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ABECMA (idecabtagene vicleucel)

Meeting Date: 15-Mar-2024

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ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
BTZ	bortezomib
CAR	chimeric antigen receptor
CFZ	carfilzomib
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cLDA	constrained longitudinal data analysis
CoD	cutoff date
COVID-19	coronavirus disease
CRR	complete response rate
CRS	cytokine release syndrome
DARA	daratumumab
DoR	duration of response
DPd	daratumumab + pomalidomide + low-dose dexamethasone
DSMB	Data Safety Monitoring Board
DVd	liposomal doxorubicin, vincristine, and low-dose dexamethasone
EHA-ESMO	European Hematology Association-European Society for Medical Oncology
EMP	extramedullary plasmacytoma
EORTC QLQ-C30	European organization for research and treatment of cancer-quality of life questionnaire-core 30 items
EORTC QLQ-MY20	European organization for research and treatment of cancer-quality of life C30 questionnaire-multiple myeloma module 20 items
EQ-5D-5L	European quality of life-5 dimensions health state classifier to 5 levels
EU	European Union
FDA	Food and Drug Administration
GHS	Global Health Status
HDAC	histone deacetylase
HR	hazard ratio
HRQoL	health related quality of life
IA	interim analysis
ide-cel	idecabtagene vicleucel
iiNT	investigator-identified neurotoxicity
IMiDs	immunomodulatory drugs
IPCW	inverse probability of censoring weighting
IRC	independent review committee
IRd	Ixazomib + lenalidomide+ low-dose dexamethasone
IRT	interactive response technology
ISS	international staging system
ITT	intent-to-treat
IXA	ixazomib
Kd	carfilzomib + low-dose dexamethasone
K-M	Kaplan-meier
LD	lymphodepleting
LEN	lenalidomide
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MM	multiple myeloma
NCCN	National Comprehensive Cancer Network
NT	neurotoxicity
ODAC	Oncology Drugs Advisory Committee

Abbreviation	Term
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PFS2	PFS on next line of therapy
PIs	proteasome inhibitors
POM	pomalidomide
PPS	post-progression survival
PRO	patient-reported outcome
QoL	quality of life
REMS	Risk Evaluation and Mitigation Strategy
RPSFT	rank preserving structural failure time
RRMM	relapsed or/and refractory multiple myeloma
SAE	serious adverse event
SLAMF7	signaling lymphocytic activation molecule family member 7
SOC	system organ class/standard of care
SPM	second primary malignancies
TCE	triple-class exposed
US	United States
VAS	visual analog scale(S)

1 EXECUTIVE SUMMARY

Abecma® (idecabtagene vicleucel, ide-cel) is a BCMA-directed genetically modified autologous T cell immunotherapy product consisting of a patient's own T cells that are harvested and genetically modified ex vivo through transduction with an anti-BCMA02 chimeric antigen receptor (CAR) lentiviral vector (LVV). Abecma® is approved in the United States (US), European Union (EU), Switzerland, Japan, Great Britain, and Israel. The initial approval by the US Food and Drug Administration (FDA) was received on 26-Mar-2021 for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody, based on the results of the BB2121-MM-001 (KarMMa) Study. A supplemental Biologics License Application (sBLA) was submitted to the FDA on 15-February 2023, based on the results of the KarMMa-3 (BB2121-MM-003, MM-003) Study, to support the proposed extension of the indication of Abecma® to the treatment of adult patients with RRMM who have received an IMiD, a PI, and an anti-CD38 antibody. To date, applications for extension of the indication based on the KarMMa-3 Study results have received approval in Japan on 06-Dec-2023 and in Switzerland on 09-Feb-2024. In the EU, a Positive Opinion was adopted by the European Medicines Agency's Committee for Medicinal Products for Human Use on 25-Jan-2024. The FDA is convening the Oncology Drugs Advisory Committee (ODAC) to have a general discussion focused on the overall survival (OS) data in the KarMMa-3 Study and the risk and benefit of Abecma® in the intended population. This briefing document reviews the following to support the overall positive benefit risk in the proposed extension of the indication.

- Substantial evidence of efficacy and safety of ide-cel compared to standard regimens, based on KarMMa-3, the **first randomized Phase 3 study of a CAR-T** therapy in patients who received 2-4 prior regimens including an IMiD, a PI and daratumumab (DARA, anti-CD38 antibody) **(triple-class exposed [TCE]),** a patient population with very high unmet need with a growing treatment gap.
- Statistically significant, clinically meaningful, and consistent results across all prespecified subgroups in KarMMa-3 **for the primary endpoint (progression free survival [PFS]) and the key secondary endpoint of overall response rate [ORR].**
- **Long treatment-free period achieved by ide-cel with a one-time therapy.**
  - Available myeloma therapies are administered continuously until progression.
- **Evidence of quality-of-life improvement in favor of ide-cel** in KarMMa-3 after a single infusion.
- **No increased ide-cel–associated mortality** compared to standard regimens.
- Interpretability of **OS data is confounded** by the patient-centric design, which allowed crossover.
  - Adjusting for crossover showed a trend towards improved OS with ide-cel versus standard regimens.
  - OS in standard regimens arm was substantially longer than expected for this patient population.

- While random variability cannot be excluded in the context of a 2:1 randomization, further analyses showed that the numerically **higher proportion of early deaths** in the ide-cel arm was driven by **patients who never received ide-cel**; most early deaths were due to disease progression.
  - Early deaths were not due to ide-cel related mortality nor due to manufacturing delays.
  - Patients with early death were enriched for high-risk factors.
  - Trial design limited bridging therapy to 1 cycle and mandated a minimum wash-out period.
- The **safety profile of ide-cel remained consistent** with the safety from the current indication.
  - Toxicity was **predictable** and **manageable,** including cytopenias, cytokine release syndrome (CRS), and CAR-T–associated neurotoxicity.
  - Deaths due to adverse events (AEs) were similar across arms.
- KarMMa-3 demonstrated a **favorable benefit–risk profile for ide-cel** compared to standard regimens in patients with RRMM who became TCE early in their treatment course, and supports the use of ide-cel in this disease setting where a treatment gap exists due to lack of approved effective therapies.
  - **Earlier use is critical** to enable optimal PFS benefit and effective bridging.
  - **Effective bridging** is required to allow patients to receive ide-cel.
  - CAR-T therapy is prescribed by dedicated experts at qualified centers who have **deep knowledge of how to treat and bridge patients to ide-cel** and manage the specific side effects.
  - Product labeling will ensure the safe use of ide-cel by informing healthcare providers about the risks associated with the use of this product and the appropriate mitigations.

1.1 Disease Background and Unmet Medical Need

Multiple myeloma (MM) is an incurable blood cancer characterized by the clonal proliferation of malignant plasma cells both within the bone marrow and at localized extramedullary sites, termed plasmacytomas. In the US, MM accounts for approximately 19% of hematologic malignancies, primarily occurring in older individuals (median age at onset of 69 years) and is very rare in individuals younger than 40 years.[1,2] In the US, 35,730 new cases of MM and 12,590 deaths due to MM were estimated in 2023.[3] The course of MM is characterized by a period of disease control after initial therapy followed by progression.[4,5] Tumors typically recur more aggressively with each relapse and with each subsequent line of therapy, leading to successive declines in disease control and ultimately, refractory MM, which is associated with poor prognosis.[6,7,8] Treatment of multiple myeloma is continuous with ongoing administration of near daily oral IMiDs, proteasome inhibitors, and/or corticosteroids as well as frequent intravenous or subcutaneous administrations of proteasome inhibitors and anti-CD38 monoclonal antibodies with few treatment breaks. Moreover, with each successive line of therapy, toxicities and comorbidities increase, performance status worsens, and death rates increase resulting in decreasing number of patients who are alive and eligible for treatment.[9] This highlights the importance of using the most effective therapies early in the treatment paradigm.

No effective standard of care exists in RRMM patients who become TCE, early in the course of their treatment.[10] TCE is defined as having received at least one drug in each of the 3 main classes of anti-myeloma therapies: IMiD, PI, and anti-CD38 monoclonal antibody. In recent years, the expanded availability and use of DARA-based regimens in frontline and early line relapse patients has contributed to OS improvement in MM; however, this has also led to the emergence of a new subset of patients who become TCE as early as second line [11,12,13,14,15] The proportion of TCE patients in the 3rd line setting has increased steadily from 9.8% in 2017 to 24.5% in 2020.[16] Although therapies with novel mechanisms of action currently available for TCE patients have been approved in 5th line setting and beyond, a therapeutic gap remains for patients who become TCE prior to 5th line of therapy. Additionally, given the treatment until progression approach with conventional therapies in myeloma, many patients who are triple class exposed are also triple class refractory. Refractoriness is defined as having progressed while on treatment or within 60 days of treatment discontinuation. Triple class refractoriness limits even further available treatment options and increases with each subsequent line of therapy[17].

A clear unmet need exists for safe and effective treatments with novel modes of action for RRMM patients who become TCE earlier during the course of their treatment.[18] The continuous oral and frequent intravenous/subcutaneous treatments lead to chronic exposure to these 3 classes over months and years. This profoundly impacts the disease course and biology, and leads to limited treatment options upon relapse with poor clinical outcomes.[7,19,20,21,22,23] Real world data as well as data from contemporary clinical trials in patients with TCE RRMM indicate that disease control with conventional therapies is poor, with short median PFS of approximately 4 months and OS of about 9-22 months.[6,24,25,26,27,28]

Ide-cel is a treatment option with a novel, non-cross-resistant mechanism of action, that is capable of achieving deep and durable responses with a manageable safety profile. Importantly, ide-cel offers prolonged disease control and a meaningful break from the typical continuous therapy that is standard for the treatment of TCE RRMM patients. This briefing book includes results from the pivotal, Phase 3 KarMMa-3 Study, which demonstrated the benefit of ide-cel compared with the standard regimens that are commonly utilized in current clinical practice for this patient population with high unmet medical need.

1.2 Study KarMMa-3 (BB2121-MM-003)

1.2.1 Study Design

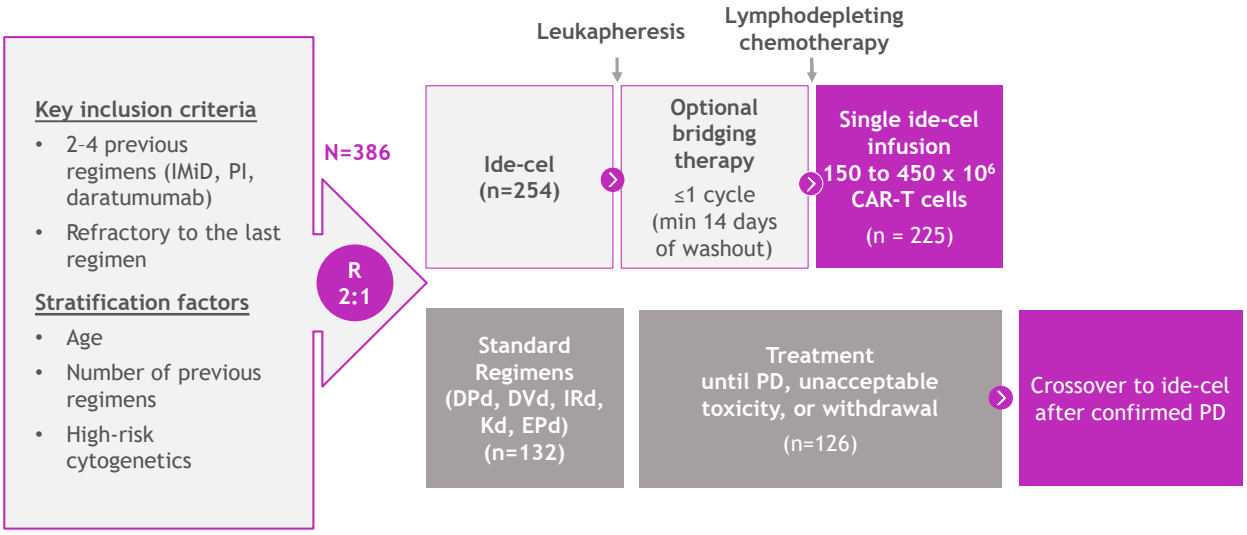
The KarMMa-3 Study enrolled patients with RRMM, who received 2 to 4 prior regimens, including an IMiD, a PI, and daratumumab. Patients were required to be refractory to the last regimen, defined as documented disease progression during or within 60 days of completing treatment with the last anti-myeloma regimen before study entry.

Patients were randomized 2:1 to the ide-cel or standard regimens arm, respectively. Randomization stratification factors included:

- age (< 65 years vs ≥ 65 years)

- number of previous regimens (2 vs 3 or 4)
- high-risk cytogenetics (presence of t(4;14) or t(14;16) or del 17p vs absence/unknown)

Figure 1.2.1-1: KarMMa-3 study design



Note: Based on the evolving treatment landscape for the patient population included in this study, 2 additional standard regimen options (EPd and Kd) were added via protocol Amendment 2.0 dated 17-Dec-2019.

To avoid bias in the selection of one of the five standard regimens for the control arm subjects, investigators chose a standard regimen prior to randomization. The 5 standard regimen choices were:

- Daratumumab, pomalidomide, dexamethasone (DPd)
- Daratumumab, Velcade (bortezomib), dexamethasone (DVd)
- Ixazomib, Revlimid (lenalidomide), dexamethasone (IRd)
- Kyprolis (carfilzomib), dexamethasone (Kd)
- Elotuzumab, pomalidomide, dexamethasone (EPd)

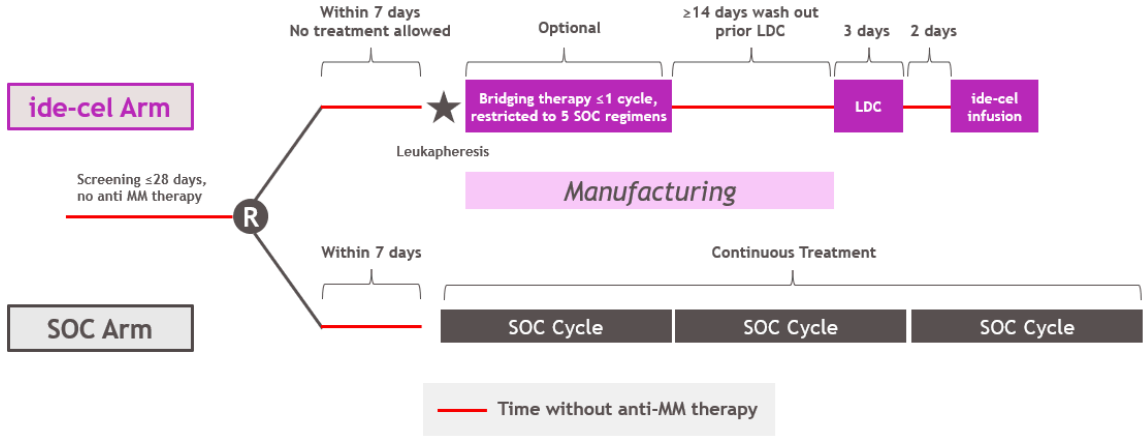
In subjects randomized to ide-cel arm, the respective standard regimen was to be used as bridging therapy, given at Investigator's discretion, or as standard regimens arm therapy if the subject were randomized to the standard regimens arm.

Ide-cel arm: Patients randomized to the ide-cel arm underwent leukapheresis within 7 days of randomization. At investigator's discretion, up to one cycle of bridging therapy was allowed during the manufacturing process for disease control (Figure 1.2.1-1), A minimum 14 days of washout after bridging therapy was required per protocol.

Lymphodepleting (LD) chemotherapy consisting of fludarabine and cyclophosphamide, not an effective anti-myeloma therapy, was administered over 3 consecutive days. After the completion of LD chemotherapy, subjects underwent a 2-day rest period followed by the ide-cel infusion at a dosing range of 150-450 x 10^6 chimeric antigen receptor (CAR) + T cells (Figure 1.2.1-2).

Standard Regimens arm: Patients randomized to the standard regimen arm were to start treatment within 7 days of randomization. Treatment was given until progression, unacceptable toxicity, or withdrawal of consent. After confirmation of disease progression by the IRC, patients were eligible to cross-over to undergo leukapheresis and receive ide-cel.

Figure 1.2.1-2: KarMMa-3: Planned Time Course to Treatment



Patient population:

KarMMa-3 Study enrolled a total of 386 patients, 226 in North America, 151 in Europe, and 9 in Japan. Baseline demographics were generally balanced between the ide-cel and standard regimens arms. Of the 207 patients enrolled in the United States (US), 35 (16.9%) were African Americans.

The study patient population is representative of a high-risk, highly refractory population with RRMM TCE who received 2-4 prior lines of therapy (median of 3) (Table 3.4.3-1). This included:

- High-risk cytogenetics in KarMMa-3 (43.5%) was higher than typical for TCE populations (18.5% to 23.7%).[29]
- Higher percentage of subjects with extramedullary disease in KarMMa-3 (24.1%) than usually seen in relapsed myeloma (3.4% to 14%).[30,31]
- Majority of subjects being DARA (94.6%) and triple class refractory (65.5%).

1.3 KarMMa-3 Efficacy Results

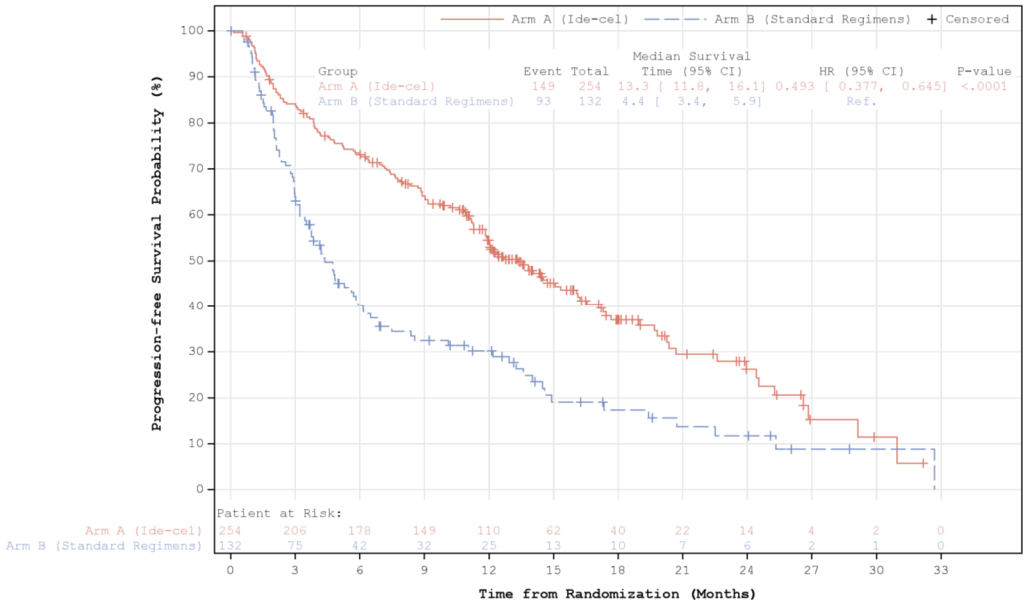
Primary Endpoint: Progression Frees Survival

As part of the sBLA submission, the results of the pre-planned interim analysis (IA) 2 for PFS (at 84% information fraction), based on a data cutoff date of 18-Apr-2022 were submitted and reviewed by FDA. As of 18-Apr-2022, with a median follow-up of 18.6 months (range: 0.4, 35.4), the primary endpoint of PFS by IRC assessment was met in this highly refractory myeloma population. Ide-cel demonstrated a statistically significant and clinically meaningful reduction in the risk of progression or death by 51% (hazard ratio [HR]) = 0.493; 95.0% CI: 0.377, 0.645) compared to treatment with standard regimens (median PFS: 13.3 vs 4.4 months; p-value < 0.0001; (Figure 1.3-1 and Table 4-1). Separation of the Kaplan-Meier (K-M) curves favoring ide-cel over standard regimens occurred early, and this treatment effect was sustained through the period of follow up. The benefit of ide-cel over standard regimens was consistent across all preplanned

subgroups (Figure 4.1-2). The median PFS in the standard regimens arm is consistent with real world data and contemporary clinical trials with conventional therapies (3.4 to 4.9 months) in this patient population[24,25,28,32,33] and reinforces the clinical significance of the ide-cel benefit and strengthens the external validity of the KarMMa-3 Study results.

While median PFS in the standard regimens arm was generally consistent across prior lines of therapy, greater benefit was observed for ide-cel when used in earlier treatment lines (15.1 months after 2 prior lines, 12.5 months after 3, 11.2 months after 4, respectively), which supports the importance of earlier use of ide-cel to allow patients to derive the greatest benefit from ide-cel treatment with the longest treatment-free interval (Figure 4.1-1). Moreover, a lower dropout rate from leukapheresis to ide-cel infusion was observed in patients with a lower number of prior regimens (2L: 5.3%, 3L: 10.5%, 4L: 12.7%), further supporting its use in earlier in the treatment course.

Figure 1.3-1: Kaplan-Meier Curve of PFS Based on IMWG Criteria - IRC Review, FDA Censoring Rules - ITT Population (18-Apr-2022 data cutoff)



Key Secondary Endpoint: Overall Response Rate

For the key secondary endpoint of ORR, which was hierarchically tested, ide-cel demonstrated a statistically significant improvement compared with standard regimens; ORR = 71.3% in the ide-cel arm vs 41.7% in the standard regimens arm; p-value < 0.0001 (Figure 4.2-1 and Table 4-1). Similar to PFS, the ORR benefit of ide-cel over standard regimens was consistent across preplanned subgroups.

Notably, 38.6% patients in the ide-cel arm compared to 5.3% patients in the standard regimens arm achieved a complete response or better. Among subjects with a response of CR or better, 20.1% subjects (95% CI: 15.2, 25.0) in the ide-cel arm and 0.8% subjects (95% CI: 0.0, 2.2) in the standard regimens arm achieved minimal residual disease (MRD)-negative status. The median

duration of response (DoR) was longer with ide-cel compared to standard regimens (14.8 months [95% CI: 12.0, 18.6] versus 9.7 months [95% CI: 5.4, 16.3]).

Key Secondary Endpoint: Overall Survival

KarMMa-3 Study Amendment 2.0 (dated 17-Dec-2019), which was implemented one year into the trial, allowed patients randomized to the standard regimens to cross over to receive ide-cel after IRC confirmed progression. The amendment was deemed ethical and appropriate based on the promising ide-cel data from the KarMMa Study and the strong demand from patients and investigators for access to ide-cel.

It is important to note that KarMMa-3 Study was not powered to detect an OS benefit and the cross-over confounds the interpretation of the OS results.

At the most recent data cutoff date (CoD) of 28-Apr-2023, with a median follow-up of 30.9 months (range: 12.7 - 47.8) and 74% information fraction, the OS analysis in the intent-to-treat (ITT) population showed a HR of 1.012 (95% CI: 0.731, 1.400) with a median OS of 41.4 months (95% CI: 30.9, NA) in the ide-cel arm versus 37.9 months (95% CI: 23.4, NA) in the standard regimens arm (Figure 1.3-2 and Table 4.3.1-1). The median OS in both arms vastly exceeds the historical data (9-22 months) (Table 1.3-1) with conventional therapies in this patient population. The long median OS in the standard regimens arm suggests that patients who received ide-cel post progression in the context of the cross-over study design benefited from ide-cel treatment.

The following interpretation of OS is provided in subsequent sections:

- Factors that confounded the interpretability of OS
  - Cross-over
- Factors that did not contribute to observed early deaths:
  - Early death differences are not due to ide-cel toxicity
  - Manufacturing delays did not contribute to early deaths
- Factors that could have contributed to observed early deaths:
  - Protocol constraints of bridging therapy
  - Random variability in the context of a 2:1 randomization

Figure 1.3-2: Kaplan-Meier Curves of Overall Survival - ITT Population (28-Apr-2023 data cutoff)

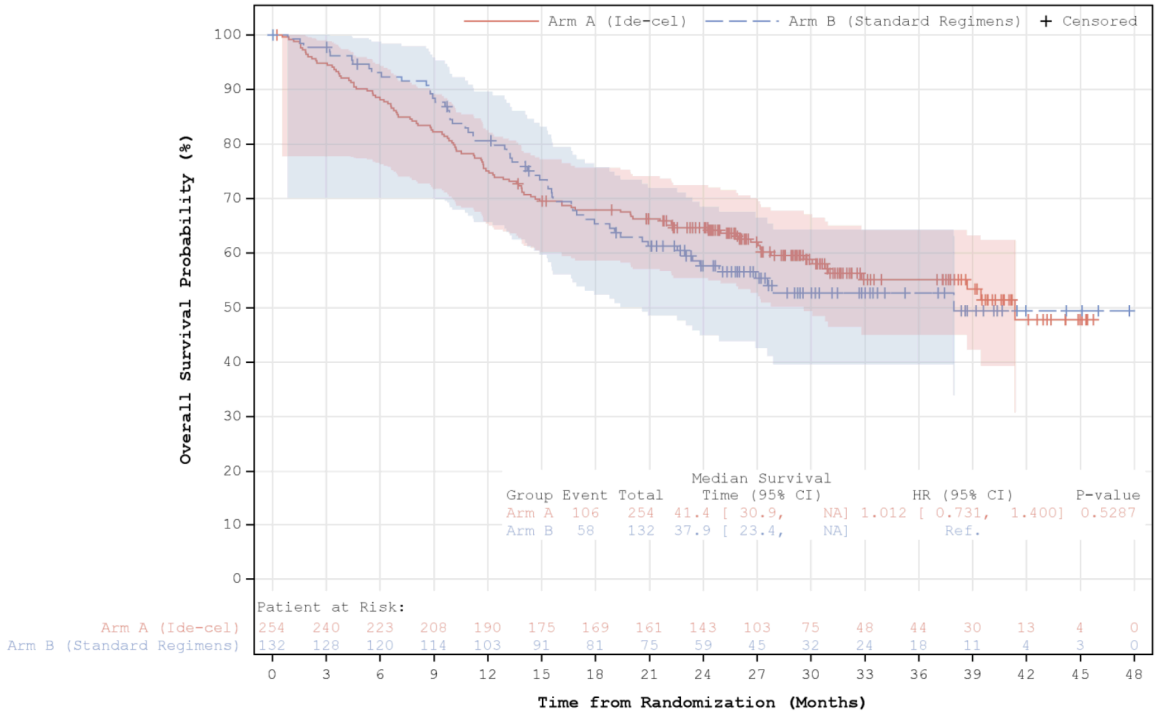


Table 1.3-1: Historic Overall Survival in TCE RRMM Patients

	KarMMa-3		PREAMBLE N = 194	CONNECT-MM N = 232	Flatiron N = 897	COTA Vantage N = 795	LocoMMotion N = 248	MAMMOTH N = 275
	Ide-cel Arm N = 254	Standard Regimens Arm N = 132						
Median OS, mo.	41.4	37.9	18.3	12.5	22.3	20.4	13.8	9.3
(95% CI)	(30.9, NA)	(23.4, NA)	(14.0, 25.9)	(10.2, 15.3)	(19.0, 25.8)	(17.8, 23.6)	(10.8, 17.0)	(8.1, 10.6)

Gandhi et al.[6]; Ramasamy et al.[24]; Lee et al.[25]; Lee et al. [26]; Mateos et al.[27]; Moreau et al.[28]

The Interpretability of the OS Results is Confounded by Cross-over

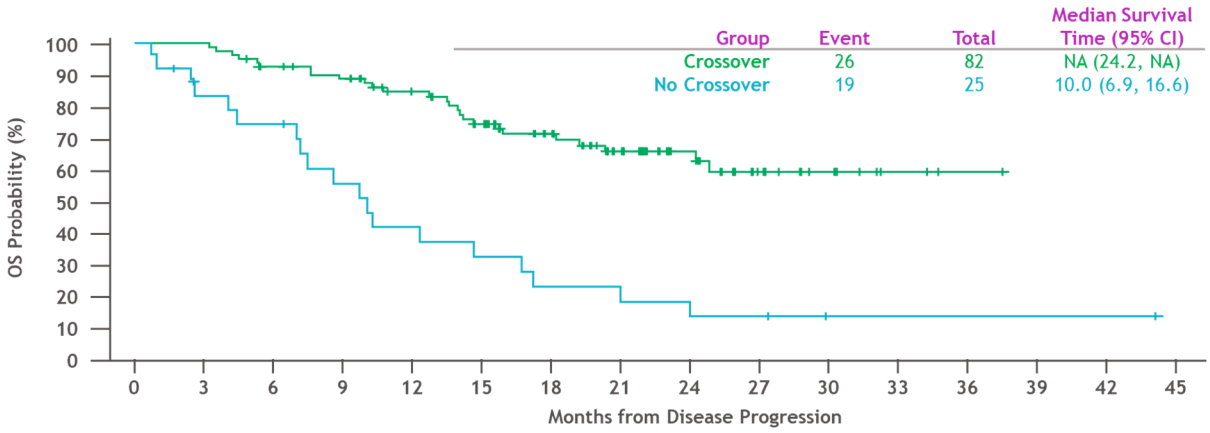
The interpretability of the OS results in KarMMa-3 is confounded by cross-over. As of the 28-Apr-2023 data cutoff, more than half of the subjects (74/132, 56.1%) in the standard regimens arm received ide-cel. Because of the short median PFS in the standard regimens arm (ie, 4.4 months), the cross-over impacted the OS curves early on. The median time from randomization to ide-cel infusion in the standard regimens arm was 8.1 months (range 2.9 - 36.7), with 75% of the cross-over patients having received their ide-cel infusion by Month 16 (Q1- Q3: 5.3, 16.3).

Two pre-specified sensitivity analyses, a 2-stage accelerated failure time model[34,35] and a rank preserving structural failure time (RPSFT) model,[36] respectively, as well as 1 post-hoc analysis

using the inverse probability of censoring weighting (IPCW) method[37,38,39] (at the request of the European Union (EU) Committee for Medicinal Products for Human Use [CHMP]) have been employed to estimate the OS treatment effect that would have been observed had cross-over not occurred. See APPENDIX 1 for additional details. Although all 3 methods rely on certain statistical assumptions, they consistently show HR estimates below 1 (Figure 4.3.2-1, Figure 4.3.2-2,Figure 4.3.2-3, and Figure 4.3.2-4).

The median OS in the standard regimens arm was substantially longer than expected in this patient population. A post-hoc analysis was conducted in the standard regimen arm analyzing post-progression survival (PPS) in patients who crossed-over and patients who did not cross-over. Acknowledging that this analysis is not protected by randomization, the median PPS of patients who crossed-over (ie, underwent leukapheresis with the intent to receive ide-cel) was not reached (95% CI: 24.2, NA), whereas patients who did not cross over had a median PPS of 10.0 months (95% CI: 6.9, 16.6); Figure 1.3-3.

Figure 1.3-3: Standard Regimens Arm: Post-progression Overall Survival is Better in Patients Who Crossed Over*



*Crossed-over includes patients who underwent leukapheresis with or without ide-cel infusion

Early Death Differences are Not Due to Ide-cel Toxicity or Delays in Manufacturing

Death by time intervals from randomization showed that the death rate in the ide-cel arm was numerically higher compared to the standard regimens arm during the first 6 months (30 [11.8%]) versus (9 [6.8%]); Table 1.3-2. The piecewise OS analysis reflects this numerical difference in early deaths, where the HRs of ide-cel versus standard regimens were 1.85 (95% CI: 0.88, 3.91) in the first 6-month interval and 0.85 (95% CI: 0.59, 1.23) after 6 months from randomization, respectively (Figure 1.3-4). A post-hoc landmark analysis of OS for all randomized subjects with more than 6 months of survival (Figure 1.3-5) supports this observation, with superimposable curves between 6-15 months followed by a clear separation of curves with a numerical trend favoring ide-cel over standard regimens afterwards (HR [95% CI] = 0.85 [0.592, 1.23]).

Figure 1.3-4: Overall Survival: Piecewise Hazard Ratio (HR) indicates a positive trend after 6 months from randomization (28-Apr-2023 data cutoff)

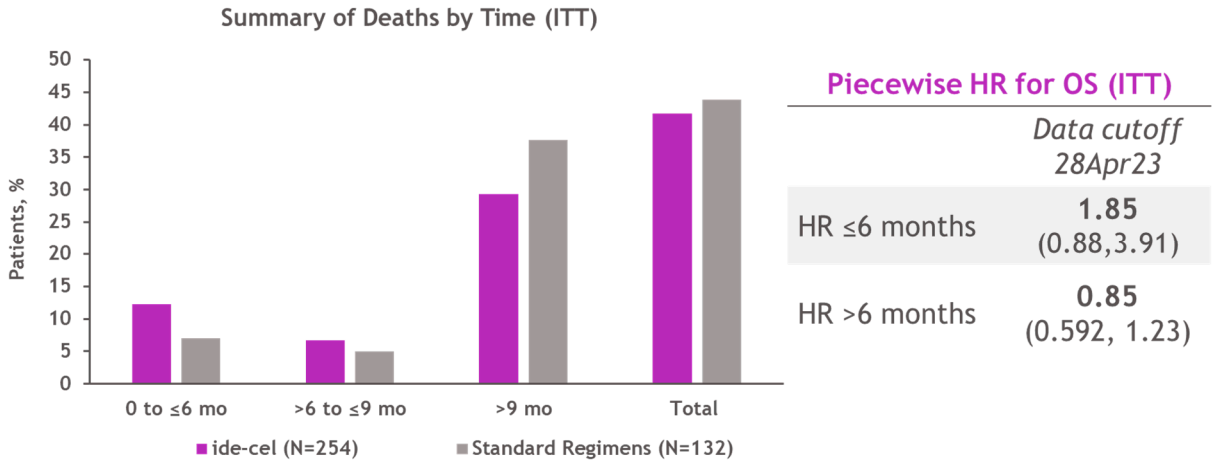
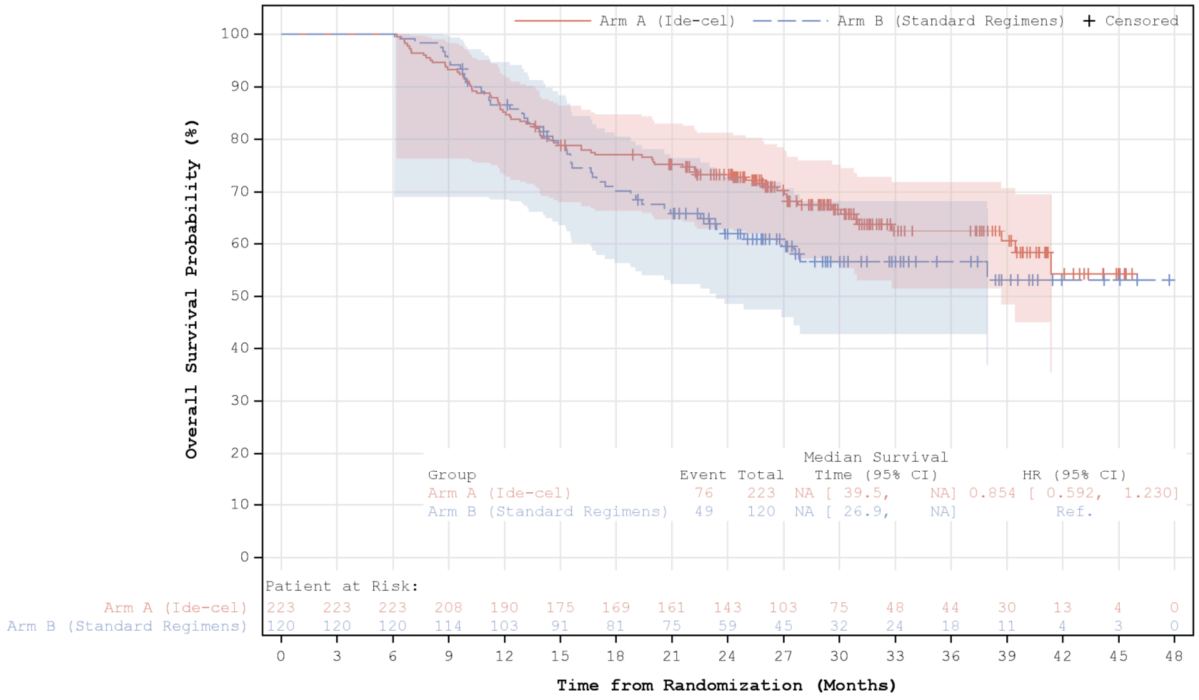


Figure 1.3-5: Landmark Analysis of Overall Survival - All Randomized Subjects with more than 6 Months of Survival (28-Apr-2023 data cutoff)



The 95% Hall-Wellner confidence bands are presented. HR is estimated from the stratified Cox proportional hazard model.

In the ide-cel arm, the majority of early deaths (17/30; 56.7%) occurred in patients who never received ide-cel treatment; of those 17 patients, 13 died from disease progression (Table 1.3-2). The early death rate among patients who received the allocated study treatment was similar between arms (5.1% in the ide-cel arm vs 6.8% in the standard regimens arm); therefore, the

numerical difference between treatment arms is driven entirely by early deaths among untreated patients in the ide-cel arm. In both arms, most early deaths were attributed to myeloma disease progression. Early deaths due to AEs among patients who received the allocated study treatment were similar between treatment arms (2.0% versus 2.3%, respectively), which indicates the numerical differences in early death rates were not associated with ide-cel related mortality.

Table 1.3-2: Differences in Early Death Rate are Driven by Patients Who Did Not Receive Ide-cel (28-Apr-2023 data cutoff)

	Ide-cel (n=254) n (%)	Standard Regimens (n=132) n (%)
Number of patients who died ≤ 6 months	30 (11.8)	9 (6.8)
Number of patients who received study treatment	13 (5.1)	9 (6.8)
Primary reason for death		
AE	5 (2.0)	3 (2.3)
Progressive disease	5 (2.0)	6 (4.5)
Other cause[a]	3 (1.2)	0
Number of patients who did not receive study treatment	17 (6.7)	0
Primary reason for death		
AE	3 (1.2)	0
Progressive disease	13 (5.1)	0
Other cause	1 (0.4)	0

[a] Cause of death unknown for these 3 subjects (one withdrew consent, death details not available). 2 subjects had evidence of disease progression prior to death

Ide-cel manufacturing was uniform and reliable, with consistent median turn-around times in patients with early death and in the ITT population (35 days and 34 days, respectively), and of the 3 manufacturing failures in the ITT population 1 occurred in a patient with early death. Therefore, there are no differences in turnaround time or manufacturing success between patients with or without early death.

Protocol Constraints of Bridging Therapy

Subjects in both arms who died within 6 months from randomization were enriched for high-risk factors portending poor outcome, including R-ISS stage III, high-risk cytogenetics, presence of EMP, high tumor burden, triple class refractoriness, albumin level < 3.5 g/dL, beta-2-microblobulin level ≥ 5.5 mg/L, LDH above the upper limit of normal, and shorter median time to progression on the last prior anti-myeloma therapy, compared to the overall ITT population in each respective arm.

Among the 30 patients with an early death event in the ide-cel treatment arm, 25 (83.3%) received bridging therapy. This rate was similar to that in the overall ide-cel ITT population where 83.5%

of subjects received bridging therapy. There are thus no obvious differences in the use of bridging therapy between patients with or without early death. However, it is important to note that the protocol specifications on bridging therapy (up to 1 cycle, minimum 14 days wash-out period) resulted in a long time without anti-MM treatment in the ide-cel arm, which did not seem to adequately control the disease in these patients enriched in high risk features and resulted in 17 patients who experienced early death without having received ide-cel.

Random Variability

It is important to note that during the first 6 months post-randomization, the CI bands for the OS KM curves are largely overlapping and as such, random variability cannot be excluded in the context of 2:1 randomization and the small number of OS events (Figure 1.3-2).

Taken together, the interpretability of OS is confounded by cross-over, and while random variability cannot be excluded, the numerical differences in early death events are driven by patients who never received ide-cel and are not caused by ide-cel toxicity.

Patient Reported Outcomes Results

In the KarMMa-3 Study, patients highlighted the benefits of single infusion ide-cel compared to continuous treatment, including better efficacy, reduced clinic visits, and avoidance of ongoing side-effects.[40] Previous studies have shown patients with multiple myeloma experience detriments to health-related quality of life as assessed through patient reported outcomes.[41] KarMMa-3 included three validated patient-reported outcomes (PRO) measures: the EORTC QLQ-C30[42], EORTC QLQ-MY20[43], and the EQ-5D-5L.[44] These were used to assess the subject's symptoms and physical, social, emotional, and functional well-being; Compliance rates were > 80% at most visits, and rates were similar between the two treatment arms. There were meaningful improvements for most PRO domains favoring ide-cel (See Section 4.4).

Efficacy Conclusions

Taken together, these data highlight the high-risk and highly refractory myeloma population enrolled in Study KarMMa-3, in which ide-cel demonstrated statistically significant and clinically meaningful improvements in PFS and ORR along with consistent benefit across all subgroups including patients with high-risk factors. Ide-cel showed evidence of an improvement in quality of life in the context of a long treatment-free interval. This is a unique benefit of ide-cel's one-time treatment over the chronic, continuous treatment with conventional therapies in MM.

The interpretability of OS is confounded by cross-over, and while random variability cannot be excluded, the numerical differences in early death events are driven by patients who never received ide-cel and are not caused by ide-cel toxicity. Sensitivity analyses employed to estimate the OS treatment effect that would have been observed had cross-over not occurred showed a consistent point estimate of HR<1 suggesting a potential OS benefit in favor of ide-cel.

The numerical difference in early deaths between treatment arms are driven entirely by early deaths among untreated patients in the ide-cel arm. The rates of deaths due to AEs in both arms among

treated patients with early death were similar and indicate that the numerical difference in early deaths were not due to ide-cel related mortality.

Patients who experienced early death events were enriched for high-risk factors, particularly high-risk cytogenetics, high tumor burden, R-ISS III, and EMP. It is important to note that optimal disease control during ide-cel manufacturing is critical in this highly refractory myeloma population and requires effective bridging therapy appropriately tailored to the patients' prior treatment history and disease characteristics.

In the commercial setting protocol specified bridging therapy restrictions do not apply and physicians can choose from a greater number of treatment options, and should reduce time without anti-MM disease control by administering more than 1 treatment cycle and reducing wash-out periods. Physicians should be cognizant when making therapeutic decisions that high-risk features and indicators of fast disease kinetics may impact patient's ability to receive ide-cel, however, should also recognize that the majority of patients with high-risk are able to receive ide-cel and benefit from it.

Taken together, these data substantiate the value of ide-cel as an effective and safe treatment option in a population with high unmet medical need for which existing standard regimens are suboptimal.

1.4 KarMMa-3 Safety Results

The overall safety profile of ide-cel in the KarMMa-3 population was consistent with the known safety profile in patients with TCE RRMM who had received 4 or more prior lines of therapy, with no new safety signals (Table 1.4-1). As expected, notable differences between ide-cel and standard regimens arms for adverse event of special interests (AESIs) that are specific to CAR T-cell therapy were observed, with the frequency and severity of AEs, Grade 3 or 4 and serious adverse events (SAEs) numerically higher in the ide-cel arm compared with the standard regimens arm. The AESIs with ide-cel were consistent with the known safety profile and were manageable.

The size of the KarMMa-3 safety database and duration of follow-up are considered adequate to provide a reasonable estimate of adverse reactions that may occur with ide-cel treatment. No new clinically relevant concerns were identified for ide-cel.

Safety summaries were provided for the KarMMa-3 Treated Population and the Safety Population unless otherwise specified.

Table 1.4-1: Overall Summary of Safety - Pivotal Study KarMMa-3

Safety Parameters	No. of Subjects (%)	
	Ide-cel Arm	Standard Regimens Arm
ITT Population	**N = 254**	**N = 132**
Deaths[a], n (%)	106 (41.7)	58 (43.9)
Primary Reason for Death		
Death due to multiple myeloma[b], n (%)	64 (25.2)	37 (28.0)
Death from other cause[b,c], n (%)	23 (9.1)	12 (9.1)
Death from AE [b], n (%)	17 (6.7)	8 (6.1)
Death from second primary malignant disease, or complication due to second primary malignant disease[b], n (%)	2 (0.8)	1 (0.8)

Safety Parameters[d]	Adverse Event Grades			
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Treated Population	**N = 250**		**N = 126**	
SAEs	130 (52.0)	107 (42.8)	48 (38.1)	43 (34.1)
AEs	248 (99.2)	233 (93.2)	123 (97.6)	94 (74.6)
Safety Population	**N = 225**		**N = 126**	
Treatment-related SAEs	37 (16.4)	31 (13.8)	19 (15.1)	15 (11.9)
Treatment-related AE	217 (96.4)	155 (68.9)	104 (82.5)	74 (58.7)
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)	10 (4.4)	-	-
iiNT	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)
Neutropenia	193 (85.8)	189 (84.0)	57 (45.2)	51 (40.5)
Thrombocytopenia	126 (56.0)	99 (44.0)	37 (29.4)	23 (18.3)
SPM	13 (5.8)	-	5 (4.0)	-
MAS	5 (2.2)	5 (2.2)	0	0
Autoimmune Disorders	1 (0.4)	-	0	-

[a] Deaths are based on 28-Apr-2023 data cutoff date

[b] Primary cause categories are from CRF. Deaths are sorted by descending frequency of primary cause categories first, and then by descending frequency of SOCs within each primary cause category, and then by descending frequency of PTs within each SOC for the last column under Ide-cel Arm

[c] Deaths due to other causes in the ide-cel arm were death (n = 18), hemothorax (n = 1), respiratory failure (n = 1), cardiac failure (n = 1), cerebral hemorrhage (n = 1), and shock (n = 1). Deaths due to other causes in the standard regimens arm were death (n = 9), acute respiratory failure (n = 1), cytokine release syndrome (n = 1), and euthanasia (n = 1). 20 (7.9%) of the 23 subjects reported as death due to other cause in the ide-cel arm had IRC-confirmed disease progression and 14 (5.5%) had received at least one subsequent anti-myeloma therapy. 7 (5.3%) of the 12 subjects reported as death due to other cause in the standard regimens arm had IRC-confirmed disease progression and 6 (4.5%) had received a subsequent anti-myeloma therapy.

[d] All Safety Parameters except for deaths were based Data Cutoff Date of 18-Apr-2022

Note: The treated population was defined as all subjects in the ITT population who underwent leukapheresis, bringing therapy, lymphodepleting chemotherapy or ide-cel infusion in the ide-cel arm, and those who received any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dex in the standard regimens arm. The safety population was defined as all subjects in the treated population who received any study treatment, including ide-cel infusion for the ide-cel arm and any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dex for the standard regimens arm.

AESIs included: ≥ Grade 3 adverse event of CRS, ≥ Grade 3 AE of MAS, ≥ Grade 3 AE of NT, ≥ Grade 3 AE of infection, new malignancies including SPMs, new diagnosis or exacerbation of autoimmune-like or rheumatologic disorder, and new diagnosis of hematologic disorder

Safety Conclusion

There were no new safety concerns identified with ide-cel in KarMMa-3 and the safety profile was consistent across subgroups. Overall, the safety profile of ide-cel in KarMMa-3 was generally consistent with data from other supportive studies including subjects with 4L+ relapsed or refractory multiple myeloma (same as in the approved indication), and in those studies with subjects with similar baseline characteristics. The data from study KarMMa-3 allow for a thorough assessment of the ide-cel safety profile in the intended patient population, including characterization of common AEs and SAEs, and informing labeling and risk management strategies. No new clinically relevant concerns were identified for ide-cel and the safety profile is overall in line with previous experience. There were no events of parkinsonism or Guillain-Barré syndrome reported. There were no cases of T cell malignancies in the study. Importantly, there was no increase in ide-cel related mortality.

1.5 Positive Benefit / Risk Of Ide-Cel in the Proposed Indication

Table 1.5-1: Positive Benefit / Risk of Ide-cel in the Proposed Indication

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In the US, MM accounts for approximately 19% of hematologic malignancies, primarily occurring in older individuals (median age at onset of 69 years).[1,2] • In the US, 35,730 new cases of MM and 12,590 deaths due to MM were estimated in 2023.[3] • In recent years, the expanded availability and use of DARA-based regimens in frontline and early line relapse patients has contributed to OS improvement in MM; however, this has also led to the emergence of a new subset of patients who become TCE (ie, to IMiDs, PIs, and anti-CD38 mAbs) as early as second line[11,12,13,14,15] • The proportion of TCE patients in the 3rd line setting has increased steadily from 9.8% in 2017 to 24.5% in 2020.[16] • Real world data and data from contemporary clinical trials in patients with TCE RRMM indicate that disease control with conventional therapies is poor, with short median PFS of approximately 4 months and OS of about 9-22 months.[6,24,25,26,27,28]	• TCE RRMM is a serious and life-threatening condition.
Current treatment options	• No effective standard of care exists in RRMM patients who become TCE early in the course of their treatment.[10] • Therapeutic options after the first or second relapse are largely driven by the type, response, and tolerability of prior therapies received, and are comprised of regimens including next generation IMiDs or PIs, anti-CD38 mAbs, anti-SLAMF7 mAbs, HDAC inhibitors, nuclear export inhibitors, and alkylating chemotherapies.[10,45] Treatment of multiple myeloma is continuous with ongoing administration of near daily oral IMiDs, proteasome inhibitor, and corticosteroids as well as frequent intravenous or subcutaneous administrations of proteasome inhibitors and anti-CD38 monoclonal antibodies with few treatment breaks.	• Although therapies with novel mechanisms of action currently available for TCE patients have been approved in 5th line setting and beyond, a therapeutic gap remains for patients who became TCE prior to 5th line of therapy.
Benefits	• Ide-cel achieved a statistically significant, clinically meaningful, and consistent results across all prespecified subgroups in KarMMa-3 for both primary the primary endpoint of PFS) and the key secondary endpoint of ORR – Greatest PFS benefit and lowest dropout rates were observed in earlier treatment lines • Long treatment-free period achieved by ide-cel with a one-time therapy	• Ide-cel achieved a clinically meaningful improvement in PFS after a one time infusion with a long treatment-free period

Table 1.5-1: Positive Benefit / Risk of Ide-cel in the Proposed Indication

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Evidence of quality-of-life improvement in favor of ide-cel in KarMMa-3 after a single infusion • Interpretability of OS data is confounded by the patient-centric design, which allowed crossover • Adjusting for crossover showed a trend towards improved OS with ide-cel versus standard regimens • OS in the standard regimens arm is substantially longer than expected for this patient population • No increased ide-cel–associated mortality compared to standard regimens	
Risk and risk management	• The numerically higher proportion of early deaths in the ide-cel arm was driven by patients who never received ide-cel; most early deaths were due to disease progression • Early deaths were not an ide-cel related mortality nor due to manufacturing delays • Patients with early death were enriched for high-risk factors, a group where effective bridging therapy is critical – Trial design limited bridging therapy to 1 cycle – Minimum wash-out period required • The safety profile of ide-cel remained consistent with the safety from the current indication. – Toxicity was **predictable** and **manageable** including cytopenias, CRS, and CAR-T–associated neurotoxicity – Deaths due to AEs were similar across arms	• CAR-T therapy is **administered by CAR-T cell experts** at qualified centers who are used to managing the specific side effects of ide-cel • Product labeling will ensure the safe use of ide-cel by informing healthcare providers about the risks associated with the use of this product and the appropriate mitigations. • All hospitals and their associated clinic(s) must be certified and enrolled in the ide-cel REMS to be able to dispense ide-cel. • An observational registry captures safety and efficacy data from ide-cel treated patients.
Benefit / risk Assessment	• KarMMa-3 demonstrated a **favorable benefit–risk profile for ide-cel** compared to standard regimens in patients with RRMM who became TCE early in their treatment course, and supports the use of ide-cel in this disease setting where a treatment gap exists due to lack of approved effective therapies – **Earlier use is critical** to enable optimal PFS benefit and effective bridging – **Individualized bridging** is required to allow patients to receive ide-cel	

Abbreviations: AEs = adverse events; CAR = chimeric antigen receptor; CRS = DARA = daratumumab; HDAC = histone deacetylase; IMiDs = immunomodulatory drugs; mAb = monoclonal antibody; MM = multiple myeloma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PIs = proteasome inhibitors; REMS = Risk Evaluation and Mitigation Strategy; RRMM = relapsed or/and refractory multiple myeloma; SLAMF7 = signaling lymphocytic activation molecule family member 7; TCE = triple-class exposed; US = United States

Additional details on positive benefit / risk of ide-cel in the proposed indication is provided in Section 6.

2 INTRODUCTION

2.1 Current Indication for Abecma® and Sponsor's Proposed Indication in sBLA 125736/218

Abecma® (ide-cel) was approved by the US Food and Drug Administration (FDA) on 26-Mar-2021 for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

As part of the supplemental Biologics License Application (sBLA) 125736/218, the Sponsor is proposing to extend the indication of Abecma® to the treatment of adult patients with relapsed or refractory MM who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

3 BACKGROUND

3.1 Disease Background

MM is an incurable blood cancer characterized by the clonal proliferation of malignant plasma cells both within the bone marrow and at localized extramedullary sites, termed plasmacytomas. The malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein or free light chains in the serum and urine and may result in bone marrow failure with cytopenias, immunosuppression, renal insufficiency, and debilitating bone lesions. In the US, MM accounts for approximately 19% of hematologic malignancies, primarily occurring in older individuals (median age at onset of 69 years), and is very rare in individuals younger than 40 years.[1,2] In the US, 35,730 new cases of MM and 12,590 deaths due to MM were estimated in 2023.[46] African Americans are disproportionately affected by MM[46], with higher incidence rates than for Whites reported overall (males: 15.9 vs. 7.5 cases per 100,000; females: 11.7 vs 4.5 cases per 100,000), a trend that also extends to mortality (males: 7.6 vs 4.0 deaths per 100,000; females: 5.6 vs. 2.4 MM deaths per 100,000.[47]

The course of MM is characterized by a period of disease control after initial therapy followed by progression.[4,5] Tumors typically recur more aggressively with each relapse and with each subsequent line of therapy, leading to successive declines in rate (ORR), depth (CRR), and duration (DoR) of response, and ultimately, refractory MM, which is associated with poor prognosis.[6,7,8] Moreover, with each successive line of therapy, toxicities and comorbidities increase, performance status worsens[8], and death rates increase resulting in decreasing number of patients who are alive and eligible for treatment.[9] This highlights the importance of using the most effective therapies early in the treatment course. Progress has been made in improving disease control and OS in patients with MM. The increase in survival has been driven by the availability of newer therapies and novel combination approaches, as well as by improved supportive care.[45] However, even with optimal frontline therapy with multi-class combinations, most patients with MM progress or relapse, and need further treatment. Despite the significant improvement in patients' survival over the past 20 years, MM remains largely incurable with an estimated 5-year

survival rate of 59.8%[48] and only 10%-15% of patients achieve or exceed expected survival compared with the matched general population.[49,50]

3.2 Standard Treatment Options and Unmet Medical Need

No clear effective standard of care exists in relapsed or/and refractory multiple myeloma (RRMM) patients who become TCE, early in the course of their treatment.[10] TCE is defined as having received at least one drug in each of the 3 main classes of anti-myeloma therapies: 1) immunomodulatory agent (eg, thalidomide, lenalidomide, pomalidomide, [IMiDs]), 2) proteasome inhibitor (e.g. bortezomib, carfilzomib, ixazomib, [PIs]), and 3) anti-CD38 monoclonal antibody (eg, daratumumab [DARA], isatuximab). Treatment options in frontline consist mostly of the use 3 and 4 drug combination regimens, including IMiDs and PIs, with or without DARA (NCCN[45] and EHA-ESMO[10] guidelines). Therapeutic options after the first or second relapse are largely driven by the type, response, and tolerability of prior therapies received, and are comprised of regimens including next generation IMiDs or PIs, anti-CD38 mAbs, anti-SLAMF7 mAbs, histone deacetylase (HDAC) inhibitors, nuclear export inhibitors, and alkylating chemotherapies.[10,45] In recent years, the expanded availability and use of DARA-based regimens in frontline and early line relapse patients has contributed to OS improvement in MM; however, this has also led to the emergence of a new subset of patients who become TCE (ie, to IMiDs, PIs, and anti-CD38 mAbs) as early as second line.[11,12,13,14,15] The proportion of TCE patients in the 3rd line setting has increased steadily from 9.8% in 2017 to 24.5% in 2020.[16] With the positive read out of the PERSEUS trial, it is expected that the TCE in 2nd line setting will increase further.[51] As the therapies currently available in TCE patients have been approved in 5th line and beyond (ie, CAR T, bispecifics: teclistamab, elranatamab, talquetamab), a therapeutic gap remains for patients who became TCE prior to 5th line of therapy. Additionally, given the treatment until progression approach with conventional therapies in myeloma, many patients who are triple class exposed are also triple class refractory. Triple class refractoriness increases with each subsequent line of therapy[17] and limits even further available treatment options.

Exposure to these 3 classes of standard therapies profoundly impacts the disease course and biology, and leads to limited treatment options with poor clinical outcomes.[7,17,19,20,21,51] Notably, in a prospective observational study in TCE RRMM patients who received a median of 4 prior regimens, survival outcomes were similarly poor regardless of the number of prior therapies received, which further underscores that it is the content of prior regimens rather than the number of prior regimens received that most strongly impact clinical outcomes from subsequent therapies.[52] Despite several therapies having been recently approved for TCE RRMM patients, they are for patients with at least 4 prior lines of therapy, under the premise that the number of prior lines of therapy accurately pinpoints patients with an unfavorable prognosis based on existing treatments. However, in a fast-paced drug development environment and with assimilation of new agents in earlier disease settings, such a premise may likely result in a therapeutic vacuum for TCE patients in early line relapse.[53]

A clear unmet need exists for safe and effective treatments with novel modes of action for RRMM patients who became TCE earlier during the course of their treatment.[18] Exposure to these 3 classes of standard therapies profoundly impacts the disease course and biology, and leads to limited treatment options with poor clinical outcomes.[7,19,20,21,22,23] Conventional therapies in the early relapse setting have been evaluated and approved in populations that are not exposed to more than 2 classes of therapies in the early relapse setting. Given the increasing use of anti-CD38 mAb containing regimens in frontline and early line relapse, therapeutic options in TCE patients in this disease setting consist largely of between or within class switch regimens and treatment guidelines are non-specific. Not only does the limited effectiveness of conventional therapies reflect the high unmet medical need in TCE RRMM patients, but it also highlights the challenges in selecting effective bridging therapies in this disease setting. A treatment option with a novel, non-cross-resistant mechanism of action, that is capable of achieving deep and durable responses with a manageable safety profile, and offers the opportunity for prolonged disease control and treatment-free intervals for TCE RRMM patients, is warranted given the current RRMM therapeutic landscape.

3.3 Ide-cel Clinical Development Program

Ide-cel is currently under investigation for the treatment of MM in several company-sponsored clinical studies. Pivotal Study KarMMa-3 is an ongoing open-label, global, randomized, controlled Phase 3 study comparing the efficacy and safety of ide-cel with standard treatment regimens in subjects with RRMM who have received 2 to 4 prior regimens, including an IMiD, a PI, and DARA and have documented disease progression on their last prior therapy. The safety of ide-cel is also supported by 3 Phase 2 studies (MM-001, MM-001-Japan, and MM-002) and 2 Phase 1 studies (CRB-401 and MM-004), in addition to a long-term follow-up study conducted in accordance with FDA guidance "Long Term Follow-Up After Administration of Human Therapy Products".[54]

3.4 Pivotal Phase 3 KarMMa-3 Study (BB2121-MM-003)

MM-003 is an ongoing, open-label, multi-center, global, randomized, controlled Phase 3 study comparing the efficacy and safety of ide-cel vs standard regimens in subjects with RRMM (Figure 1.2.1-1).

3.4.1 Study Design

The KarMMa-3 Study enrolled patients with RRMM, who received 2 to 4 prior regimens, including an IMiD, a PI, and daratumumab. Patients were required to be refractory to the last regimen, defined as documented disease progression during or within 60 days of completing treatment with the last anti-myeloma regimen before study entry.

Patients were randomized 2:1 to the ide-cel or standard regimens arm, respectively. Randomization stratification factors included:

- age (< 65 years vs ≥ 65 years)
- number of previous regimens (2 vs 3 or 4)
- high-risk cytogenetics (presence of t(4;14) or t(14;16) or del 17p vs absence/unknown)

The standard regimens allowed in the study consisted of DPd, DVd, or IRD, and from Protocol Amendment 2.0 (17-Dec-2019) onwards, 2 additional regimens (EPd or Kd) were allowed, which provides further evidence of the lack of consensus in standard of care. To avoid bias in the selection of one of the five standard regimens for the control arm subjects, investigators chose a standard regimen prior to randomization. Investigator's choices were governed by the RRMM therapeutic guidelines (ie, subject's clinical features, disease history, and prior tolerability) as well as by protocol requirements prohibiting the reuse of regimens used as most recent prior therapy. In subjects randomized to ide-cel arm, the respective standard regimen was to be used as bridging therapy, given at Investigator's discretion, or as standard regimens arm therapy if the subject were randomized to the standard regimens arm. Subjects in the standard regimen arm had the option to receive ide-cel upon IRC confirmation of disease progression and confirmed eligibility.

Ide-cel arm: Patients randomized to the ide-cel arm underwent leukapheresis within 7 days of randomization. At investigator's discretion, up to one cycle of bridging therapy was allowed during the manufacturing process for disease control (Figure 1.2.1-2), and 212 (83.5%) of patients randomized to the ide-cel arm received bridging therapy. The most frequently administered regimen as bridging therapy was EPd.[55] A minimum 14 days of washout after bridging therapy was required per protocol. The 24 days median time from end of bridging therapy to the date of ide-cel infusion (range: 12 - 75) reflects the longer time without effective anti-myeloma therapy in the ide-cel arm (Figure 1.2.1-2).

LD chemotherapy consisting of fludarabine and cyclophosphamide, not an effective anti-myeloma therapy, was administered over 3 consecutive days. After the completion of LD chemotherapy, subjects underwent a 2 day rest period followed by the ide-cel infusion at a dosing range of 150-450 x 10^6 chimeric antigen receptor (CAR) + T cells (Figure 1.2.1-2).

Standard Regimens arm: Patients randomized to the standard regimen arm were to start treatment within 7 days of randomization; the median time from randomization to first study drug dose was 5 days (range:1-24). Treatment was given until progression, unacceptable toxicity, or withdrawal of consent. 82 (62.1%) patients were eligible to cross-over and underwent leukapheresis and 74 (56.1%) received ide-cel infusion after confirmation of disease progression by the IRC. The median time from randomization to ide-cel infusion in the standard regimens arm was 8.1 months (range 2.9 - 36.7, Q1 5.3, Q3 16.3).

3.4.2 Statistical Considerations

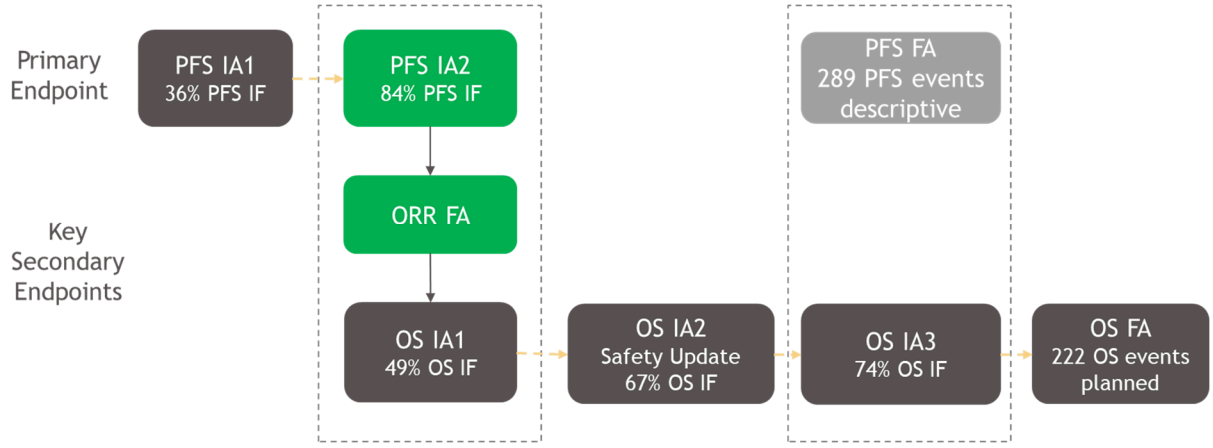
The primary analyses on efficacy were conducted using the ITT Population, defined as all subjects who are randomized to one of the two treatment arms. The primary endpoint of PFS and key secondary endpoints of ORR and OS are evaluated using a hierarchical testing strategy to maintain an overall type I error of 0.025 (one-sided); Figure 3.4.2-1. There were 2 PFS interim analyses planned for this study: the first one for futility (105 PFS events [36% information fraction]) and the second one for efficacy (at least 232 PFS events [80% information fraction]). The PFS final analysis was planned to occur when 289 PFS events are observed. A group sequential procedure with an alpha-spending function of the O'Brien-Fleming type was used to control the Type I error rate. At PFS IA2 (242 PFS events [84% information fraction] observed), ide-cel demonstrated a

statistically significant improvement in both PFS and ORR compared to standard regimens, and the study proceeded to test OS.

At the time of the first IA for OS conducted at the pre-specified PFS IA2, based on the data CoD of 18-Apr-2022 at 49% OS information fraction, the p-value for OS did not cross the significance boundaries for either efficacy or futility. During the pre-sBLA Meeting held on 01-Dec-2022, the Agency advised for OS data to be available for almost all subjects and recommended that the Sponsor provides as much data as possible. Given the feedback from the Agency, an additional OS IA2 was conducted with a data CoD of 03-Oct-2022. OS was formally tested again at the pre-specified OS IA3 at the time of planned PFS FA when 289 PFS events by IRC were accumulated, 74% OS information fraction, with a data CoD of 28-Apr-2023. The final OS analysis is planned to occur when approximately 222 OS events are observed.

Additional details are provided in APPENDIX 1.

Figure 3.4.2-1: KarMMa-3: Statistical considerations



Abbreviations: IA = Interim Analysis, FA = Final Analysis, IF = Information Fraction

3.4.3 Patient Population

Study KarMMa-3 enrolled a total of 386 patients in North America (N = 226), Europe (N = 151), and Japan (N = 9). Baseline demographics were generally balanced between the ide-cel and standard regimens arms. Of the 207 patients enrolled in the United States (US), 35 (16.9%) were African Americans.

The study patient population is representative of a high-risk, highly refractory myeloma population with RRMM TCE who received 2-4 prior lines of therapy (median of 3), as reflected by the high percentages of patients who harbored high-risk cytogenetic abnormalities, had extramedullary disease, and had high tumor burden at baseline (Table 3.4.3-1). The rate of high-risk cytogenetics in KarMMa-3 (43.5%) was higher than typical for TCE populations (18.5% to 23.7%).[56] There was a higher percentage of subjects with extramedullary disease in KarMMa-3 (24.1%) than usually seen in relapsed myeloma, where the reported incidence of extramedullary disease is 3.4%

to 14%.[57,58] The refractory nature and difficult-to-treat disease course in this patient population is evident based on the majority of subjects being DARA (94.6%) and triple class refractory (65.5%).

Table 3.4.3-1: Key Baseline Disease Characteristics - ITT Population in KarMMa-3

Parameters	Ide-cel Arm (N=254)	Standard Regimens Arm (N=132)	Total (N=386)
ECOG Performance Status, n (%)[a]			
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)
Time since Initial Diagnosis (year)			
n	251	131	382
Median (Min, Max)	4.1 (0.2, 21.8)	4.0 (0.7, 17.7)	4.1 (0.2, 21.8)
R-ISS at Baseline (Derived), n (%)[b]			
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 Abnormalities, n (%)[c]			
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)
Presence of Extramedullary Plasmacytoma, n (%)			
Yes	61 (24.0)	32 (24.2)	93 (24.1)
No	192 (75.6)	100 (75.8)	292 (75.6)
Missing/Unknown	1 (0.4)	0	1 (0.3)
Tumor Burden, n (%)[d]			
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 Autologous Stem Cell Transplant for Multiple Myeloma, n (%)			
Yes	214 (84.3)	114 (86.4)	328 (85.0)
Number of Prior Anti-myeloma 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 Anti-myeloma Regimens, n (%)			
2	78 (30.7)	39 (29.5)	117 (30.3)

Table 3.4.3-1: Key Baseline Disease Characteristics - ITT Population in KarMMa-3

Parameters	Ide-cel Arm (N=254)	Standard Regimens Arm (N=132)	Total (N=386)
3	95 (37.4)	49 (37.1)	144 (37.3)
4	81 (31.9)	44 (33.3)	125 (32.4)
Number of Prior Anti-myeloma Regimens per Year Since Diagnosis, n	251	131	382
Median (Min, Max)	0.7 (0.1, 8.1[e])	0.7 (0.2, 3.2)	0.7 (0.1, 8.1[e])
Refractory Status to Prior Therapies, n (%)			
Immunomodulatory Agent (IMiD)	224 (88.2)	124 (93.9)	348 (90.2)
Proteasome Inhibitor (PI)	189 (74.4)	95 (72.0)	284 (73.6)
Anti-CD38 Antibodies	242 (95.3)	124 (93.9)	366 (94.8)
Triple-class Refractory, n (%)[f]			
Yes	164 (64.6)	89 (67.4)	253 (65.5)
Time to Progression on Last Prior Anti-Myeloma Therapy (Months)[g]			
Median (Min, Max)	7.1 (0.7, 67.7)	6.9 (0.4, 66.0)	6.9 (0.4, 67.7)

Note: Baseline value is defined as the last non-missing value before or on the date of first leukapheresis for ide-cel Arm and before or on Month 1 Day 1 for Standard Regimens Arm. If a subject does not perform leukapheresis in ide-cel arm or is not treated in standard regimens arm, then the last assessment on or before randomization +7 days is used as baseline value.

[a] All subjects had ECOG score 0 or 1 at screening, but the ECOG score may be >1 at baseline.

[b] Derived ISS is calculated using baseline values of Albumin and Beta-2-microglobulin. R-ISS is derived using baseline ISS stage, cytogenetic abnormality, and serum lactate dehydrogenase.

[c] To determine cytogenetic risks, the centralized lab data at screening will be considered first, if centralized data are not available, the last value from historical tests including at diagnosis collected on the CRF will be used. If neither the centralized lab nor the CRF data are available, the data will be imputed from the IRT system. Cytogenetic risk 'High' is defined as presence of any of the following abnormality: del17p13 (a probe reflective of del17p), t(14;16) or t(4;14); 'Not High' risk is defined as absence of all three abnormalities. The cytogenetic risk is not evaluable or missing if the status of one or more probes is not available.

[d] Tumor burden is determined by the higher value between bone marrow aspiration and bone marrow biopsy CD138+ plasma cell. Low tumor burden: < 50%, High tumor burden: ≥ 50%.

[e] Range maximum reflects data entry error; corrected after database lock.

[f] Triple-class refractory is defined as refractory to at least one immunomodulatory agent, one PI and one anti-CD38 antibody. For KarMMa-3, refractory to a medication was ascertained relative to the last (ie, most recent) regimen the respective medication was part of. Specifically, a subject was determined as refractory to that medication if the subject was either nonresponsive on therapy (defined as failure to achieve at least minimal response) or progressed on or within 60 days of the last dose of the respective medication (inclusive).

[g] Time to progression calculated based on summary statistics instead of Kaplan-Meier estimator.

4 EFFICACY

In the ITT population (data CoD: 18-Apr-2022), ide-cel demonstrated a clinically meaningful and statistically significant improvement in PFS, per IRC assessment (stratified log-rank test p-value of < 0.0001) and for the key secondary endpoint of ORR per IRC assessment (Cochran-Mantel-Haenszel test p-value < 0.0001) compared with standard regimens that are commonly utilized in

current clinical practice for this patient population with unmet medical need (Table 4-1). The OS results (data CoD: 28-Apr-2023) in the ITT population showed a HR of 1.012 (95% CI: 0.731, 1.400) with a median OS of 41.4 months (95% CI: 30.9, NA) in the ide-cel arm versus 37.9 months (95% CI: 23.4, NA) in the standard regimens arm (Table 4.3.1-1).

Table 4-1: Summary of Progression-free Survival and Objective Response Rate - ITT Population (18-Apr-2022 data cutoff)

	Ide-cel (N = 254)	Standard Regimens (N = 132)
Primary Endpoint		
PFS per IRC		
Events (Progressed/Died), n (%)	149 (58.7)	93 (70.5)
Censored, n (%)	105 (41.3)	39 (29.5)
Median PFS (95% CI)[a], mo.	13.3 (11.8, 16.1)	4.4 (3.4, 5.9)
Stratified HR (97.2% CI)[b], one-sided p-value[c]	0.493 (0.365, 0.666); p < 0.0001	
Stratified HR (95% CI)[b]	0.493 (0.377, 0.645)	
Event-free rate % (SE)[d]		
6-month	73.4 (2.8)	40.3 (4.6)
12-month	54.5 (3.3)	30.2 (4.4)
Key Secondary Endpoint (Hierarchically Tested)		
ORR[e] per IRC		
N responders (%),	181 (71.3)	55 (41.7)
95% CI[f]	(65.7, 76.8)	(33.3, 50.1)
Common rate difference[g] (97.2% CI)	29.3 (18.1, 40.5); p < 0.0001[h]	
Common rate difference[g] (95.0% CI)	29.3 (19.3, 39.3)	
Common odds ratio[g], (97.2% CI)	3.54 (2.14, 5.85)	
Common odds ratio[g], (95.0% CI)	3.54 (2.26, 5.54)	
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)

[a] Median and corresponding 95% confidence interval are based on Kaplan-Meier approach

[b] Stratified and unstratified HR are based on the univariate Cox proportional hazards model. Confidence interval is two-sided. Additional two-sided 97.2% CI for stratified HR is to match the one-sided superiority boundary 0.014 in p-value scale used for this interim analysis.

[c] P-value is one-sided based on a log-rank test stratified by stratification factors (age, < 65 vs ≥ 65; Number of prior antimyeloma regimens, 2 vs 3 or 4; High risk cytogenetic abnormalities, t(4;14) or t(14;16) or del 17p presence vs absence/unknown).

[d] SE is based on Greenwood formula.

[e] Overall response rate is defined as the rate of subjects whose response is PR or better (ie, sCR or CR or VGPR or PR); Complete response rate is defined as the rate of subjects whose response is CR or better (ie, sCR or CR). The denominator used for rate calculation is the number of subjects in the designated study population.

[f] Two-sided Wald confidence interval

[g] Common rate difference, odds ratio and CI are based on CMH estimate. Additional two-sided 97.2% CI for common risk difference and odds ratio is to match the one-sided superiority boundary 0.014 in p-value scale used for this interim analysis.

4.1 Progression-free Survival

As of 18-Apr-2022, the data cutoff for the pre-planned IA2 for PFS (at 84% information fraction), with a median follow-up of 18.6 months (range: 0.4, 35.4), KarMMa-3 Study met its primary endpoint of PFS by IRC in this highly refractory myeloma population. Ide-cel demonstrated a statistically significant and clinically meaningful reduction in the risk of progression or death by 51% (HR = 0.493 (95.0% CI: 0.377, 0.645) compared to treatment with standard regimens (median PFS: 13.3 vs 4.4 months, p-value <0.0001) (Table 4-1 and Figure 1.3-1). Separation of the K-M curves favoring ide-cel over standard regimens occurred early, and this treatment effect was sustained through the period of follow up. The benefit of ide-cel over standard regimens was consistent across all preplanned subgroups, including high-risk subgroups (HR < 1) (eg, high-risk cytogenetics, high tumor burden, R-ISS III, or EMP) (Figure 4.1-2), supporting the internal consistency of the study results. The median PFS in the standard regimens arm is consistent with real world data[24,25,27,32,33] with conventional therapies (3.4 to 4.9 months) in this patient population and reinforces the clinical significance of the ide-cel benefit and strengthens the external validity of the KarMMa-3 study results.

While median PFS in the standard regimens arm was generally consistent across prior lines of therapy, greater benefit was observed for ide-cel when used in earlier treatment lines (15.1 months after 2 prior lines, 12.5 months after 3, 11.2 months after 4, respectively), which supports the importance of earlier use of ide-cel to allow patients to derive the greatest benefit from ide-cel treatment with the longest treatment-free interval.(Figure 4.1-1). Moreover, a lower dropout rate from leukapheresis to ide-cel infusion was observed in patients with a lower number of prior regimens (2L: 5.3%, 3L: 10.5%, 4L: 12.7%), further supporting its use in earlier in the treatment course.

Figure 4.1-1: KarMMa-3: Greatest PFS benefit of ide-cel in earlier treatment line (18-Apr-2022 data cutoff)

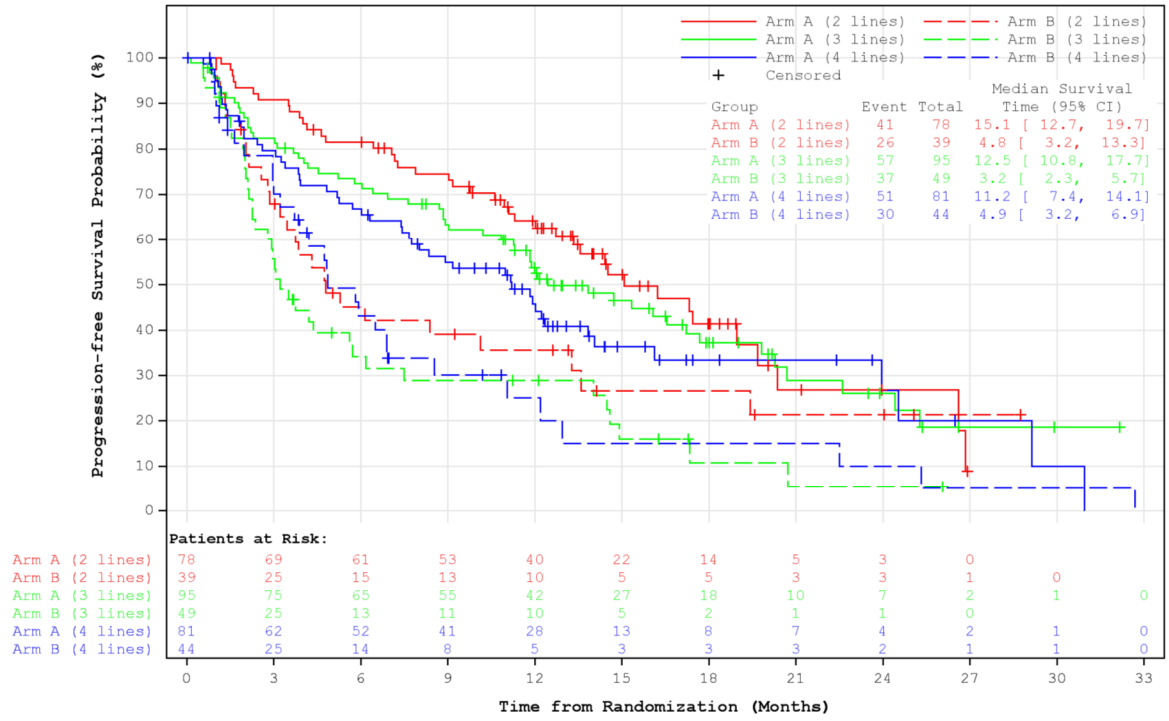


Figure 4.1-2: Forest Plot for PFS Hazard Ratios Based on IMWG Criteria - IRC Review FDA Censoring Rules - ITT Population (18-Apr-2022 data cutoff)

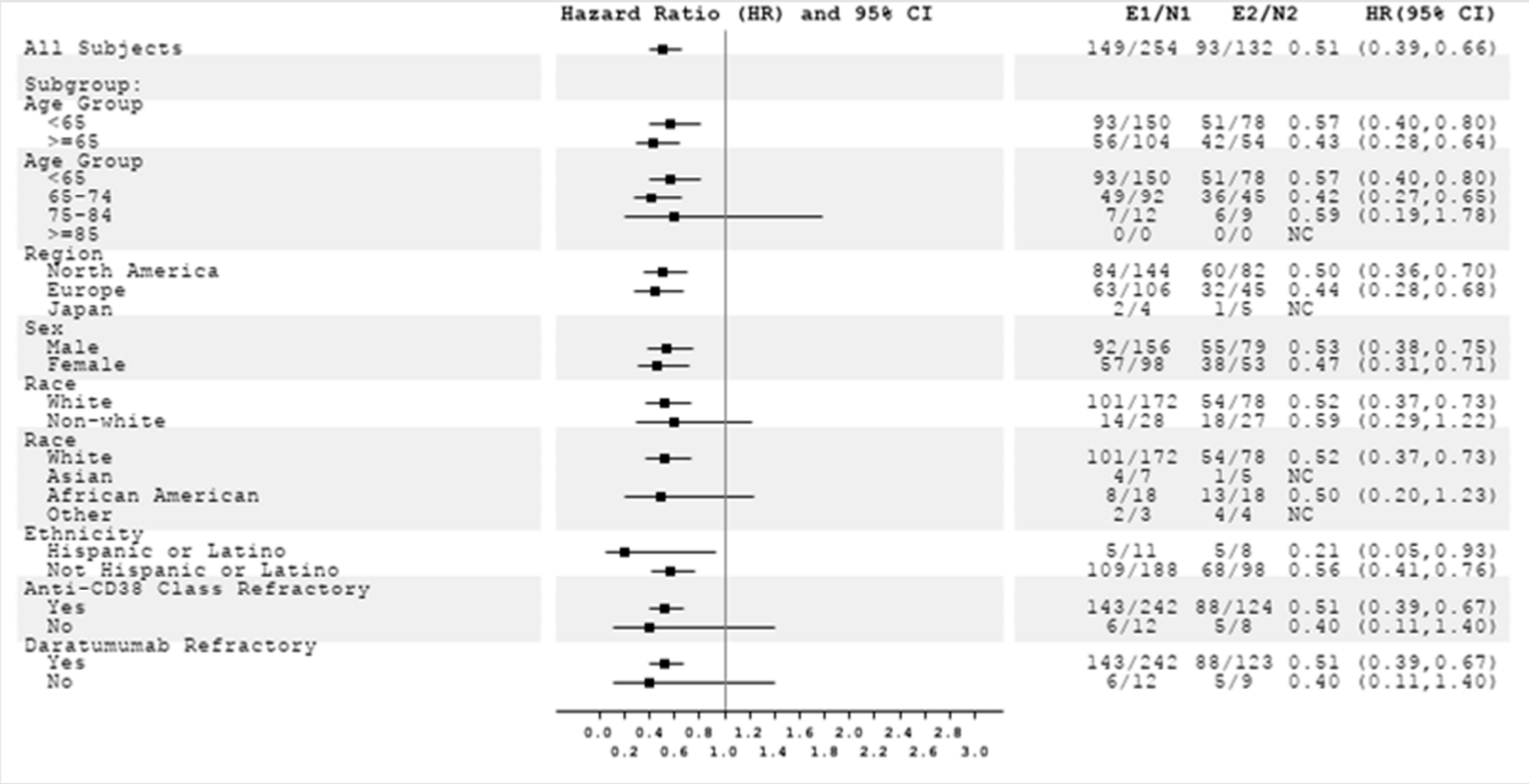
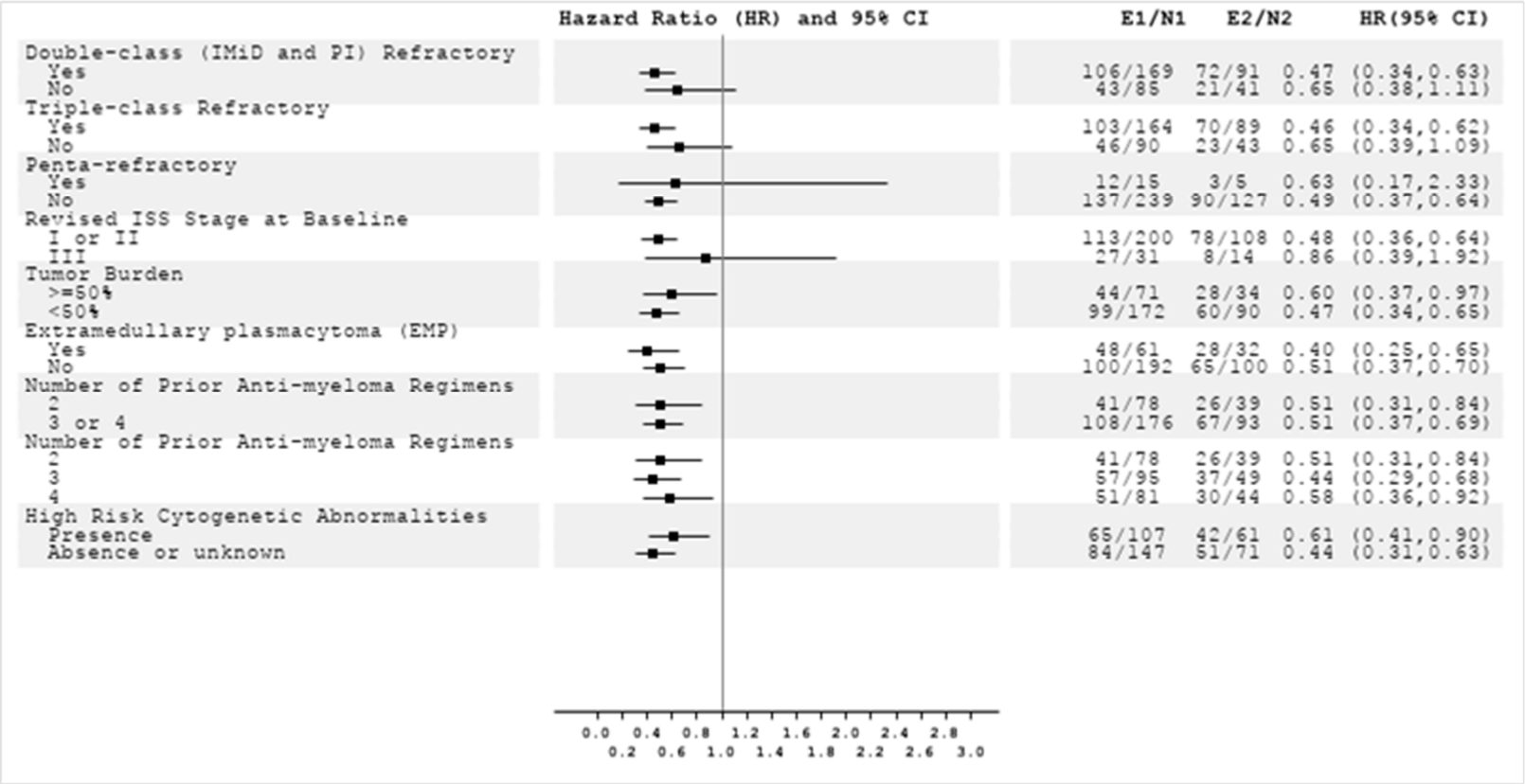


Figure 4.1-2: Forest Plot for PFS Hazard Ratios Based on IMWG Criteria - IRC Review FDA Censoring Rules - ITT Population (18-Apr-2022 data cutoff)



E1/N1 = number of events/number of subjects assigned to Ide-cel Arm in the subgroup.

E2/N2 = number of events/number of subjects assigned to Standard Regimens Arm in the subgroup.

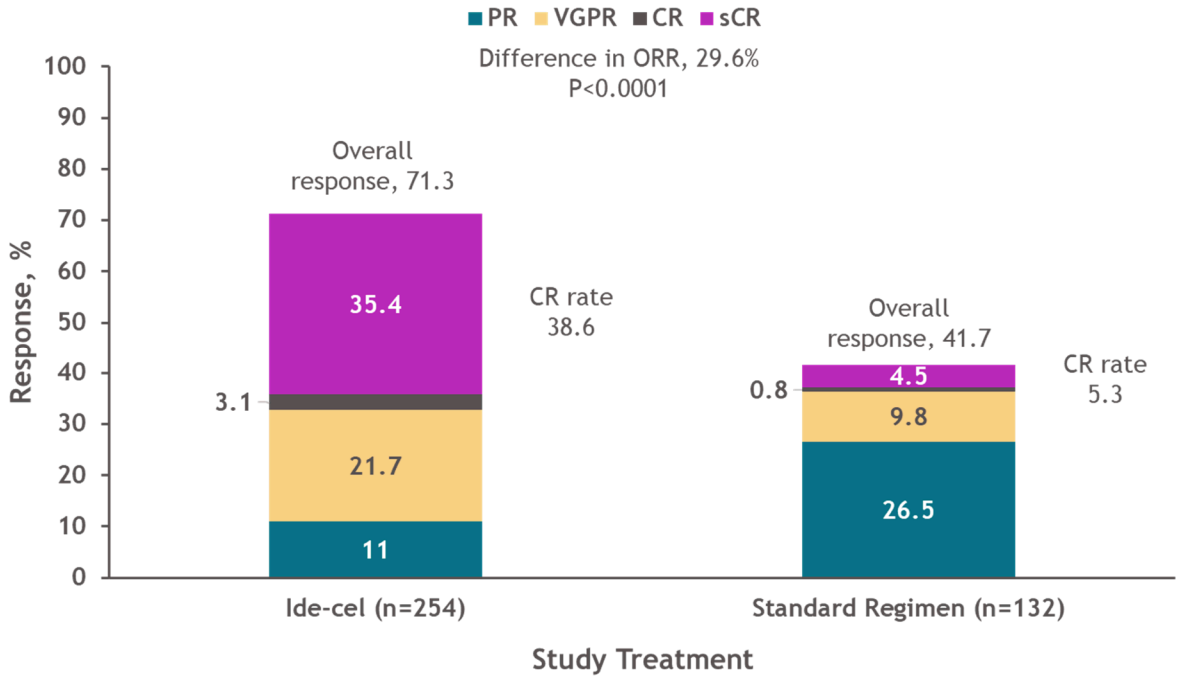
Note: HR is unstratified HR for ide-cel arm vs standard regimens arm based on the univariate Cox proportional hazards model. CI is two-sided. HR is not computed for subgroups if both N1 and N2 are less than 10. NC = Not calculated.

4.2 Objective Response Rate

For the key secondary endpoint of ORR, which was hierarchically tested, ide-cel demonstrated a statistically significant improvement compared with standard regimens; ORR = 71.3% in the ide-cel arm vs 41.7% in the standard regimens arm; p-value < 0.0001 (Table 4-1 and Figure 4.2-1). Ide-cel demonstrated a 3.54 (95% CI: 2.26, 5.54) fold higher odds of achieving a response compared to standard regimens. Similar to PFS, the ORR benefit of ide-cel over standard regimens was consistent across preplanned subgroups.

Notably, 38.6% patients in the ide-cel arm compared to 5.3% patients in the standard regimens arm achieved a complete response or better. Among subjects with a response of CR or better, 20.1% subjects (95% CI: 15.2, 25.0) in the ide-cel arm and 0.8% subjects (95% CI: 0.0, 2.2) in the standard regimens arm achieved MRD-negative status. The median DoR was longer with ide-cel compared to standard regimens (14.8 months [95% CI: 12.0, 18.6] versus 9.7 months [95% CI: 5.4, 16.3]).

Figure 4.2-1: Ide-cel demonstrates significant improvement in ORR by IRC review (ITT) - 18-Apr-2022 data cutoff



CR = complete response; PR = partial response; sCR = Stringent complete response; VGPR = very good partial response

4.3 Overall Survival

Due to the size and power of the KarMMa-3 Study, the ability to show a difference in overall survival was limited. The cross-over allowed upon IRC confirmed progression, via Amendment 2.0, dated 17 Dec 2019, for patients in the standard regimens arm to receive ide-cel confounds the interpretation of the OS results. The interpretation of OS results follows the approach described in Section 1.3.

Results from the pre-specified OS IA3 when the prespecified 289 PFS events by IRC were accumulated (ie, at the planned final PFS analysis), 74% information fraction, with a data CoD of 28-Apr-2023 are summarized below. Section 3.4.2 provides details on all OS IAs conducted.

4.3.1 Overall Survival Analysis Based on 28-Apr-2023 data cutoff - ITT Population

At the most recent data CoD of 28-Apr-2023, with a median follow-up of 30.9 months (range: 12.7 - 47.8) and 74% information fraction, the OS results in the ITT population showed a HR of 1.012 (95% CI: 0.731, 1.400) with a median OS of 41.4 months (95% CI: 30.9, NA) in the ide-cel arm versus 37.9 months (95% CI: 23.4, NA) in the standard regimens arm (Table 4.3.1-1 and Figure 1.3-2). The median OS in both arms vastly exceeds the historical data (9-22 months) with conventional therapies in this patient population (Table 1.3-1).

At the time of Amendment 2.0 implementation, 9 subjects in the standard regimen arm had PD and thus did not have the opportunity to cross-over. Overall, 82 patients were eligible to cross-over and underwent leukapheresis, and 74 (56.1%) received ide-cel infusion after confirmation of disease progression by the IRC.

The long median OS in the standard regimens arm suggests that patients who received ide-cel post progression in the context of the cross-over study design benefited from ide-cel treatment.

Table 4.3.1-1: Summary of Overall Survival - ITT Population (28-Apr-2023 data cutoff)

	Ide-cel Arm (N = 254)	Standard Regimens Arm (N = 132)
Overall Survival (OS) status, n (%)	254 (100.0)	132 (100.0)
Censored, n (%)	148 (58.3)	74 (56.1)
Died, n (%)	106 (41.7)	58 (43.9)
OS Survival Time (months)[a]		
25th Percentile (95% CI)	12.1 (10.0, 14.9)	14.6 (10.9, 17.0)
Median (95%CI)	41.4 (30.9, NA)	37.9 (23.4, NA)
75th Percentile (95% CI)	NA (NA, NA)	NA (NA, NA)
Survival probability		
6 Months Event-Free % - (95% CI)	88.1 (83.5, 91.6)	93.1 (87.1, 96.3)
12 Months Event-Free - % (95% CI)	75.1 (69.3, 80.0)	80.6 (72.7, 86.5)
18 Months Event-Free - % (95% CI)	67.9 (61.8, 73.3)	65.4 (56.4, 73.0)
24 Months Event-Free - % (95% CI)	64.6 (58.4, 70.2)	57.6 (48.4, 65.8)
P-value[b]	0.5287	
Stratified Hazard Ratio (95% CI)[c]	1.012 (0.731, 1.400)	Ref.
Unstratified Hazard Ratio (95% CI)[c]	0.930 (0.675, 1.281)	Ref.

Note: No adjustment for subjects in standard regimens arm who received ide-cel infusion. “Ref.” is used to indicate standard regimens arm as the reference for HR calculation.

[a] The 25th and 75th percentile, median and corresponding 95% confidence interval are based on Kaplan-Meier approach.

[b] P-value is based on a log-rank test stratified by stratification factors (age, <65 vs ≥ 65; Number of prior anti-myeloma regimens, 2 vs 3 or 4; High risk cytogenetic abnormalities; t(4;14) or t(14;16) or del 17p, presence vs absence/unknown).

[c] Stratified and unstratified hazard ratio are based on the univariate Cox proportional hazards model. Confidence interval is two-sided.

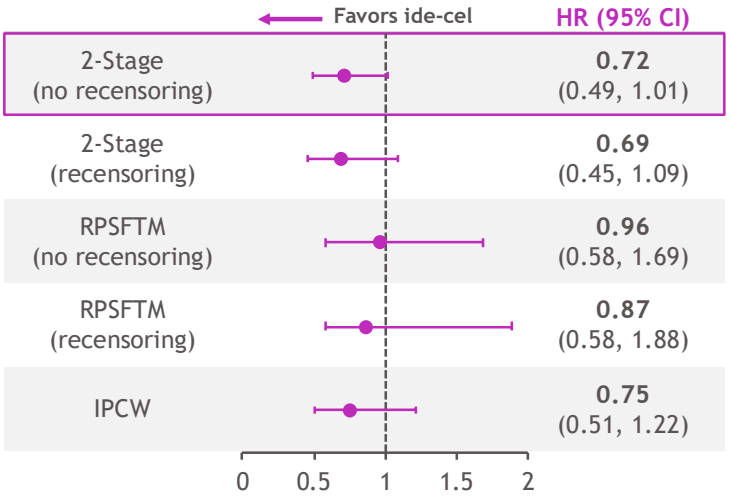
4.3.2 The Interpretability of the OS Results is Confounded by Cross-over

The interpretability of the OS results in KarMMa-3 is confounded by cross-over. Per the patient-centric study design, subjects randomized to the standard regimens arm were allowed, after IRC confirmation of disease progression, to receive ide-cel as subsequent anti-myeloma therapy. As of the 28-Apr-2023 data cutoff, more than half of the subjects (74/132, 56.1%) in the standard regimens arm received ide-cel. Because of the short median PFS in the standard regimens arm, the cross-over impacted the OS curves early on. The median time from randomization to ide-cel infusion in the standard regimens arm was 8.1 months (range 2.9 - 36.7), with 75% of the cross-over patients having received their ide-cel infusion by Month 16 (Q1- Q3: 5.3, 16.3).

Two pre-specified analyses (ie, a 2-stage model,[34,35]and a RPSFT model[36] as well as 1 post-hoc analysis using the IPCW method[37,38,39] (at the request of the EU CHMP) have been employed to estimate the OS treatment effect that would have been observed had cross-over not occurred; see APPENDIX 1 for additional details. Although all 3 methods rely on certain statistical assumptions, they consistently indicate a trend in OS benefit in favor of ide-cel over standard regimens, with HR estimates below 1 (Figure 4.3.2-1, Figure 4.3.2-2, Figure 4.3.2-3, and Figure 4.3.2-4).

The median OS in the standard regimens arm was substantially longer than expected in this patient population. A post-hoc analysis was conducted in the standard regimen arm analyzing PPS, in patients who crossed-over and patients who did not cross-over. Acknowledging that this analysis is not protected by randomization, the median PPS of patients who crossed-over (ie, underwent leukapheresis with the intent to receive ide-cel) was not reached (95% CI: 24.2, NA), whereas patients who did not cross over had a median PPS of 10.0 months (95% CI: 6.9, 16.6); Figure 1.3-3.

Figure 4.3.2-1: Estimated HR From Sensitivity Analysis Adjusting for Crossover (28-Apr-2023 data cutoff)



IPCW = inverse probability of censoring weighting; RPSFTM = rank preserving structural failure time

Figure 4.3.2-2: Kaplan-Meier Curve of Overall Survival by Two-stage Model with Re-censoring - ITT Population (28-Apr-2023 data cutoff)

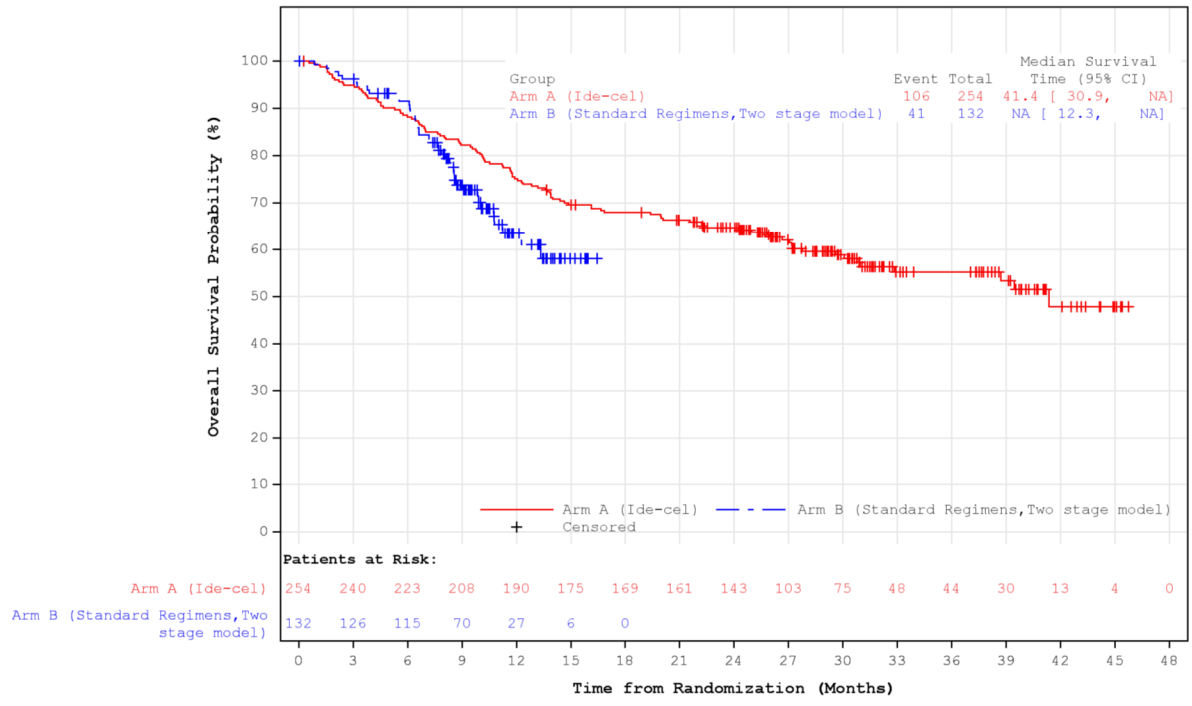


Figure 4.3.2-3: Kaplan-Meier Curve of Overall Survival by Rank Preserving Structural Failure Time (RPSFT) Model with Re-censoring - ITT Population (28-Apr-2023 data cutoff)

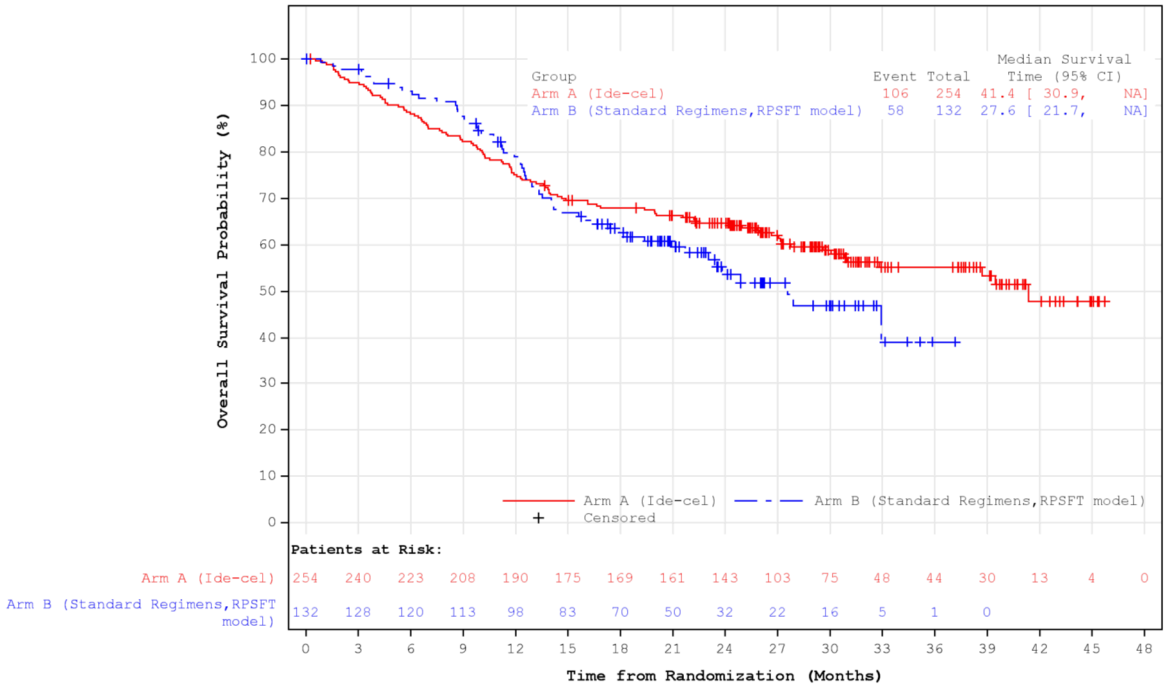
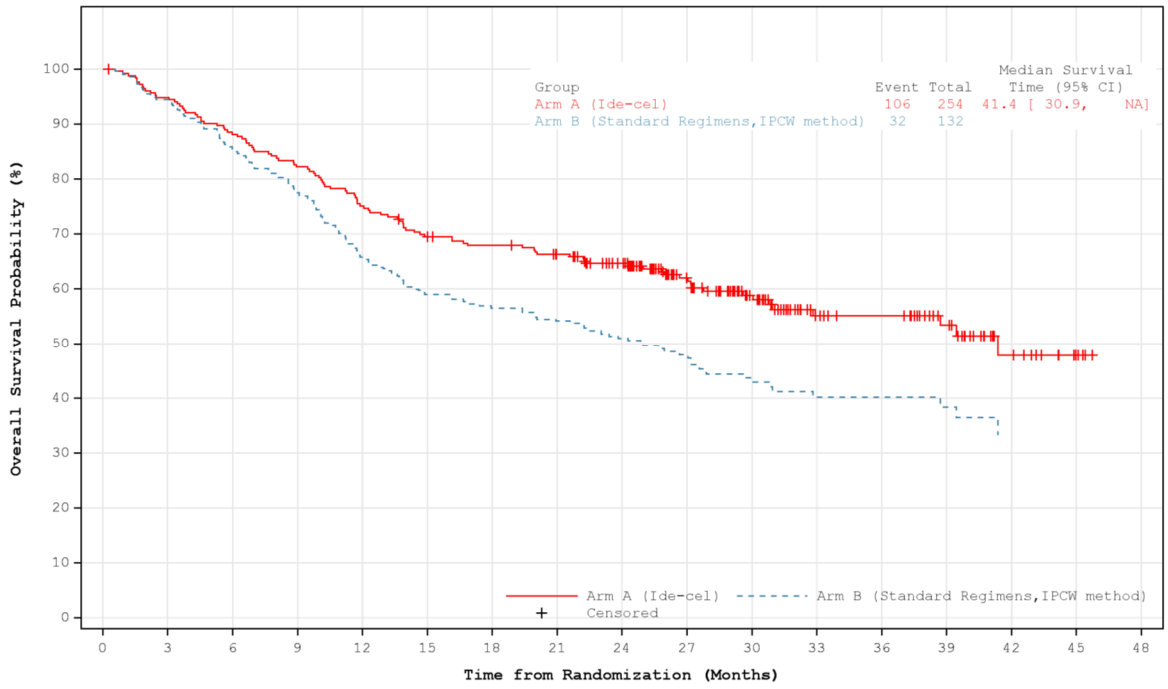


Figure 4.3.2-4: Kaplan-Meier Curve of Overall Survival by Inverse Probability of Censoring Weighting (IPCW) Method - ITT Population (28-Apr-2023 data cutoff)



4.3.3 Imbalance in Early Deaths are Not Due to Ide-cel Toxicity or Delays in Manufacturing

Despite crossing of the OS curves at 15 months (Figure 1.3-2), the piecewise HR pinpoints the imbalance largely to the first 6 month from randomization (Figure 1.3-4). Death by time intervals from randomization showed that death rates in the ide-cel arm were numerically higher than that in the standard regimens arm during the first 6 months (30 [11.8%]) versus (9 [6.8%]); Table 1.3-2. The piecewise OS analysis reflects this numerical difference in early deaths, where the HRs of ide-cel versus standard regimens were 1.855 (95% CI: 0.88, 3.91) in the first 6-month interval and 0.85 (95% CI: 0.59, 1.23) after 6 months from randomization, respectively. A post-hoc landmark analysis of OS for all randomized subjects with more than 6 months of survival (Figure 1.3-5) supports this observation, with superimposable curves between 6-15 months followed by a clear separation of curves with a numerical trend favoring ide-cel over standard regimens afterwards (HR [95% CI] = 0.85 [0.592, 1.23]).

In the ide-cel arm, a majority of subjects who died within 6 months of randomization (17/30; 56.7%) occurred in patients who never received ide-cel treatment; (Table 1.3-2); this includes 13 (5.1%) subjects who died from disease progression, 3 (1.2%) subjects who had an AE leading to death (sepsis shock [2 subjects], CMV infection [1 subject]), and 1 (0.4%) subject with unknown cause of death. The rate of early death among patients who received study treatment was similar between arms (5.1% in the ide-cel arm vs 6.8% in the standard regimens arm); therefore, the numerical difference between treatment arms **is driven entirely by early deaths among untreated patients**. In both arms, most early deaths were attributed to myeloma disease progression. Early deaths due to AEs among patients who received the allocated study treatment were similar between treatment arms (2.0% versus 2.3%, respectively), which indicates the numerical differences in early death rates were not associated with ide-cel related mortality.

Ide-cel manufacturing was uniform and reliable, with consistent median turn-around times in patients with early death and in the ITT population (35 days and 34 days, respectively), and of the 3 manufacturing failures in the ITT population 1 occurred in a patient with early death. Therefore, there are no differences in turnaround time between patients with or without early death.

4.3.4 Protocol Constraints of Bridging Therapy

Subjects in both arms who died within 6 months from randomization were, not surprisingly, enriched for high-risk factors portending poor outcome compared to the overall ITT population in each respective arm. High-risk factors included R-ISS stage III, high-risk cytogenetics, presence of EMP, high tumor burden, triple class refractoriness, albumin level < 3.5 g/dL, beta-2-microblobulin level ≥ 5.5 mg/L, LDH above the upper limit of normal, and shorter median time to progression on the last prior anti-myeloma therapy, compared to the overall ITT population in each respective arm.

Per KarMMa-3 protocol, bridging therapy was allowed at investigators' discretion (one of the 5 standard regimens), with the intent of stabilizing the disease during manufacturing, for up to 1 cycle with a minimum of 14 days of washout. Among the 30 subjects with an early death event in the ide-cel treatment arm, 25 (83.3%) received bridging therapy. This was similar to the overall

ide-cel ITT population where 83.5% of subjects received bridging therapy. There are thus no obvious differences in the use of bridging therapy between patients with or without early death. However, it is important to note that the protocol specifications on bridging therapy (up to 1 cycle, minimum 14 days wash-out period) resulted in a long time without anti-MM treatment in the ide-cel arm, which did not seem to adequately control the disease in patients with high risk disease and resulted in 17 patients who experienced early death without having received ide-cel.

During the first 6 months post-randomization, the CI bands for the OS KM curves are largely overlapping and as such, random variability cannot be excluded in the context of 2:1 randomization and the small number of OS events (Figure 1.3-2).

Taken together, the interpretability of OS is confounded by cross-over, and while random variability cannot be excluded, the numerical differences in early death events are driven by patients who never received ide-cel and are not caused by ide-cel toxicity.

4.4 Patient Reported Outcomes (PROs)

Previous studies have shown patients with multiple myeloma experience detriments to health-related quality of life as assessed through patient reported outcomes.[41] KarMMa-3 included three validated PRO instruments: the EORTC QLQ-C30[42], EORTC QLQ-MY20[43], and EQ-5D-5L.[44] These were used to assess the subject's symptoms as well as physical, social, emotional, and functional well-being. The compliance rates were equivalent across the PRO measures, were>75% at most visits, and rates were similar between the two arms. See APPENDIX 1 for additional details.

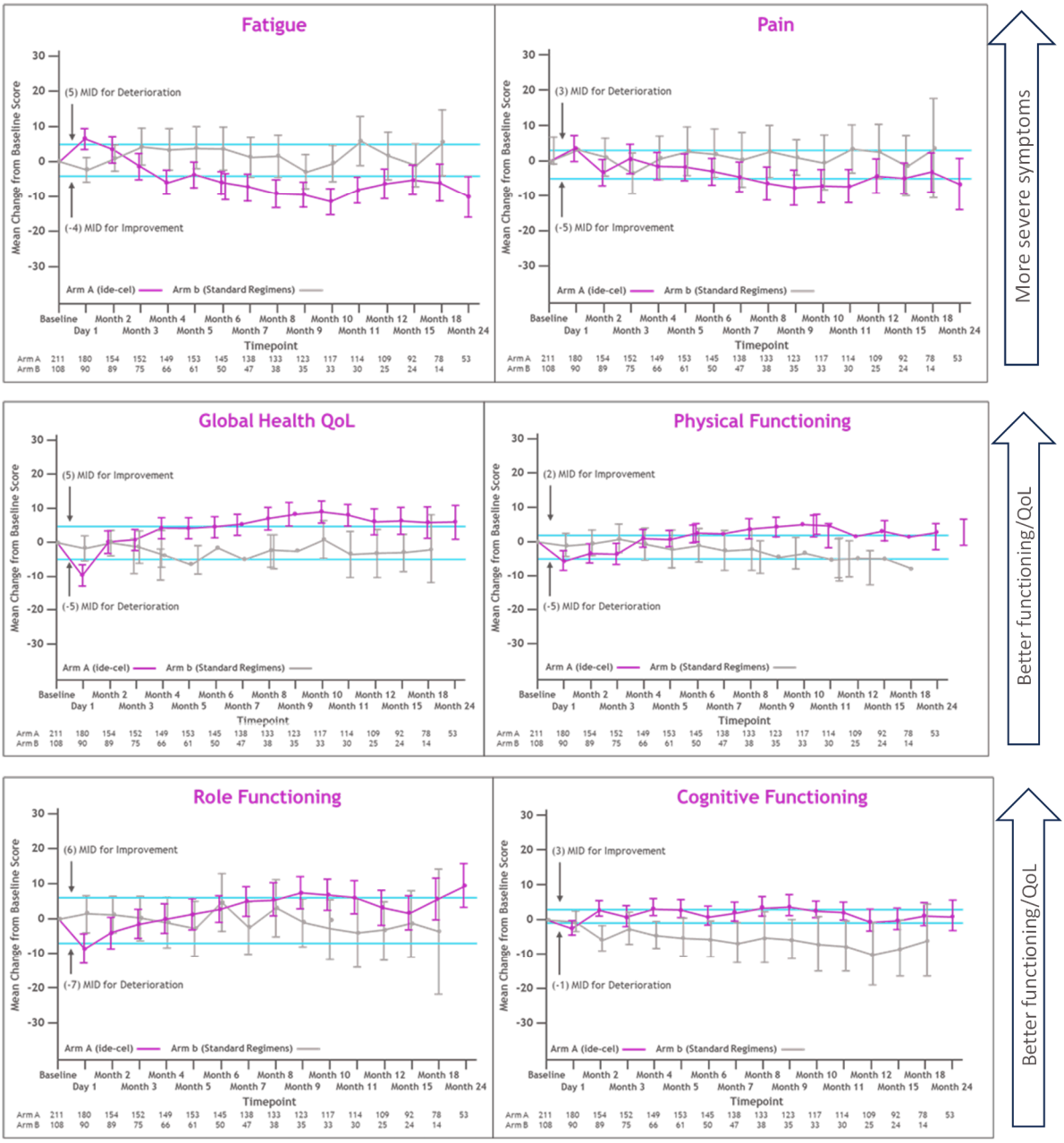
4.4.1 Descriptive Changes in the HRQoL Based on Mean Changes in PRO Scores Changes from Baseline

Group-level observed mean change from baseline on EORTC QLQ-C30 domains (Fatigue, Pain, Physical Functioning, Cognitive Functioning, and Global Health Status (GHS)/QoL) after ide-cel consistently demonstrated clinically meaningful improvements compared with those of the standard regimens arm, which were stable or worsened over time. After a transient decline on Day 1, fatigue, functioning domains (physical, role, cognitive), and GHS/QoL in particular, showed clinically meaningful improvements from baseline with ide-cel as well as differences between arms, in favor of ide-cel (Figure 4.4.1-1).

The EORTC QLQ-C30 Pain domain and EORTC QLQ-MY20 Disease Symptoms also demonstrated improvement or stability over time in the ide-cel arm.

Findings were similar for other PRO domains. When evaluating within-patient change, the proportion of subjects with meaningful improvement or that were stable was consistently higher across domains in the ide-cel arm compared to standard regimens.

Figure 4.4.1-1: Line Graph of Mean Change in Scores from Baseline by Timepoint EORTC QLQ-C30 (Select Primary Domains) - ITT Population (18-Apr-2022 data cutoff)



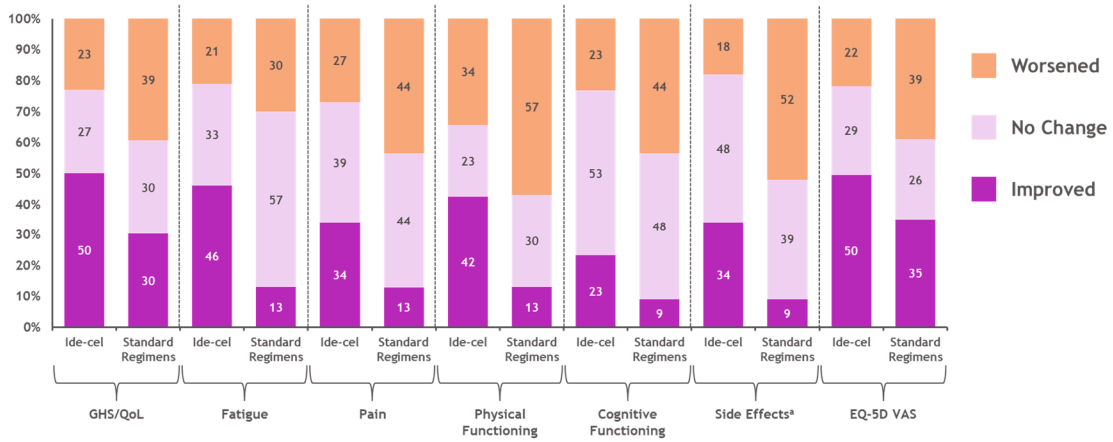
Notes: Baseline is defined as the last available assessment on or prior to randomization. Error bars represent 95% confidence intervals. The line graphs for mean changes are produced for each timepoint with n ≥ 10. Higher scores for symptoms represent more severe symptoms. Higher scores for functioning/HRQoL represent better functioning/QoL.

4.4.2 Proportion of Subjects Showing Improvement or Worsening in PRO Domains Over Time

The proportion of subjects reporting meaningful improvement, no change, or worsening compared to baseline was evaluated for post-baseline visits based on pre-specified responder

definitions.[43,59,60] Across domains higher proportions of subjects in the ide-cel arm improved or were stable compared with the standard regimens arm (Figure 4.4.2-1).

Figure 4.4.2-1: Proportion of patients improved based on pre-specified thresholds (12 months) - 18-Apr-2022 data cutoff



a Side effect domain from MY20

4.4.3 *Comparative Effects of Treatments on HRQoL Overall Mean Changes in PRO Domains from Baseline to Month 20 using Constrained Longitudinal Data Analysis Models*

The constrained longitudinal data analysis (cLDA) showed more favorable changes over time for the ide-cel arm across most PRO domains. The estimand favored ide-cel arm for most PRO domains evaluated, including fatigue, pain, physical functioning, and overall quality of life. Additionally, most domains showed clinically meaningful improvement in the ide-cel arm based on the group-level meaningful change thresholds..[43,59,60]

4.4.4 *Time to Confirmed Improvement and Deterioration between the Ide-cel and the standard regimen treatment arms*

The ide-cel arm showed shorter times to clinically meaningful improvement than the standard regimens group in nearly all PRO domains. Time to confirmed improvement was significantly shorter in favor of the ide-cel arm and was generally longer or similar for meaningful deterioration in most domains compared with the standard regimens.

Figure 4.4-2: Forest plot for between group differences in overall LS mean change from baseline

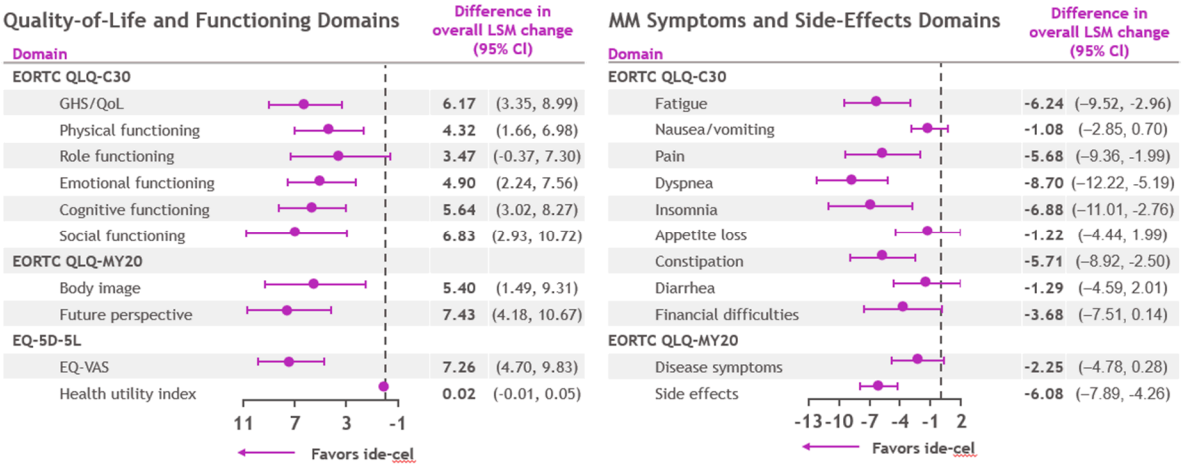


Table 4.4-1: Time-to-event Analyses in Ide-cel versus Standard Regimens (18-Apr-2022 data cutoff)

Instrument/domain	Time to confirmed deterioration HR (95% CI; nominal *P* value)[a,b,c]	Time to confirmed improvement HR (95% CI; nominal *P* value)[a,b,c]
EORTC QLQ-C30		
Global health status/QoL	0.92 (0.48, 1.74; 0.793)	3.87* (1.91, 7.82; <0.001)
Physical functioning	0.74 (0.44, 1.24; 0.251)	3.17* (1.56, 6.44; 0.001)
Role functioning	0.93 (0.51, 1.71; 0.821)	1.72 (0.89, 3.34; 0.108)
Emotional functioning	0.45* (0.24, 0.86; 0.015)	2.58* (1.44, 4.62; 0.001)
Cognitive functioning	0.30* (0.15, 0.59; <0.001)	4.46* (1.55, 12.79; 0.005)
Social functioning	0.55 (0.30, 1.01; 0.055)	4.52* (1.89, 10.79; 0.001)
Fatigue	0.97 (0.53, 1.80; 0.933)	5.15* (2.35, 11.30; <0.001)
Nausea and vomiting	0.73 (0.22, 2.46; 0.618)	4.96* (1.07, 22.92; 0.040)
Pain	0.71 (0.38, 1.33; 0.288)	2.08* (1.03, 4.17; 0.040)
Dyspnea	0.28* (0.13, 0.60; 0.001)	6.60* (1.54, 28.21; 0.011)
Insomnia	0.38* (0.17, 0.84; 0.018)	2.09* (1.01, 4.35; 0.048)
Appetite loss	1.48 (0.50, 4.42; 0.483)	3.55* (1.30, 9.70; 0.013)
Constipation	0.33* (0.12, 0.86; 0.023)	4.35* (1.28, 14.77; 0.018)
Diarrhea	0.60 (0.22, 1.63; 0.317)	2.28 (0.78, 6.70; 0.133)
Financial difficulties	0.79 (0.32, 1.95; 0.605)	2.05 (0.75, 5.58; 0.160)
EORTC QLQ-MY20		
Disease symptoms	0.68 (0.32, 1.44; 0.309)	2.58* (1.06, 6.26; 0.037)
Side effects of treatment	0.38* (0.19, 0.75; 0.005)	5.54* (1.98, 15.53; 0.001)
Body image	0.80 (0.38, 1.68; 0.548)	1.97 (0.81, 4.81; 0.137)

Table 4.4-1: Time-to-event Analyses in Ide-cel versus Standard Regimens (18-Apr-2022 data cutoff)

Instrument/domain	Time to confirmed deterioration HR (95% CI; nominal *P* value)[a,b,c]	Time to confirmed improvement HR (95% CI; nominal *P* value)[a,b,c]
Future perspective	0.63 (0.28, 1.41; 0.258)	2.18* (1.31, 3.62; 0.003)
EQ-5D-5L		
Health utility index	0.72 (0.38, 1.36; 0.308)	2.08 (0.89, 4.82; 0.089)
EQ-VAS	0.66 (0.33, 1.30; 0.230)	3.09* (1.65, 5.77; <0.001)

[a] The HR (95% CI and nominal *P* value) of ide-cel versus std regimens was estimated from the stratified Cox proportional hazards regression model by the randomization stratification factors.

[b] Confirmed improvement/deterioration is defined as improvement/deterioration from baseline at least at the prespecified threshold and lasting for ≥84 days after the onset of improvement/deterioration.

[c] HR <1 indicates delayed time to deterioration for ide-cel; HR >1 indicates faster time to improvement for ide-cel.
CI, confidence interval; cLDA, constrained longitudinal data analysis; HR, hazard ratio; LSM, least squares mean; MID, minimal important difference; mo, month; std, standard;

4.5 Efficacy Summary

Taken together, these data highlight the high-risk, and highly refractory myeloma population enrolled in KarMMa-3 Study, in which ide-cel demonstrated statistically significant and clinically meaningful improvements in PFS and ORR along with consistent benefit across all subgroups including patients with high-risk factors. Ide-cel showed evidence of an improvement in quality of life in the context of a long treatment-free interval. This is a unique benefit of ide-cel's one-time treatment over the chronic, continuous treatment with conventional therapies in MM.

The interpretability of OS is confounded by cross-over, and while random variability cannot be excluded, the numerical differences in early death events are observed in patients who never received ide-cel and are not caused by ide-cel toxicity. Sensitivity analyses employed to estimate the OS treatment effect that would have been observed had cross-over not occurred showed a consistent point estimate of HR<1 suggesting a potential OS benefit in favor of ide-cel. The numerical difference in early death rates between treatment arms being driven entirely by early deaths among untreated patients in the ide-cel arm, and the similar rates of early deaths due to AEs among treated patients in both arms indicate the early deaths were not associated with ide-cel related mortality.

Patients who experienced early death events were enriched for high-risk factors, particularly high-risk cytogenetics, high tumor burden, R-ISS III, and EMP. It is important to note that disease control during ide-cel manufacturing is critical in this highly refractory myeloma population and requires effective bridging therapy appropriately tailored to the patient prior treatment history and disease characteristics.

In the commercial setting, protocol-specified bridging therapy restrictions do not apply, and physicians can choose from a greater number of treatment options, and should reduce time without anti-myeloma disease control by administering more than 1 treatment cycle and reducing washout

periods. Physicians should be cognizant when making therapeutic decisions that high-risk features and indicators of fast disease kinetics may impact the patients' ability to receive and benefit from ide-cel treatment, but should also recognize that the majority of patients with high-risk are able to receive ide-cel and benefit from it. Taken together, these data substantiate the value of ide-cel as an effective and safe treatment option in a population with high unmet medical need for which existing standard regimens are suboptimal.

5 SAFETY

The overall safety profile of ide-cel in the KarMMa-3 population was consistent with the known safety profile in patients with TCE RRMM who had received 4 or more prior lines of therapy, with no new safety signals. As expected, notable differences between ide-cel and standard regimens arms for AESIs that are specific to CAR T-cell therapy were observed, with the frequency and severity of AEs, Grade 3 or 4 and SAEs numerically higher in the ide-cel arm compared with the standard regimens arm. The AESIs with ide-cel were consistent with the known safety profile and were manageable (Table 1.4-1).

The size of the KarMMa-3 safety database and duration of follow-up are considered adequate to provide a reasonable estimate of adverse reactions that may occur with ide-cel treatment. No new clinically relevant concerns were identified for ide-cel.

Safety summaries are provided for the KarMMa-3 Study from the Treated Population and the Safety Population unless otherwise specified.

5.1 Deaths, Serious Adverse Events, and Adverse Events of Special Interest (AESIs)

In the ITT population, similar proportions of subjects died in the ide-cel and standard regimens arms (Table 1.4-1) with the causes of death being similar between both arms. Most deaths were due to disease progression in both arms and a similar percentage of subjects died due to AEs in each arm, indicating no excess toxicity associated with ide-cel treatment. At latest data cutoff (28-Apr-2023), similar proportions of subjects had died in the ide-cel and standard regimens arms (106 [41.7%] and 58 [43.9%] respectively).

The frequencies of SAEs were higher in the ide-cel arm than the standard regimens arm (Table 1.4-1) with the most frequently reported SAEs in the ide-cel arm being general physical health deterioration, pneumonia, pyrexia, CRS, and febrile neutropenia and in the standard regimens arm being pneumonia, COVID-19 pneumonia, and general physical health deterioration.

As expected, among subjects who received any study treatment, the frequency of AESIs (including known side effects specific to CAR T-cell therapy) was greater in the ide-cel arm than in the standard regimens arm. The majority of AESIs reported in both arms were manageable with protocol-specified guidelines and/or local standards of care and no new clinically important events were identified for ide-cel. In the ide-cel arm, 197 (87.6%) subjects experienced at least one event of CRS with a median time to first onset of CRS of 1.0 day (range 1.0 to 14.0) and a median duration of CRS of 3.5 days (range: 1.0 to 51.0). Most CRS events were of Grade 1 or 2 severity, graded according to the Lee criteria 2014.[61] A small proportion of subjects had severe events

(Grade 3: 2.7%; Grade 4: 1.3%, and Grade 5: 0.9%). 1 subject had ongoing CRS at time of death (cause of death was sepsis).

There were no Grade 5 events due to macrophage activation syndrome (MAS) reported in KarMMa-3 and the rate of MAS (2.2%) in KarMMa-3 is lower than the rate in the current ide-cel label (4%).

In KarMMa-3, investigators were asked to identify those events which they would attribute to and classify as CAR T-associated neurologic toxicity (investigator-identified neurotoxicity [iiNT]). In the ide-cel arm, 34 (15.1%) subjects experienced at least one event of iiNT, with a median time to first onset of any iiNT AEs of 3.0 days (range: 1.0, 317.0) and a median duration of iiNT of 2.0 days (range: 1.0, 37.0). The majority of iiNT AEs were of Grade 1 or 2 severity. 7 (3.1%) subjects reported Grade 3/4 iiNT. No Grade 5 iiNT events were reported. 1 subject developed encephalopathy at Day 317 (not suspected to be related to ide-cel by the investigator). There were no events of parkinsonism or Guillain-Barré syndrome reported.

The rates of Grade 3/4 neutropenia (97.7%) and Grade 3/4 thrombocytopenia (64.8%) seen in the ide-cel arm, are consistent with the known safety profile of ide-cel, and were managed well with growth factors and transfusions. The median time to recovery for subjects with prolonged cytopenias, defined as Gr 3-4 cytopenias on/beyond day 30 after ide-cel infusion, was 1.7 months for neutropenia and 1.9 months for thrombocytopenia.

Despite the higher rates of Grade 3/4 neutropenia in the ide-cel arm within the month post infusion, infection rates including severe infections and types were largely similar between the two arms. Grade 3/4 infection rates were 4.9% in the first month after ide-cel infusion, and in the standard regimens arm were 4.0% in the first month of treatment. Thereafter, rates dropped in both arms, with the rate of Grade 3/4 infection in the ide-cel arm ranging between 0-2.2% from month 2 after ide-cel infusion (with the exception of month 5 after ide-cel infusion when the rate was 3.6%), and in the standard regimens arm, ranging from 0-2.4% from month 3 after commencing treatment.

The percentage of subjects with any second primary malignancy (SPM) reported was very low, and similar between the treatment arms (Table 1.4-1). As of the data cut-off of 18-Apr-2022, the rates of SPM per 100 person-years calculated as per IMWG[62] were similar between the two arms. The SPM rate was 4.37 (95% CI 2.53, 7.52) in the ide-cel arm and 5.43 (2.26, 13.05) per 100 person years in the standard regimens arm. Nine (4.0%) subjects in the ide-cel arm and 3 subjects (2.4%) in the standard regimens arm had invasive SPMs, of which 3 (1.3%) and 0 were hematologic respectively. The 3 cases of hematologic malignancy in the ide-cel arm were myelodysplastic syndrome (MDS, 2 (0.9%) and acute myeloid leukemia (AML, 1(0.4%)). There were no cases of T cell malignancies in the study.

As of the 03-OCT-2022, SPMs had been reported in a total of 15 subjects (6.7%) in the ide-cel arm and 5 subjects (4.0%) in the standard regimens arm (safety population). Of these, 11 (4.9%) and 3 (2.4%) respectively were invasive SPMs. This included 2 additional haematological malignancies (both myelodysplastic syndrome) in the ide-cel arm, for a total of 5 (2.2%) in the ide-cel arm, with none reported at the time of data cutoff in the standard regimens arm. The median

time to onset of haematological SPM in the ide-cel arm was a median of 14.0 months (range 10.7-27.6).

5.2 Safety Conclusion

There were no new safety concerns identified with ide-cel in KarMMa-3 and the safety profile was consistent across subgroups. Overall, the safety profile of ide-cel in KarMMa-3 was generally consistent with data from other supportive studies including subjects with 4L+ relapsed or refractory multiple myeloma (same as in the approved indication), and in those studies with subjects with similar baseline characteristics. The data from study KarMMa-3 allow for a thorough assessment of the ide-cel safety profile in the intended patient population, including characterization of common AEs and SAEs, and informing labeling and risk management strategies. No new clinically relevant concerns were identified for ide-cel and the safety profile is overall in line with previous experience. Importantly, there was no increase in ide-cel related mortality.

6 POSITIVE BENEFIT / RISK OF IDE-CEL IN THE PROPOSED INDICATION

KarMMa-3 provides substantial evidence of efficacy and safety of ide-cel in the proposed indication of treatment of adult patients with relapsed or refractory MM who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody. The trial design was rigorous, well controlled and conducted in a high-quality manner. Bias in treatment allocation and confounding in treatment effect assessment were minimized by randomization, stratification of key prognostic factors, and allocation of a standard regimen prior to randomization. While the use of multiple standard regimens introduced a level of heterogeneity in the control arm clinical benefit, it also enhanced the external validity of the study given the global lack of standard of care in this disease setting. Efficacy was assessed per the International Myeloma Working Group (IMWG) response guidelines by a blinded IRC to avoid assessment bias and ensure integrity of study results. The subjects enrolled in the study were representative of the TCE RRMM patient population, as reflected by the high percentages of patients who harbored high risk cytogenetic abnormalities, had extramedullary disease, and had high tumor burden at baseline.

In recent years, the expanded availability and use of DARA-based regimens in 1st and 2nd line settings has contributed to OS improvement in MM; however, this has also led to the emergence of a new subset of patients who become TCE earlier in the course of their treatment who represent a population with very high unmet need. As no therapies are currently approved in patients who become TCE earlier in the course of their treatment, conventional therapies typically used in these patients are associated with poor outcomes with median PFS of 4 months and OS of 9-22 months.[6,24,25,26,27,28]. The median PFS of 4.4 months in the standard regimens arm in the KarMMa-3 study reflects the short benefit of the most utilized treatment options available today. Importantly, the median PFS was similar in the standard regimen arm among patients with 2, 3 or 4 prior lines of therapy (4.8, 3.2, and 4.9 months, respectively) adding to the notion that exposure to the 3 common classes of therapy is more important than number of prior lines of therapy. Additionally, with each subsequent line of therapy, tumors recur more aggressively and become more refractory to conventional therapies, toxicities and comorbidities increase, performance status worsens[8], and

death rates increase which results in progressively reduced pool of patients who alive and eligible for treatment.[9] This highlights the importance of using the most effective therapies early in the treatment course. Novel non-cross resistant therapies such as bispecific T-cell engagers or CAR-T cell therapies are restricted to patients in the 5th line setting. Considering the significant attrition from 1st line to this late line setting, the clinical deterioration over the course of the treatment journey, and the increasing refractoriness which limits the ability to bridge patients to the CAR-T cell infusion, it is of critical importance to making these treatments available earlier in the treatment paradigm.

In this context, the KarMMa-3 study demonstrates in this earlier line, highly refractory, high-risk, myeloma population a statistically significant and clinically meaningful improvement in PFS and ORR, with consistent benefit across all subgroups including patients with high-risk factors. Ide-cel showed evidence of improvement in quality of life in the context of a long treatment-free interval. The estimated 51% reduction in the risk of progression or death with median PFS benefit of 13.3 months in the ide-cel arm vs 4.4 months in the standard regimens arm is clinically meaningful in this high unmet medical need population. The largest PFS benefit was seen in patients after 2 lines of therapy (15.1 months) vs after 3 or 4 prior lines of therapy (12.5 months, 11.2 months, respectively) which supports the importance of earlier use of ide-cel to allow patients to derive the greatest benefit from ide-cel treatment with the longest treatment-free interval.

The interpretability of the OS results is confounded by cross-over. Multiple analyses correcting for cross-over resulted in consistent trend of OS benefit in favor of ide-cel. While random variability cannot be excluded, an imbalance in early death events was observed in patients with multiple high-risk features who could not be adequately bridged to ide-cel. The protocol-restricted bridging therapy for patients in the ide-cel arm led to a prolonged time without anti-MM disease control and indicate that optimal disease control during ide-cel manufacturing is critical in this high-risk, highly refractory TCE population and requires effective bridging therapy appropriately tailored to the patients' prior treatment history and disease characteristics. Physicians should be cognizant when making therapeutic decisions that high-risk factors and indicators of fast disease kinetics may impact the ability of those patients to receive ide-cel treatment. Therefore, selection of patients best suited for ide-cel treatment as well as selection of the optimal, individualized bridging therapy approach based on patients' comorbidities and treatment history should be ultimately based on treating physician's clinical judgement. In this context, it is important to note that the dropout rate from leukapheresis to ide-cel infusion was greatest in patients who had 4 prior lines of therapy (2L: 5.3%, 3L: 10.5%, 4L: 12.7%) and the number of patients with triple class refractory disease increased with more prior lines of therapy in KarMMa-3 (refractoriness after 2, 3, or 4 prior lines, 50.4%, 61.1%, or 84.8%, respectively). This further underscores the use of ide-cel earlier in the treatment course to ensure effective bridging can be applied and patients are able to receive and benefit from ide-cel therapy.

The safety profile of ide-cel remained consistent with the safety profile from the approved indication.

Taken together, these data substantiate the value of ide-cel as an effective and safe treatment option, a favorable benefit/risk profile, in patients with TCE RRMM, a population with high unmet medical.

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APPENDIX 1 KARMMA-3 STUDY STATISTICAL CONSIDERATIONS

The sample size calculations were based on the assumption that the overall PFS distribution is exponential with a constant failure (hazard) rate. With 2:1 (ide-cel arm: standard regimens arm) randomization, two interim analyses, one for futility at approximately 33% information fraction and one for superiority at approximately 80% information fraction, a total of approximately 289 PFS events would be required for the final PFS analysis to provide 94% overall power to detect a hazard ratio of 0.643 using a one-sided log rank test with an overall significance level of 0.025. A group sequential procedure with an alpha-spending function of the O'Brien-Fleming type was used to control the Type I error rate. The planned sample size of 381 subjects also would provide at least 90% power for detecting a difference in ORR by assuming that ORR would be approximately 68% in ide-cel arm and 50% in standard regimens arm. A total of 222 OS events were planned with approximately 50% OS power at one-sided significance level of 0.025, based on the assumption of an improvement of median OS from 20 months in standard regimens arm to 27 months in ide-cel arm, corresponding to a target OS hazard ratio of 0.74.

Efficacy Analyses

All primary efficacy analyses were conducted using ITT population, defined as all subjects who are randomized to one of the two treatment arms. The primary analysis for the study was to compare PFS between ide-cel arm and standard regimens arm. An improvement in median PFS from 9 months for standard regimens arm to 14 months for ide-cel arm was considered clinically relevant.

The primary endpoint PFS and key secondary endpoints ORR and OS were to be tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate. The O'Brien-Fleming boundary alpha spending function was used to adjust multiplicity for the second PFS interim analysis. The null hypotheses were to be rejected if the p-value associated to the test was smaller than or equal to 0.014 based on the actual information fraction (84%, 242 out of 289 planned events) at the time of the second PFS interim analysis.

To select the best response, the following order of response was used: stringent CR > CR > VGPR > PR > MR > SD > PD > no evaluation after baseline. CMH test stratified by stratification factors was used to compare ORR (assessed by both IRC and investigator(s)); the percentage together with 95% CIs are provided. The OS was to be analyzed using the same method as that for PFS (see above), as well as median OS and the corresponding 2-sided 95% CI, survival rate at specific time points and K-M survival curve.

OS Sensitivity Analyses Accounting for Cross-over

For OS results in subjects randomized to standard regimens arm who received ide-cel after disease progression, the following analyses were to be performed as sensitivity analyses: a 2-stage Weibull approach, also called 2-stage accelerated failure time model[63,64] and rank preserving structural failure time (RPSFT) method.[65] In addition, 1 post-hoc analysis using the inverse probability of censoring weighting (IPCW) method[66,67,68] (at the request of the European Union (EU) Committee

for Medicinal Products for Human Use [CHMP]) have been employed to estimate the OS treatment effect that would have been observed had cross-over not occurred.

- **RPSFT Model**

In the RPSFT model, survival times of patients in the standard regimens Arm who crossed over were adjusted multiplicatively by an acceleration factor e^{ψ_0} as:

$$U_i = T_{B_i} + e^{\psi_0} T_{A_i},$$

where U_i is the counterfactual survival time (that would have been observed had treatment switching not occurred) for patient i in the standard regimens Arm, T_{B_i} is the survival time when patient is on standard regimens treatment, e^{ψ_0} is the multiplicative acceleration factor associated with the active treatment, and T_{A_i} is the event time when the patient is on the active treatment (ide-cel). The acceleration factor e^{ψ_0} was estimated by G-estimation. Survival times of all patients randomly assigned to the standard regimens Arm were then re-censored to maintain the assumption of noninformative censoring.

Observed survival times in the ide-cel Arm were compared with adjusted survival times in the standard regimens Arm using a stratified Cox proportional hazards model. The bootstrap method was used to estimate the 95% CIs of ψ_0 and HR.

The RPSFT model is based on the common treatment assumption that the treatment effect of active treatment (ie, ide-cel) is the same for all individuals, regardless of when treatment is received.

- **Two-stage Model**

In stage 1 of the 2-stage model, a Weibull model was developed to estimate the effect of treatment switching (ie, cross-over) by comparing subjects in the standard regimens Arm who switched and those who did not. It accounts for baseline prognostic factors (age, number of prior antimyeloma regimens, cytogenetic risk, triple refractory status, tumor burden, and extramedullary disease status), treatment switch indicator as a time-varying covariate, and parameters (ECOG status, LDH value) at secondary baseline (ie, at the time of disease progression). The estimated treatment effect due to switching was then used to adjust survival times in patients who crossed over to receive ide-cel. To maintain the assumption of noninformative censoring, survival times for patients in the standard regimens Arm were re-censored.

In the second stage, observed survival times in the ide-cel Arm were compared with adjusted survival times in the control arm and analyzed with a stratified proportional hazards model. The bootstrap method was used to estimate the 95% CIs of the multiplicative acceleration factor and treatment effect HR.

The 2-stage model assumes that there are no unmeasured confounders, that is, the covariates included in the model capture reasons for treatment switching that are also linked to survival.

- **Inverse Probability of Censoring Weighting (IPCW) Method**

The IPCW method first censors cross-over patients in the standard regimens arm at the time of their treatment switch, then re-weights all subjects in the standard regimens arm by the inverse probability of not switching. The time-varying weights were calculated according to subject's

baseline (including age, number of prior antimyeloma regimens, cytogenetic risk, triple refractory status, tumor burden, and extramedullary disease status) and time-dependent disease characteristics (including ECOG score, LDH value [with log transformation], and Investigator assessed disease progression status). These were then used in a weighted stratified cox proportional hazard model to estimate the OS HR, with the 95% CI estimated by bootstrap method.

The IPCW method assumes that there are no unmeasured confounders, that is, all factors that influence both switch and survival are included in the model.

Safety Analyses

Safety summaries were provided for the KarMMa-3 from the Treated population and the Safety population, as appropriate, unless otherwise specified. Treated population is defines as all subjects in the ITT population who underwent leukapheresis, bringing therapy, lymphodepleting chemotherapy or ide-cel infusion in Ide-cel Arm, and those who receive any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dex in standard regimens arm and Safety population is defined all subjects in the Treated Population who received any study treatment, including ide-cel infusion for ide-cel arm and any dose of DARA, POM, LEN, BTZ, IXA, CFZ, ELO, or dex for standard regimens arm.

AEs were coded according to MedDRA version 24.1. Descriptive statistics of safety were presented using NCI-CTCAE v4.03 by treatment arm.

Patient-Reported Outcomes Analyses

The key pre-specified PRO domains of interest were EORTC QLQ-C30 Fatigue, Pain, Physical Functioning, Cognitive Functioning, and Global Health/QoL subscales, and the EORTC QLQ-MY20 symptom subscales (Disease Symptoms and Side Effects).

As the power for the study was calculated based on the primary endpoint, all PRO analyses should be interpreted as descriptive. Missing values were addressed according to questionnaire guidelines.

Key analyses included:

- Data completion (fixed denominator) and compliance rates (variable denominator)
- Group descriptive analyses and mean changes from baseline (within-group clinically meaningful change thresholds were prespecified in the SAP)
- Responder analysis including proportion of patients with clinically meaningful change based on pre-defined thresholds (categorized into improved, no change, and worsened)
- Constrained longitudinal data analysis
- Time to confirmed improvement and deterioration

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