chemotherapy	70 (27.6)	65 (49.2)
Autologous BCMA CAR T therapy	0	74 (56.1)
Autologous BCMA CAR T therapy off protocol	3 (1.2)	3 (2.3)
Antibody drug conjugates	27 (10.6)	14 (10.6)

Type of Subsequent Therapy	Arm A (Ide-cel) (N=254) n (%)	Arm B (Standard Regimens) (N=132) n (%)
Monoclonal antibodies	92 (36.2)	40 (30.3)
Immunomodulatory agents	69 (27.2)	35 (26.5)
Proteasome inhibitors	81 (31.9)	73 (55.3)
Transplant	-	-
HDT+ASCT	8 (3.1)	6 (4.5)
Allogeneic transplant	4 (1.6)	1 (0.8)
Other cellular therapies	1 (0.4)	1 (0.8)
Other therapies	53 (20.9)	17 (12.9)

Source: Applicant IR, April 28, 2023, Data cutoff.
Abbreviations: ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T-cell; HDT, high-dose therapy.

8.4 Second Primary Malignancies in KarMMa 3

Table 24. Second Primary Malignancies in Ide-cel Arm, KarMMa 3

Malignancy	N=222
Acute myeloid leukemia	1
Myelodysplastic syndrome	4
Breast cancer	2
Malignant melanoma	2
Rectal adenocarcinoma	1
Pancreatic adenocarcinoma	1
Basal cell carcinoma*	2
Squamous cell carcinoma of skin*	1
Squamous cell carcinoma of thoracic wall	1
Squamous cell carcinoma of skin in situ	1
Total	15

Source: FDA analysis
Data cutoff October 3, 2022 (safety update)
*One subject developed both squamous cell carcinoma and basal cell carcinoma is included under both categories
The table does not include one subject who received nonconformal ide-cel and developed renal cell carcinoma

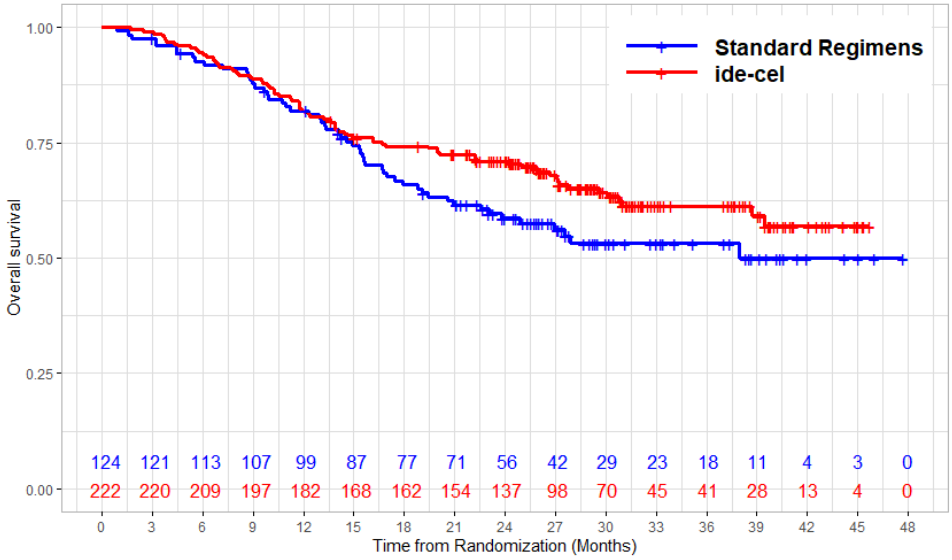
Table 25. Second Primary Malignancies in SOC Arm, KarMMa 3

Malignancy	N=126
Developed prior to ide-cel	
Metastatic bronchial carcinoma	1
Lentigo maligna	1
GI stromal tumor	1
Developed after ide-cel infusion	
Metastatic squamous cell carcinoma skin (ear)	1
Squamous cell carcinoma of skin	1
Metastatic carcinoma of unknown primary	1
Total	6

Source: FDA analysis
Data cutoff October 3, 2022.(Safety update)

8.5 Overall Survival and Disposition of Subjects Who Did Not Receive Ide-cel and Died Within 9 Months

Figure 5. Overall Survival, Safety Population



Source: FDA analysis
April 28, 2023, Data cutoff, excluding five subjects receiving nonconformal ide-cel

Figure 6. Disposition of 20 Subjects Who Did Not Receive Ide-cel and Died Within 9 Months