25 January 2024
EMA/64311/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abecma

International non-proprietary name: Idecabtagene vicleucel

Procedure No. EMEA/H/C/004662/II/0031

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Abbreviation	Definition
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AMT	antimyeloma therapy(ies)
Ang	angiopoietin
ASCT	autologous stem cell transplant
BCMA	B-cell maturation antigen
BLA	Biologics License Application
BMS	Bristol Myers Squibb
BTZ	bortezomib
C1	Cohort 1
CAR	chimeric antigen receptor
CFZ	carfilzomib
CI	confidence interval
Cmax	maximum observed concentration
CMC	Chemistry, Manufacturing, and Controls
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
Cy	cyclophosphamide
DARA	daratumumab
DBL	database lock
d/c	discontinued
ddPCR	droplet digital polymerase chain reaction
dex	dexamethasone
DKd	daratumumab, carfilzomib, and low dose dexamethasone
DoR	duration of response
DPd	daratumumab, pomalidomide, and low dose dexamethasone
DSMB	Data Safety Monitoring Board
DVd	daratumumab, bortezomib, and low dose dexamethasone
ECD	extracellular domain
EE	Efficacy evaluable
EFS	event free survival
ELO	elotuzumab
EMP	extramedullary plasmacytoma
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer-quality of life questionnaire-core 30 items
EORTC QLQ-MY20	EORTC quality of life questionnaire-multiple myeloma module 20 items
EOT	end of treatment
EPd	elotuzumab, pomalidomide, and low dose dexamethasone
EQ-5D-5L	European quality of life-5 dimensions health state classifier to 5 levels
E-R	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
Flu	fludarabine
GH	global health
HDAC	histone deacetylase
HR	hazard ratio
HRQoL	Health-related Quality of Life
IA	interim analysis
ICH	International Council for Harmonisation
ide-cel	idecabtagene vicleucel (also known as bb2121 or Abecma®)
IHC	immunohistochemistry
IL	interleukin
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IND	Investigational New Drug
iiNT	investigator identified neurotoxicity
IRC	Independent Response Committee
IRd	ixazomib, lenalidomide, and dexamethasone
IRT	Interactive Response Technology
ISA	isatuximab

Abbreviation	Definition
ITT	intent to treat
IV	intravenous
IXA	ixazomib
Kd	carfilzomib and dexamethasone
K-M	Kaplan-Meier
LD	lymphodepleting
LEN	lenalidomide
LLOQ	a. lower limit of quantification
LPLV	last patient last visit
LTFU	long-term follow-up
LVV	lentiviral vector
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MAS	b. macrophage activation syndrome
Max	maximum
MedDRA	c. Medical Dictionary for Regulatory Activities
Min	minimum
MM	multiple myeloma
mo	month
mPFS	median progression free survival
MRD	minimal residual disease
NA	not applicable
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NDMM	newly diagnosed multiple myeloma
NGS	next generation sequencing
NT	neurotoxicity
ORR	overall response rate
OS	overall survival
PD	pharmacodynamics or progressive disease
PFS	progression-free survival
PFS2	progression-free survival after next line of therapy
PI	proteasome inhibitor
PK	pharmacokinetics
POM	pomalidomide
PR	partial response
d. PRIME	e. PRIority MEdicines
PRO	patient reported outcomes
PT	preferred term
QoL	quality of life
qPCR	quantitative Polymerase Chain Reaction
f. RP2D	recommended Phase 2 dose
RRMM	relapsed and refractory multiple myeloma
SAE	serious adverse event
SAP	Statistical Analysis Plan
sBMCA	soluble B-cell maturation antigen
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
sCR	stringent complete response
sCRS	CRS (cytokine release syndrome) requiring steroid
SCS	Summary of Clinical Safety
SE	standard error
SLAMF-7	signaling lymphocytic activation molecule F7
SMQ	Standardized MedDRA Query
SmPC	Summary of Product Characteristics
SOC	system organ class
SPM	second primary malignancy
TCE	triple class exposed
tCRS	CRS (cytokine release syndrome) requiring tocilizumab
Tmax	maximum observed concentration
TNF	tumor necrosis factor
TTP	time to progression
TTR	time to response
Tx	treatment
UK	United Kingdom
US	United States
VAS	visual analog scale
VGPR	very good partial response

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 6 March 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD-38 antibody and have demonstrated disease progression on the last therapy for Abecma (idecabtagene vicleucel, ide-cel), based on results from study BB2121-MM-003 (MM-003, KarMMa-3). This is a Phase 3, multicentre, randomised, open-label study to compare the efficacy and safety of ide-cel versus standard regimens in subjects with RRMM. As a consequence, sections 2.1, 2.2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3, 6.4 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 3.0 of the RMP has also been submitted. Furthermore, the PI is brought in line with the Guideline on core SmPC, Labelling and Package Leaflet for advanced therapy medicinal products (ATMPs) containing genetically modified cells.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Abecma, was designated as an orphan medicinal product EU/3/17/1863 on 20 April 2017. Abecma was designated as an orphan medicinal product in the following indication: Treatment of multiple myeloma.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0068/2021 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH did not seek Protocol Assistance from the CAT/CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CAT were:

Rapporteur: Rune Kjeken Co-Rapporteur: Heli Suila

Timetable	Actual dates
Submission date	6 March 2023
Start of procedure	25 March 2023
CAT Rapporteur's preliminary assessment report circulated on	17 May 2023
PRAC Rapporteur's preliminary assessment report circulated on	24 May 2023
CAT Co- Rapporteur's preliminary assessment report circulated on	1 June 2023
Updated PRAC Rapporteur's assessment report circulated on	2 June 2023
PRAC RMP advice and assessment overview adopted by PRAC on	8 June 2023
Updated CAT Rapporteur(s) (joint) assessment report circulated on	12 June 2023
Request for supplementary information adopted by the CAT on	16 June 2023
MAH's responses submitted to the CAT on	31 August 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	25 September 2023
CAT Rapporteur(s) preliminary joint assessment report on the MAH's responses circulated on	9 October 2023
PRAC RMP advice and assessment overview adopted by PRAC on	26 October 2023
Updated CAT Rapporteur(s) joint assessment report on the MAH's responses circulated on	27 October 2023
2nd request for supplementary information adopted by the CAT on	31 October 2023
MAH's responses submitted to the CAT on	20 November 2023
CAT Rapporteur(s) preliminary joint assessment report on the MAH's responses circulated on	21 December 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	3 January 2024
SAG Oncology experts meeting to address questions raised by the CAT	9 January 2024
PRAC RMP advice and assessment overview adopted by PRAC on	11 January 2024
Updated CAT Rapporteur(s) joint assessment report on the MAH's responses circulated on	16 January 2024

Timetable	Actual dates
CAT Opinion adopted on	19 January 2024
CHMP Opinion adopted on	25 January 2024
The CAT/CHMP adopted a report on similarity of Abecma with Farydak, Kyprolis, Darzalex, Ninlaro, Blenrep, Carvykti and Talvey on date	19/25 January 2024
The CAT/CHMP adopted a report on the novelty of the indication/significant clinical benefit for Abecma in comparison with existing therapies	19/25 January 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The present variation application concerns treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Claimed therapeutic indication

The initial proposed indication for Abecma extension of indication was:

Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Epidemiology and risk factors, screening tools/prevention

Multiple myeloma (MM) accounts for about 10% to 18% of hematologic malignancies (Moreau, 2017). In Europe, MM accounts for 1%-1.8% of all cancers and is the second most common haematological malignancy (after non-Hodgkin's lymphoma [NHL]) with an estimated incidence of 4.5-6.0/100,000/year (Dimopoulos, 2021). The mortality is 4.1/100,000/year. In Europe, the median age at onset of MM is 72 years (Moreau, 2017). MM primarily affects older individuals and is very rare in patients younger than 40 years old (Howlader, 2019). The course of MM is characterized by a period of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapy (Moreau, 2017).

Biologic features, aetiology and pathogenesis

Multiple myeloma is a malignant B-cell neoplasm, characterised by the clonal proliferation of malignant plasma cells both within the bone marrow (BM) and at localized extramedullary sites termed plasmacytomas, which remains mainly incurable. Plasma cells in MM patients typically secrete high levels

of monoclonal immunoglobulins (IgG, IgA, IgD or IgE, termed "M protein") or Bence-Jones protein (monoclonal K or h light chains), while the production of normal immunoglobulin is impaired. The cause of a myeloma cell's failure to differentiate is unknown.

MM has a heterogeneous progression pathway, with multiple relapses over time, whereby several MM cell subclones coexist at baseline and compete for dominance over time, leading to the evolution of drug-resistance clones (Laubach, 2014). Drug resistance to prior regimens in patients with relapsed/refractory (RR) MM is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time (Anderson, 2008). B-cell maturation antigen (BCMA) was selected as a therapeutic target, because BCMA is consistently expressed on plasma cells and myeloma cells from patients with MM, where the expression of BCMA is thought to support tumour cell survival in the BM niche (Carpenter, 2013). Normal, nonhematopoietic tissues do not express BCMA (Carpenter, 2013). In contrast, benign and malignant plasma cells contain high levels of BCMA messenger ribonucleic acid, and concentrations of soluble BCMA (sBCMA) within serum correlate with disease status (i.e., disease burden), response to therapy, and overall survival (OS) (Sanchez, 2012).

Clinical presentation, diagnosis and prognosis

In MM, the malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein (M-protein) in the serum and urine and may result in BM failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures (Munshi, 2012).

The criteria for diagnosis of MM, as defined by the International Myeloma Working Group (IMWG), requires the presence of one or more myeloma defining events (MDE) in addition to evidence of either 10% or more clonal plasma cells on BM examination or a biopsy-proven bony or extra-medullary plasmacytoma. MDE consists of established CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) features as well as 3 specific biomarkers: clonal BM plasma cells $\geqslant$60%, serum free light chain (FLC) ratio $\geqslant$100 (provided involved FLC level is $\geqslant$100 mg/L), and more than one focal lesion on MRI.

The Revised International Staging System (R-ISS) is a widely accepted classification used for prognostic evaluation. It combines elements of tumour burden (ISS) and disease biology (presence of high-risk cytogenetic abnormalities or elevated lactate dehydrogenase level).

Despite progress in its current treatment landscape and management, MM remains incurable. Although autologous stem cell transplant (ASCT) has extended survival in newly diagnosed MM, practically all patients eventually relapse, and the remission duration in relapsed MM decreases with each regimen. In a study based on data collected from existing medical records from multiple centres, patients with relapsed MM, who had received at least three prior lines of therapy, were refractory to both an immunomodulatory agent (IMiD; lenalidomide or pomalidomide) and a proteasome inhibitor (PI; bortezomib or carfilzomib), and had been exposed to an alkylating agent, the median OS was reported to be 13.0 months and median PFS was 5.0 months (Kumar, 2017). In relapsed disease, refractoriness to several drug classes represents a major therapeutic challenge. The aim of the treatment is to achieve deep and durable responses that extend patient survival and afford the opportunity for treatment-free intervals and improved quality of life.

Management

The treatment algorithm for MM is evolving rapidly and the therapeutic field for the management of the condition is continually changing. Current treatment includes glucocorticoids, chemotherapy, primarily alkylating agents, high-dose chemotherapy followed by ASCT, PIs (bortezomib, carfilzomib and ixazomib), IMiDs (thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs; daratumumab, isatuximab and elotuzumab), histone deacetylase inhibitors (panobinostat), XPO1 inhibitors (selinexor), and several therapies targeting BCMA such as the antibody drug conjugate belantamab mafodotin, CAR-T cell products (ide-cel and ciltacabtagene autoleucel [cilta-cel]), and the recently approved bispecifc antibodies: teclistamab targeting the CD3 receptor expressed on the surface of T-cells and BCMA on myeloma cell and talquetamab targeting CD3 expressed on the surface of T-cells and GPRC5D expressed on myeloma cells.

Many factors influence the choice of therapy in the RRMM setting, including age; performance status; comorbidities; type, efficacy, and tolerability of the prior AMT; the number of prior treatment lines; the available remaining treatment options; the interval since the last therapy; and the type of relapse (clinical versus biochemical) (Moreau, 2017).

For RRMM patients with second or subsequent relapses, European Hematology Association (EHA) and European Society for Medical Oncology (ESMO) clinical practice guidelines recommended options are triplet regimens, however, no single treatment algorithm exist, and the choice of treatment regimen depends on prior drug exposure and responsiveness/refractoriness (Dimopoulos, Ann Oncol. 2021; 32(3): 309-322). As most patients receive frontline therapy with a backbone of an IMiD and/or a PI, the development of disease that is refractory to both of these classes represents a major therapeutic challenge. Given the increasing use of anti-CD38 antibody containing regimens in frontline and early line relapse, therapeutic options in patients previously exposed to these 3 anti-myeloma therapies (AMT) classes consist largely of between or within class switch regimens. RRMM patients, particularly those exposed to multiple prior AMTs, those exposed to an anti-CD38 antibody, or those refractory to major classes of AMT, has low response rates to conventional therapies, short duration of response (DoR), and poor survival. Thus, an unmet medical need exists for more treatment options capable of achieving deep and durable responses with the opportunity for treatment-free intervals and improved quality of life (QoL) for patients with RRMM who have received at least 2 prior therapies, including an IMiD, a PI, and an anti-CD38 antibody.

2.1.2. About the product

Abecma (idecabtagene vicleucel; ide-cel; product code bb2121) consists of T cells transduced with an anti-BCMA02 chimeric antigen receptor (CAR) lentiviral vector (LVV). Autologous T cells transduced *ex vivo* with the anti-BCMA02 CAR LVV express the anti-BCMA CAR on the T cell surface. The CAR is comprised of a murine extracellular single-chain variable fragment specific for recognising BCMA followed by a human CD8α hinge and transmembrane domain fused to the T cell cytoplasmic signalling domains of CD137 (4-1BB) and CD3ζ chain, in tandem. Binding of ide-cel to BCMA-expressing target cells leads to signalling initiated by CD3ζ and 4-1BB domains, and subsequent CAR+ T cell activation. Antigen-specific activation of ide-cel results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Abecma was originally granted a conditional marketing authorisation in the EU/EEA via the centralised procedure (Procedure No. EMEA/H/C/004662) on 18-Aug-2021 and is currently indicated for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. The approved

target dose is 420 x 10^6 CAR-positive viable T cells within a range of 260 to 500 x 10^6 CAR-positive viable T cells.

2.1.3. The development programme/compliance with CHMP guidance

Abecma was granted Priority Medicines (PRIME) scheme eligibility (EMA/PRIME/17/062) by the CHMP and Committee for Advanced Therapies (CAT) on 10 Nov 2017.

Abecma was designated as an orphan medicinal product EU/3/17/1863 on 20 Apr 2017 in the following condition: treatment of multiple myeloma.

MM-003 is the confirmatory phase 3 study for the conditional marketing authorisation and was discussed as part of the PRIME kick-off meeting held on 14-Mar 2018. During this meeting, the Rapporteur suggested to include as comparator for this study a limited number of options instead of 1 regimen. The Rapporteur's comment was implemented, and the comparator arm included a choice of 5 standard regimens.

2.1.4. General comments on compliance with GCP

No concerns were raised about compliance with GCP, related regulatory or ethical requirements, and a request for a GCP inspection has not been adopted.

2.2. Quality aspects

2.2.1. Introduction

The supportive quality information submitted provides an overall summary to support idecabtagene vicleucel (ide-cel) finished product manufacturing for the BB2121-MM-003 trial.

The following updates were made to Module 2 and Module 3 to support the change:

Module 2:

- Summary of clinical and CMC for the finished product used to support clinical trial BB2121-MM-003.

Module 3:

- New section 3.2.S.3.1 to provide phenotypic and functional characterisation for MM-003 trial finished product lots.
- New section 3.2.S.3.1 to provide clinical correlative analysis for MM-003 trial.
- New section 3.2.P.5.4 to provide batch analysis for trial MM-003.
- New section 3.2.P.5.6 to provide the rationale and statistical analysis to justify 4L+ specification for the 3L+ patient population.

2.2.2. Lentiviral vector

Manufacturer – lentiviral vector

A list of anti-BCMA02 CAR LVV manufacturing, release and stability testing and storage facilities has been presented.

Manufacturing process - lentiviral vector

Plasmids are used to transfect the HEK293T cells to produce the LVV.

Control of raw materials - lentiviral vector

The compendial as well as non-compendial raw materials used in the production of anti-BCMA02 CAR LVV are listed.

Control of lentiviral vector

The release specifications for clinical anti-BCMA02 CAR LVV have been provided. The vector specifications were updated throughout the development lifecycle of the LVV as further understanding of the process and product was gained. Analytical procedures are described.
Analytical comparability assessments have been provided by retrospectively assessing all release attributes.

Stability Summary - lentiviral vector

Anti-BCMA02 CAR LVV lots were placed on stability at the intended long-term storage condition to evaluate chemical and physical stability over time. These studies were conducted as per the requirements of ICH Q1A(R2) and Q1E where data were gathered in real time and stability was assessed at designated time points.

Data gathered from the three stability studies were first overlaid on graphs for a direct comparison. Based on both statistical analysis and data visual representations it was concluded that the results were comparable with similar trends from long-term stability studies. This also demonstrated that the vectors remained stable in long-term storage conditions with similar degradation profiles.

2.2.3. Finished Product

Manufacturing Process and Controls – finished product

The ide-cel manufacturing process follows the same manufacturing controls as originally defined in the approved MAA.

Control of finished product

The specifications and test methods are the same for the clinical finished products. All quantitative release critical quality attributes (CQAs) were evaluated. Quality attributes of ide-cel finished product were assessed against pre-defined equivalence criteria.

Retrospective analysis of manufacturing data from the MM 003 clinical study

The retrospective assessment of patient finished product data was composed of ide-cel finished product lots manufactured to support the MM-003 study.

Data from quantitative finished product release attributes were shown. A summary of the data for each CQA was included.

Ide-cel dose is determined based on the total number of CAR-positive T cells, any shift in CAR-positive T cell percentage will be accounted for in the final dose that is provided to the patient. All patients received a dose within the specified range regardless of the CAR-positive T cell percentage of the finished product.

The MAH's conclusion

Although differences were observed, data from the normal healthy donor SDM as well as the clinical retrospective analysis suggests that the per CAR+ T cell effector functionality is preserved and there are high levels of similarity across finished products. Consistency in potency data as well as similarity in finished product CQAs and functional characterisation attributes between finished products supports that the mechanism of action is maintained. Clinical outcome and correlative analysis summarized overall support that minor differences in product quality observed in analytical comparability were not associated with differences on clinical efficacy or safety outcomes.

Stability summary - finished product

All stability attributes demonstrated that there are no significant changes in the stability indicating product quality attributes for up to 12 months when stored in the vapor phase of liquid nitrogen. All lots were manufactured using normal healthy donor (NHD) material and stored at the long-term stability condition (≤ -130ºC) in the approved finished product container closure system (CryoStore CS50 or CS250 cryopreservation bags).

2.2.4. Discussion and conclusions on quality aspects

Supportive quality information is submitted for the manufacture of idecabtagene vicleucel (ide-cel) finished product for the BB2121-MM-003 trial.

Clinical data associated with the MM-003 trial were reviewed in totality as the MAH considered differences in product quality to not be associated with differences on clinical efficacy or safety outcomes.

Supportive quality information has been provided in module 2. As only summary information is provided, assessment according to regulatory quality requirements has not been performed. Conclusions on comparability for neither the vector nor the finished product can therefore be made, but differences between the various processes are highlighted. Analytical methods remain essentially the same. The manufacturer for ide-cel finished product remains unchanged. The ide-cel manufacturing process is also the same.

A retrospective analysis of batch data from the MM-003 trial is also presented. All quantitative release critical quality attributes were assessed against pre-defined equivalence criteria. The MAH justifies the differences observed to be within the historical manufacturing experience and by similar associated effector functions. All patients received a dose within the specified range regardless of the CAR-positive T cell percentage of the finished product.

Long-term stability data for three batches manufactured from healthy donors are available up to 12 months (≤ -130ºC). The stability attributes indicate no significant changes in the stability indicating product attributes.

New sections are also provided in module 3. The phenotypic and functional characterisation for MM-003 finished product batches is acknowledged. A correlative analysis for the ide-cel finished product batches was performed to determine whether correlations exist between finished product quality attributes and clinical safety, efficacy, and pharmacokinetic parameters. Overall, the correlative analyses claim no impact to previously implemented product characterisation, which is noted.

The batch results from trial MM-003 are included as well as a new section to provide the rationale and statistical analysis to justify the 4L+ (three or more prior lines of therapies) specification for the 3L+ (two or more prior lines of therapies) patient population. The same approved commercial manufacturing process was used to produce finished products for all patients.

To conclude based on the supportive quality data provided, some differences for the anti-BCMA02 lentiviral vector are observed. The differences observed are overall as expected. Comparability on the ide-cel CAR-T product level has been studied, but limited information is provided and therefore a final conclusion on comparability cannot be reached. However, the manufacturing process is the same for ide-cel finished product and the differences observed in the retrospective analysis of batch data from the MM-003 trial do not seem to translate into differences in efficacy or safety for ide-cel CAR-T product.

As the efficacy and safety of the final ide-cel CAR-T product manufactured do not seem to have substantially affected the clinical outcome of the trial, it is considered acceptable to use the data to support this extension of indication application. No further questions are raised from a quality perspective. The remaining uncertainties regarding comparability need to be considered in the context of the overall benefit/risk decision.

The CHMP endorse the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

2.3. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CAT. The environmental risk of idecabtagene vicleucel is not affected by the proposed extension of indication.

The CHMP endorse the CAT conclusions on the non-clinical aspects as described above.

2.4. Clinical aspects

2.4.1. Introduction

The current submission regards the extension of indication to third- and later lines of RRMM therapy (i.e., "have received at least two prior therapies"), and concerns data from the pivotal Phase 3 Study BB2121-MM-003 (**MM-003**). Studies supporting the current application for an extension of the indication are summarised in the below table.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study/ Region	Design/ *Primary Objective*	Population	Treatment Groups	Study Status/ Number of Subjects	Data Cutoff Dates
Phase 3					
BB2121-MM-003 (Canada, EU, Japan, UK, US)	Multicenter, randomized, open-label study comparing the efficacy and safety of ide-cel vs standard regimens *Efficacy of ide-cel compared to standard regimens in subjects with RRMM as measured by PFS per IRC*	Subjects (≥ 18 years), with RRMM who had received 2-4 prior myeloma regimens including DARA, an IMiD, and a PI, with documented disease progression during or within 60 days after the last therapy	Arm A (Ide-cel): 150 to 450 × 10^6 CAR+ T cells[a] Arm B (Standard Regimens):[b] One of the following standard therapies: • DARA + POM + dex (DPd) • DARA + BTZ + dex (DVd) • IXA + LEN + dex (IRd) • CFZ + dex (Kd) • ELO + POM + dex (EPd)	Ongoing for follow-up (enrollment closed) **Planned**: 381 Ide-cel: 254 Standard Regimens: 127 **Randomized:** 386 Ide-cel: 254 Standard Regimens: 132 **Treated:** 376 Ide-cel: 250 Standard Regimens: 126 **Safety Population:** 351 Ide-cel: 225 Standard Regimens: 126	18-Apr-2022
Phase 2					
BB2121-MM-001 (Canada, EU, US)	Multicenter, open-label, single-arm study to evaluate the efficacy and safety of ide-cel *Efficacy of ide-cel in subjects with RRMM as measured by ORR per IRC*	Subjects (≥ 18 years) with RRMM who had received least 3 prior therapies, including: an IMiD, a PI, and an anti-CD38 antibody, and who were refractory to their last prior treatment regimen	150 to 450 × 10^6 CAR+ T cells[a]	Ongoing for follow-up (enrollment closed) Planned: 140 Enrolled: 140 Treated: 128	Efficacy: 14-Jan-2020 Safety: 07-Apr-2020
Phase 1					
CRB-401 (US)	Multicenter, open-label, single-arm, 2-part (dose escalation [Part A] and dose expansion [Part B]), study to evaluate the safety and efficacy of ide-cel *Part A: to determine the MTD of ide-cel in subjects with MM whose tumors expressed BCMA and to select a RP2D for future studies.* *Part B: to confirm the safety of the dose(s) chosen in Part A.*	Subjects (≥ 18 years) with: Part A: RRMM who had received at least 3 different prior lines of therapy, including a PI and IMiD or had double refractory disease (progression on or within 60 days of treatment) to a PI and IMiD Part B: RRMM who had previous exposure to a PI, IMiD, and DARA and were refractory (based on IMWG criteria) to their last line of therapy.	Part A (dose escalation) 50, 150, 450, or 800 × 10^6 CAR+ T cells[c] Part B (dose expansion) Target doses ranging from 150 to 450 × 10^6 CAR+ T cells/infusion	LPLV achieved Closeout CSR under development Part A: Enrolled: 24 / Treated: 21 Part B: Enrolled: 43 / Treated: 41	07-Apr-2020
Long-term Follow-up					
LTF-305 US (aligns with parent study CRB-401)	Multicenter, open-label, non-randomized, long-term safety and efficacy follow-up	Subjects with MM who were treated with ide-cel in Study CRB-401	No treatment administered	Enrollment completed Study closed Enrolled: 20	Safety: 22- Jul-2019
GC-LTFU-001 (Canada, EU, Japan, UK, US; aligns with corresponding parent study)	Multicenter, open-label, non-randomized, long-term safety and efficacy follow-up	Subjects previously treated with gene- modified T cells in Sponsor's studies	No treatment administered	Ongoing Enrolled: 46	Aligns with parent study

a The current clinical dose range for Studies MM-001, and MM-003 is 150 to 540 x 10^6 CAR+ T cells; dose exceeding 20% of the upper limit constituted overdose.

b The choice of study treatment is dependent on the subject's most recent antimyeloma treatment regimen (Section 3.1 of MM-003 Protocol).[25]

c In CRB-401, only patients in the 150 to 450 × 10^6 CAR+ T cells dose range were included.

Source: MM-003 Primary CSR,[24] SCE,[26] SCS.[27]

2.4.2. Pharmacokinetics

Introduction

The clinical pharmacology profile of ide-cel in subjects with RRMM had been previously characterised, during the initial marketing authorisation procedure, based on the results of pivotal Phase 2 study MM-001 (at the target dose levels of 150-450 × 10^6 CAR+ T cells) and supportive Phase 1 Study CRB-401. The current submission concerns data from the pivotal Phase 3 Study MM-003 (see Table below), including pharmacokinetics (PK) and exposure-response (ER) analysis, dose response regression analysis, and PD analysis.

Table 1. BMS-Sponsored MM-003 Study Supporting the Clinical Pharmacology for the Proposed RRMM Indication

Study Design/ Primary Objective	No. Planned Subjects (N)	Population	Dose / Schedule	No. of Ide-cel Treated (N)/ No. included in Analysis	Design of the Clinical Pharmacology Related Components	Supports
Pivotal Study MM-003						
Phase 3, multicenter, randomized (2:1), open-label study ide-cel vs standard regimens *PFS*	Ide-cel: 254 Standard regimens: 127	RRMM with 2-4 prior anti-myeloma regimens, including an IMiD, a PI, and daratumumab	Ide-cel: 150 to 450 x 10^6 CAR+ T cells/ IV infusion after LD chemo (3 consecutive days of fludarabine 30mg/m^2 and cyclophosphamide 300 mg/m^2 IV) Standard regimens dependent on the subject's most recent anti-myeloma treatment regimen (DPd, DVd, IRd, Kd or EPd)	225 in the ide-cel arm / 220 included in the PK characterization and E-R analysis; 225 included in the dose-response and IMG analyses	PK and E-R: whole blood ddPCR transgene data IMG: Serum ADA	Efficacy, safety, PK, E-R, IMG, pharmacodynamics,

Bioanalytics

Cellular kinetics

A *pan gag ddPCR assay* to quantify CAR T vector copy number (VCN) in human whole blood was validated to support MM-003. The results are reported as gag copies per µg of genomic DNA, which is determined based on the number of copies of RPPH1. The ddPCR assay is sensitive, selective, reproducible and met the pre-specified acceptance criteria. The ddPCR assay was applied to all MM-003 subjects qualified for PK evaluation (N=284, including 225 in the idecabtagene vicleucel arm).

A validated *qPCR assay* was also used to quantitate gene expression (MM-003, N =133, including 126 in the idecabtagene vicleucel arm).

PK parameters were not pooled due to the different primary PK assays used *i.e.* qPCR (CD3+ sorted cells, MM-001) and ddPCR (whole blood, MM-003).

Antidrug antibody

Formation of anti-CAR antibodies (ADA to the ECD of the CAR, which binds to BCMA) in serum has been evaluated in study MM-003 using a multi-tiered approach including a screening assay, a confirmatory assay, and a titer assay. The validated ECL immunoassay was the same as the assay used in studies MM-001 and CRB-401.

Table 2. Bioanalytical study reports assessed in the MAA procedure

Method	Validation report	Studies	Within study validation
Cellular kinetics			
qPCR (BIOMMG 09) Real-Time PCR Detection and Quantification of Lentiviral Psi-Gag	RLZV2	MM-001 CRB-401	RJBR – Legacy CSR; RJBR 2; RFCZ; RGQG2 (long term follow-up of subjects treated with bb2121)
ADA			
ECL immunoassay	BB2121-DMPK-2634	MM-001 CRB-401	BB2121-MM-001-ADA-interim-legacy CSR; MM-001-ADA-Interim-3; CRB-401-ADA-interim-Legacy CSR
Cellular immunogenicity			
ELISPOT	BB2121-DMPK-2671	MM-001	BB2121-MM-BA1-Legacy CSR

ADA = antidrug antibody; ECL = electrochemiluminescence; ELISPOT = interferon (IFN) gamma enzyme-linked immunosorbent; qPCR = real-time quantitative polymerase chain reaction.

Pharmacokinetic data analysis

Analysis datasets were created using SAS version 9.4 (SAS Institute Inc., North Carolina). The PK parameters of ide-cel were evaluated using the time course ddPCR-quantified CAR transgene copy numbers through NCA methods, using the software program Phoenix WinNonlin 8.1 (Certara, Princeton, USA). Individual exposure parameters were calculated as a basis for a covariate evaluation and dose-exposure and E-R analyses. PK characterisation, ER evaluations and simulations were performed in R version 4.0.3.

The specific cell expansion (i.e. PK) parameters were Cmax (maximum transgene level occurring at Tmax), AUC0-28D (AUC of the transgene level from the time of dosing to 28 days, and Cmax/Tmax (T cell expansion rate). Primary exposure metric was AUC0-28D (linked to efficacy event), while Cmax/Tmax was assumed to correlate with onset and severity of cytokine release syndrome (CRS), and was used for ER safety analysis.

In arm A of study MM-003 (investigational treatment) blood samples for PK and ADA analysis were collected as detailed in the Table below. The PK evaluable population was defined as subjects who received ide-cel infusion and had detectable transgene levels (i.e. at least one measurable timepoint post-infusion).

Table 3. Selected parts of the table of events for treatment arm A

	Screening Period			Treatment Period		PFS Follow-up Period (28-day month)								Follow-up Period	
	Screening	Leukapheresis[a]	Baseline[b]	LD Chemotherapy[c]	bb2121 infusion[d]	M1			M2-M6	M7-M12	M13-M24	≥ M25 every 3 months	PFS discon[e] ≤7 days from PD or discon decision	28 days after PFS Discon	SFU every 3 months
	-28 to randomization			D-5 D-4 D-3	D1	D2-8	D9-15	D18 D22 D25	D1	D1	D1	D1		+3	±14
Visit Window (Days)					+7			±1	±2	±3	±3	±3			
Peripheral blood sample for immunogenicity to bb2121 (PBMC)	-	X[aa]	-	-	-	-	-	-	M2, M3, M4	-	-	-	X	-	-
Peripheral blood for PK[cc]	-	X[aa]	-	-	-	D3, D5 D8	D10 D12 D15	D18 D22	X	M7 M10	M13 M16 M19 M22	M25 then every 6 months	X	-	X[ff]

d. bb2121 infusion will be administered on Day 1 and subjects must be infused no more than 7 days from the planned infusion day. If bb2121 infusion cannot take place by Day 8, subjects must wait 4 weeks to receive a second LD chemotherapy prior to bb2121 infusion. Subjects that are enrolled and unable to receive bb2121 infusion will be followed for 28 days for safety from the last study procedure (leukapheresis, LD chemotherapy or bridging therapy). Tocilizumab must be available at the site prior to infusion of the subject.
aa. Assessments should be done at least ≤ 3 days prior to initiating leukapheresis
cc. Peripheral blood for CAR T PK will be collected as indicated for all subjects. If CAR T vector is detected in ≥ 1% of cells at any time point ≥12 months after last bb2121 infusion, the pattern for vector integration sites will be analysed.

Evaluation and Qualification of Models

Population pharmacokinetic modelling has not been conducted.

Dose-exposure was investigated assuming a linear relationship. Dose was treated as a continuous or a categorical variable (<300, 300-460, and >460-540 x 10^6 CAR-T cells).

The ER analyses of **MM-003** data were conducted to characterise relationships between individual exposure parameters and efficacy or safety response variables based on logistic regression or time-to-event multivariable models (Cox Proportional Hazard), with potential covariate effects on the ER relationship also assessed. A sigmoid Emax ER relationship was also evaluated to improve the characterisation of the ER relationships.

Dose-response analysis (ORR, safety endpoints) were investigated using logistic regression models. A linear CPH model was used to assess the relationship between actual dose and PFS.

Statistical methods

Covariate evaluation

Potential correlations between exposure parameters and the covariates of interest were assessed by graphical evaluation. A linear working base model was formed using covariates identified previously from **MM-001** analyses and additional prespecified covariates. For cellular kinetics these included baseline ferritin, body weight, baseline soluble BCMA, actual dose, type of LVV, number of prior lines.

Candidate/evaluated covariates were for example in the following categories:

- Baseline demographic factors (*e.g.* sex, age, body weight, BSA, BMI, race, ethnicity);

- Disease factors (*e.g.* number of prior MM regimens, last prior MM therapy, bridging therapy, extramedullary disease, ECOG performance status, prior STC, triple refractory, ISS system stage derived);
- Baseline/Pre-infusion variables (*e.g.* ferritin, bone marrow % plasma cells, soluble BCMA1, urine and serum monoclonal protein (m-protein); IL-6, IL.-15, TNF-α, free light chain, soluble CD137);
- Immunogenicity (post-infusion ADAs);
- Product attributes.

For assessment of categorical covariates, generally at least 10% of the subjects were to be present in each category. Ide-cel actual dose was treated as a continuous variable in all regression analyses; in addition, dose was also explored as a categorical variable with following dose categories: $<300\times10^6$, $300\text{-}460\times10^6$, or $>460\text{-}540\times10^6$ CAR+ T cells. Ide-cel actual dose was assessed as a predictor for PK characterisation.

The exposure parameter represented by AUC0-28D was normalised to a dose of 300×10^6 CAR+T cells for analysis of impact of covariates on cellular kinetics.

Exploratory graphical evaluation

A graphical evaluation preceded any modelling analyses. Prior to the covariate evaluations, several summaries of the (non-dose normalised) exposure parameters (Cmax, AUC0-28D, and Cmax/Tmax) were generated. Specifically, tabular and graphical summaries were made of the distributions of the exposure parameters by dosing categories. Other investigations included potential correlations between exposure metrics, tabulated descriptive statistics of exposure quartiles, potential correlations between exposure parameters and the covariates of interest (linear regression for continuous and box-plots for categorical/binary covariates).

An initial graphical evaluation was performed to identify potential ER relationships. For binary endpoints, stacked bar graphs were created which summarised the proportion of responders by exposure quartile for each of the three PK parameters (Cmax, AUC0-28D, and Cmax/Tmax). For time-to-event endpoints, Kaplan-Meier curves were constructed per exposure quartile for the PK parameters.

Statistical evaluation

For cellular kinetics and ER analysis, candidate covariates were tested individually by adding to the working base model. The statistically significant covariates identified from the univariable screening step (ΔBayesian Information Criterion, ΔBIC<0) and the preselected covariates were subjected to multivariable modelling step. For variables that were highly correlated (>0.8), selection was based on consideration of clinical relevance. Final model was developed by a backward deletion procedure until no more non-significant covariates were left in the model (Δ BIC>0) for use in subsequent simulations.

Target population

Cellular kinetics in study MM-003

At data cut-off 01.03.2022, 224 patients were randomised to the ide-cel arm (arm A), and 224 patients had post-infusion PK samples. Median follow up of patients in arm A was 18.7 months. The PK characterisation dataset (*i.e.* subjects who received ide-cel infusion and had evaluable exposure parameters) is given in the Table below. Median age and body weight were 63 years and 82.7 kg, respectively, and the majority of patients were males (63%) and Caucasians/whites (69%). See also section 5.5 for further details on baseline demographics. Mean (range) ide-cel dose administered was 441.8 (174.9-529.0) $x10^6$ CAR T cells.

Table 4. Number of subjects in analysis dataset per dose category (×10^6 CAR+ T cells) for each exposure parameter in MM-003

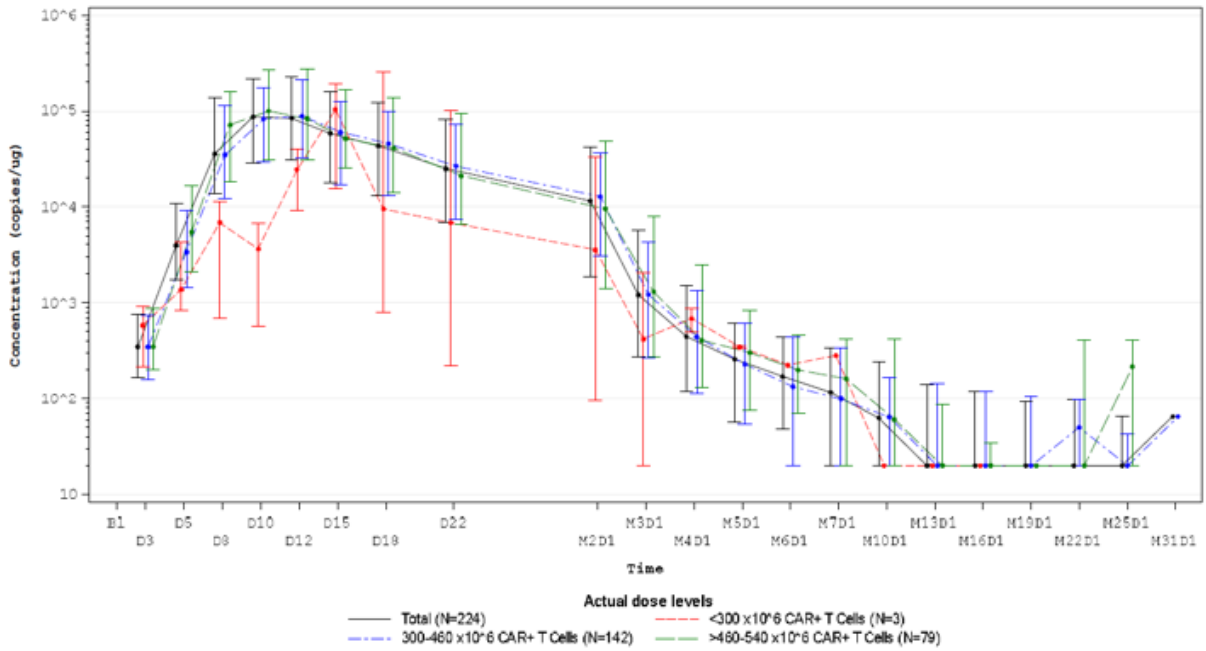
Parameter	Dose Category (×10^6 CAR+ T Cells)			
	<300	300-460	>460-540	Total
Cmax	3	139	78	220
AUC0-28D	3	137	78	218
Cmax/Tmax	3	139	78	220

Analysis-Directory: /global/pkms/data/CA/bb2121/mm-sbla/prd/ppk/final
Program Source: Analysis-Directory/sas/samples_ie.sas
Source: Analysis-Directory/reports/table3.3.1-2.rtf

Cellular kinetics

Following ide-cel infusion, the cells proliferated and underwent rapid multi-log expansion, with the maximum peak expansion occurring at a median of 11 days across the ide-cel actual doses (Figure below).

Figure 1. Median (Q1, Q3) concentration of idecabtagene vicleucel transgene (copies/µg) over time - whole blood matrix (idecabtagene vicleucel arm) – PK Analysis Population MM-003



There appeared to be lack of strong association between dose and exposure (represented by AUC0-28D). The inter-subject variability as measured by the geometric coefficient of variation was > 200% for most PK parameters, resulting in substantial overlap of ide-cel exposure across the actual dose levels.

Longer term exposures (see Tables below), AUC0-6M and AUC0-9M, also increased with increasing ide-cel dose. Comparing the extent of cell expansion over time, the geometric mean estimates of AUC0-6M and AUC0-9M were similar (within ~10%) to AUC0-3M. Furthermore, the extent of cell expansion during the first month post infusion (AUC0-28D) represents more than 80% of the cumulative exposure at 3 months (AUC0-3M) post infusion. Persistence data of ide-cel (measured as detectable transgene level by ddPCR) over time suggest that approximately 70% and 40% of PK evaluable subjects had measurable

ide-cel levels at 6 months (Visit of Month 7 Day 1) and 12 months (Visit of Month 13 Day 1) post infusion, respectively. These data demonstrate that ide-cel persists in peripheral blood up to 1-year post-infusion.

Table 5. Summary of ide-cel PK parameters - whole blood matrix (Ide-cel Arm) - PK Analysis Population - MM-003

	Treatment Ide-cel Arm by Actual Dose Levels			
Parameter Statistics	<300 x10^6 CAR+ T Cells (N=3)	300-460 x10^6 CAR+ T Cells (N=142)	>460-540 x10^6 CAR+ T Cells (N=79)	All Subjects (N=224)
Cmax (copies/ug)				
Geometric Mean [N]	21039.59 [3]	112557.30 [139]	129756.57 [78]	115700.97 [220]
(Geo%CV)	(5999.66)	(204.02)	(223.94)	(222.69)
AUC0-28D (copies*days/ug)				
Geometric Mean [N]	200793.01 [3]	1079609.47 [137]	1165951.07 [78]	1084348.85 [218]
(Geo%CV)	(2086.96)	(218.20)	(229.43)	(230.94)
AUC0-3M (copies*days/ug)				
Geometric Mean [N]	225584.71 [3]	1318013.24 [135]	1409567.80 [77]	1317250.75 [215]
(Geo%CV)	(2471.78)	(234.08)	(248.91)	(249.31)
AUC0-6M (copies*days/ug)				
Geometric Mean [N]	230405.11 [3]	1368055.29 [134]	1454981.01 [77]	1364221.69 [214]
(Geo%CV)	(2537.65)	(234.79)	(250.41)	(250.53)
AUC0-9M (copies*days/ug)				
Geometric Mean [N]	230889.37 [3]	1391741.76 [133]	1468728.44 [77]	1383641.31 [213]
(Geo%CV)	(2546.55)	(234.94)	(250.66)	(250.86)
Tmax (Days)				
Median [N]	11.00 [3]	11.00 [139]	9.000 [78]	11.00 [220]
(Min - Max)	(2.000 - 16.00)	(7.000 - 31.00)	(4.000 - 21.00)	(2.000 - 31.00)
Tlast (Days)				
Median [N]	111.00 [3]	168.00 [139]	167.50 [78]	168.00 [220]
(Min - Max)	(28.00 - 169.00)	(14.00 - 839.00)	(22.00 - 671.00)	(14.00 - 839.00)

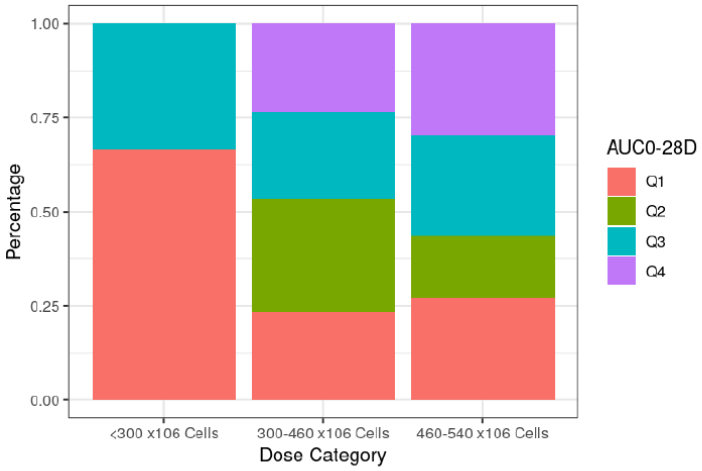
PK parameters are excluded from analysis if the following criteria are met: For AUC0-3M, if Tlast < 3 months and %AUC Extrapolation, pred > 35%; For AUC0-6M, if Tlast < 6 months and %AUC Extrapolation, pred > 35%; For AUC0-9M, if Tlast < 9 month and %AUC Extrapolation, pred > 35%.

Table 6. Persistence of ide-cel over time - whole-blood matrix (ide-cel arm) - PK Analysis Population - MM-003

Scheduled Visit (Post Infusion)	Total Number of Observations	Number of Observations with Measurable Values (%)	Number of Observations <LLOQ (%)
Month 2 Day 1	202	201 (99.5)	1 (0.5)
Month 3 Day 1	177	167 (94.4)	10 (5.6)
Month 4 Day 1	150	133 (88.7)	17 (11.3)
Month 5 Day 1	147	121 (82.3)	26 (17.7)
Month 6 Day 1	136	104 (76.5)	32 (23.5)
Month 7 Day 1	125	88 (70.4)	37 (29.6)
Month 10 Day 1	84	45 (53.6)	39 (46.4)
Month 13 Day 1	51	21 (41.2)	30 (58.8)

Source: Table 9.1-2 of the MM-003 Primary CSR

Figure 2. Distribution of AUC0-28D Quartiles by Dose Categories in MM-003



Analysis-Directory: /global/pkms/data/CA/bb2121/mm-sbla/prd/ppk/final/
Program Source: Analysis-Directory/R/scripts/MM003ARMA-PK.Rmd
Source: Analysis-Directory/R/plots/MM003ARMA-AUCquartile_by_DOSECAT.tiff;

Note: Q1-Q4 are the first (Q1), second (Q2), third (Q3) and fourth (Q4) quartiles of the AUC0-28D distribution.

Cellular kinetics in responders vs non-responders

The cell expansion was found to be higher in responders vs non-responders (Table below) and in patients with negative vs non-negative MRD status (not shown).

Table 7. Descriptive statistics of exposure parameters by ORR (≥ PR) - MM-003

Exposure	Median Exposures (N, %)		Ratio of Median Exposures of Responders vs Non-responders
	Responders	Non-responders	
Cmax (copies/µg)	163,546 (180, 81.8%)	30,337 (40, 18.2%)	5.39
AUC0-28D (days*copies/µg)	1,457,106 (180, 82.6%)	266,258 (38, 17.4%)	5.47
Cmax/Tmax (copies/µg/day)	16,510 (180, 81.8%)	2,730 (40, 18.2%)	6.05

Source: Table 5.2.1.1-1 of the PK characterization and E-R report[8]

Arm B patients receiving ide-cel

Patients in Arm B had the option to receive ide-cel upon confirmation of progressive disease (PD) by the IRC based on the IMWG criteria and confirmed eligibility. Peak exposures in the 57 patients from arm B receiving ide-cel (300-540x10^6 CAR T cells) were comparable to those observed for patients in arm A (**MM-003** CSR, Figure 14.2.7.1.3), however follow-up was much shorter (up to M4D1) and no further comparison has been made.

Covariate investigations

No association was found between the number of prior anti-MM therapies and cell expansion parameters.

Table 8. Effect of Covariates on Dose- Log AUC0-28D full model in MM-003

	Percentile Value	Change in Exposure Relative to Reference (%)	95% CI
Baseline Ferritin 5th Percentile (µg/L)	25.5	-8.144	-31.276 to 22.775
Baseline Ferritin 95th Percentile (µg/L)	1836.25	11.728	-23.499 to 63.175
Baseline Body Weight 5th Percentile (kg)	54.97	24.834	3.074 to 51.188
Baseline Body Weight 95th Percentile (kg)	115.845	-36.385	-56.954 to -5.986
Baseline Soluble BCMA 5th Percentile (ng/mL)	13.3	-31.967	-54.467 to 1.652
Baseline Soluble BCMA 95th Percentile (ng/mL)	487.4	21.69	-0.831 to 49.326
Baseline IL-15 5th Percentile (pg/mL)	14	-43.936	-60.617 to -20.19
Baseline IL-15 95th Percentile (pg/mL)	100.4	54.849	18.58 to 102.212
Formulation		-32.557	-54.394 to -0.263
No. of prior MM Regimens (3 vs 2)		-14.58	-43.461 to 29.053
No. of prior MM Regimens (4 vs 2)		-18.366	-47.124 to 26.033
Baseline Extramedullary Plasmacytoma (Yes vs No)		-39.567	-59.968 to -8.769
Post-infusion ADA Positive (Yes vs No)		58.747	10.29 to 128.494

Analysis-Directory: /global/pkms/data/CA/bb2121/mm-sbla/prd/ppk/final/
Program Source: Analysis-Directory/R/scripts/MM003ARMA-PK.Rmd
Source: Analysis-Directory/R/export/MM003ARMA-AUC_continuousCov_effects.csv; MM003ARMA-AUC_categoricalCov_effects.csv
Note: Reference value for baseline ferritin, soluble BCMA and IL-15 are their respective medians 163 (µg/L), 144.5(ng/mL) and 43 (pg/mL). Reference value for baseline body weight is 75 kg.

Special populations

Gender

Gender was not found to impact on cellular kinetics.

Race

The PK dataset (study **MM-003**) included primarily Caucasians/Whites (>69%), and 20% of patients were categorised as unknown.

Body weight

Body weight was estimated to be a significant covariate with a modest effect on exposure (AUC0-28D). Exposure was ~25% higher in low-weight (5th percentile) subjects, and ~36% lower in high-weight (95th percentile) subjects relative to the reference subject with body weight 75 kg.

Baseline soluble BCMA

Baseline sBCMA were identified as statistically significant covariate with a modest effect on exposure.

Elderly

Median (range) age at baseline was 63 (30-81) years. Age (continuous and binned by <65 years and ≥65) was not found to impact ide-cel pharmacokinetics in the covariate analyses.

Children

Ide-cel has not been investigated in children. A PIP waiver has been granted for treatment of mature B-cell neoplasms in the paediatric population from birth to 18 years of age.

Immunogenicity

In multivariable regression analyses the presence of post-infusion ADAs was associated with higher exposure. This positive covariate effect should be interpreted with caution, since it was potentially associated with higher likelihood of observing positive ADA status in responders who had both better cell expansion and longer follow-up period than non-responders.

Drug-drug Interactions

Of the 197 subjects who reported CRS signs or symptoms in the safety population (N=225), 161 (71.6%) subjects received tocilizumab, and 3 (1.3%) subjects received siltuximab. For management of iiNT, 15 (6.7%) subjects received steroids and no subjects received tocilizumab, anakinra, or siltuximab. Exposures by binary safety events have been tabulated, as shown below for AUC0-28D.

Table 1. Descriptive Statistics of AUC0-28D by Binary Safety Event in MM-003

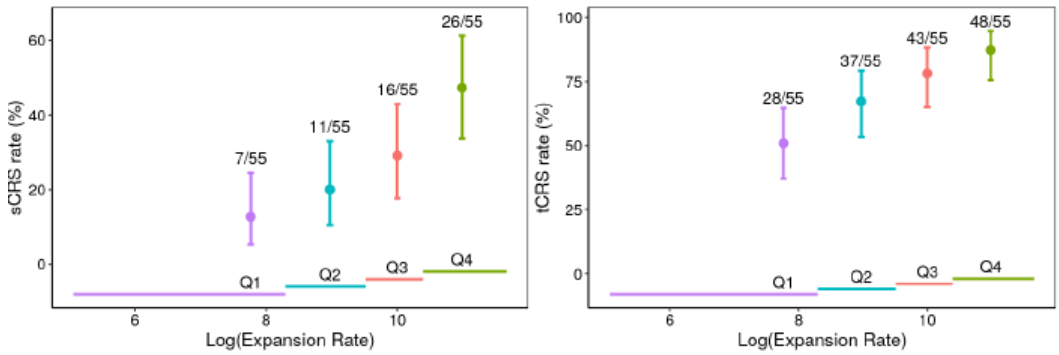
Endpoint	Subject Group	N	%	Median AUC0-28D (days*copies/µg)	Ratio of Median AUC0-28D of Subjects with AE vs. without AE
sCRS	0	158	72.48	950901.27	2.37
	1	60	27.52	2257369.54	
All-grade CRS	0	28	12.84	573398.71	2.40
	1	190	87.16	1375728.94	
CRS (Gr3+)	0	210	96.33	1246611.26	3.18
	1	8	3.67	3963815.68	
tCRS	0	63	28.90	525066.44	2.94
	1	155	71.10	1544466.68	
iiNT (Gr2+)	0	199	91.28	1253179.91	3.61
	1	19	8.72	4527389.98	
Cytopenia	0	101	46.33	786697.40	2.27
	1	117	53.67	1783136.91	

Analysis-Directory: /global/pkms/data/CA/bb2121/mm-sbla/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/MM003ARMA-ER-DR-Safety.Rmd
Source: Analysis-Directory/R/export/MM003ARMA-AUC_Safety_Summary_table.csv
Note: Subject group 0 and 1 indicate lack and presence of safety event respectively.

sCRS = CRS requiring corticosteroid treatment; tCRS = CRS requiring tocilizumab or siltuximab treatment.

ER safety was characterised (graphically and by multivariable regression) with respect to CRS requiring tocilizumab, siltuximab or corticosteroids.

Figure 3. Graphical evaluation of ER relationship for safety Events and log(Cmax/Tmax) - MM-003



sCRS = CRS requiring corticosteroid treatment; tCRS = CRS requiring tocilizumab or siltuximab treatment.
Note: Dots represent observed mean safety event rate with associated 95% CI for quartiles of log(Cmax/Tmax) displayed as error bar. Both are plotted at the median log(Cmax/Tmax) of each quartile (Q1-Q4). Horizontal lines represent log(Cmax/Tmax) ranges of each quartile. The numbers above the error bars (x/y) represent the number of subjects who achieved the response (x) and the total number of subjects (y) within each of the quartiles.

E-R regression modelling analyses for tCRS or sCRS suggested that the relationship between expansion rate (i.e., Cmax/Tmax) and tCRS or sCRS was well described by the linear logistic regression model. Following univariable screening and multivariable regression model development, only post-infusion ADA was identified a significant covariate (on tCRS only). Based on the model parameter estimates, no covariates appeared to influence the dose-tCRS or -sCRS relationship.

2.4.3. Pharmacodynamics

Pharmacodynamics

Pharmacodynamic (biomarker) investigations in study **MM-003** included immune-related soluble factors (27 soluble factors, focused on the CAR T cell mechanism), soluble BCMA (peripherally accessible biomarker of MM disease burden independent of the secreted monoclonal immunoglobulin subtype), tumour BCMA expression by IHC, and BCMA target antigen expression at disease progression. Limited data of the latter were available at data cut-off, and sBCMA was used as a surrogate measure of BCMA-expressing cells. Also, sBCMA was prospectively tested as a biomarker of response durability. A brief summary of the results of selected biomarker analyses (clinical data cutoff date of 18-Apr-2022) are summarised below.

Immune-related soluble factors (cytokines, chemokines, CRP, ferritin):

Univariate testing with multiplicity adjustment (adjusted p-value threshold of 0.05) across different soluble factors was performed (subjects in the ide-cel arm only). Potential relationships with dose (300-460 x 10^6 cells vs >460-540 x 10^6 CAR-T cells), number of prior anti-myeloma regimens, baseline disease characteristics, efficacy and safety end-points were explored.

- Immune-related soluble factors characteristic of T cell activation and proliferation were induced after ide-cel infusion; peak elevation was generally observed within one week and levels subsequently returned to baseline. Pre-infusion and Cmax concentrations did not differ across dose subgroups. Pre-infusion and Cmax concentrations were also similar across number of prior regimens subgroups with the exception that pre-infusion levels of C-Reactive Protein (CRP) were higher in subjects who had received 3 or 4 prior regimens vs 2.
- Pre-infusion concentrations of a subset of cytokines, potentially indicative of basal inflammation, were associated with high tumour burden or high-risk tumour features and suboptimal depth of clinical response. Higher peak concentrations of IL-15, a T-cell homeostatic cytokine, were observed in subjects who achieved CR/sCR vs < CR.

- On the day of ide-cel infusion, Ang-2 concentrations were positively associated with CRS grade; no other pre-infusion soluble factor levels were associated with incidence or grade of CRS. Substantially overlapping Ang-2 concentration ranges were observed across CRS grades and the prognostic value may be limited.
- On the day of infusion Ang-2 and IL-8 were higher in subjects with Grade 2+ iiNT vs Grades 0-1 iiNT; no other pre-infusion soluble factor levels were associated with iiNT incidence or grade. Substantially overlapping concentration ranges were observed for both factors across iiNT grades and the prognostic value may be limited.
- Post-infusion peak concentrations of soluble factors associated with inflammation were correlated with CRS and iiNT incidence and grade, consistent with the mechanisms of action of ide-cel and etiology of CRS/iiNT.

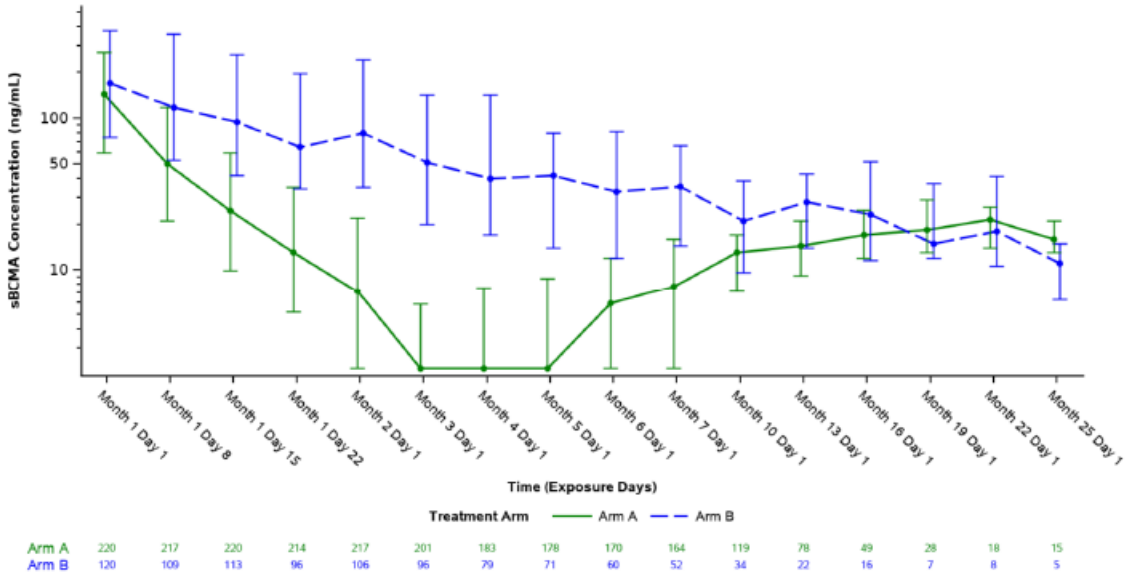
Tumour associated factors

The percentage of CD138-positive BMPCs expressing BCMA was measured by IHC to evaluate the presence of target antigen on tumour cells; proportions of subjects in the safety population with available baseline biopsies were 60.9% (137/225) and 60.3% (76/126) in the ide-cel and standard regimens arms, respectively. BCMA expression was only evaluated in biopsies with at least 3% CD138+ tumour cells. Relatively few bone marrow biopsy samples were collected at the time of disease progression and available for evaluation at the time of data cut-off (Arm A, N=6; Arm B, N=12). Baseline BCMA expression was not associated with response for subjects in either treatment arm.

Serum sBCMA concentrations correlate with the total number of BCMA-expressing normal and malignant plasma cells, and was used as a peripherally accessible biomarker of MM disease burden independent of the secreted monoclonal immunoglobulin subtype which is measurable even in subjects with non-secretory disease. Univariate testing (p-value threshold of 0.05) was performed to identify potential relationships between sBCMA and dose (300-460 x 10^6 cells vs >460-540 x 10^6 CAR-T cells), number of prior anti-myeloma regimens, baseline disease characteristics, efficacy and safety endpoints.

- Day of infusion levels of sBCMA was positively correlated with a subset of high tumour burden or high-risk tumour features, and with grade of CRS and iiNT.
- Day of infusion levels of sBCMA were higher in subjects not achieving a clinical response (<PR) and in subjects with < CR versus CR/sCR in both treatment arms, indicating the association may not be specific to the BCMA-directed CAR T mechanism of action.
- sBCMA clearance was observed in both treatment arms, and nadir levels were deeper and occurred earlier in ide-cel treated subjects versus standard regimens. sBCMA nadir correlated with depth of clinical response (Figure below).
- The nadir and frequency of sBCMA clearance was not different across dose subgroups, but the frequency of subjects clearing sBCMA <LLOQ was higher in subjects who received 2 prior regimens versus 3-4 prior regimens supporting the benefit of ide-cel for subjects in earlier treatment lines.
- sBCMA clearance at 2 months post-infusion (Month 3 Day 1 visit) and ongoing clearance at 6 months (Month 7 Day 1 visit) post-infusion were associated with more favourable mPFS. Detectable sBCMA at these timepoints identified subjects at higher risk of progression.
- Evidence of BCMA expression (directly via BCMA+ IHC result, or indirectly via detectable sBCMA) was observed in all evaluable subjects at screening, and in 97.6% (82/84) of evaluable subjects at the time of progression, suggesting antigen loss was not a primary driver of treatment resistance/relapse.

Figure 4. Median (Quartile) sBCMA concentration over time by treatment arm - Safety Population - MM-003



All concentrations below the LLOQ (4.4 ng/mL) were imputed to LLOQ/2 (2.2 ng/mL). Semi-log scale. Q1 and Q3 are displayed as upper and lower limit. Arm A is ide-cel treatment arm. Arm B is standard regimens arm.

Source: Figure 4.2.1-1 of the MM-003 biomarker report.

Immunogenicity

Treatment-induced anti-CAR antibodies were detected in 56.9% (128/225) of the subjects in **MM-003**, which is similar to the incidence observed in **MM-001** + **CRB-401** (50.5%, 93/184). Moreover, the onset of anti-CAR antibody response was also similar (around 3- 4 months) in all these studies. Based on the consistent immunogenicity response across the trials, the immunogenicity data from these studies were pooled in the SmPC. The combined ADA incidence was 54% (221/409).

Table 10. Summary of Anti-CAR Antibodies, Ide-cel Safety Population - Pooled MM-001, CRB-401 and MM-003 Studies

	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T Cells (N = 184)	MM-003 (N = 225)	Pooled MM-001, CRB-01 and MM-003 (N = 409)
Anti-CAR-Antibodies		n (%)	
Pre-positive[a]			
Pre-positive and post-positive[b]	8 (4.3)	5 (2.2)	13 (3.2)
Pre-positive andpost-negative[b]	6 (3.3)	2 (0.9)	8 (2.0)
Missing post data	1 (0.5)	2 (0.9)	3 (0.7)
Pre-negative[a]	172 (93.5)	214 (95.1)	386 (94.4)
Pre-negative and post-positive[b]	93 (50.5)	128 (56.9)	221 (54.0)
Pre-negative and post-negative[b]	78 (42.4)	84 (37.3)	162 (39.6)
Missing post data	1 (0.5)	2 (0.9)	3 (0.7)
Missing pre data	4 (2.2)	6 (2.7)	10 (2.4)
Post-positive[b]	3 (1.6)	5 (2.2)	8 (2.0)
Post-negative[b]	0	1 (0.4)	1 (0.2)
Missing post data	1 (0.5)	0	1 (0.2)

[a] Pre-positive is defined as the last value before or on ide-cel infusion date is positive; Pre-negative is defined as the last value before or on ide-cel infusion date is negative.

[b] Post-positive is defined as at least one positive value post ide-cel infusion; post-negative is defined as all negative values post ide-cel infusion.

Cut-off dates: CRB401:07Apr20, MM-001:07Apr20, MM-003:18Apr22

Source: Table 7.6.3 in Appendix 2

During the first 3 months of follow up, the majority of subjects in the ide-cel arm (PK evaluable population) (>77%) were ADA negative. No apparent (<2 fold) difference was observed in the transgene levels between subjects who were ADA positive and ADA negative through Month 1 (i.e., Visit of Month 2 Day 1).

- At Month 5 Day 1 and beyond, ≥50% of subjects were ADA positive and the median transgene level for subjects who were ADA positive was ~3-fold lower than that of subjects who were ADA negative.
- Data from the longer follow up suggests that the incidence of positive ADAs increases over time. In addition, the median transgene levels in ADA positive subjects at Month 10 Day 1 and beyond were largely undetectable.

In the ide-cel arm, exposure parameters of four subjects who were baseline ADA-positive were generally comparable to the PK parameters of 210 subjects who were baseline ADA-negative. Geometric Mean PK parameters for 135 PK evaluable subjects who had at least one visit with detectable ADA post infusion were ≤ 70% higher than those observed in 85 PK evaluable subjects without detectable ADA post infusion (Table below), suggesting modest difference in PK parameters between the two groups in the light of large inter-subject PK variability (>~200% geometric CV% in PK parameters).

Table 112. PK parameters in subjects who have at least one positive and all negative post-baseline ADA (idecabtagene vicleucel arm - PK Analysis population - MM-003)

	Post-Baseline ADA Status					
	Positive (N=135)			Negative (N=87)		
Parameter Statistics	n	Geometric Mean	Geometric CV%	n	Geometric Mean	Geometric CV%
Cmax (copies/ug)	135	140799.70	177.54	85	84706.47	286.85
AUC0-28D (copies*days/ug)	135	1261991.04	189.27	83	847233.30	299.18
AUC0-3M (copies*days/ug)	133	1523143.74	205.81	82	1040801.81	322.27
Parameter Statistics	n	Median	Range	N	Median	Range
Tmax (days)	135	9	4-28	85	11	2-31
Tlast (days)	135	168	26-839	85	146	14-511

Source: Table 11.1.1-2 of the MM-003 Primary CSR[2]

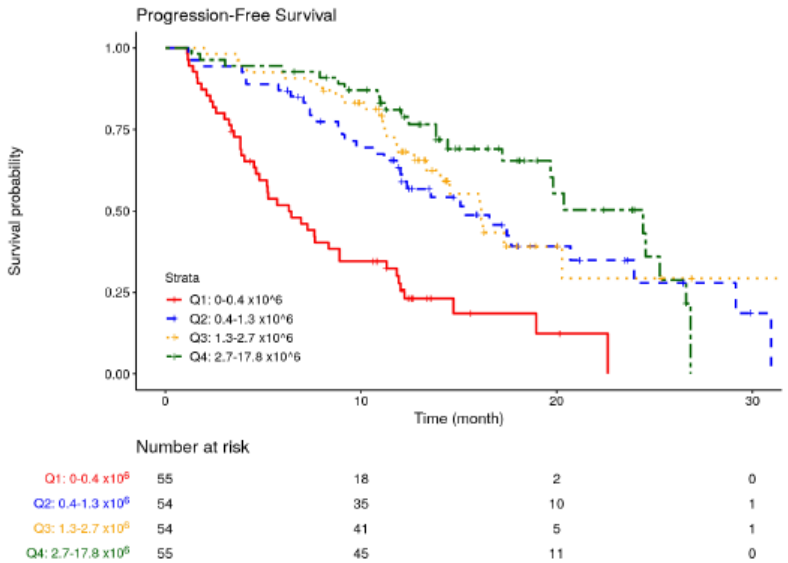
2.4.4. PK/PD modelling

Univariate- and multivariate regression analysis were performed using data from **MM-003** to explore potential relationships between CAR-T dose or exposure and key efficacy and safety endpoints. Subject-level exposures were calculated through NCA methods. The exposure or covariate effects on responses were determined to be statistically significant if the 95% CI of parameter estimates excluded the null value of 0.

ER efficacy analysis

A total of 218 subjects (Arm A) with both evaluable PK parameters and efficacy endpoints were included. Key efficacy endpoints were PFS, ORR, DoR, and MRD (IRC adjudicated assessment according to IMWG Uniform Response Criteria for Multiple Myeloma. The cell expansion was found to be higher in responders vs non-responders, in subjects with longer DoR, and in MRD negative CR subjects. Apparent ER relationships were observed for primary and key secondary efficacy endpoints PFS and ORR, with a shorter median PFS (Figure below) and a lower proportion of responders, respectively, observed in the lowest exposure quartile.

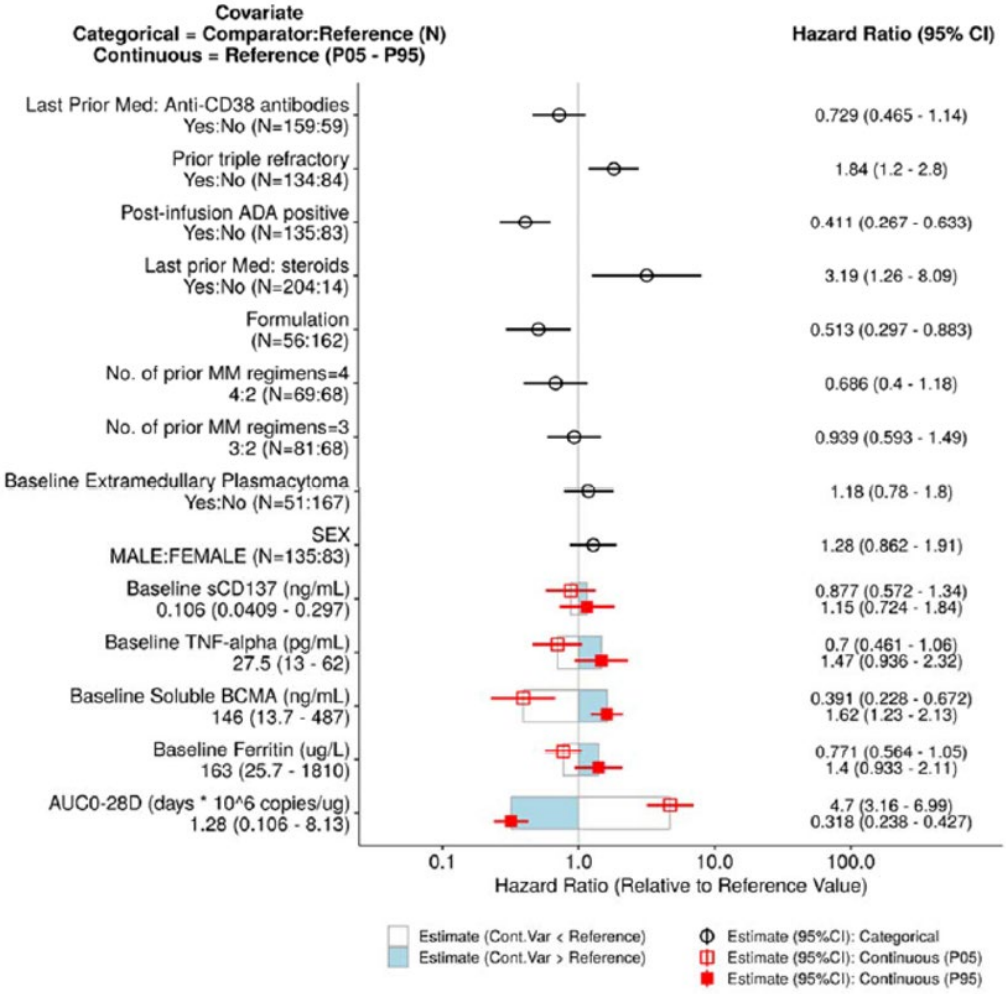
Figure 5. Kaplan-Meier Curves for PFS by AUC0-28D Quartiles - MM-003



Note: Median PFS = ~6.3, ~15, ~16, and ~24 months in Q1, Q2, Q3, and Q4 of AUC0-28D, respectively
Source: Figure 5.2.1.3-2 of the PK characterization and E-R report

Multivariable regression model development based on the **MM-003** data, identified several significant covariates for PFS and ORR for the ide-cel arm (Table below):

Table 12. Covariates and exposure effect plot for PFS ER full model - MM-003



Note: The reference values for continuous variables were set at the median values.
Source: Figure 5.2.3.3-1 of the PK characterization and E-R report[8]

PFS: The risk of disease progression was higher (shorter PFS) in subjects with prior triple refractory history status and subjects who received last prior treatment of steroids in the ide-cel arm; whereas the risk of disease progression was lower (longer PFS) in subjects with lower baseline sBCMA, and subjects with positive post-infusion ADA status in the ide-cel arm. However, the findings on last prior treatment of steroids, and positive post-infusion ADA status should be interpreted with caution.

ORR: Presence of extramedullary plasmacytoma was associated with lower odds of response in the ide-cel arm.

ER safety

A total of 220 subjects (Arm A) with both evaluable PK parameters and safety endpoints were included. Safety events that were evaluated in relation to AUC0-28D included: tCRS, sCRS, all grade CRS, Grade 3+ CRS, Grade 2+ iiNT, and cytopenia. Overall, the cell expansion measured by exposure parameters was found to be higher in subjects with tCRS, sCRS, all-grade CRS, Grade 3+ CRS, Grade

2+ iiNT, or cytopenia, respectively (exemplified by Table below). Apparent ER relationships were observed for tCRS and sCRS, which were further investigated in the regression modeling analyses.

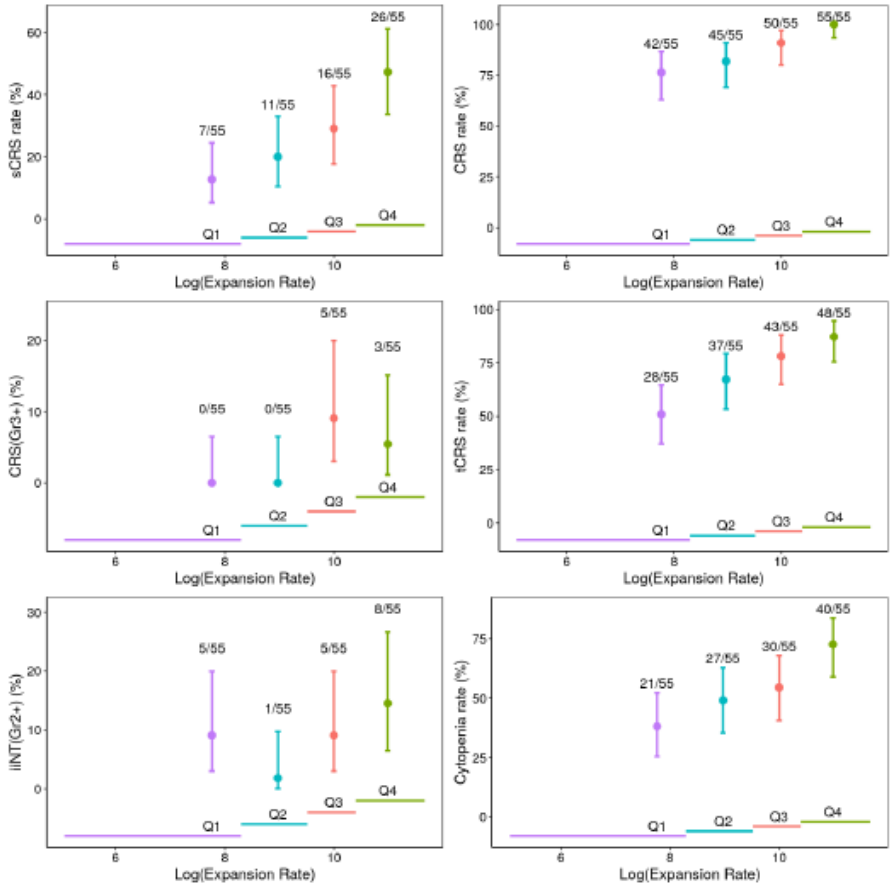
- Higher rates of these safety events were associated with higher exposure quartiles.
- The relationships between expansion rate (i.e., Cmax/Tmax) and tCRS or sCRS were well described by the linear logistic regression model.
- The post-infusion ADA status was identified to be a significant covariate for tCRS but not for sCRS, with the lower odds ratio in subjects with positive post-infusion ADA status vs those with negative post-infusion ADA.

Table 13. Descriptive statistics of Cmax/Tmax by binary safety event - MM-003

Endpoint	Subject Group	N	%	Median Cmax/Tmax (copies/µg/day)	Ratio of Median Cmax/Tmax of Subjects with AE vs. without AE
sCRS	0	160	72.73	9693.70	2.75
	1	60	27.27	26683.76	
All-grade CRS	0	28	12.73	4754.35	3.35
	1	192	87.27	15908.08	
CRS (Gr3+)	0	212	96.36	12605.38	2.33
	1	8	3.64	29379.82	
tCRS	0	64	29.09	5530.66	3.41
	1	156	70.91	18837.99	
iiNT (Gr2+)	0	201	91.36	12698.49	2.40
	1	19	8.64	30426.83	
Cytopenia	0	102	46.36	8899.51	1.95
	1	118	53.64	17349.52	

Note: Subject group 0 and 1 indicate lack and presence of safety event respectively.
Source: Table 5.3.1.1-3 of the PK characterization and E-R report[8]

Figure 6. Graphical Evaluation of E-R relationship for safety events and log(Cmax/Tmax) - MM-003



Note: Dots represent observed mean safety event rate with associated 95% CI for quartiles of log(Cmax/Tmax) displayed as error bar. Both are plotted at the median log(Cmax/Tmax) of each quartile (Q1-Q4). Horizontal lines represent log(Cmax/Tmax) ranges of each quartile. The numbers above the error bars (x/y) represent the number of subjects who achieved the response (x) and the total number of subjects (y) within each of the quartiles.
Source: Figure 5.3.1.2-1 of the PK characterization and E-R report

(Dose-)Exposure-response

No apparent relationships between actual dose and ORR/PFS/iiNT(Grade 2+) were observed. Model based analyses also showed lack of statistically significant relationship between dose and these endpoints. A statistically non-significant positive relationship was also found between dose and tCRS/sCRS. The linear regression model suggested a significant positive relationship between dose and CRS (Grade 3+), which should be interpreted with caution, as the visual inspection suggested potential inconsistency between data and model prediction at the high doses.

2.4.5. Discussion on clinical pharmacology

Pharmacokinetics

The cellular kinetics were investigated in a similar manner as in the MAA procedure. The findings (PK, ER, dose response) were overall consistent with the previous analysis.

The cellular kinetics in the target population has been adequately described and investigated based on data from study MM-003. Similar as in the original MAA submission, the MAH has used standard NCA to describe ide-cel cellular kinetics. It is not possible to separate the cellular kinetic processes, expansion and persistence, from presentations of NCA parameters. Modelling approaches could

possibly have disentangled and quantified variability in these pharmacokinetic processes (Stein et al, CPT Pharmacometrics Syst. Pharmacol 2019;285-295, Kimmel et al. 2019(bioRxiv, doi: https://doi.org/10.1101/717074). However, within the current application it is considered acceptable to use NCA.

PK assessments were made using blood samples taken at prespecified time points. Apparently, although not explicitly stated, actual sampling and dosing time were used.

Appropriate exposure metrics (Cmax, AUC0-28D, Cmax/AUC0-28D) were used to describe PK, and to investigate covariate and ER relationships. The new/additional PK parameter Cmax/Tmax is used as a measure of T cell expansion rate (instead of AUC0-3M) and is primarily used to evaluate the ER safety (i.e. CRS) relationship. Tlast is considered the most appropriate measure of ide-cel persistence.

Population PK modelling has not been performed for this submission. Although the MAH has conducted statistical analyses of exposure (as measured by AUC0-28D), there is currently no model describing the relationship between dose and exposure. (Dose-)Exposure-response modelling has been performed for both efficacy and safety end points using adequate methodology for model development and covariate investigation (similar to those applied to MM-001 data). The models developed as part of this application are empirical, without mechanistic elements. They are of low regulatory impact, and can be used for descriptive purposes only (e.g. characterisation of ER relationship).

As pointed out in previous procedures, dose normalisation is not considered appropriate for CAR+ T products and may have confounded the results of the exploratory covariate analyses. Exposures used for graphical evaluation were not dose-normalised. This is acceptable, as a linear dose-exposure relationship is generally not expected for CAR T-cell products.

The MAH initially used graphical analyses to explore possible covariates that may impact ide-cel exposure, and subsequently used linear fixed effect regression modelling to further characterise the relationships. Assumptions for the regression models have not been tested or discussed.

While this methodology could allow identification of highly influential covariates, it is limited by sensitivity towards to the accuracy of the NCA-based PK parameters and potential imbalances in individual PK sampling times or drop-outs. Further, it does not allow an understanding of which processes that may be influenced (e.g. early/late expansion or persistence), and it does not readily allow combining data across dose levels. The population approach (i.e. non-linear mixed effects modelling) is generally the preferred methodology for covariate analysis because it overcomes these limitations.

Comprehensive data in this application continue to support the clinically meaningful benefit of ide-cel at the approved dose range of 260 to 500 $\times 10^6$ CAR+ viable T cells in subjects with RRMM. Overall, the results are comparable to previous knowledge (MM-001 data), although lower exposure is noted which could be attributed to different BA method used in the MM-003 study. In general, bioanalytical methods used have been appropriately described and validated, and deemed fit for purpose.

In MM-003 the majority of patients (63%) received doses of 300-460x10^6 CAR T cells, only three patients received doses of <300x10^6 CAR T cells and the maximum dose given was 540x10^6 CAR T cells. In study MM-01 results indicated that ide-cel may have threshold dose above which robust expansion is more likely, as hypothesised by Dasyam et al. Br J Clin Pharm 2020;1-12. In study MM-003, exposure levels were lower in the patients receiving the lowest dose (<300x10^6 CAR T cells), however interpretation is limited by the small group size. As expected for this cell-based therapy, there was a lack of correlation between exposure (AUC0-28D) and dose across the two dose levels 300-460 vs. >460-540x10^6 CAR T cells. Exposure in the first month (AUC0-28D) and Cmax were highly correlated, indicating that expansion is the main driver of AUC0-28D. Further, the expansion in the

first month also represents the majority (<75%) of exposure, and AUCs do therefore not reflect ide-cel persistence. Tlast is a better indicator of persistence, with median of 168 days (range 14-839 days). Similarly, as for MM-001, the MM-003 data indicate that ide-cel could persist in blood for >1year.

Presence of post-infusion ADAs and higher baseline levels of IL-15 and sBCMA were associated with higher ide-cel exposure, and increased BW and presence of baseline extramedullary plasmacytoma was associated with decreased exposure. The impact on exposure of other investigated factors was not statistically significant.

No dedicated studies of ide-cel cell kinetics in special populations have been conducted. The MAH has performed exploratory analyses with data from study MM-003 to detect covariates that may affect ide-cel NCA-based cellular exposure parameters. The results obtained are overall in agreement with previous investigations (MAA procedure). No changes have been proposed to the SmPC in section 4.2 or 5.2 regarding special populations (with the exception of an updated age range), which is accepted.

Considering the substantial PK variability, the impact of BW is not considered clinically relevant.

Overall, the conducted covariate analyses are accepted for the current use, although they are considered exploratory and should be interpreted with caution.

CRS rate was associated with higher exposures, hence management of CRS with tocilizumab, siltuximab and/or corticosteroids was more common in patients with higher exposure/cellular expansion.

Compared to the MM-001 study, siltuximab was an additional agent used to treat CRS (in three patients) in study MM-003 (along with tocilizumab and corticosteroids). Based on the presented data, it is not possible to conclude on whether administration of medicinal drug products used to treat CRS have a negative impact on the expansion or persistence of ide-cel, albeit this must be considered likely, given their known MoA.

The SmPC section 4.5 has been updated with information on concomitant treatment with siltuximab. The proposed SmPC text is accepted.

Considering the potential formulation effect and that study MM-003 is ongoing, the MAH has committed to provide updated summary documents and final reports following study completion.

In general, the proposed text in SmPC sections 4.5 and 5.2 are acceptable.

Pharmacodynamic

The same panel of selected biomarkers as studied in MM-01, including immune- and tumour-associated soluble factors, that could be associated with dose and/or exposure and potentially predict safety and efficacy outcomes were explored using data from MM-003 (data cut off 18-Apr-2022). Also, tumour associated factors (sBCMA and BCMA expression) and MRD were explored.

Biomarkers such as cytokines/chemokines and sBCMA were assessed using commercial assays. Clinical markers of inflammation (CRP and ferritin) were measured locally at each clinical site. Target antigen BCMA expression was measured by immunohistochemistry (IHC), and MRD was evaluated using NGS.

Ide-cel anti-tumour activity is mediated by recognition of BCMA antigen on malignant plasma cells leading to activation, proliferation, and cytolytic activity. Overall, biomarker results were comparable to those from study MM-001. The soluble factors characteristic of T-cell activation demonstrated a profile of induction, elevation, and subsequent clearance. Generally, peak concentrations were observed within the first seven days, and then returned to baseline levels within one month post ide-

cel infusion. Peak levels (e.g. IL-15 post-infusion) were higher in responders compared to non-responders. In MM-003, however, no dose relationship was apparent across the two dose levels investigated (300-460 vs 460-540x 10^6), and pre-infusion and Cmax concentrations of soluble biomarkers were similar regardless of prior therapies (2 vs 3-4).

Elevated/presence of baseline tumour burden measures (sBCMA, EMP) and indicators of basal inflammation were associated with less optimal responses to ide-cel. Baseline sBCMA was not different by number of prior regimens, but a higher proportion of subjects with 2 vs 3-4 prior regimens achieved sBCMA clearance and this may have suggested that additional patient factors may be favourable in subjects with two prior regimens leading to more optimal sBCMA clearance supporting the currently applied indication. MRD negativity was associated with improved PFS in the ide-cel arm.

All evaluable MM-003 subjects had evidence of BCMA expression prior to ide-cel infusion. Due to limited progression biopsy results at data cutoff, sBCMA was used as a surrogate measure of BCMA-expressing cells. Consistent with MM-01, target antigen loss was not associated with disease progression. Results indicated that detectable sBCMA at M3D1 post-infusion and/or shorter duration of sBCMA clearance (*i.e.* detectable sBCMA at M7D1) could be potentially used to identify subjects at risk of earlier relapse.

Induction of proinflammatory cytokines has been associated with inflammation-related CAR T cell toxicities including CRS and iiNT, and the magnitude of proinflammatory cytokine induction was associated with grades of CRS and iiNT in the current study.

The biomarker investigations were explorative in nature with no impact on clinical conclusions. Additionally, due to the premature nature of the investigations, an updated biomarker report should be made available at time of study completion**.**

The validated ECL immunoassay that was used to detect the presence of anti-CAR antibodies in MM-003 study was the same as used in MM-001 and CRB-401 studies. Neutralising activity has not been investigated (which was adequately justified in the MAA procedure). According to the MAH, the impact of pre-existing ADA on cellular expansion appears to be limited, and only a modest impact of (post-infusion) ADA status on PK with no apparent effect on efficacy and safety of idecabtagene vicleucel were observed. There are no data on ADAs following re-treatment with ide-cel in study MM-003.

The available immunological data appear consistent across studies (MM-001 and -003). As there is a substantial time lag from administration to onset of immune responses, impact on cellular expansion is expected to be limited. However, negative impact on ide-cell persistence and long-term outcome, or on cellular expansion/outcome following ide-cel re-treatment, cannot be ruled out based on available data. Updated immunogenicity analysis should be provided at MM-003 study completion.

Pooled immunogenicity data from study MM-001 and MM-003 at the target dose are given in the SmPC which is accepted.

Overall, results from empirical exposure-response models are consistent with findings from study MM-001. The exposure metrics are positively associated with improved outcomes (PFS, ORR). The median Cmax and AUC0-28D was higher in responders vs the non-responders, and increasing AUC0-28D was also associated with longer PFS. Similarly, a higher cell expansion was observed in subjects with tCRS, sCRS, all-grade CRS, Grade 3+ CRS, Grade 2+ iiNT, and cytopenia. Apparent E-R relationships were observed for CRS requiring steroids or tocilizumab.

There was no apparent relationship between dose (300-540 x 10^6 CAR-T cells) and efficacy and safety outcomes. There were limited data on the lowest dose (<300 x 10^6 CAR-T cells). Although not discussed by the Applicant, the two highest dose groups included in the analysis appeared overall comparable with respect to baseline demographic and disease characteristics.

The impact of potential covariates were explored in multivariate regression analysis. Several covariates showed statistically significant effect on the identified ER relationships; however, no firm conclusions can be drawn due to the methodology issues raised.

The models developed are empirical without mechanistic elements, and are considered qualified for descriptive purposes only.

2.4.6. Conclusions on clinical pharmacology

The cellular kinetics in the target population has been adequately described based on data from study MM-003. Considering that the study MM-003 is ongoing, relevant final clinical pharmacology reports should be submitted after study completion.

The following measures are considered necessary to address issues related to pharmacology:

The MAH has committed to provide the relevant clinical pharmacology final reports (PK, ER, biomarker reports) when available following MM-003 study completion.

The CHMP endorse the CAT assessment regarding the conclusions on the Clinical pharmacology as described above.

2.5. Clinical efficacy

2.5.1. Main study

Title of Study

Phase 3, Multicenter, Randomized, Open-Label Study To Compare The Efficacy And Safety Of BB2121 Versus Standard Regimens In Subjects With Relapsed And Refractory Multiple Myeloma (RRMM) (KARMMA-3)

Study BB2121-MM-003 (KarMMa-3)

The primary evidence of efficacy of ide-cel in the indication extension to MM in an earlier treatment line is obtained from study BB2121-MM-003 (KarMMa-3, hereafter referred to as MM-003), which is an ongoing, open-label, multi-center, global, randomised, controlled phase 3 study comparing the efficacy and safety of ide-cel vs standard regimens (ie, daratumumab, pomalidomide, and dexamethasone (DPd), daratumumab, bortezomib and dexamethasone (DVd), ixazomib, lenalidomide and dexamethasone (IRd), carfilzomib and dexamethasone (Kd) or elotuzumab, pomalidomide, and dexamethasone (EPd)) in subjects with RRMM who had received 2 to 4 prior myeloma regimens, including daratumumab (DARA), an IMiD, and a PI and had documented disease progression during or within 60 days after the last therapy.

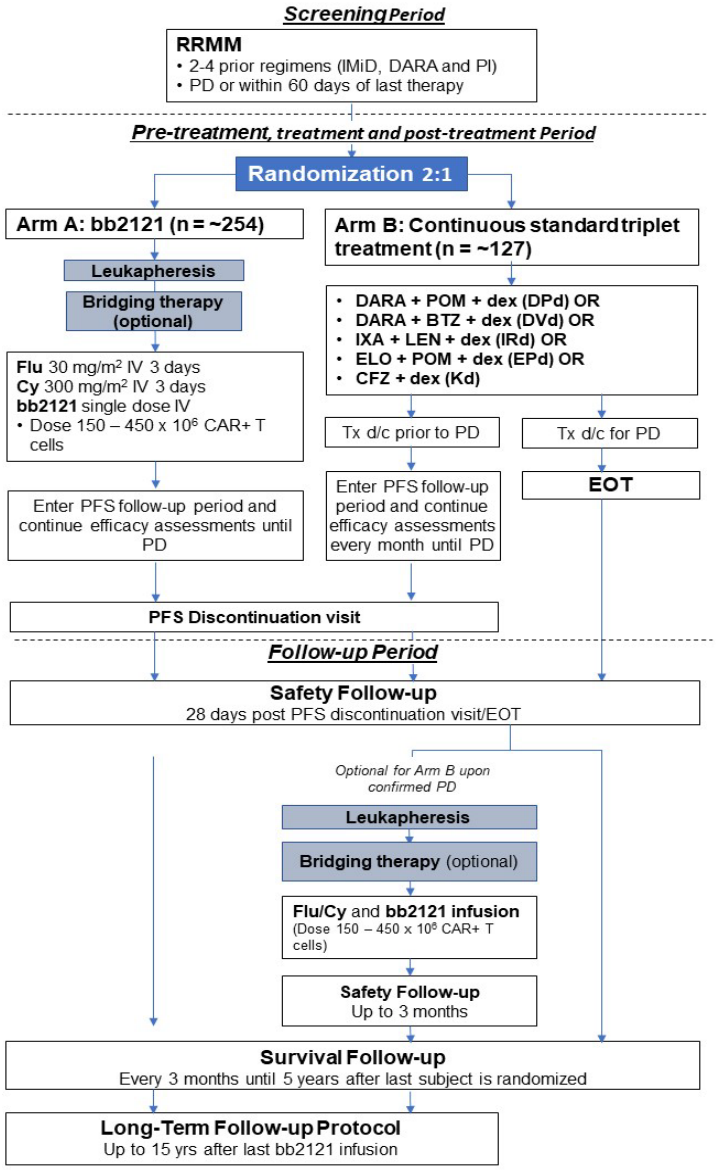
An overview of the study design is provided in Figure below.

Upon enrolment, eligible subjects were randomized in a 2:1 ratio to arm A (lymphodepleting chemotherapy (LDC) followed by ide-cel infusion) or arm B (standard regimens: DPd, DVd, IRd, Kd, or EPd)), stratified by age (< 65 years vs ≥ 65 years), number of prior antimyeloma regimens (2 vs 3 or 4 prior antimyeloma regimens) and high-risk cytogenetic abnormalities (presence vs absence or unknown presence of t(4;14) or t(14;16) or del 17p).

At the time of the data cut-off (DCO) date (18-Apr-2022), the study was ongoing, and subjects will be followed until the end of the trial.

Two interim analyses (IAs) for PFS were planned for MM-003. An independent data safety monitoring board (DSMB) was responsible for review of the analyses. The data presented are based on efficacy results from the pre-specified interim analysis PFS IA2 (at least 232 PFS events [80% information fraction]; data cut-off: 18 Apr 2022), on the primary and key secondary endpoints comparing ide-cel vs standard regimens. The primary endpoint of PFS and key secondary endpoints of 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. Updated data for PFS, ORR, DoR and OS from the final PFS analysis (DCO 28-Apr-2023) has been provided.

Figure 7. Study design



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

Methods

Study participants

Main inclusion criteria

1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Subject has documented diagnosis of MM and measurable disease, defined as:

a. M-protein (serum protein electrophoresis [sPEP] or urine protein electrophoresis [uPEP]): sPEP ≥ 0.5 g/dL or uPEP ≥ 200 mg/24 hours and/or

b. Light chain MM without measurable disease in the serum or urine: Serum immunoglobulin free light chain ≥ 10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free light chain ratio

3. Subject has received at least 2 but no greater than 4 prior MM regimens. Note: induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered as one regimen.
4. Subject has received prior treatment with DARA, a PI, and an IMiD-containing regimen for at least 2 consecutive cycles.
5. Subject must be refractory to the last treatment regimen. Refractory is defined as documented progressive disease during or within 60 days (measured from the last dose of any drug within the regimen) of completing treatment with the last anti-myeloma regimen before study entry.
6. Subject achieved a response (minimal response [MR] or better) to at least 1 prior treatment regimen.
7. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Recovery to Grade 1 or baseline of any non-hematologic toxicities due to prior treatments, excluding alopecia and Grade 2 peripheral neuropathy.
9. Adequate vascular access for leukapheresis.
10. Only subjects that would be considered for any of the 5 proposed standard regimens (DPd, DVd, IRd, Kd or EPd), as judged by the Investigator, should be included in the study.

Main exclusion criteria

1. Subject has non-secretory MM.
2. Subject has any of the following laboratory abnormalities:
    a. Absolute neutrophil count (ANC) < 1,000/µL
    b. Platelet count: < 75,000/µL in subjects in whom < 50% of bone marrow nucleated cells are plasma cells and platelet count < 50,000/µL in subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells (it is not permissible to transfuse a subject to reach this level)
    c. Haemoglobin < 8 g/dL (< 4.9 mmol/L) (it is not permissible to transfuse a subject to reach this level)
    d. Serum creatinine clearance (CrCl) < 45 mL/min

e. Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L)

f. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN)

g. Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome

h. International normalized ratio (INR) or activated partial thromboplastin time (aPTT) > 1.5 × ULN, or history of Grade ≥ 2 haemorrhage within 30 days, or subject requires ongoing treatment with chronic, therapeutic dosing of anticoagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors)

3. Subject has inadequate pulmonary function defined as oxygen saturation (SaO_2) < 92% on room air.

4. Subject has prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years with the exception of the following non-invasive malignancies:

    a. Basal cell carcinoma of the skin

    b. Squamous cell carcinoma of the skin

    c. Carcinoma *in situ* of the cervix

    d. Carcinoma *in situ* of the breast

    e. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system) or prostate cancer that can be treated with curative intent.

5. Subject has active or history of plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis.

6. Subject with known central nervous system (CNS) involvement with myeloma.

7. Subject has clinical evidence of pulmonary leukostasis and disseminated intravascular coagulation.

8. Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) 50% of predicted normal. Note that forced expiratory testing (FEV1) is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is < 50% of predicted normal.

9. Subject has a history or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, subarachnoid haemorrhage or other CNS bleed, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.

10. Subject was treated with DARA in combination with POM with or without dexamethasone (DP±d) as part of their most recent anti-myeloma treatment regimen, cannot receive DPd as bridging therapy but may receive DVd, IRd, Kd or EPd as bridging as per Investigator's discretion if randomized to Treatment Arm A.

11. Subject was treated with DP±d as part of their most recent anti-myeloma treatment regimen, cannot receive DPd if randomized to Treatment Arm B but may receive DVd, IRd, Kd or EPd as per Investigator's discretion.

12. Subject was treated with DARA in combination with BTZ with or without dexamethasone (DV±d) as part of their most recent anti-myeloma treatment regimen, cannot receive DVd as bridging therapy but may receive DPd, IRd, Kd or EPd as bridging as per Investigator's discretion if randomized to Treatment Arm A.
13. Subject was treated with DV±d as part of their most recent anti-myeloma treatment regimen, cannot receive DVd if randomized to Treatment Arm B but may receive DPd, IRd, Kd or EPd as per Investigator's discretion.
14. Subject was treated with IXA in combination with LEN with or without dexamethasone (IR±d) as part of their most recent anti-myeloma treatment regimen, cannot receive IRd as bridging therapy but may receive DPd, DVd, Kd or EPd as bridging as per investigator's discretion if randomized to treatment arm A.
15. Subject was treated with IR±d as part of their most recent anti-myeloma treatment regimen, cannot receive IRd if randomized to Treatment Arm B but may receive DPd, DVd, Kd or EPd as per investigator's discretion.
16. Previous history of an allogeneic hematopoietic stem cell transplantation, treatment with any gene therapy-based therapeutic for cancer, investigational cellular therapy for cancer or BCMA targeted therapy.
17. Subject has received autologous stem cell transplantation (ASCT) within 12 weeks prior to randomization.
18. Subject has received any of the following within the last 14 days prior to randomization:
    a. Plasmapheresis
    b. Major surgery (as defined by the Investigator)
    c. Radiation therapy other than local therapy for myeloma-associated bone lesions
    d. Use of any investigational agents and systemic anti-myeloma drug therapy
19. Echocardiogram (ECHO) or multigated acquisition (MUGA) with left ventricular ejection fraction (LVEF) < 45%.
20. Ongoing treatment with chronic immunosuppressants (eg, cyclosporine or systemic steroids at any dose). Intermittent topical, inhaled, or intranasal corticosteroids are allowed.
21. Subject is positive for human immunodeficiency virus (HIV-1 and HIV-2), chronic or active hepatitis B or active hepatitis A or C.
22. Subject has uncontrolled systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antimicrobial treatment) or requiring IV antimicrobials for management.
23. Subject has a history of class III or IV congestive heart failure (CHF) or severe non-ischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months prior to randomization.
24. Hypersensitivity to DARA, thalidomide, lenalidomide, POM, BTZ, IXA, CFZ, ELO or dexamethasone. This includes rash ≥ Grade 3 during prior thalidomide, POM or lenalidomide therapy.

25. Subject with known hypersensitivity to any component of ide-cel, cyclophosphamide, fludarabine, and/or tocilizumab or hypersensitivity to the excipients contained in the formulation of DARA, POM, LEN, IXA, BTZ, CFZ, ELO or dexamethasone.
26. Subject is a female who is pregnant, nursing, or breastfeeding, or who intends to become pregnant during the participation in the study.
27. For a subject randomized to Treatment Arm B and will be on a POM- or LEN-containing regimen; unable or unwilling to undergo protocol required thromboembolism prophylaxis.
28. Subject is intolerant to bortezomib, or has acute diffuse infiltrative pulmonary and pericardial disease, subject cannot receive DVd as bridging therapy if randomized to Treatment Arm A or cannot receive DVd if randomized to Treatment Arm B.
29. Subject was treated with K±d as part of their most recent anti-myeloma treatment regimen, cannot receive Kd if randomized to Treatment Arm B but may receive DPd, DVd, IRd or EPd as per Investigator's discretion.
30. Subject was treated with EP±d as part of their most recent anti-myeloma treatment regimen, cannot receive EPd if randomized to Treatment Arm B but may receive DPd, DVd, Kd or IRd as per Investigator's discretion.

Treatments

Ide-cel arm (Arm A)

The ide-cel pre-treatment/treatment phase includes leukapheresis, bridging chemotherapy (optional) and LDC (Figure 8).

A leukapheresis collection was performed on each subject to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the generation of the ide-cel drug product. According to the protocol, leukapheresis should occur within 7 calendar days of randomization.

Treatment with therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 14 days prior to leukapheresis was not allowed. Physiologic replacement, topical, intranasal and inhaled steroids were permitted. Bridging therapy, if needed, should not be initiated prior to leukapheresis.

Antimyeloma bridging therapies

If necessary, selected anti-myeloma bridging treatment for disease control was allowed while ide-cel was being manufactured, as long as the last dose was administered > 14 days prior to the initiation of lymphodepletion chemotherapy (LDC). Bridging therapy included up to 1 cycle of DPd or DVd or IRd or Kd or EPd, dependent on the subject's most recent anti-myeloma treatment regimen.

A standard regimen was assigned to each subject by the investigator prior to randomization. In subjects randomized to arm A, the respective standard regimen was to be used as bridging therapy, if clinically indicated.

For standard regimens arm subjects elected to receive ide-cel after confirmed progression, bridging therapy could include corticosteroids, alkylating agents, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 antibodies as single agents or in combination, based on Investigator's discretion.

After the ide-cel drug product has been manufactured, baseline evaluations were performed prior to initiation of LD chemotherapy. In subjects who received bridging anti-myeloma therapy, baseline

evaluations for disease staging were to be repeated following completion of bridging therapy and prior to starting LD chemotherapy.

Lymphodepleting chemotherapy

Subjects received fludarabine 30 mg/m^2 IV and cyclophosphamide 300 mg/m^2 IV as LD chemotherapy for 3 days starting 5 days prior to ide-cel infusion followed by two days of rest.

Ide-cel infusion

After the completion of LD chemotherapy, ide-cel was administered as a single IV infusion at a dose ranging from 150 to 450 x 10^6 CAR+ T cells on Day 1.

Standard regimens arm (Arm B)

Subjects received study treatment with a standard regimen (DPd, DVd, IRd, Kd or EPd) that was selected by investigators based on the subject's most recent anti-myeloma treatment regimen. Re-treatment with the same regimen the subject received as their last prior therapy was not allowed.

The doses/schedules for standard regimens were selected based on approved labels and are shown in the. table below:

Table 14. Selection and timing of dose

Treatment	Drug	Dose	Timing of Dose
Ide-cel Arm (Arm A)			
LDC	Cyclophosphamide	300 mg/m^2 IV infusion over 30 minutes	Days -5, -4, and -3
	Fludarabine	30 mg/m^2 IV infusion over 30 minutes administered immediately after cyclophosphamide (fludarabine dose should be reduced based on renal function)[a]	Days -5, -4, and -3
Ide-cel	ide-cel [b,c]	At a dose range of 150 to 450 × 10^6 CAR+ T cells/infusion[d]	Day 1 (+ 7-day window)
Standard Regimens Arm (Arm B)			
DPd	DARA	Starting dose of 16 mg/kg, IV	Months 1 and 2 on Days 1, 8, 15 and 22 of a 28-day month Months 3 to 6 on Days 1 and 15 of a 28-day month Months ≥ 7 on Day 1 of a 28-day month
	POM	4 mg/day, orally	Days 1 to 21 of a 28-day month
	dex[e]	40 mg (> 75 years 20 mg)	Days 1, 8, 15 and 22 of a 28-day month.
DVd	DARA	Starting dose of 16 mg/kg, IV	Months 1 to 3 on Days 1, 8 and 15 of a 21-day month Months 4 to 8 on Day 1 of a 21-day month Months ≥ 9 on Day 1 of a 28-day month
	BTZ[f]	Starting dose of 1.3 mg/m^2, subcutaneously	Months 1 to 8 on Days 1, 4, 8 and 11 of a 21-day month
	dex	Starting dose of 20 mg[g,h]	Months 1 to 8 on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day month
IRd	IXA	Starting dose of 4 mg/day, orally	Days 1, 8 and 15 of a 28-day month
	LEN	25 mg/day	Days 1 to 21 of a 28-day month
	dex	40 mg/day	Days 1, 8, 15 and 22 of a 28-day month

Treatment	Drug	Dose	Timing of Dose
Kd	CFZ	20 mg/m² (Cycle 1), IV 56 mg/m² (Cycle 1 and 2)	Days 1 and 2 of first 28-day month (Cycle 1) Days 8, 9, 15, and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15 and 16 for each 28-day month thereafter (Cycle 2 and onwards)
	dex	20 mg/day	Days 1, 2, 8, 9, 15, 16, 22 and 23 of a repeated 28-day month
EPd	ELO	10 mg/kg (Cycle 1 and 2), IV 20 mg/kg (Cycle ≥ 3)	Days 1, 8, 15, and 22 of 28-day month (Cycle 1 and 2) Day 1 of 28-day month (Cycle ≥ 3)
	POM	4 mg/day	Days 1 to 21 of 28-day month
	dex	≤ 75 years: weeks with ELO dosing: 28 mg orally + 8 mg IV and 40 mg orally on non-ELO dosing weeks > 75 years: weeks with ELO dosing: 8 mg orally + 8 mg IV and 20 mg orally on non-ELO dosing weeks	Days 1, 8, 15 and 22 of each cycle

[a] Subjects with CrCl of 50 to 70 mL/min should have a 20% dose reduction of each daily fludarabine dose; subjects with CrCl of 30 to 49 mL/min should have a 40% dose reduction of each daily fludarabine dose. The Cockcroft Gault formula should be used to calculate renal function. Fludarabine should not be administered to subjects with CrCl < 30 mL/min.

[b] Premedication should occur approximately 30 minutes prior to the infusion and should include acetaminophen 650 mg orally and diphenhydramine 12.5 mg IV or 25 to 50 mg orally (or equivalent). Subjects should not receive corticosteroids as premedication.

[c] During pre-treatment period, subjects had undergone a leukapheresis collection to obtain a sufficient quantity of PBMCs for the production of the ide-cel IP. If technical issue during the procedure or in the processing of the product, the subject could have second collection procedure performed. More than one ide-cel product lot could be combined to meet the protocol target dose range.

[d] The protocol planned dose range was 150 to 450 × 10^6 CAR+ T cells; dose exceeding 20% of the upper limit constituted overdose.

[e] For subjects ≤ 75 years, dex was dosed as 20 mg IV before the DARA infusion and 20 mg orally after the DARA infusion. For subjects > 75 years, dex was dosed as 20 mg IV before the DARA infusion.

[f] BTZ dosing must be discontinued after Month 8.

[g] For subjects ≤ 75 years, dex was dosed as 20 mg IV before DARA infusion and 20 mg orally the day after DARA infusion. On non- DARA dosing days, dex was dosed as 20 mg orally For subjects who are > 75 years, underweight (BMI < 18.5), have poorly controlled diabetes mellitus or prior intolerance/AE to steroid therapy, the dex dose may be administered at a dose of 20 mg weekly.

[h] Dex dosing must be discontinued after M8.

If requested by the investigator, subjects in treatment arm B were allowed to receive ide-cel upon central confirmation of progression and confirmed eligibility.

Objectives

Primary Objective:

To compare the efficacy of ide-cel, defined as PFS per IRC assessment, to standard regimens in subjects with RRMM.

Key secondary objectives:

To evaluate additional efficacy parameters of ide-cel, defined as ORR and OS, compared to standard regimens.

Other secondary objectives:

To evaluate additional efficacy parameters of ide-cel compared with standard regimens such as CR rate, DoR, TTR, EFS, PFS2, time to next antimyeloma treatment, MRD negativity rates and PRO.

Outcomes/endpoints

Primary endpoint:

The primary endpoint was PFS by IRC assessment.

PFS was defined as the time from randomization to the first documented progression in months based on the IMWG Uniform Response Criteria for Multiple Myeloma (Kumar, 2016) assessed by an IRC or death due to any cause on study, whichever occurred first. The time from randomization to PFS events or censoring was calculated as event date/censoring date – randomization+1.

Key secondary endpoint - ORR by IRC:

ORR was defined as the proportion of subjects who achieved a best overall response of PR or better according to IMWG Uniform Response Criteria for Multiple Myeloma (Kumar, 2016) as assessed by IRC.

To select the best response, the following order of response was used: stringent complete response (sCR) > complete response (CR) > very good partial response (VGPR) > partial response (PR) > minimal (MR) response > stable disease (SD) > progressive disease (PD) > no evaluation after baseline.

Key secondary endpoint - OS:

OS was defined as time from randomization to time of death due to any cause.

Subjects who die on/before the cut-off date was considered as having events on the date of death.

Subjects who were alive or lost to follow-up was censored on the last known alive date. For subjects whose last date of follow-up confirmed that the subject was alive at the data cut-off (i.e. valid date after cut-off), the subject was censored at the date of data cut-off.

The primary endpoint PFS and key secondary endpoints ORR and OS were tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate. In addition, OS analysis was conducted at the second PFS interim analysis and the PFS final analysis for safety and efficacy considerations regardless of whether PFS and ORR were tested positive.

Other secondary endpoints:

Table 15. Other secondary efficacy endpoints

CR rate by IRC	Percentage of subjects who achieved CR or better according to IMWG Uniform Response Criteria for MM as assessed by an IRC
DoR	Time from first documentation of response (PR or better) to first documentation of disease progression or death from any cause, whichever occurs first
TTR	Time from randomization to the first documentation of response (PR or better)
EFS	Time from randomization to the first documentation of PD, first day when subject receives another anti-myeloma treatment or death due to any cause, whichever occurs first

PFS2	Time from randomization to second objective PD on subsequent therapy (Arm A: PD observed after the next antimyeloma regimen that is different from ide-cel regimen; Arm B: subsequent therapy including ide-cel) or death from any cause, whichever is first
Time to next antimyeloma treatment	Calculated as the time from randomization to the first day when subjects receive another antimyeloma treatment, which includes ide-cel for subjects in Treatment Arm B.
MRD negativity	Evaluate subjects for MRD status using NGS
PRO	Changes in subject-reported health related quality of life and multiple myeloma-related symptoms as measured by the selected domains of EORTC QLQ-C30, specifically Global Health Status/QoL, physical functioning, pain, fatigue, and cognitive functioning and the disease symptoms and side effects of treatment measured by EORTC QLQ-MY20

Sample size

The primary analysis for the study was to compare PFS between Treatment Arm A (ide-cel) and Treatment Arm B (DPd or DVd or IRd or Kd or EPd). An improvement in median PFS from 9 months for Treatment Arm B to 14 months for Treatment Arm A was considered clinically relevant. It was assumed that the overall PFS distribution is exponential with a constant failure (hazard) rate. With 2:1 (A:B) randomization, two interim analyses, one for futility at approximately 33% information and one for superiority at approximately 80% information, a total of approximately 289 events was 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. O'Brien-Fleming type of alpha and beta spending functions were used to determine the superiority and futility boundaries, respectively.

The median PFS (9 months versus 14 months) in the statistical assumption was calculated from randomization for both treatment arms. Considering the potential non-proportional hazard function due to the delayed study treatment in Treatment Arm A (ide-cel) by approximately 1 month post randomization, the statistical power was still estimated to be > 85%. Assuming a 76% event rate, a total of 381 subjects (254 in Treatment Arm A and 127 in Treatment Arm B) were planned to be randomized.

The above calculated sample size of 381 subjects also provides at least 90% power for detecting a difference in ORR by assuming that ORR was approximately 68% in Treatment Arm A and 50% in Treatment Arm B.

The primary endpoint PFS and key secondary endpoints ORR and OS were tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate. In addition, OS analysis was conducted at the second PFS interim analysis and the PFS final analysis for safety and efficacy considerations regardless whether PFS and ORR were tested positive.

For the key secondary endpoint, OS, an improvement of median from 20 months for Treatment Arm B to 27 months for Treatment Arm A (with a hazard rate ratio of 0.74) was considered clinically relevant. With two OS interim analyses (one conducted at the second PFS interim analysis and the other conducted at the PFS final analysis), and the final OS analysis conducted at the time when approximately 222 OS events were reached, an overall power of at least 50% could be achieved at one-sided significance level of 0.025.

Randomisation

The study was anticipated to randomize approximately 381 subjects with RRMM in a 2:1 ratio as follows:

~ 254 subjects randomized to receive Treatment Arm A: ide-cel

~ 127 subjects randomized to receive Treatment Arm B: standard regimens dependent on the subject's most recent anti-myeloma treatment regimen.

After informed consent had been obtained, subjects underwent screening procedures to determine eligibility. Eligible subjects were randomized using an Interactive Response Technology (IRT), stratified by age (< 65 years, ≥ 65 years), number of prior anti-myeloma regimens (2, 3 or 4), and high risk cytogenetic abnormalities (t[4;14] or t[14;16) or del 17p: presence of known high risk cytogenetic abnormalities versus absence or unknown presence of high risk cytogenetic abnormalities).

The stratification based on data from case report form (CRF) and centralized lab analysis with missing values imputed by the values from IRT was used for stratified analyses and subgroup analyses. For the determination of cytogenetic risks, the centralized lab data at screening was considered first, if centralized data were not available, the last value from historical tests including at diagnosis collected on the CRF were used. If neither the centralized lab nor the CRF data were available, the data were imputed from the IRT system. Key stratified analyses could also be conducted using the stratification based on the IRT data only.

Blinding (masking)

MM-003 is an open-label study; investigators and subjects were unblinded to treatment assignment for individual subjects. The clinical team from the sponsor, statisticians, and statistical programmers could see individual treatment assignments when reviewing subject-level clinical data; however, no summaries or analyses by treatment group were performed before this DBL for IA2 or the sponsor was allowed to be unblinded by the DSMB. Hence, data processing, and adjudication of treatment response were performed in blinded manner prior to database lock for primary analysis. The investigators who delivered treatments and randomized subjects were unblinded to treatment assignment. The clinical team from the sponsor were blinded to treatment assignment when reviewing data. Personnel from the study team such as statisticians and statistical programmers as well as IRC members involved in data processing and treatment response adjudication, were blinded. One statistical programmer was identified to perform unblinded data transfer.

The IRC, which was responsible to review data related to disease response assessments during the study and determine relapse for the primary analysis, were blinded to the treatment arm assigned to the subjects, even in case of expedite reviews for subjects in Arm B with the intent to receive ide-cel treatment.

Statistical methods

Statistical analyses

The primary analyses on efficacy were conducted using the ITT population. Analysis using the EE population was performed as supportive analysis for selected efficacy endpoints, including the primary endpoint PFS, the key secondary endpoints ORR and OS, and other endpoints of clinical importance such as CR rate.

The analyses for efficacy endpoints were based primarily on the data provided by IRC and secondarily on investigator assessment using the IMWG Uniform Response Criteria). Efficacy results generally were

reported by treatment arms (Arm A versus Arm B) and were considered statistically significant after consideration of the strategy for controlling the familywise type I error rate. For all statistical tests, the corresponding p-values using significance level of 1-sided 0.025 and two-sided 95% CIs for intended point estimates were reported, unless otherwise specified. The hypothesis testing was based on the overall comparison between Treatment Arm A and Arm B.

In addition, study visits and key efficacy assessments including response evaluation, efficacy laboratory data, etc. impacted by COVID-19 were evaluated. Either summaries or listing(s) on number of days from one visit to the next and number of missing assessments at each visit on key efficacy parameters was presented if possible.

The Kaplan-Meier (KM) product limit methods was used to estimate the PFS and the median PFS, and the two-sided 95% CI for the median was computed. 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; presence of t(4;14) or t(14;16) or del 17p vs absence) was used as the primary analytic method to compare PFS between the treatment arms, and p-value were calculated.

PFS rate at time T was defined as the probability that a subject had not progressed and was alive at time T following randomization. PFS rates at fixed time points (e.g. 6 months, depending on the minimum follow-up) were defined as the probability that a subject had not progressed and was alive at time T following randomization. The univariate Cox proportional hazards model stratified by stratification factors was used to compute the hazard rate (risk) ratio between treatment arms for the PFS.

Censoring

Censoring rules based on Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance for cancer trial endpoints (FDA Guidance 2015, EMA Guidance, 2013) were applied for PFS. The PFS analysis were primarily based on the FDA censoring rules and the PFS analysis based on EMA censoring rules were used as supportive analysis. The Table below specifies the definition of events and censoring for PFS. Censoring rules based on FDA guidance (FDA Guidance 2015, Appendix C and D) were used for additional sensitivity analyses as appropriate.

Table 16. Event and Censoring Rules for Progression-Free Survival

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

Sensitivity analyses

Considering the potential non-proportional hazard function due to the delayed study treatment in Treatment Arm A (ide-cel) by approximately 1 month post randomization, if non-proportional hazards were observed to the extent that a hazard ratio will not reliably represent the differences between treatment arms then piecewise weighted log-rank test would be used by placing zero weight for the treatment effect during the time frame of 48 days from randomization as sensitivity analyses. The 48-day time cut was selected based on the median infusion time from leukapheresis in KarMMa and KarMMa-2 studies as well as impact from COVID-19. The medians from leukapheresis to ide-cel infusion were 40 and 42 days for KarMMa and KarMMa-2 studies, respectively. Adding 3 days from randomization to leukapheresis and about 4 days from COVID-19's impact on product delivery to 41 days, 48 days from randomization was used as the cut time for the piecewise weighted log-rank test. The calculation of the hazard ratio for the ide-cel arm (Treatment Arm A) versus the standard regimen arm (Treatment Arm B) was also based on the events occurred after the time cut, i.e., starting at Day 49 from randomization.

Several additional sensitivity analyses on the primary endpoint of PFS were conducted to support the primary analysis

1. In relation to intercurrent events of PD prior to study drug administration, an analysis was conducted to reflect study drug effect in clinical practice by removing PD events that occurred after randomization and prior to the administration of the investigational products. The subjects who had the PD events removed had to have PR or better responses after the administration of the investigational products as

well as receiving the infusion within 48 days from randomization. Proportional hazard model were applied in this sensitivity analysis. The event starting time was at randomization.

2. Sensitivity analysis could also be performed by excluding subjects with important protocol deviation for the primary endpoint, if applicable. The definition of protocol deviation was defined before unblinding and database lock.

3. The imbalance in dropouts between treatment arms as well as the informative censoring was evaluated. However, since the comparable subjects who drop out in Treatment Arm B may not be identified at a time that was similar to subjects in Treatment Arm A who dropped out before ide-cel infusion, the imbalance in dropouts between treatment groups could only be assessed at a specific time point that can be used for both treatment arms. Therefore, the following evaluation were conducted:

- evaluation of such dropout imbalance two months after randomization
- evaluation of dropouts throughout the entire study period

Based on the evaluation, appropriate sensitivity analyses were conducted to address any imbalance in dropouts between treatment arms, as applicable, and/or any informative censoring identified.

Analysis of PFS using investigator's assessment was performed as a supportive analysis. In addition, descriptive statistics on PFS as well as other efficacy endpoints such as ORR, CRR or DOR by specific treatment regimens in Treatment Arm B were performed. If a difference on median PFS or other efficacy endpoints was observed among the five regimens, exploratory analyses were performed to understand the difference.

OS was defined as the time from randomization to death due to any cause. Subjects who die on/before the cut-off date were considered as having events on the date of death. Subjects who were alive or lost to follow-up will be censored on the last known alive date. For subjects whose last date of follow-up confirms that the subject was alive at the data cut-off (i.e. valid date after cut-off), the subject was censored at the date of data cut-off.

The OS was analyzed using the same method as that for PFS stated. Median OS and the corresponding 2-sided 95% CI were provided. Survival rate at specific time points and KM survival curve was also provided.

For OS, as subjects from standard regimens in Treatment Arm B had the possibility to receive ide-cel after disease progression, the following analyses could be performed as sensitivity analyses: a 2-stage Weibull approach, also called 2-stage accelerated failure time model if data permitted it, and rank preserving structural failure time (RPSFT) method.

In the 2-stage Weibull model, confirmation of PD for Treatment Arm B patients was considered as the secondary baseline for Treatment Arm B subjects. By fitting the Weibull model using the baseline prognostic factors, treatment switch indicator as time-varying covariate, and the parameters at secondary baseline, the treatment effect of switching can be obtained by comparing those who switched and who did not in Treatment Arm B. The obtained treatment effect due to switching was used to adjust survival times observed in patients who received ide-cel to derive counterfactual survival times in Treatment Arm B. A stratified Cox proportional hazards regression model was then fitted to the observed group who received ide-cel survival times and the counterfactual control group survival times to estimate a treatment switching-adjusted HR. The following covariates measured at baseline and at the time of secondary baseline could be considered in the model: age, sex, ECOG performance status, and other potentially predictive and/or prognostic baseline and disease characteristics such as R-ISS, cytogenetic abnormalities, number of prior anti-myeloma regimens, refractoriness categories and selected baseline lab parameters.

The RPSFT approach, relied on a simple model for survival times that assumed that the effect of treatment is multiplicative on time, and that the size of the benefit was the same regardless of whether subjects were randomized initially to Treatment Arm A or Arm B subjects who received ide-cel treatment. The proposed one-parameter model was:

$$U_i = T_{Bi} + e^{\psi 0} * T_{Ai}$$

where U_i is the counterfactual event time for Arm B, T_{Bi} is the event time when the patient is on the control treatment, eψ0 is the acceleration factor associated with the intervention and T_{Ai} is the event time when the patient is on the intervention treatment. Similar to the 2-stage Weibull model, a stratified Cox proportional hazards regression model was then be fitted to the observed ide-cel group (Treatment Arm A) survival times and the counterfactual control group (Treatment Arm B) survival times to estimate a treatment switching-adjusted HR.

Censoring could be problematic for the RPSFT model due to the potential informative censoring issue between counterfactual censor time and observed survival time. Re-censoring approach was applied to avoid possible bias by breaking the dependence between censoring time and treatment received.

Subgroup Analyses

Efficacy subgroup analyses were performed on following subgroups for at least but not limited to the primary and key secondary efficacy endpoints:

☐ Age group (< 65, ≥ 65; <65; 65-74, 75-84, ≥85)

☐ Region (North America, Europe, Japan)

☐ Sex (male, female)

☐ Race (White vs Non-white; White, Asian, African American, and Other)

☐ Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

☐ Anti-CD38 class (Daratumumab, Isatuximab, and MOR202) refractory (yes, no)

☐ Double (IMiD and PI) refractory (yes, no)

☐ Triple refractory (yes, no)

☐ Daratumumab refractory (yes, no)

☐ Revised ISS stage at baseline (I or II, III)

☐ Tumor burden at baseline (bone marrow % plasma cells ≥, < 50%)

☐ Extramedullary plasmacytoma (EMP) (yes, no)

☐ Number of prior anti-myeloma regimens: (2 vs 3 or 4; 2 vs 3 vs 4)

☐ High risk cytogenetic abnormalities: High risk (presence of t(4;14) or t(14;16) or del 17p)

versus absence or unknown

☐ ide-cel dose category (<300, 300 to 460, and >460 to 540×10^6 CAR+ T cells) – Arm A only

Values recorded on the CRFs with missing values imputed by the values from IRT when missing on CRF for age categories, number of prior anti-myeloma regimens, high risk cytogenetic was used in the subgroup analysis.

Subgroup analyses were only performed if there were a reasonable number of subjects in each subgroup within each treatment arm for meaningful results. Some grouping of classes were considered if there were too few subjects in some subgroups.

Multiplicity

The primary endpoint PFS and key secondary endpoints ORR and OS were tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate. In addition, OS analysis was conducted at the second PFS interim analysis and the PFS final analysis for safety and efficacy considerations regardless of whether PFS and ORR were tested. The O'Brien-Fleming boundary alpha spending function was used to adjust multiplicity for the second PFS interim analysis. The null hypotheses were rejected if the p-value associated to the test was smaller than or equal to 0.012, at the time of the second PFS interim analysis. At the PFS final analysis, the null hypothesis was rejected if the p-value associated to the test was smaller than or equal to 0.021 for PFS. The significant level for the ORR interim analysis (conducted at the second PFS interim analysis) and the significant levels for two OS interim analyses (one conducted at the second PFS interim analysis and the other conducted at the PFS final analysis) were specified. The significance level at the final analysis for ORR and OS was determined based on the correlation of the test statistics at their corresponding interim and final analyses (Haybittle-Peto boundary).

Interim Analyses

Two interim analyses, one for futility and one for superiority of efficacy, were planned for this study. The first interim analysis was at approximately 33% information for futility, the second interim at approximately 80% information for superiority. Summaries of both efficacy and safety information for each interim analysis were performed by an independent statistical organization and the results were presented to the DSMB for review.

For the primary efficacy endpoint PFS, a group sequential procedure with an alpha-spending function and beta-spending function of the O'Brien-Fleming type to control the Type I error rate and Type II error rate, respectively, was used. For safety, confidence intervals for adverse event rates of special interest may be developed to provide evidence for early stopping in the face of unacceptable toxicity.

The primary efficacy endpoint, PFS, was compared between Treatment Arm A and Treatment Arm B using a group sequential log-rank test specified. The purpose of the first interim analysis was to stop for futility in case of no efficacy signal on PFS at 33% information time (~96 PFS events) between ide-cel treated subjects compared to standard regimens. Enrolment continued while this interim analysis was being conducted.

The boundary for futility of Treatment Arm A compared with Treatment Arm B at the first interim analysis with approximately 33% information was based on a beta-spending function of the O'Brien- Fleming type with overall $\beta = 0.06$. The p-value using one-sided log-rank test were calculated and a recommendation to terminate was to be made if the p-value is higher than the nominal p-value corresponding to the futility boundary.

The table below gave the nominal p-values for failing to reject the null hypothesis for PFS corresponding to the O'Brien-Fleming boundaries. The boundary for declaring superiority of Treatment Arm A over Treatment Arm B at the second interim analysis with approximately 80% information (~232 PFS events) was based on an alphaspending function of the O'Brien-Fleming type with overall $\alpha = 0.025$, one-sided.

The p-value using one-sided log-rank test was calculated and compared with the upper (superiority) boundary. If the value of the log-rank p-value was lower than this superiority boundary, superiority claim based on PFS for Treatment Arm A to Treatment Arm B would be made. The futility boundary was nonbinding for the study at first interim analysis. The Table below provides the nominal one-sided p-

values for either failing to reject the null hypothesis (futility) at the first PFS interim analysis or rejecting the null hypothesis (superiority) at the second PFS interim analysis and the PFS final analysis, corresponding to the O'Brien- Fleming boundaries.

In addition to the log-rank test comparing the 2 treatment arms, estimates of the hazard ratio and its 95% confidence interval was also calculated at each interim analysis. The primary endpoint PFS and key secondary endpoints ORR and OS was tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate. In addition, OS analyses was conducted at the second PFS interim analysis and the PFS final analysis for safety and efficacy considerations regardless of whether PFS and ORR were tested positive.

The other secondary endpoints were also summarized at the time when the primary efficacy endpoint (PFS) is tested positive. No formal stopping rules was employed for these endpoints. For ORR, one interim analysis for superiority was conducted at the second PFS interim analysis for superiority, and the final ORR analysis was conducted at the PFS final analysis. The superiority boundary for the interim ORR analysis was the same as for the second PFS interim analysis, and the superiority boundary for the final ORR analysis was determined following the Haybittle-Peto boundary based on the actual alpha spent and actual information fraction used at the interim analysis to retain the overall alpha of 0.025 one-sided.

For OS, two interim analyses were conducted: one at the second PFS interim analysis and another one at the PFS final analysis. The final OS analysis will be conducted when approximately 222 OS events have occurred. A one-sided non-binding futility boundary of 0.8 and an administrative one-sided superiority boundary of 0.001 would be applied for the OS interim analysis conducted at the second PFS interim analysis, and a one-sided superiority boundary of 0.01 would be used for the OS interim analysis conducted at the PFS final analysis. The superiority boundary for the final OS analysis will be determined following the Haybittle-Peto boundary based on the actual alpha spent and actual information fraction used at the two OS interim analyses to retain the overall alpha of 0.025 one-sided.

Table 17. Analysis Timing and Boundaries for Primary and Key Secondary Endpoints

Timing for Analysis	PFS		ORR[a]	OS	
	Superiority Boundary (Cum. α Spent)	Futility Boundary (Cum. β Spent)	Superiority Boundary (Cum. α Spent)	Superiority Boundary (Cum. α Spent)	Futility Boundary (Cum. β Spent)
PFS Interim #1 at 33% IF	N/A (N/A)	0.847 (0.001)	N/A (N/A)	N/A (N/A)	N/A (N/A)
PFS Interim #2 at 80% IF	0.012 (0.012)	N/A (N/A)	0.012 (0.012)	0.001 (0.001)	0.8 (TBD[c])
PFS Final	0.021 (0.025)	0.021 (0.06)	TBD[b] (0.025)	0.01 (TBD[b])	N/A (TBD[c])
OS Final				TBD[b] (0.025)	TBD[c] (0.5)

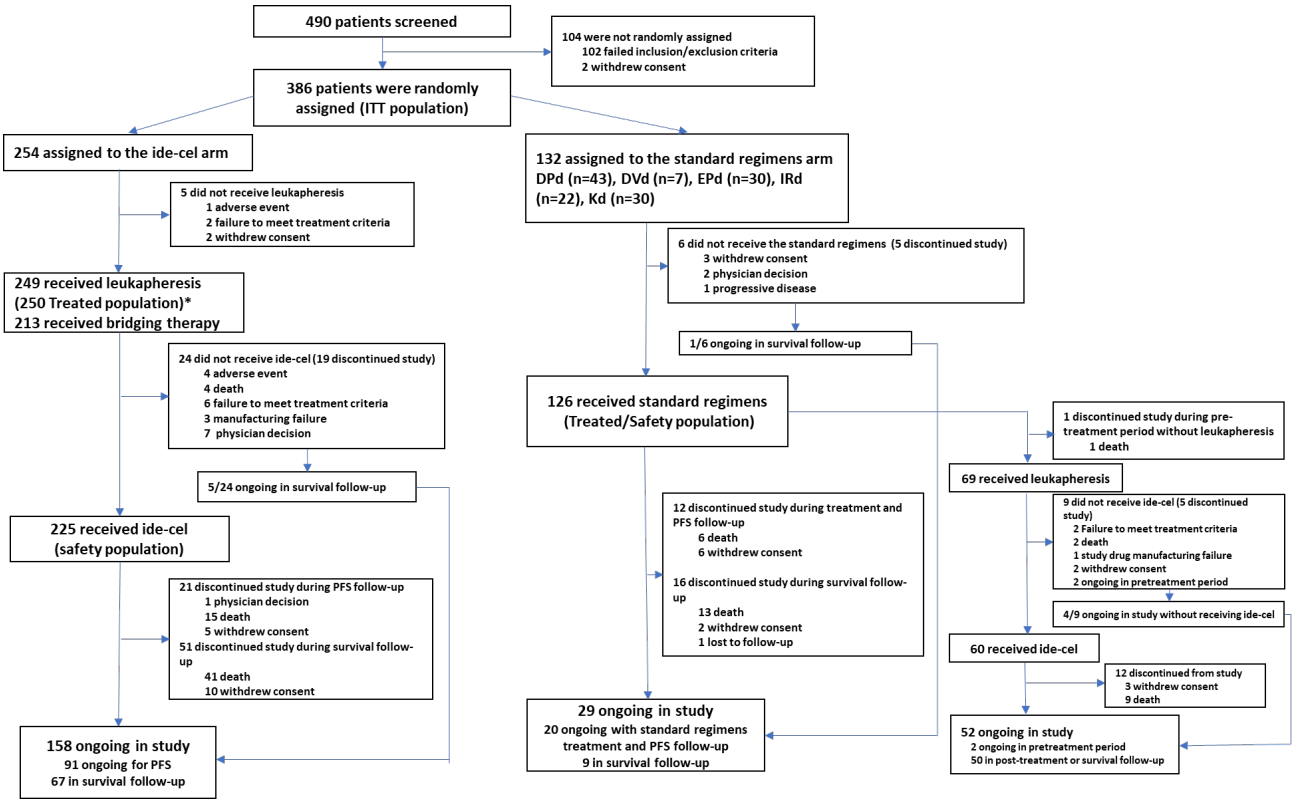
Cum. = Cumulative; IF = Information fraction; N/A = not applicable; PFS = Progression-free survival; ORR = Overall response rate; OS = Overall survival; TBD = To be determined.
Critical one-sided p-values computed using the East (Version 6) Software (Cytel Inc. 2005).
a No futility test will be performed for ORR interim analysis.
b To be determined following the Haybittle-Peto boundary based on the actual alpha spent and actual information fraction used at the interim analysis to retain the overall alpha of 0.025 one-sided.
c To be determined by interpolated spending function based on the actual beta

Results

Participant flow

Of the 490 patients screened in MM-003 at the DCO of 18-Apr-2022, 388 fulfilled the eligibility criteria. Two patients withdraw consent; thus, 386 patients were randomly assigned (ITT population). The most frequently failed inclusion/exclusion criteria were; subject has certain predefined laboratory abnormalities; absolute neutrophil count (ANC) <1,000/uL (35/102), subject willing and able to adhere to the study visit schedule and other protocol requirements within this protocol, and for subjects in arm A – agrees to continued follow-up for up to 15 years (14/102) as well as subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study (9/102). A total of 254 subjects was assigned to the ide-cel arm and 158 (62.2%) of these subjects were still ongoing in the study. For the standard regimens arm, 132 patients were assigned and 81 (61.4%) of these subjects were still ongoing in the study, of which 52 after cross-over to ide-cel treatment post progression. At the final PFS analysis (DCO 28-Apr-2023), 74 (56.1%) of the patients in the standard regimens arm had received ide-cel after PD.

Figure 8. Patient disposition in study MM-003 as of the DCO of 18-Apr-2022



*Note: One subject in the ide-cel arm, treated population, received bridging therapy, but not leukapheresis.

Disposition of standard regimens arm subjects who were planned to receive ide-cel after IRC confirmation of progression

In standard regimens arm, at investigator's request after confirmation of disease progression by the IRC, 75 subjects were screened for potential treatment with ide-cel, of whom 69 (92.0%) underwent leukapheresis. Failure to meet treatment criteria (3 [4.0%]) was the primary reason for not receiving

leukapheresis. Of the 69 subjects who underwent leukapheresis, 60 (87.0%) received ide-cel infusion. 12 (20.0%) discontinued from the study after receiving ide-cel infusion; the primary reason for discontinuation was death.

Recruitment

A total of 386 patients were enrolled in the MM-003 study, at 49 sites in 12 countries (Belgium, Canada, France, Germany, Italy, Japan, Netherlands, Norway, Spain, Switzerland, UK, and US), and 151 (39.1%) of the patients were enrolled in Europe.

Study initiation date was 16-Apr-2019, enrolment is closed, last patient was randomized to the ide-cel arm on 04-Feb-2022, and last patient was randomized to the comparator arm on 08-Apr-2022. The study is ongoing for follow-up. Subjects will be followed in the survival follow-up every 3 months until the end of trial, defined as 5 years after the last subject has been randomized.

The DCO date for the primary analysis, a pre-specified interim analysis (PFS IA2), was 18-Apr-2022, and the study is ongoing. Updated OS data were provided from an additional interim analysis, OS IA2, with DCO date of 03-Oct-2022.

At the DCO, the median follow-up was 18.7 months for the ide-cel arm and 18.1 months for the standard regimens arm. Minimum follow-up was 2.4 months for the ide-cel arm and 0.4 months for the standard regimens arm.

Conduct of the study

Protocol amendments

The original protocol for this study was dated 13-Jul-2018. As of the 18 Apr 2022 data cut-off date, there were 4 global amendments.

Table 183. Summary of key changes to MM-003 study protocol

Document (Amendment) Date	Summary of Key Changes	Rationale	Planned Sample Size	Subjects Randomized at time of Protocol Amendment
Amendment 1.0 11-Dec-2018	An independent DSMB was added to review cumulative study data quarterly over the course of the study to evaluate safety and efficacy, protocol conduct, and scientific validity and integrity of the study. Also added the following, 1.1 Interim analysis, AEs and mortality data were added to be provided as evidence for potential early stopping in the event of unacceptable toxicity. This was included as part of the DSMB review of interim results; DSMB may recommend that the study be stopped for superiority or futility or that modification of the study is required.	NA	381	0

Document (Amendment) Date	Summary of Key Changes	Rationale	Planned Sample Size	Subjects Randomized at time of Protocol Amendment
	1.2 Safety and efficacy data were to be monitored by the Sponsor Medical Monitor, Clinical Research Scientist and Safety Physician on an ongoing basis throughout the study. 1.3 Should a significant safety or efficacy issue be identified, all Investigators were to be notified immediately and the DSMB was to be convened in an expedited fashion to make a recommendation on future conduct of the study. 1.4 Based on the changes above, the criteria for pausing the study were removed from the protocol.			
Amendment 2.0 17-Dec-2019	2 additional standard regimen options were added: EPd and Kd. Subjects in Treatment Arm B were given the opportunity to receive ide-cel treatment following confirmed progression on the standard regimen in Treatment Arm B and confirmed eligibility. Subjects in Treatment Arm B who received ide-cel were to be followed for safety for a period of 3 months post-ide-cel infusion.	These changes were based on the evolving treatment landscape for the patient population included in this study (RRMM with 2 to 4 prior regimens) and feedback received from Investigators and health authorities.	381	68
Amendment 3.0 21-Aug-2020	Revised Management Guidelines for CRS and Neurologic Toxicities.	This was done to clarify guidance and management options for subjects who rapidly deteriorate despite first line interventions and was prompted by reports of non-relapse mortality within the first 2 months of ide-cel infusion.	381	168
Amendment 4.0 08-Nov-2021	The second interim analysis for the primary endpoint, PFS, at approximately 67% information fraction (or approximately 193 PFS events) was replaced by an interim analysis at approximately 80% information fraction (or approximately 232 PFS events)	Per FDA's recommendation received on 12-Oct-2021 to perform an interim analysis for superiority with a higher information fraction allowing for an accurate and reproducible estimate of treatment effect. The FDA recommendation was part of the review of the SAP included in the meeting package submitted to FDA to get feedback on the content/format of the planned sBLA for Study BB2121-MM-003. This change was further supported by similar feedback on the information fraction and maturity of PFS data at the time of IA, received	381	382

Document (Amendment) Date	Summary of Key Changes	Rationale	Planned Sample Size	Subjects Randomized at time of Protocol Amendment
		from ex-US health authorities for other clinical studies.		
	The timing for OS interim analyses was adjusted. The superiority and futility boundaries for PFS and OS interim and final analyses were updated accordingly	According to FDA's feedback, OS analysis was to be conducted at the second PFS interim analysis and the PFS final analysis for safety and efficacy considerations regardless of whether PFS and ORR were tested positive. The rationale was that OS is not only an efficacy but also an important safety endpoint.		

Changes to planned analyses

Updates made to the planned analysis in the MM-003 SAP v2.0 are described below.

Pre-specified analyses not conducted:

- The sensitivity analysis for the primary endpoint (PFS per IRC) in relation to intercurrent events of PD prior to study drug administration, by removing those PD events and including the responses after the study drug administration, was not conducted. This was because the IRC adjudication of the response results was done in a blinded manner and the adjudication stopped upon PD (ie, no further assessment was conducted beyond the PD). Similarly, the sensitivity analysis based on investigator assessments, as described above, was also not conducted because most PDs were confirmed by investigator and no assessments after a confirmed PD should be included for response assessments per IMWG 2016 criteria.
- The sensitivity analysis "excluding subjects with unmeasurable disease after bridging therapy for the analyses of efficacy endpoints" was not and will not be conducted, since the measurability post bridging therapy is a post baseline characteristic and should not impact the analysis based on ITT principle.

Post-hoc analyses conducted:

- MRD negativity rates based on MRD-evaluated subjects and subjects who achieved at least CR as the denominator were included as appropriate in addition to the ITT population.
- The analysis was modified for the calculation of second primary malignancies (SPM) incidence rate per 100 person-years to include both treatment arms, regardless subjects in Arm B had received ide-cel infusion or not because the occurrence of SPM was not only limited to subjects who received ide-cel infusion. The start date of person-year calculation was changed from leukapheresis date to randomization date for the comparison of SPM occurrence between treatment arms and to align with other AESI analysis. In addition, person-years calculation was conducted separately for Arm B subjects who underwent leukapheresis vs not.
- The PRO analyses population was changed from PRO evaluable set, which included subjects who have a baseline and at least one post baseline assessment that was analysable in the ITT population to the full ITT population.

Exploratory analyses added analysis of DoR by response group: DoBR in different best response categories was added to analysis in addition to the DoR analysis. DoBR is defined as the time from the first documentation of the designated best response category to the first documentation of disease progression or death from any cause, whichever occurs first.

Protocol deviations

The total number of subjects with important protocol deviations was 141 (55.5%) in the ide-cel arm and 58 (43.9%) in the comparator arm. The largest category of important protocol deviations was "laboratory", which includes samples not collected and procedures not done per protocol including central laboratory samples for efficacy, local samples for safety, and PK/PD samples (36.6% in the ide-cel arm and 22.7% in the comparator arm). Most of these were PK/PD samples not collected per protocol (25.2% and 13.6% for arm A and arm B, respectively). According to the MAH, the laboratory deviations did not substantially impact the assessment of primary and key secondary endpoints, or on the assessment of the adequacy of the trial conduct. The second most reported category was "other" which mostly included SAE reporting not having occurred within the protocol required timeframe (10.2% arm A and 3.0% in arm B).

Baseline data

Table 19. Key demographics and baseline characteristics summary - ITT population

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

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.

Table 20. Key baseline disease characteristics - ITT population

• 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 Abnormality, 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)
Radiological Only	6 (2.4)	2 (1.5)	8 (2.1)
Both Clinical and Radiological	55 (21.7)	30 (22.7)	85 (22.0)
No	192 (75.6)	100 (75.8)	292 (75.6)
Missing/Unknown	1 (0.4)	0	1 (0.3)
Bone Marrow Aspirate Plasma Cell (%)			
n	216	105	321
Median (Min, Max)	6.0 (0.0, 98.0)	4.0 (0.0, 85.0)	6.0 (0.0, 98.0)
Bone Marrow Biopsy CD138+ Plasma Cell (%)			
n	215	112	327
Median (Min, Max)	20.0 (0.0, 95.0)	20.0 (0.0, 90.0)	20.0 (0.0, 95.0)
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)
Renal Function (Cockcroft-Gault CrCl [ml/min]), n (%)			
<30	3 (1.2)	0	3 (0.8)
30-<45	5 (2.0)	4 (3.0)	9 (2.3)
45-<60	29 (11.4)	20 (15.2)	49 (12.7)
60-<80	59 (23.2)	33 (25.0)	92 (23.8)
≥80	158 (62.2)	75 (56.8)	233 (60.4)
Prior Radiation Therapies for Multiple Myeloma, n (%)			
Yes	90 (35.4)	46 (34.8)	136 (35.2)
No	164 (64.6)	86 (65.2)	250 (64.8)
Prior Autologous Stem Cell Transplant for Multiple Myeloma, n (%)			
Yes	214 (84.3)	114 (86.4)	328 (85.0)
1 transplant	167 (65.7)	87 (65.9)	254 (65.8)
>1 transplant	47 (18.5)	27 (20.5)	74 (19.2)
No	40 (15.7)	18 (13.6)	58 (15.0)
Number of Prior Antimyeloma Regimens			
Median (Min, Max)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Distribution of Prior Antimyeloma Regimens, n (%)			
2	78 (30.7)	39 (29.5)	117 (30.3)
3	95 (37.4)	49 (37.1)	144 (37.3)
4	81 (31.9)	44 (33.3)	125 (32.4)

• Parameters	• Ide-cel Arm (N=254)	• Standard Regimens Arm (N=132)	• Total (N=386)
Number of Prior Antimyeloma 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)
Refractory Status to Prior Therapies, n (%)			
IMiD	224 (88.2)	124 (93.9)	348 (90.2)
PI	189 (74.4)	95 (72.0)	284 (73.6)
Anti-CD38 Antibodies	242 (95.3)	124 (93.9)	366 (94.8)
Double-class Refractory, n (%)[f]			
Yes	169 (66.5)	91 (68.9)	260 (67.4)
No	85 (33.5)	41 (31.1)	126 (32.6)
Triple-class Refractory, n (%)[f]			
Yes	164 (64.6)	89 (67.4)	253 (65.5)
No	90 (35.4)	43 (32.6)	133 (34.5)
Penta-drug Refractory, n (%)[f]			
Yes	15 (5.9)	5 (3.8)	20 (5.2)
No	239 (94.1)	127 (96.2)	366 (94.8)
Refractory to Last Regimen, n (%)			
Yes	253 (99.6)[g]	132 (100.0)	385 (99.7)
No	1 (0.4)[h]	0	1 (0.3)

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] Upper end of range reflects one data entry error that has since been corrected in EDC after data cut-off date.
[f] Double-class refractory is defined as refractory to at least one immunomodulatory agent and one PI; triple-class refractory is defined as refractory to at least one immunomodulatory agent, one PI and one anti-CD38 antibody; penta-drug refractory is defined as refractory to LEN, POM, BTZ, CFZ and anti-CD38 antibodies.
[g] Includes 1 subject who had a best response of PD to last regiment, but the PD date was more than 60 days after the last dose date of the regimen
[h] Protocol deviation (PD date was > 60 days [62 days] after last dose date)

Prior Antimyeloma Therapy

Retreatment with the last regimen received prior to study enrolment was not allowed, given subjects were required to have been refractory to that regimen. In MM-003, there was no retreatment with the same regimen that they received immediately prior to entering the study.

Per protocol all subjects in the ITT population were exposed to an IMiD, a PI, and DARA, and the majority of subjects were also refractory to these agents. With regards to DARA refractoriness, 94.6% of subjects were DARA refractory, of whom 69.9% were refractory to DARA received as part of their last prior antimyeloma regimen (immediately before study entry) and 24.6% of subjects were refractory to DARA as part of an earlier antimyeloma regimen.

Time to progression (TTP) on last prior antimyeloma therapy (AMT)

In the ITT population, the most common (≥ 25% of subjects) last non-steroid AMT agents received by subjects across both treatment arms before entering the study were DARA (72.3% of subjects), and pomalidomide (38.1% of subjects). The median (min, max) TTP on the last prior AMT before study entry was 7.1 months (0.7, 67.7) in the ide-cel arm and 6.9 months (0.4, 66.0) in the standard regimens arm.

Treatment

Ide-cel arm

Antimyeloma bridging therapies

In the ITT population, the majority of subjects (83.9%) in the ide-cel arm received bridging therapy for myeloma control during the ide-cel manufacturing period. The median (min, max) duration of bridging therapy was 22.0 days (1.0, 101.0). The most commonly received (≥ 25% of subjects) antimyeloma bridging therapy agents were pomalidomide (48.4%), daratumumab (31.9%), and elotuzumab (26.4%).

Lymphodepleting chemotherapy (LDC)

In the ide-cel arm (treated population), 227 (90.8%) patients received LDC, all but two of whom received one 3-day cycle of LDC starting 5 days prior to ide-cel infusion, targeted to be on Day 1 (+ 7-day window). The 2 subjects in the ide-cel arm who received > 1 LDC cycle were due to interruption of the first cycle.

Based on the lymphodepletion treatment plan, most subjects were dosed with fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) for 3 days, with a median daily dose of 29.8 mg/m^2 (min, max: 16.5, 32.4) and 300.3 mg/m^2 (min, max: 240.6, 324.4) received, respectively.

Ide-cel infusion

The median dose of ide-cel was 445.3 x 10^6 CAR+ T cells (min, max: 174.9, 529.0) for the 225 subjects who received ide-cel infusion (see table below).

The median time (min, max) from leukapheresis to ide-cel administration was 49.0 days (34.0, 117.0,). The median time (min, max) from randomization to ide-cel administration was 54.0 days (35.0, 120.0).

Table 214. Ide-cel administration, ide-cel arm - safety population

•	• **Ide-cel, (N=225)**
Planned CAR+T Cells Infused (10^6 cells), n (%)	
150 – 450	225 (100.0)
Actual CAR+T Cells Infused (10^6 cells), n	225
Mean (SD)	441.8 (52.22)
Median (Min, Max)	445.3 (174.9, 529.0)
Actual CAR+T Cells Infused Grouping (10^6 cells), n (%)	
< 300	3 (1.3)
300 to 460	143 (63.6)
> 460 to 540	79 (35.1)
> 540	0

Note: The allowed dose range was 150 to 450 × 10^6 CAR+ T cells; doses in excess of 20% were considered overdose.

Table 225. Time from randomization to ide-cel administration in the ITT population

Parameters	Arm A (Ide-cel) ITT Population (N=254)	Arm A (Ide-cel) Safety Population (N=225)
Time from Randomization to Ide-cel(Arm A) Administration (days) [a]		
n	225	225
Mean	56.1	56.1
SD	13.84	13.84
Median	54.0	54.0
Min, Max	35.0, 120.0	35.0, 120.0
Time from Randomization to Leukapheresis (days) [b]		
n	249	225
Mean	4.3	4.3
SD	2.42	2.41
Median	4.0	4.0
Min, Max	0.0, 21.0	0.0, 21.0
Time from Leukapheresis to Ide-cel Product Released (days) [c]		
n	242	225
Mean	37.0	37.0
SD	11.95	11.77
Median	34.0	35.0
Min, Max	24.0, 102.0	24.0, 102.0
Time from Ide-cel Product Released to Ide-cel Infusion Administration (days) [d]		
n	225	225
Mean	14.7	14.7
SD	7.57	7.57
Median	13.0	13.0
Min, Max	1.0, 48.0	1.0, 48.0
Time from Leukapheresis to ide-cel Infusion Administration (days) [e]		
n	225	225
Mean	51.8	51.8
SD	13.59	13.59
Median	49.0	49.0
Min, Max	34.0, 117.0	34.0, 117.0
Subjects who underwent >1 leukapheresis - n (%)	13 (5.1)	8 (3.6)

Standard regimens arm

Of the 132 randomized to the standard regimens arm, 126 subjects (safety population) received treatment regimens as shown in the table below. Median treatment duration in number of days and in number of cycles was longer for subjects receiving DPd or Kd than for IRd, EPd or DVd.

Table 23. Standard regimen therapy in the standard regimens arm- safety population

• Standard Regimen (N=126)	• DPd	• DVd	• Ird	• Kd	• EPd
n (%)	41 (32.5)	7 (5.6)	20 (15.9)	28 (22.2)	30 (23.8)

Table 24. Treatment duration for standard regimens arm - safety population

	Arm B (Standard Regimens)				
	DPd (N=41)	DVd (N=7)	IRd (N=20)	Kd (N=28)	EPd (N=30)
Treatment Duration (Days) [a]					
Median (Min, Max)	178.0 (11, 967)	86.0 (15, 195)	120.0 (21, 623)	178.0 (28, 604)	119.5 (14, 399)
Number of Cycles Dosed [b]					
Median (Min, Max)	6.0 (1, 35)	5.0 (1, 10)	5.0 (1, 22)	6.5 (2, 21)	4.5 (1, 14)

[a] Treatment duration = Last dose date of the regimen - first dose date of the regimen + 1.
[b] Cycle refers to the "Month" defined per protocol, which is 21 days for DVd, and 28 days for all other standard regimens.

The median dose of ide-cel was 456.9 x 10^6 CAR+ T cells (min, max: 366.2, 539.3) for standard regimens arm subjects who received ide-cel at investigator's request after IRC confirmation of progression.

Concomitant medication

Concomitant medications and procedures/surgeries of interest in the ide-cel arm

All 225 subjects in the ide-cel arm, safety population, received at least 1 concomitant medication of interest and 122 (54.2%) had at least 1 concomitant procedure of interest.

The most commonly used concomitant medications of interest during the study included antivirals (98.7%), antibiotics (98.2%), antimycotics (71.6%), anti-cytokine drugs (72.0%), CSFs (58.7%), and IVIGs (32.9%). The anti-cytokine drugs tocilizumab, anakinra, and siltuximab were received by 72.0%, 4.4%, and 1.3% of subjects, respectively.

The most frequently reported concomitant procedures of interest included RBC transfusions (48.4%) and platelet transfusions (31.6%).

Concomitant medications and procedures/surgeries of interest in the standard regimens arm

In the standard regimens arm, safety population, 123 (97.6%) subjects had at least 1 concomitant medication of interest and 27 (21.4%) had at least 1 concomitant procedure of interest.

The most commonly used concomitant medications of interest included antivirals (96.0%), antibiotics (71.4%), and CSFs (34.1%).

The most frequently reported concomitant procedures of interest included RBC transfusions (9.0%) and platelet transfusions (7.9%).

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarised in the table below.

Table 25. Analysis populations

• Population [a]	• Ide-cel Arm (N = 254) n (%)	• Standard Regimens Arm (N = 132) n (%)	• Total (N = 386) n (%)
Intent-to-Treat [b]	254 (100.0)	132 (100.0)	386 (100.0)
Treated [c]	250 (98.4)	126 (95.5)	376 (97.4)
Safety [d]	225 (88.6)	126 (95.5)	351 (90.9)
Efficacy Evaluable [e]	225 (88.6)	122 (92.4)	347 (89.9)
Pharmacokinetic Analysis [f]	224 (88.2)	57 (43.2)	281 (72.8)

[a] Percentages are based on the ITT Population.
[b] ITT Population: all subjects who are randomized to one of the two treatment arms.
[c] Treated population: 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.
[d] Safety Population: 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.
[e] Efficacy Evaluable population: all subjects in the ITT Population who had received any study treatment, and had a baseline and at least one post-baseline efficacy assessment.
[f] PK Analysis population: all subjects who have received ide-cel infusion and have evaluable CAR T measurements.

Outcomes and estimation

Primary endpoint

A statistically significant improvement in PFS was observed in the ITT population for patients treated with ide-cel compared to standard regimens, HR = 0.493 (95.0% CI: 0.377, 0.645) using FDA censoring rules, and HR = 0.487 (95.0% CI: 0.375, 0.633) using EMA censoring rules, and a stratified log rank test p-value of < 0.0001.

At the DCO (18-Apr-2022), 149 patients (58.7%) in the ide-cel arm and 93 patients (70.5%) in the standard regimen arm had experienced a PFS event.

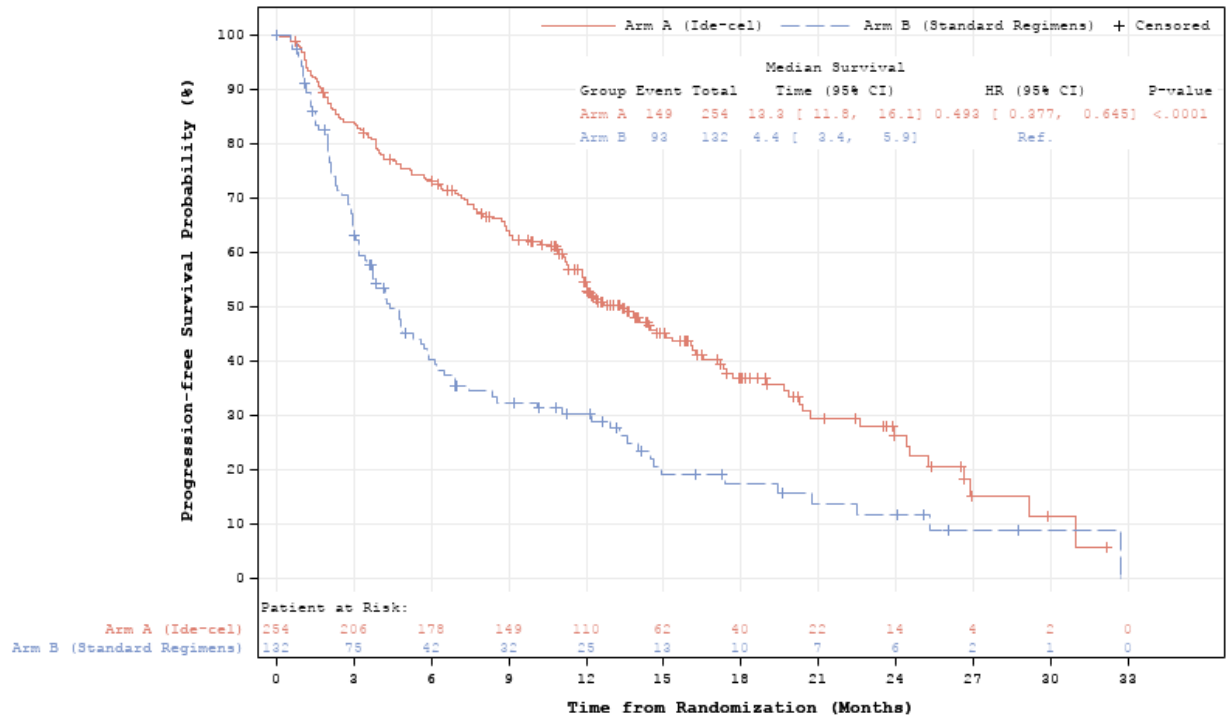
The Kaplan-Meier (KM) plot of PFS using FDA censoring rules is shown below. The KM estimate of median PFS was 13.3 months (95% CI: 11.8, 16.1) for patients receiving ide-cel compared to 4.4 months (95% CI: 3.4, 5.9) for patients receiving standard regimens. Analysis using EMA censoring rules gave a median PFS of 12.5 months (95% CI: 11.3, 15.3) for patients receiving ide-cel compared to 4.4 months (95% CI: 3.4, 5.8) for patients receiving standard regimens.

Table 266. Efficacy results on the primary endpoint; PFS per IRC assessment using FDA and EMA censoring rules. (DCO 18 April 2022)

	Ide-cel (N=254)	Standard Regimens (N=132)
Primary Endpoint		
PFS per IRC, FDA Censoring Rules		
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)
PFS per IRC, EMA Censoring Rules		
Events (Progressed/Died), n (%)	154 (60.6)	100 (75.8)
Censored, n (%)	100 (39.4)	32 (24.2)
Median PFS (95% CI)[a], mo.	12.5 (11.3, 15.3)	4.4 (3.4, 5.8)
Stratified HR (95% CI)[b]	0.487 (0.375, 0.633)	
Event-free rate % (SE)[d]		
6-month	73.3 (2.8)	39.1 (4.5)
12-month	53.4 (3.2)	28.8 (4.3)

a Median and corresponding 95% CI are based on Kaplan-Meier approach.
b Stratified and unstratified HR are based on the univariate Cox proportional hazards model. CI 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 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).
d SE is based on Greenwood formula.

Figure 9. KM plot of PFS based on IMWG criteria per IRC assessment in the ITT population using FDA censoring rules. (DCO 18 Apr 2022)



Using FDA censoring rules, 105 (41.3%) and 39 (29.5%) of subjects were censored for PFS in the ide-cel arm and standard regimens arm, respectively. The most common reasons for censoring in both the ide-cel and standard regimens arms were "ongoing without event at time of cut-off" and "discontinued study without progression/death".

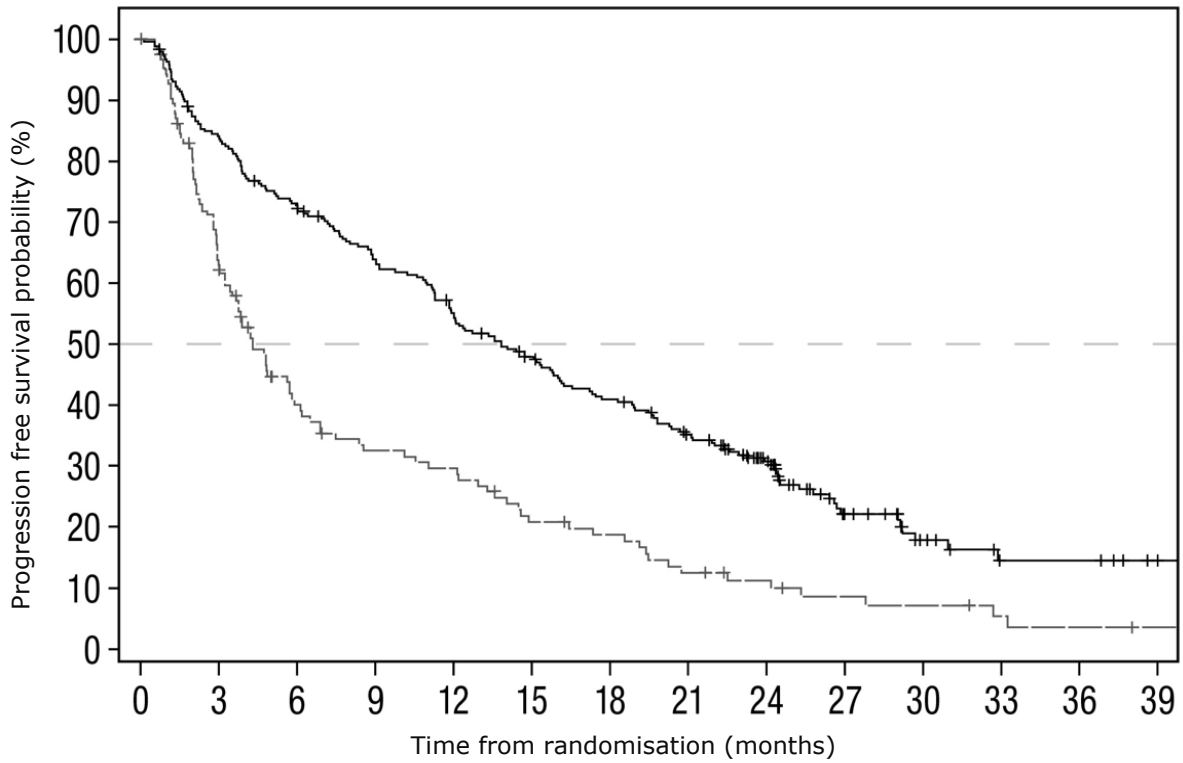
Table 277. Reasons for censoring and progression for PFS per IRC, FDA Censoring Rules - ITT Population

•	• Ide-cel Arm N=254 n (%)	• Standard Regimens Arm N=132 n (%)
Progression-free Survival (PFS) Status		
Censored	105 (41.3)	39 (29.5)
Progressed	129 (50.8)	89 (67.4)
Died Without Progression	20 (7.9)	4 (3.0)
Primary Reason of Censored [a]		
Taking New Anti-MM Therapy before PD/Death	2 (0.8)	5 (3.8)
Progression After Extended Lost to Follow-up (Two or More Missed Planned Assessments)	1 (0.4)	2 (1.5)
Death After Extended Lost to Follow-up (Two or More Missed Planned Assessments)	2 (0.8)	0
Discontinued Study Without Progression/Death	9 (3.5)	10 (7.6)
Ongoing Without Event at Time of Cutoff	91 (35.8)	22 (16.7)
Reasons of Progression [a]		
Serum M-protein increase (sPEP)	36 (14.2)	22 (16.7)
Urine M-protein increase (uPEP)	8 (3.1)	10 (7.6)
Bone Marrow Plasma Cell percentage increase	9 (3.5)	1 (0.8)
Increase in the difference between uninvolved and involved free light chain levels	55 (21.7)	49 (37.1)
Bone Lesions (new or increase in size)	16 (6.3)	10 (7.6)
Plasmacytomas (new or increase in size)	39 (15.4)	18 (13.6)

[a] The primary reason of censor is reported. A subject may have multiple reasons of progression.

Final PFS analysis (DCO 28-Apr-2023), based on the IMWG criteria per IRC and FDA censoring rules, showed a median PFS of 13.8 months (95% CI: 11.8, 16.1) for patients receiving ide-cel versus 4.4 months (95% CI: 3.4, 5.8) for patients receiving standard regimens (HR: 0.493 [95% CI: 0.384, 0.634]). At the final PFS analysis, 184 patients (72.4%) in the ide-cel arm and 105 patients (79.5%) in the standard regimen arm had experienced a PFS event. In the ide-cel arm, 70 (27.6%) of subjects were censored for PFS, and 27 (20.5%) were censored in standard regimens arm.

Figure 10. Kaplan-Meier plot of progression-free survival based on IRC assessment in KarMMa-3 study (intent-to-treat population). (DCO 28 April 2023)



Number of subjects at risk

——— Abecma

254 206 177 153 131 111 94 77 54 25 14 7 7 2

- - - - Standard regimens

132 76 43 34 31 21 18 12 9 6 5 3 2 1

Final PFS analysis using EMA censoring rules showed a stratified HR = 0.512 (95.0% CI: 0.404, 0.649), with a median PFS of 12.8 months (95% CI: 11.3, 15.7) for patients receiving ide-cel versus 4.8 months (95% CI: 3.7, 5.9) for patients receiving standard regimens.

The following additional/sensitivity analyses were conducted to assess the impact of potential biases on PFS:

PFS analysis performed for the efficacy evaluable (EE) population

Consistent with the ITT population, in the EE population, PFS median (per IRC, and FDA censoring rules) was 14.5 months (95% CI:12.2, 7.3) vs 4.7 months (95% CI: 3.4, 5.9), for ide-cel and standard regimens, respectively, stratified HR 0.415 (0.314, 0.548).

PFS analysis using investigator's assessment

Median PFS assessed by investigator (FDA censoring rules) was 12.0 months (95% CI: 10.6, 13.6) and 4.7 months (95% CI: 3.3, 5.9) for ide-cel and standard regimens, respectively, stratified HR = 0.586 (95% CI: 0.451, 0.763).

Sensitivity analysis based on piecewise log-rank test (FDA censoring rules)

Sensitivity analysis based on piecewise log-rank test (FDA censoring rules) in the ITT population showed a HR which was consistent with the primary analysis.

Table 288. Summary of PFS based on IMWG criteria - IRC review - sensitivity analysis based on piecewise log-rank test censoring rules according to FDA guideline - ITT population

Parameters		Arm A (Ide-cel) (N=254)	Arm B (Standard Regimens) (N=132)
Progression-free Survival (PFS) status [a]			
On/before cut date		30 (11.8)	33 (25.0)
Censored	n (%)	8 (3.1)	13 (9.8)
Progressed/Died	n (%)	22 (8.7)	20 (15.2)
Progressed	n (%)	17 (6.7)	19 (14.4)
Died Without Progression	n (%)	5 (2.0)	1 (0.8)
After cut date		224 (88.2)	99 (75.0)
Censored	n (%)	97 (38.2)	26 (19.7)
Progressed/Died	n (%)	127 (50.0)	73 (55.3)
Progressed	n (%)	112 (44.1)	70 (53.0)
Died Without Progression	n (%)	15 (5.9)	3 (2.3)
Piecewise weighted log-rank test p-value [a][b]		< 0.0001	
Stratified Hazard Ratio (95% CI) [c]		0.486 (0.360, 0.656)	Ref.
Stratified Hazard Ratio (97.2% CI) [c]		0.486 (0.348, 0.680)	Ref.
Unstratified Hazard Ratio (95% CI) [c]		0.506 (0.378, 0.677)	Ref.

CI=Confidence interval.
[a] The cut date for piecewise weighted log rank test (Xu, 2017) is set to 48 days after randomization. The events occurred on or before the cut date are assigned a weight of 0; whereas the events occurred after the cut date are assigned a weight of 1 in piecewise weighted log-rank test.
[b] P-value is one-sided based on a piecewise weighted 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 (HR) are based on the univariate Cox proportional hazards model for the events occurred after the cut date only, with the day after cut date as the start date for PFS. 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.

PFS per IRC assessment by ide-cel dose levels (FDA censoring rules) (DCO 18 April 2022)

Median PFS per IRC assessment across the ide-cel dose levels of < 300 x 10^6, 300 to 460 x 10^6 CAR+ T cells and > 460 to 540 x 10^6 CAR+ T cells is shown the table and figure below. Only 3 subjects were treated with dose level < 300 x 10^6 CAR+ T cells.

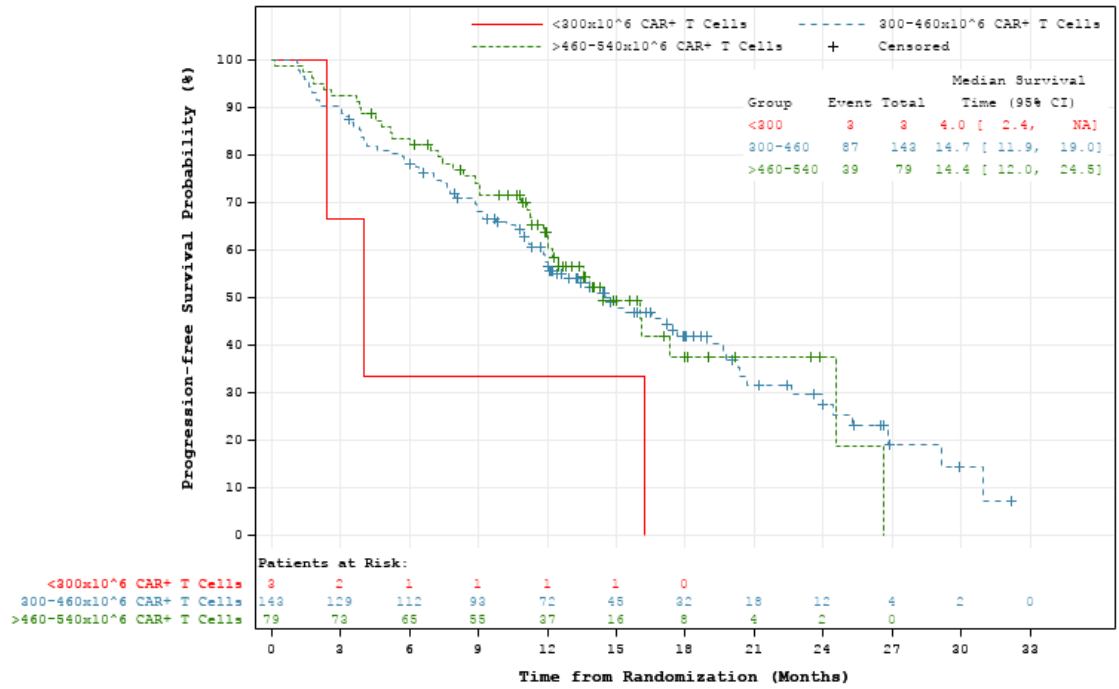
Table 299. PFS per IRC assessment by ide-cel dose levels, FDA censoring rules - safety population

• Parameters	• Ide cel Arm • < 300 × 10^6 CAR+ T Cells (N=3)	• 300 - 460 × 10^6 CAR+ T Cells (N=143)	• > 460 - 540 × 10^6 CAR+ T Cells (N=79)
Progression-free Survival (PFS) Status, n (%)	3 (100.0)	143 (100.0)	79 (100.0)
Censored, n (%)	0	56 (39.2)	40 (50.6)
Progressed/Died, n (%)	3 (100.0)	87 (60.8)	39 (49.4)
Progressed, n (%)	3 (100.0)	79 (55.2)	35 (44.3)
Died Without Progression, n (%)	0	8 (5.6)	4 (5.1)
Progression-free Survival Time (months) [a]			

•	• Ide cel Arm		
• Parameters	• < 300 × 10^6 CAR+ T Cells (N=3)	• 300 - 460 × 10^6 CAR+ T Cells (N=143)	• > 460 - 540 × 10^6 CAR+ T Cells (N=79)
25th Percentile (95% CI)	2.4 (2.4, NA)	7.2 (4.2, 9.2)	8.8 (5.2, 11.8)
Median (95%CI)	4.0 (2.4, NA)	14.7 (11.9, 19.0)	14.4 (12.0, 24.5)
75th Percentile (95% CI)	16.2 (2.4, NA)	25.3 (20.4, 30.9)	24.5 (17.3, NA)

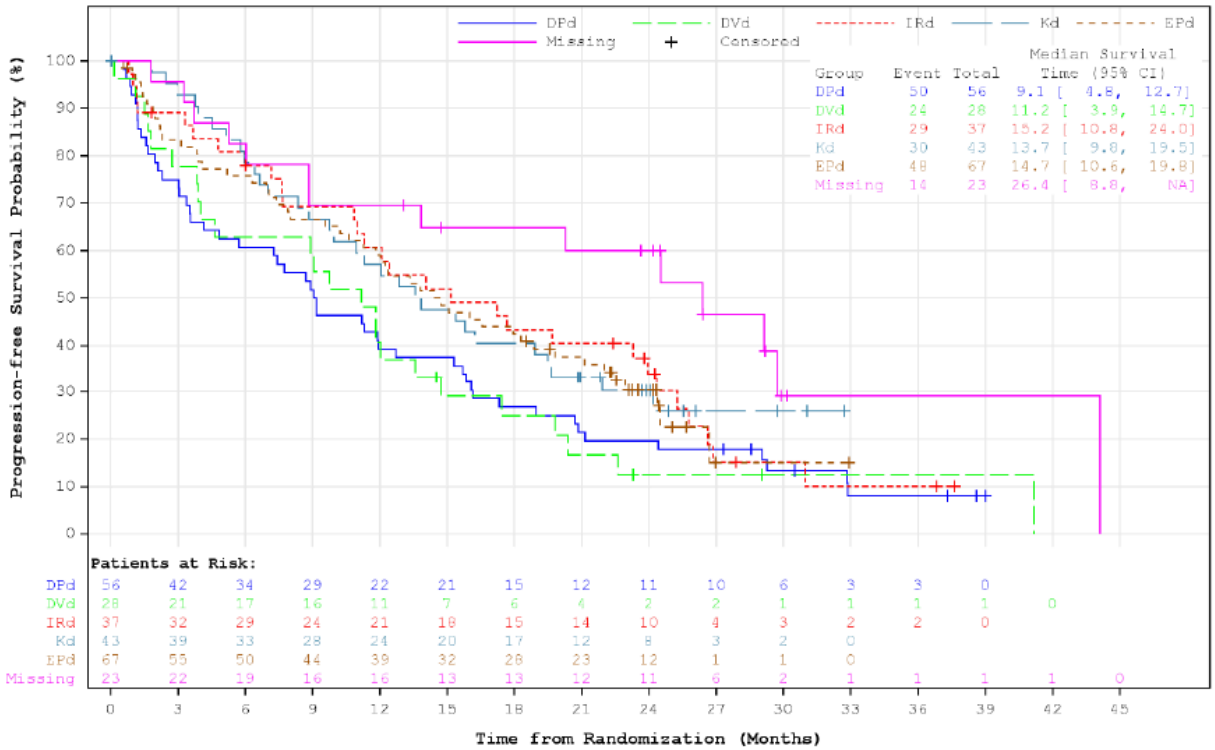
[a] The 25th and 75th percentile, median and corresponding 95% confidence interval are based on Kaplan-Meier approach.
[b] SE is based on Greenwood formula.

Figure 11. KM curve of PFS per IRC by ide-cel dose levels, FDA censoring rules - safety population



PFS for patients in Arm A according to the standard regimen they would have received should they have been randomized to Arm B.

Figure 22. KM Curve of PFS based on IMWG Criteria - IRC Review Censoring Rules According to EMA Guideline, Arm A (Ide-cel) Pseudo-ITT Population by Standard Regimens (DPd vs DVd vs IRd vs Kd vs EPd) in MM-003 (DBL 23-Jun-2023).



Note: Arm A ITT population according to the standard regimen they would have received should they have been randomized to Arm B

Missing refer to subjects for whom the investigator indicated that no bridging therapy was required.

Key secondary endpoint – ORR

ORR per IRC assessment showed a statistically significant improvement for patients treated with ide-cel compared with patients treated with standard regimens. ORR was 71.3% (95% CI: 65.7, 76.8) for the ide-cel arm compared to 41.7% (95% CI: 33.3, 50.1) for the comparator arm, with a common odds ratio at 3.54 (95% CI: 2.26, 5.54) and p-value < 0.0001 (Cochran-Mantel-Haenszel test) (DCO 18 April 2022).

ORR per investigator assessment was 65% (95% CI: 59.1, 70.8) for the ide-cel arm and 40.2% (95% CI: 31.8, 48.5) for the comparator arm.

Table 30. Summary of Best Overall Response per IRC based on IMWG criteria - ITT population (DCO 18 April 2022)

• Parameters	• Ide-cel (N=254) n (%)	• Standard Regimens (N=132) n (%)
BOR, n (%)		
sCR	90 (35.4)	6 (4.5)
CR	8 (3.1)	1 (0.8)
VGPR	55 (21.7)	13 (9.8)
PR	28 (11.0)	35 (26.5)
MR	4 (1.6)	9 (6.8)
SD	31 (12.2)	48 (36.4)
PD	24 (9.4)	10 (7.6)
Not Evaluable or Not Done [a]	14 (5.5)	10 (7.6)
ORR, n (%) [b]	181 (71.3)	55 (41.7)
95% CI [c]	65.7, 76.8	33.3, 50.1
p-value [d]	<.0001	
Common Rate Difference (97.2% CI) [e]	29.3 (18.1, 40.5)	
Common Odds Ratio (97.2% CI) [e]	3.54 (2.14, 5.85)	
CR Rate, n (%) [b]	98 (38.6)	7 (5.3)
95% CI [c]	32.6, 44.6	1.5, 9.1
Common Rate Difference (95% CI) [e]	33.1 (26.1, 40.2)	
Common Odds Ratio (95% CI) [e]	11.79 (5.19, 26.81)	
Response Rate of VGPR or better (sCR or CR or VGPR), n (%) [b]	153 (60.2)	20 (15.2)
95% CI [c]	54.2, 66.3	9.0, 21.3

Note: Only the assessments before the first progressive disease are included in the analysis. The assessments after the start of a new antimyeloma therapy are not considered.
a Including subjects who did not have any response assessment data, or whose only assessment was response not evaluable.
b 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.
c Two-sided Wald confidence interval.
d One-sided p-value from CMH test stratified by stratification factors.
e Unstratified rate difference and odds ratio are calculated based on the observed response rate with two-sided Wald CI. Common rate difference, odds ratio and CI are based on Mantel-Haenszel estimate. Additional two-sided 97.2% CI for common risk difference is to match the one-sided superiority boundary 0.014 in p-value scale used for this interim analysis.

ORR per IRC at the updated DCO (28-Apr-2023) was 71.3% (95% CI: 65.7, 76.8) for the ide-cel arm compared to 42.4% (95% CI: 34.0, 50.9) for the comparator arm.

Table 31. Summary of Overall response rate results from KarMMa-3 (intent-to-treat population) (DCO 28 April 2023)

	Abecma arm (N = 254)	**Standard regimens arm (N = 132)**
Overall response rate		
n (%)	181 (71.3)	56 (42.4)

	Abecma arm **(N = 254)**	**Standard regimens arm** **(N = 132)**
95% CI (%)[c]	(65.7, 76.8)	(34.0, 50.9)
CR or better (sCR+CR)	111 (43.7)	7 (5.3)
sCR	103 (40.6)	6 (4.5)
CR	8 (3.1)	1 (0.8)
VGPR	45 (17.7)	15 (11.4)
PR	25 (9.8)	34 (25.8)

Key secondary endpoint - OS

At the DCO (18-Apr-2022) for the pre-planned interim OS IA1 (from PFS IA2) analysis, with 49% of the events required for the final analysis (109 out of 222 events) the OS data presented with HR = 1.093 (95% CI: 0.727, 1.645), and one-sided p = 0.6657 in all randomized subjects. The CI for HR crossed 1 and the one-sided p-value for OS did not meet the significance boundaries for either superiority of efficacy (< 0.001) or futility (> 0.8).

An additional IA for OS utilizing the data lock planned for a safety update of the study (DCO: 3-Oct-2022) was performed.

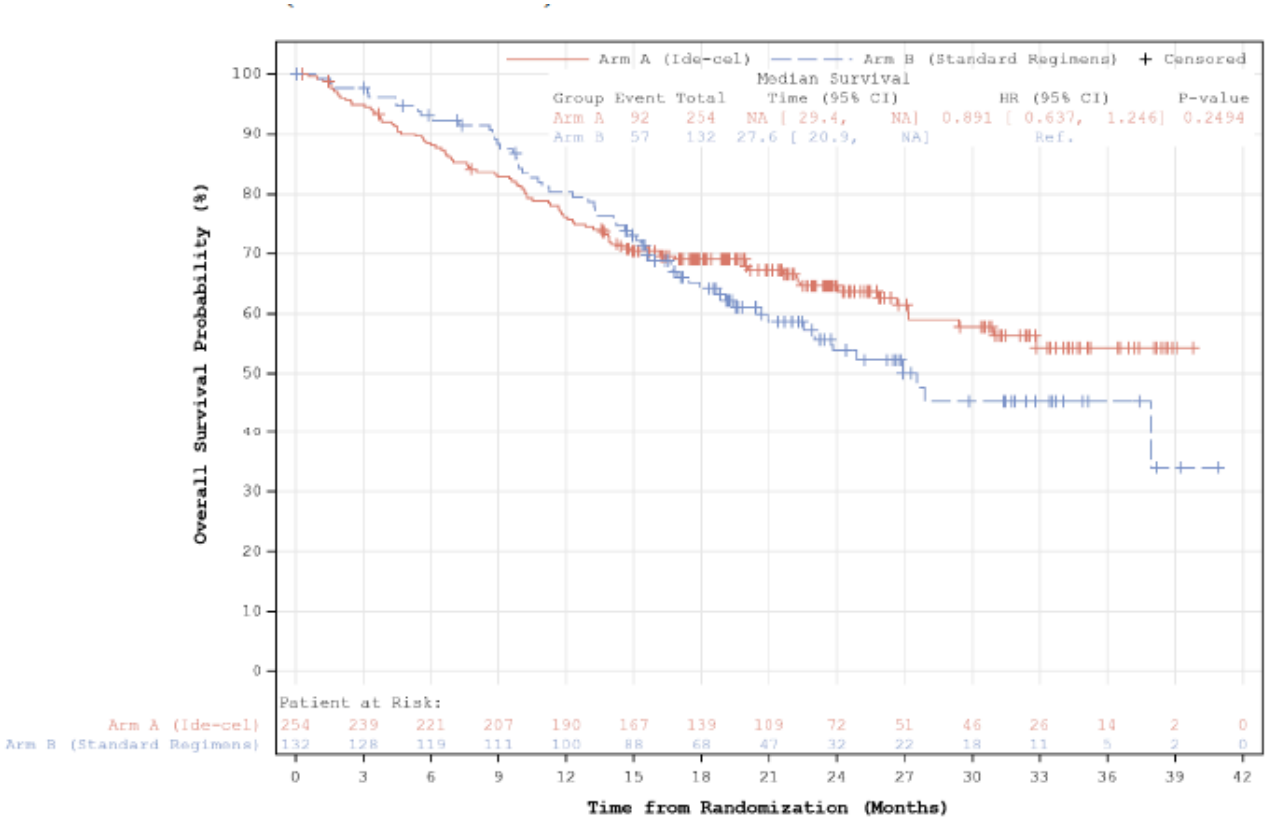
At the additional interim analysis, OS IA2, study MM-003 had a median follow-up of approximately 24 months (24.2 months [min - max: 8.0 - 41.0] for the ide-cel arm and 23.6 months [min - max: 5.9 - 40.9] for the standard regimens arm). With 67.1% of the events required for the final analysis (149 out of 222 events), OS data presented with a HR = 0.891 (95% CI: 0.637, 1.246) and a p-value of 0.2494 for all randomized subjects. The KM plot of OS for the ITT population at DCO (03-Oct-2022) for the additional interim OS IA2 is shown below.

Table 32. Summary of OS - ITT population at DCO (03-Oct-2022) for the additional interim OS IA2

	Arm A (Ide-cel) (N = 254)	Arm B (Standard Regimens) (N = 132)
Overall Survival (OS) status, n (%)	254 (100.0)	132 (00.0)
Censored, n (%)	162 (63.8)	75 (56.8)
Died, n (%)	92 (36.2)	57 (43.2)
OS Survival Time (months)[a]		
25th Percentile (95% CI)	12.4 (10.2, 16.1)	14.2 (10.4, 16.7)
Median (95%CI)	NA (29.4, NA)	27.6 (20.9, NA)
75th Percentile (95% CI)	NA (NA, NA)	NA (37.9, NA)
Survival probability [b]		
At 6 Months Event-Free- % (SE)	88.1 (2.0)	93.1 (2.2)
At 12 Months Event-Free- % (SE)	76.1 (2.7)	80.3 (3.5)
At 18 Months Event-Free- % (SE)	69.1 (2.9)	64.2 (4.4)
At 24 Months Event-Free- % (SE)	64.6 (3.2)	54.0 (5.0)
P-value [c]	0.2494	
Stratified Hazard Ratio (95% CI) [d]	0.891 (0.637,1.246)	Ref.
Unstratified Hazard Ratio (95% CI) [d]	0.825 (0.593,1.149)	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] SE is based on Greenwood formula.
[c] P-value is 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] Stratified and unstratified hazard ratio are based on the univariate Cox proportional hazards model. Confidence interval is two-sided.

Figure 33. KM plot of OS - ITT population at DCO (03-Oct-2022) for the additional interim OS IA2



Piecewise OS HRs of ide-cel versus standard regimens were 1.876 (95% CI: 0.890, 3.958) in the first 6-month interval, and 0.703 (95% CI: 0.479, 1.031) in the interval after 6 months from randomization, respectively. Hence, survival events in the first 6 months from randomization were further characterized. For subjects in the first 6 months from randomization, 30 (11.8%) death events were reported in the ide-cel arm and 9 (6.8%) in the standard regimen arm, respectively. Key baseline demographics and disease characteristics for the patients in the ide-cel arm who died within 6 months from randomization compared to the ITT population in the ide-cel arm and standard regimens arm are provided in the table below.

Table 33. Death summary - all randomized subjects who died within 6 months after randomization

	Arm A (Ide-cel) (N=254)	Arm B (Standard Regimens) (N=132)
Number of Subjects who died (%)	30 (11.8%)	9 (6.8%)
Primary Reason for Death (%)		
Death from an AE (not otherwise specified)	8 (3.1%)	3 (2.3%)
Death from Malignant Disease, or Complication due to Malignant disease	18 (7.1%)	6 (4.5%)
Death from Other Cause	4 (1.6%)	0
Number of Subjects who Did Not Receive Study Treatment and Died (%)	17 (6.7%)	0
Primary Reason for Death (%)		
Death from an AE (not otherwise specified)	3 (1.2%)	0
Death from Malignant Disease, or Complication due to Malignant Disease	13 (5.1%)	0
Death from Other Cause	1 (0.4%)	0
Number of Subjects who Received Study Treatment and Died (%)	13 (5.1%)	9 (6.8%)
Primary Reason for Death (%)		
Death from an AE (not otherwise specified)	5 (2.0%)	3 (2.3%)
Death from Malignant Disease, or Complication due to Malignant Disease	5 (2.0%)	6 (4.5%)
Death from Other Cause	3 (1.2%)	0

Table 34. Key baseline demographics and disease characteristics – all randomized subjects in ide-cel arm and standard regimens arm who died within 6 months from randomization

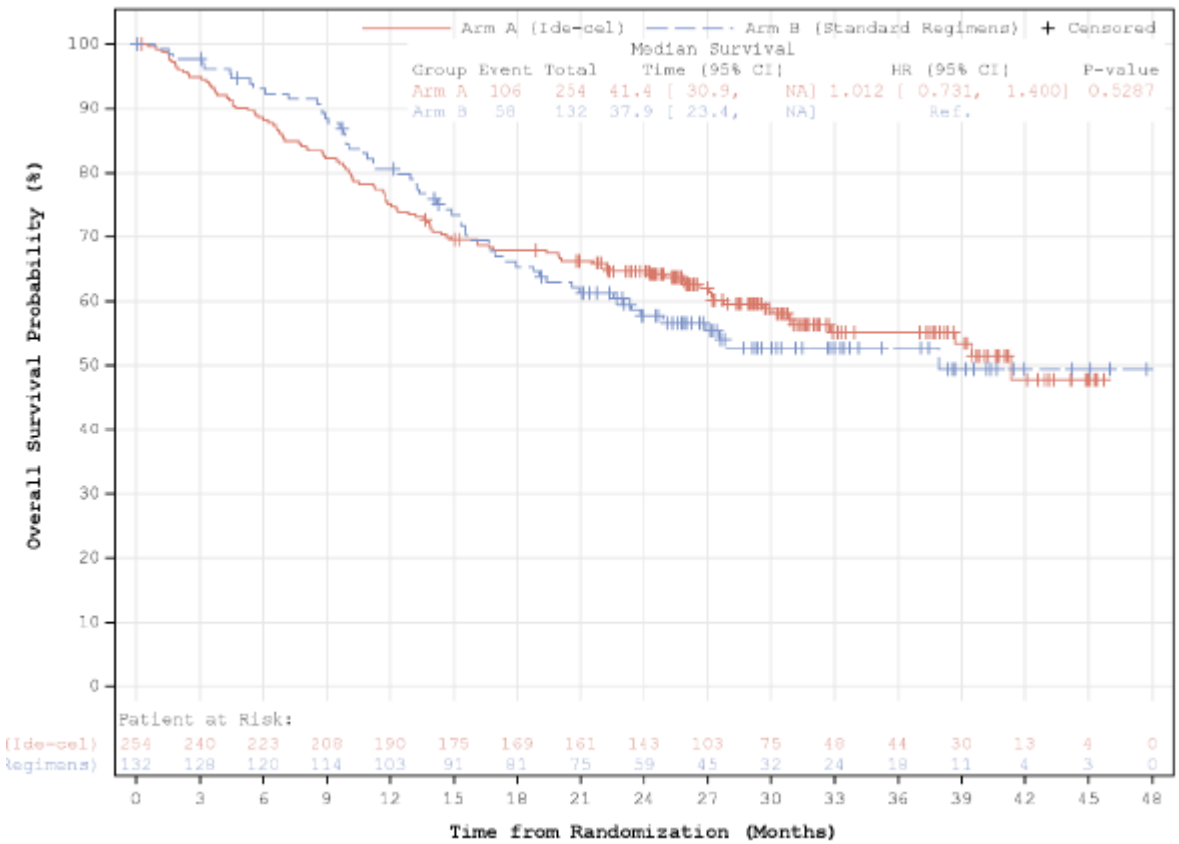
	Arm A (Ide cel)		Arm B (Standard Regimens)	
Parameters	Subjects Who Died within 6 Months from Randomisation (N=30)	ITT Population (N=254)	Subjects Who Died within 6 Months from Randomisation (N=9)	ITT Population (N=132)
ECOG Performance Status - n (%)[a]				
0	8 (26.7)	120 (47.2)	1 (11.1)	66 (50.0)
1	21 (70.0)	133 (52.4)	8 (88.9)	62 (47.0)
2	0	0	0	3 (2.3)
3	1 (3.3)	1 (0.4)	0	1 (0.8)
R-ISS, (derived) - n (%)[b]				
Stage I/II	21 (70.0)	200 (78.7)	7 (77.8)	108 (81.8)
Stage III	9 (30.0)	31 (12.2)	2 (22.2)	14 (10.6)
Missing/Unknown	0	23 (9.1)	0	10 (7.6)
Tumor Burden - n (%) [c]				
High	14 (46.7)	71 (28.0)	2 (22.2)	34 (25.8)
Low	13 (43.3)	172 (67.7)	6 (66.7)	90 (68.2)

Parameters	Arm A (Ide cel)		Arm B (Standard Regimens)	
	Subjects Who Died within 6 Months from Randomisation (N=30)	ITT Population (N=254)	Subjects Who Died within 6 Months from Randomisation (N=9)	ITT Population (N=132)
Missing/Unknown	3 (10.0)	11 (4.3)	1 (11.1)	8 (6.1)
Presence of Extramedullary Plasmacytoma - n (%)				
Yes	12 (40.0)	61 (24.0)	3 (33.3)	32 (24.2)
Radiological Only	0	6 (2.4)	0	2 (1.5)
Both Clinical and Radiological	12 (40.0)	55 (21.7)	3 (33.3)	30 (22.7)
No	17 (56.7)	192 (75.6)	6 (66.7)	100 (75.8)
Missing/Unknown	1 (3.3)	1 (0.4)	0	0
Cytogenetic Abnormality - n (%)[d]				
High Risk	21 (70.0)	107 (42.1)	6 (66.7)	61 (46.2)
Del (17p)	15 (50.0)	66 (26.0)	2 (22.2)	42 (31.8)
t (4;14)	6 (20.0)	43 (16.9)	4 (44.4)	18 (13.6)
t (14;16)	1 (3.3)	8 (3.1)	0	4 (3.0)
Non-High Risk	9 (30.0)	114 (44.9)	3 (33.3)	55 (41.7)
Not Evaluable or Missing	0	33 (13.0)	0	16 (12.1)
Triple Refractory - n(%) [e]				
Yes	26 (86.7)	164 (64.6)	7 (77.8)	89 (67.4)
No	4 (13.3)	90 (35.4)	2 (22.2)	43 (32.6)
Distribution of Prior Ani-myeloma Regimens - n (%)				
2	7 (23.3)	78 (30.7)	4 (44.4)	39 (29.5)
3	14 (46.7)	95 (37.4)	2 (22.2)	49 (37.1)
4	9 (30.0)	81 (31.9)	3 (33.3)	44 (33.3)
Time to Progression on Last Prior Anti-myeloma Therapy (months)[f]				
Median (Min, Max), months	4.6 (1.1, 21.0)	7.1 (0.7, 67.7)	3.6 (0.4, 22.5)	6.9 (0.4, 66.0)

[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] 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%.
[d] 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.
[e] Triple refractory is defined as refractory to at least one IMiD, one PI and one anti-CD38 antibody.
[f] Time to progression calculated based on summary statistics instead of Kaplan-Meier estimator.

Updated OS data from DCO 28-Apr-2023, with 74% of the events required for the final analysis (164 out of 222 events), are shown below. Median OS was 41.4 months (95% CI: 30.9, NA) for the ide-cel arm, versus 37.9 months (95% CI: 23.4, NA) for the comparator arm (HR =1.012 [95% CI: 0.731, 1.400]). At this update, 58.3% and 56.1% of the patients censored in the ide-cel arm and the standard regimens arm, respectively.

Figure 14. KM curves of OS in ITT population (DCO 28-Apr-2023)



OS analysis in subjects with no high-risk factors

To better understand the impact of the high-risk factors (high tumor burden, R-ISS stage III, presence of high-risk cytogenetic abnormalities or presence of extramedullary plasmacytoma) on OS, the MAH examined OS in subjects with none of these 4 high-risk factors and with at least one of the 4 high-risk factors. The result of the OS analysis in subjects with none of these 4 high-risk factors indicate an absence of early numerical disadvantage in the ide-cel arm and a trend in OS benefit in favor of ide-cel

with HR = 0.33 (95% CI: 0.16-0.64,). The results of the OS analysis in subjects with at least 1 of the 4 high-risk factors indicate a HR of 1.3 (95% CI: 0.9-1.89,), with the confidence interval covering 1.

Figure 15.4 KM curve of OS in patients with none of the four high-risk factors (DCO 28 April 2023)

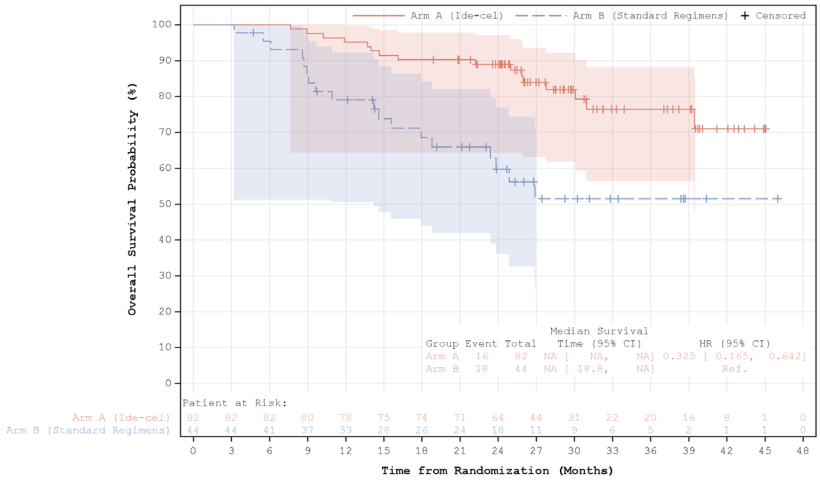
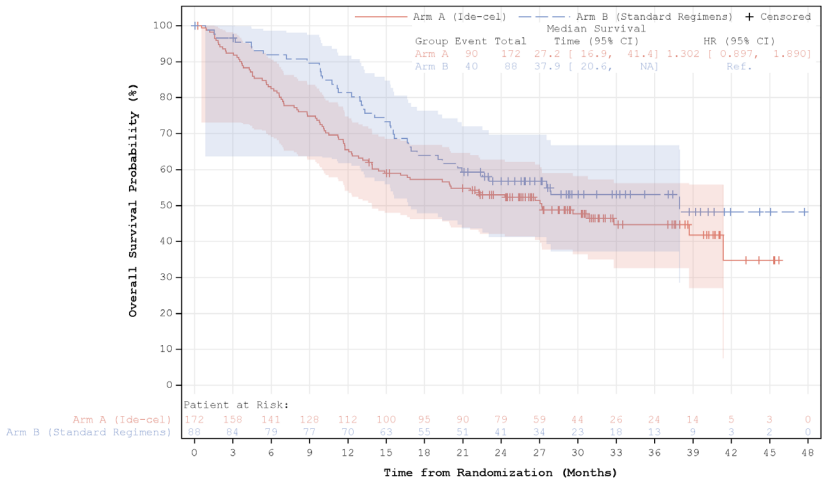


Figure 16.5 KM curve of OS in patients with at least one of the four high-risk factors (DCO 28 april 2023)



Other secondary endpoints

Duration of Response (DoR) per IRC

The median DoR (DCO 18 april 2022), based on IMWG criteria per IRC, was 13.9 months (95% CI: 11.2, 17.8) for the ide-cel arm vs 9.2 months (95% CI: 4.9, 15.7) for the comparator arm using EMA censoring rules. At the DCO 48.1% was censored in the ide-cel arm and 32.7% was censored in the standard regimens arm.

Updated data (DCO 28-Apr-2023) showed a median DoR of 16.5 months (95% CI: 12.0, 19.4) for the ide-cel arm versus 9.7 months (95% CI: 5.4, 15.5) for the comparator arm using EMA censoring rules. This estimate was based on 128 events (out of 181 responders) for the ide-cel arm and 47 events (out of 56 responders) for the comparator arm.

Other secondary endpoints

Several other secondary endpoints, such as TTR, EFS, time to next antimyeloma treatment, PFS2 and MRD negativity rates, are presented in the table below.

Table 35. Other secondary endpoints (DCO 18 April 2022)

	Ide-cel (N=254)	**Standard Regimens (N=132)**
TTR per IRC, EMA Censoring Rules, n	181	55
Median TTR[i], mo (Min, Max)	2.9 (0.5, 13.0)	2.1 (0.9, 9.4)
DoR per IRC, EMA Censoring Rules, n	181	55
Median DoR[i], mo (95% CI)	13.9 (11.2, 17.8)	9.2 (4.9, 15.7)
EFS per IRC, EMA Censoring Rules		
Events, n (%)	159 (62.6)	103 (78.0)
Censored, n (%)	95 (37.4)	29 (22.0)
Median EFS, mo (95%CI)[a]	12.4 (11.2, 14.7)	3.9 (3.1, 5.3)
Stratified HR (95% CI)[b]	0.479 (0.370, 0.619)	
Time to next antimyeloma treatment		
Median, mo (95% CI)[a]	20.3 (16.2, 24.5)	6.9 (5.3, 8.1)
Stratified HR (95% CI)[b]	0.348 (0.259, 0.467)	
PFS2		
Progressed/Died, n (%)	112 (44.1)	62 (47.0)
Censored, n (%)	142 (55.9)	70 (53.0)
Median PFS2 (95% CI)a, mo	20.0 (17.3, 24.0)	15.9 (11.8, 21.5)
Stratified HR (95% CI)[b]	0.744 (0.543, 1.021)	
MRD-negative status by NGS and ≥ CR, n (%)[j]	51 (20.1)	1 (0.8)
95% CI[f]	(15.2, 25.0)	(0.0, 2.2)

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.
f Two-sided Wald confidence interval.
i Median is based on the Kaplan-Meier estimation.
j Negative MRD values post randomization are considered. MRD negativity is determined by at least one negative MRD value within 3 months prior to achieving CR or above until time of progression/death (exclusive). ITT population is used as a denominator. The primary analysis for MRD negative response uses the sensitivity of 10^{-5}.

Table 36. Summary of MRD-negative status by NGS and ≥ CR results from KarMMa-3 (intent-to-treat population) (DCO 28 April 2023)

	Abecma arm **(N = 254)**	**Standard regimens arm** **(N = 132)**
MRD-negative status by NGS and ≥ CR		
MRD negativity rate, n (%)[d]	57 (22.4)	1 (0.8)
95% CI (%)[c]	(17.3, 27.6)	(0.0, 2.2)

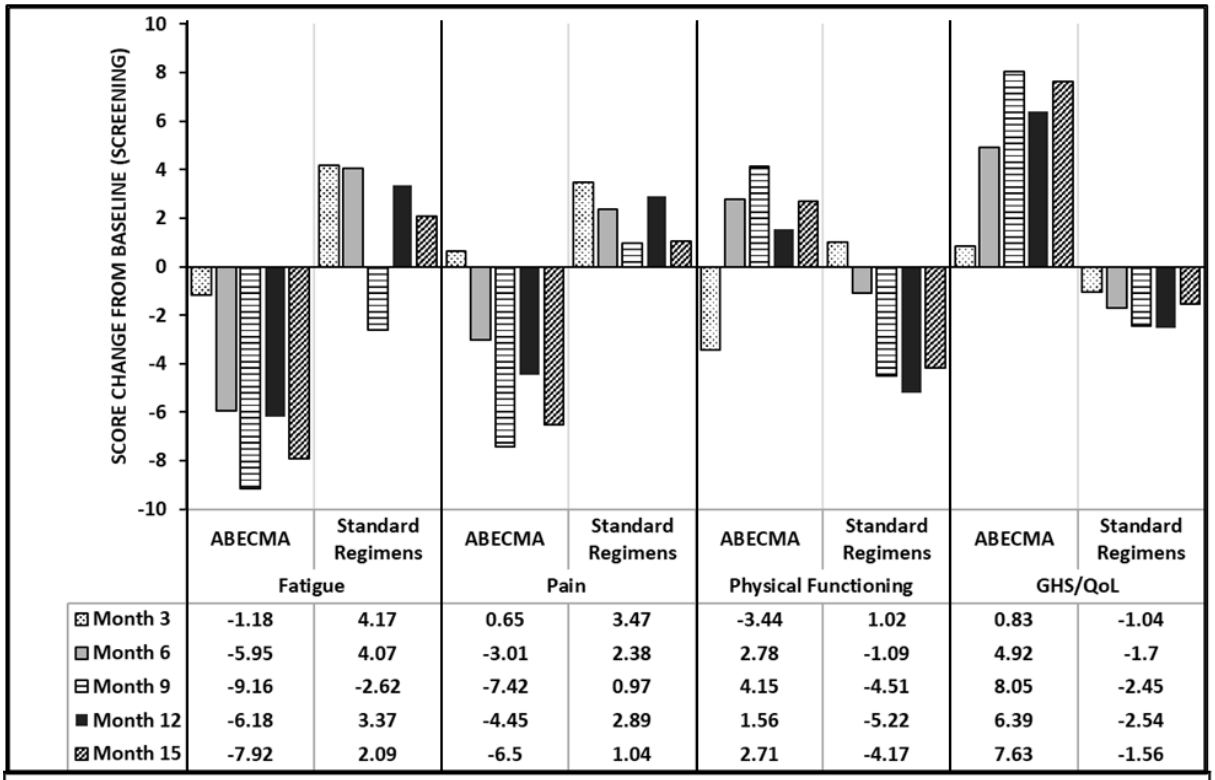
PRO

Descriptive analyses

Three PRO measures (EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D-5L) were completed at baseline (screening), monthly through month 24 and every 3 months thereafter. The completion and compliance rates were equivalent across the PRO assessments with compliance rates > 80% at most visits. Rates were similar between the two treatment arms.

Of the questionnaire responders (Abecma n = 211; standard regimens n = 108), patients treated with ide-cel experienced improvements and differences in mean score changes from baseline compared to patients treated with standard regimens in most PRO domains, including fatigue, pain, physical functioning and GHS/QoL.

Figure 17. EORTC QLQ-C30 - Mean score changes at month 3, 6, 9, 12 and 15 from baseline for fatigue, pain, physical functioning, and GHS/QoL domains in MM-003 study



	Fatigue		Pain		Physical Functioning		GHS/QoL	
	ABECMA	Standard Regimens	ABECMA	Standard Regimens	ABECMA	Standard Regimens	ABECMA	Standard Regimens
Month 3	-1.18	4.17	0.65	3.47	-3.44	1.02	0.83	-1.04
Month 6	-5.95	4.07	-3.01	2.38	2.78	-1.09	4.92	-1.7
Month 9	-9.16	-2.62	-7.42	0.97	4.15	-4.51	8.05	-2.45
Month 12	-6.18	3.37	-4.45	2.89	1.56	-5.22	6.39	-2.54
Month 15	-7.92	2.09	-6.5	1.04	2.71	-4.17	7.63	-1.56

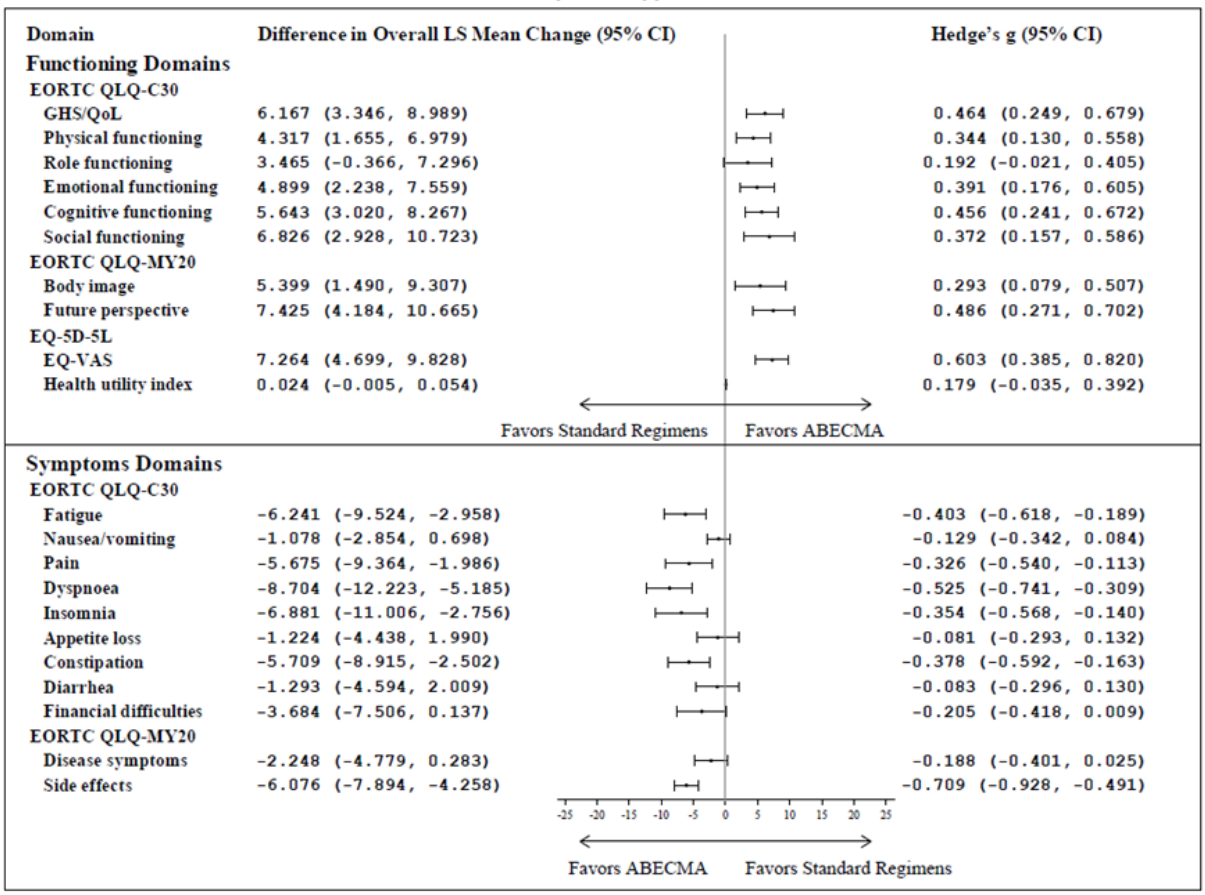
	Baseline (Screening)	Month 3	Month 6	Month 9	Month 12	Month 15
ABECMA Arm (N)	211	151	144	119	90	59
Standard Regimens Arm (N)	108	72	49	37	23	16

Negative score change from baseline represent improvement in symptoms for fatigue and pain domains, whereas positive score change from baseline represents better functioning for physical and GHS/QoL domains.

Constrained longitudinal data analyses (cLDA)

A comparison of least square (LS) mean changes from baseline to month 25 using cLDA for the EORTC QLQ-C30 domains, EORTC QLQ MY-20 domains, and EQ-5D-5L (health utility and EQ-VAS) is shown here below.

Figure 18. Forest plot of between-group differences in the cLDA overall LS mean change from baseline by treatment group in MM-003 study (Abecma n = 211; standard regimens n = 108)



CI = Confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life-of-Core 30 Questionnaire; EORTC QLQ-MY20 = European Organization for Research and Treatment of Cancer Quality of Life-of-Questionnaire Multiple Myeloma Module; EQ-VAS = Visual Analogue Scale; GHS = Global health status; LS = Least square; QoL = Quality of Life.

[a] The guideline by Cohen (1998, 1992) for the interpretation of Hedge's g values is 0.20 to be indicative of small effects; 0.50 for medium effects, and 0.80 for large effects.

[b] Primary domains of interest: EORTC QLQ-C30 domains of global health status/quality of life (QoL), physical functioning, cognitive functioning, fatigue and pain; EORTC QLQ-MY20 domains of disease symptoms and side effects of treatment; EQ-5D-5L health utility index and EQVAS. Remaining domains considered secondary domains.

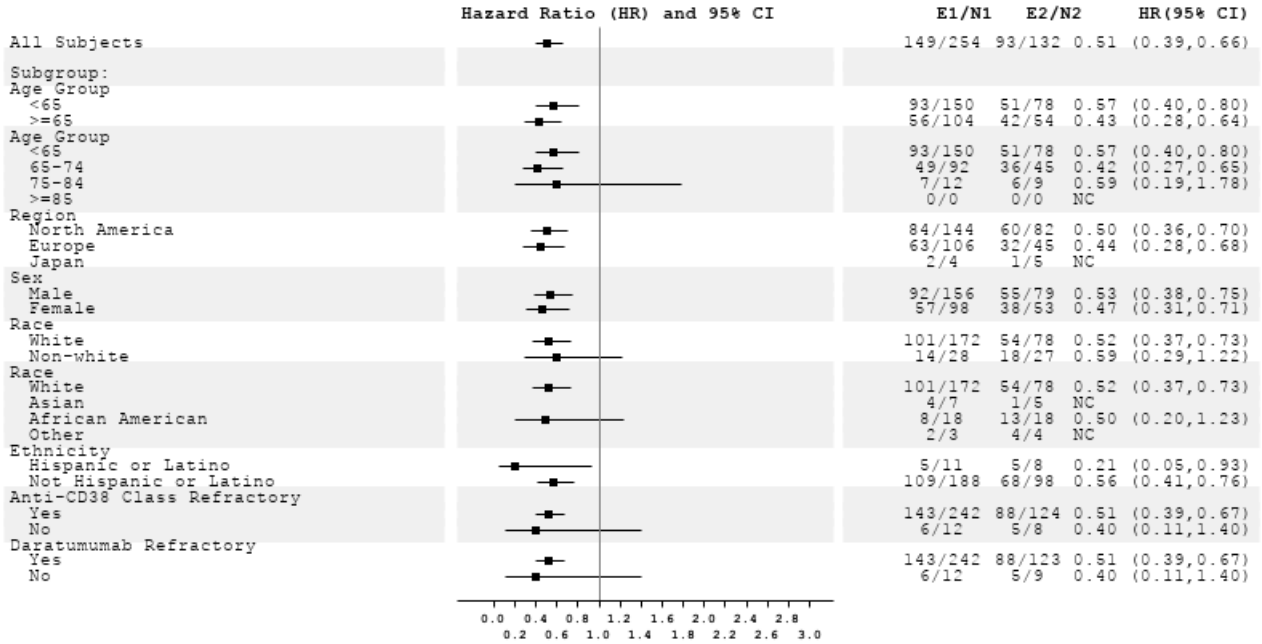
[c] Analysis did not include multiplicity adjustment.

Ancillary analyses

Subgroup Analysis on PFS (Primary Endpoint)

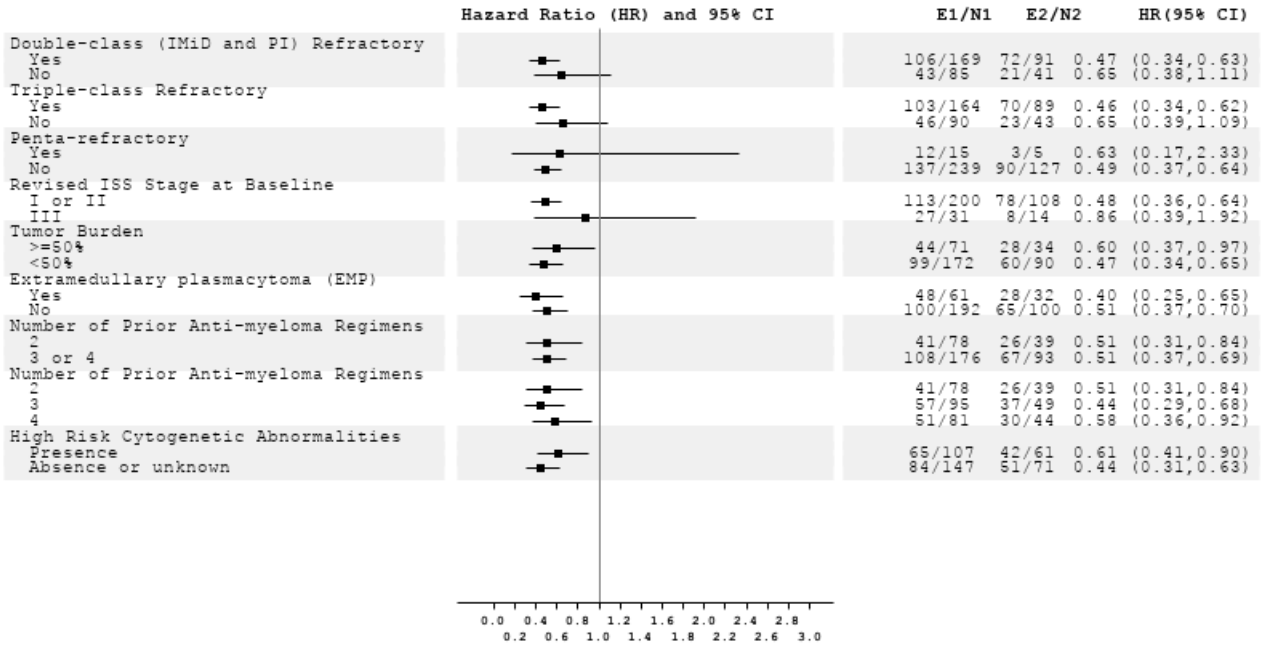
Forest plot for PFS HR for all pre-defined subgroups are shown below.

Figure 19. Forest plot for PFS hazard ratio based on IMWG criteria per IRC, FDA censoring rules - ITT population



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.

Figure 20. Forest plot for PFS hazard ratio based on IMWG criteria per IRC, FDA censoring rules - ITT population

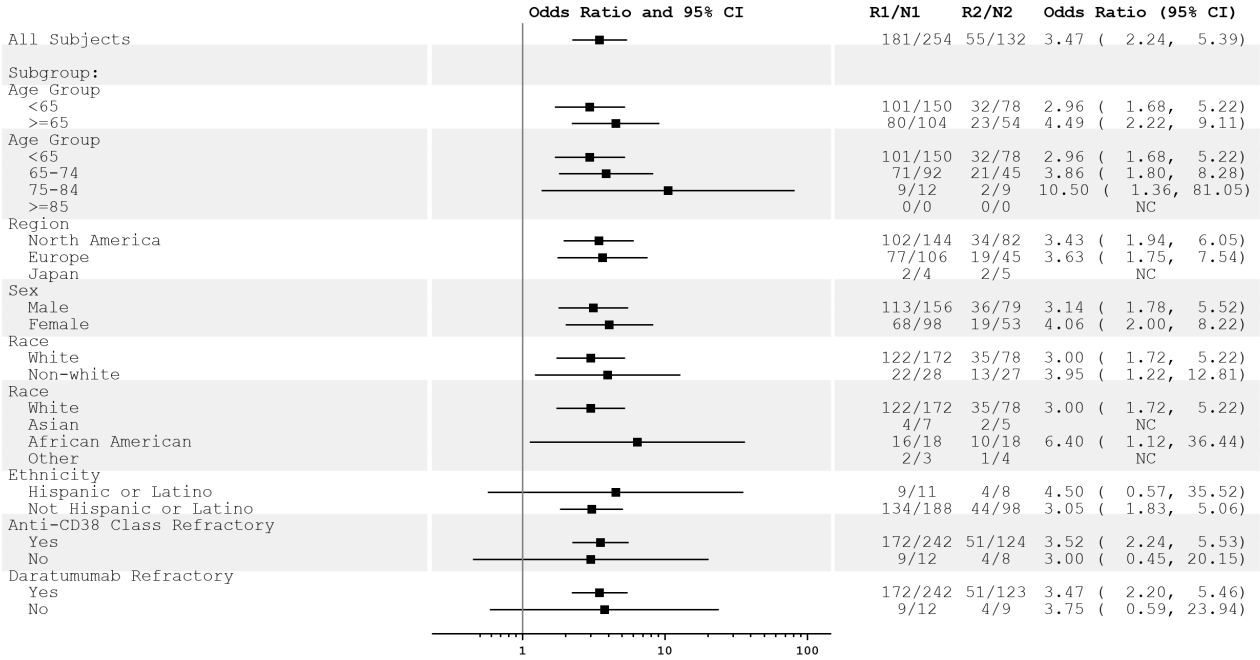


E1/N1 = number of events/number of subjects assigned to Ide-cel Arm in the subgroup.
E2/N2 = number of events/number of subjects assigned to standard regimens arm in the subgroup.
Note: HR is unstratified HR for ide-cel arm vs standard regimens arm based on the univariate Cox proportional hazards model. CI is two-sided. HR is not computed for subgroups if both N1 and N2 are less than 10. NC = Not calculated.

Subgroup Analysis on ORR (Secondary Endpoint)

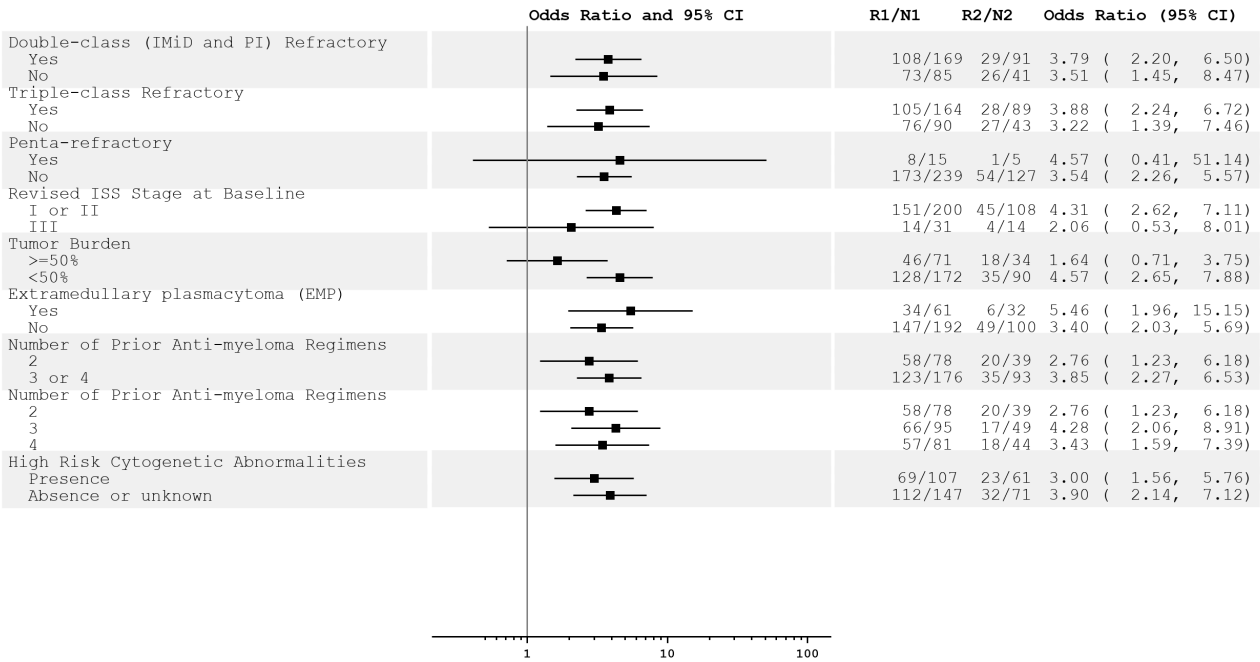
Forest plot for ORR odds ratio for all pre-defined subgroups are shown here below.

Figure 61. Forest plot for ORR odds ratio between ide-cel and standard regimens arms based on IMWG criteria per IRC, - ITT population.



R1/N1 = number of responders/number of subjects assigned to Ide-cel Arm in the subgroup.
R2/N2 = number of responders/number of subjects assigned to Standard Regimens Arm in the subgroup.
Odds ratio is unstratified and based on the observed response rate. Confidence interval (CI) is two-sided Wald CI.
Odds ratio is not computed for subgroups if both N1 and N2 are less than 10.

Figure 72. Forest plot for ORR odds ratio between ide-cel and standard regimens arms based on IMWG criteria per IRC, - ITT population.



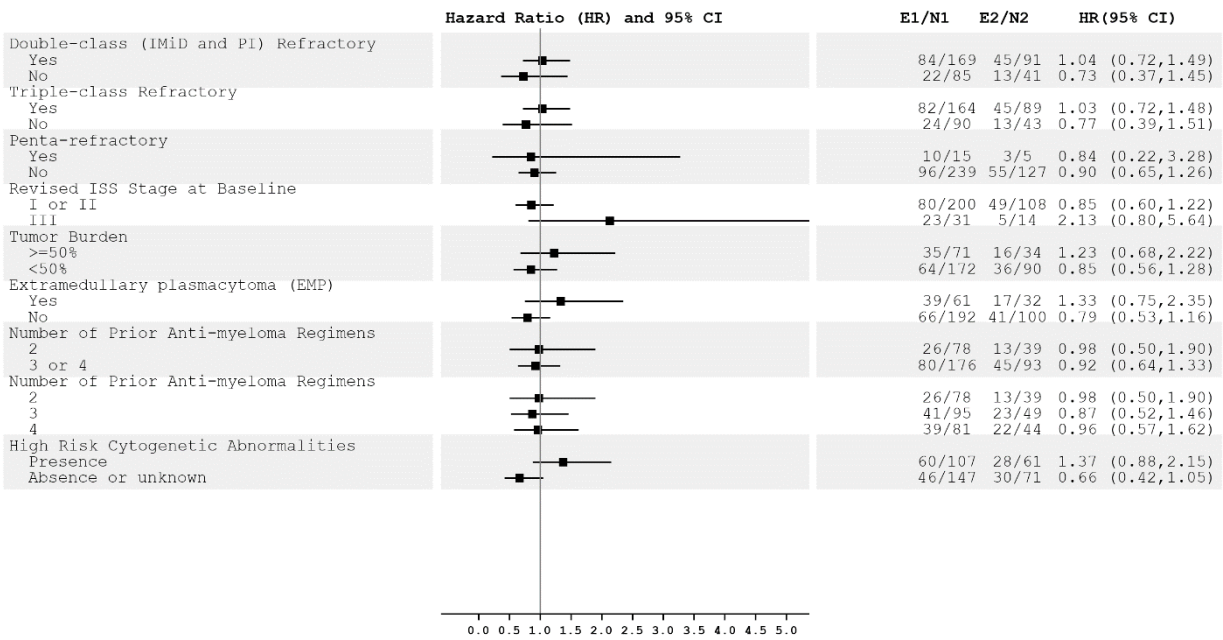
R1/N1 = number of responders/number of subjects assigned to Ide-cel Arm in the subgroup.
R2/N2 = number of responders/number of subjects assigned to Standard Regimens Arm in the subgroup.

Odds ratio is unstratified and based on the observed response rate. Confidence interval (CI) is two-sided Wald CI. Odds ratio is not computed for subgroups if both N1 and N2 are less than 10.

Subgroup Analysis on OS (Secondary Endpoint)

Forest plot for OS hazard ratio for pre-defined subgroups are shown in the figure below.

Figure 23. Forest Plot for hazard ratio based on OS - ITT population (DCO 28-Apr-2023)



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: hazard ratio (HR) is unstratified HR form ide-cel Arm vs Standard Regimens Arm based on the univariate Cox proportional hazards model. Confidence interval (CI) is two-sided. HR is not computed for subgroups if both N1 and N2 are less than 10. NC=Not calculated. CIs which exceed 5 are truncated at 5 for plotting purposes.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 3710. Summary of efficacy for MM-003

Title: A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of ide-cel versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3)	
Study identifier	BB2121-MM-003 (MM-003)
Design	A multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of ide-cel versus standard regimens in subjects with RRMM who had received 2 to 4 prior myeloma regimens including DARA, an IMiD, and a PI. Eligible subjects were randomized in a 2:1 ratio to ide-cel (Arm A) or standard regimens (Arm B) using an IRT, stratified by the following factors: age (< 65 years versus ≥ 65 years), number of prior antimyeloma regimens (2, 3, or 4), and high risk cytogenetic abnormalities (t[4;14] or t[14;16] or del 17p: presence of these known (from baseline or historical cytogenetic results) high risk cytogenetic abnormalities versus absence or unknown presence of these high risk cytogenetic abnormalities)

	Duration: FPFV: 16-Apr-2019; LPLV (clinical cut-off date): 18-Apr-2022; clinical DBL for the primary CSR:14-Jul-2022. The study is ongoing.	
Hypothesis	For this interim analysis, the null hypothesis was to be rejected if the p-value was ≤ 0.014 for the comparison of PFS in subjects with RRMM, treated with ide-cel or standard regimens.	
Treatment groups	**Ide-cel Arm**: 150 to 450 × 10^6 CAR+ T cells/ IV infusion following LD chemotherapy (3 consecutive days of fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 IV) **Standard regimens Arm:** One of the following standard treatment regimens: DARA in combination with POM and low-dose dexamethasone (DPd) DARA in combination with BTZ and low-dose dex (DVd) IXA in combination with LEN and low-dose dex (IRd) CFZ in combination with low-dose dex (Kd) ELO in combination with POM and low-dose dex (EPd)	
ENDPOINTS AND ANALYSES		
Objectives	**Efficacy Endpoint**	**Endpoint Description**
Primary		
To compare the efficacy of ide-cel to standard regimens in subjects with RRMM	PFS by IRC	Time from randomization to the first documentation of progressive disease based on the IMWG Uniform Response Criteria for MM as assessed by an IRC or death due to any cause, whichever occurs first
Key Secondary (Hierarchically Tested)		
Evaluate additional efficacy parameters of ide-cel compared to standard regimens in subjects with RRMM	ORR	Percentage of subjects who achieved PR or better according to IMWG Uniform Response Criteria for MM as assessed by an IRC.
	OS[a]	Time from randomization to time of death due to any cause
Other Secondary		
Evaluate additional efficacy parameters of ide-cel compared to standard regimens	CR rate	Percentage of subjects who achieved CR or better according to IMWG Uniform Response Criteria for MM
	DoR	Time from first documentation of response (PR or better) to first documentation of disease progression or death from any cause, whichever occurs first
	TTR	Time from randomization to the first documentation of response (PR or better)
	EFS	Time from randomization to the first documentation of progressive disease, first day when subject receives another antimyeloma treatment or death due to any cause, whichever occurs first

	PFS2	Time from randomization to second objective disease progression on subsequent therapy (Arm A: PD observed after the next antimyeloma regimen that is different from ide-cel regimen; Arm B: subsequent therapy including ide-cel) or death from any cause, whichever is first
	Time to Next Antimyeloma Treatment	Time from randomization to the first day when subjects receive another antimyeloma treatment, which includes ide-cel for subjects in Treatment Arm B.
Evaluate the percentage of subjects who attain MRD negative status by NGS	MRD negativity	The proportion of subjects with ≥ CR who are MRD negative at any time point within 3 months prior to achieving ≥ CR until the time of progression or death. at sensitivity level of 10^{-5} nucleated cells using NGS.
Evaluate the impact of bb2121 compared to standard regimens on the changes in HRQoL	PRO	Changes in subject-reported health related quality of life and multiple myeloma-related symptoms as measured by the selected domains of EORTC-QLQ-C30, specifically GH/QoL, physical functioning, pain, fatigue, and cognitive functioning and the disease symptoms and side effects of treatment measured by EORTC-QLQ-MY20

[a] The p-value for OS did not cross the significance boundaries for either efficacy or futility at this interim analysis; therefore, the study team remains blinded to OS results.

Database Lock	14-Jul-2022 (data cutoff: 18-Apr-2022)
Analysis Population	The ITT population (N=386) includes all subjects in the screened population who are randomized to one of the two treatment arms. This is the primary analysis population for efficacy.

RESULTS AND ANALYSES

Summary of Efficacy

	Ide-cel Arm (N=254)	**Standard Regimens Arm (N=132)**
Primary Endpoint		
PFS per IRC, FDA Censoring Rules		
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)
PFS per IRC, EMA Censoring Rules		
Events (Progressed/Died), n (%)	154 (60.6)	100 (75.8)
Censored, n (%)	100 (39.4)	32 (24.2)
Median PFS (95% CI)[a], mo.	12.5 (11.3, 15.3)	4.4 (3.4, 5.8)
Stratified HR (95% CI)[b]	0.487 (0.375, 0.633)	
Event-free rate % (SE)[d]		
6-month	73.3 (2.8)	39.1 (4.5)
12-month	53.4 (3.2)	28.8 (4.3)
	Ide-cel Arm (N=254)	**Standard Regimens Arm (N=132)**
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)
Other Secondary Endpoints		
CR Rate per IRC[e], n (%)	98 (38.6)	7 (5.3)
95% CI[f]	32.6, 44.6	1.5, 9.1
TTR per IRC, EMA Censoring Rules, n	181	55
Median TTR[i], mo (Min, Max)	2.9 (0.5, 13.0)	2.1 (0.9, 9.4)
DoR per IRC, EMA Censoring Rules, n	181	55
Median DoR[i], mo, (95% CI)	13.9 (11.2, 17.8)	9.2 (4.9, 15.7)
EFS per IRC, EMA Censoring Rules		
Events, n (%)	159 (62.6)	103 (78.0)
Censored, n (%)	95 (37.4)	29 (22.0)
Median EFS, mo (95%CI)[a]	12.4 (11.2, 14.7)	3.9 (3.1, 5.3)
Stratified HR (95% CI)[b]	0.479 (0.370, 0.619)	
Event-free Rate % (SE)[d]		
6-month	71.9 (2.8)	36.3 (4.4)

12-month	52.4 (3.2)	27.2 (4.1)
Time to next antimyeloma treatment		
Median, mo (95% CI)[a]	20.3 (16.2, 24.5)	6.9 (5.3, 8.1)
Stratified HR (95% CI)[b]	0.348 (0.259, 0.467)	
	Ide-cel Arm (N=254)	**Standard Regimens Arm (N=132)**
PFS2		
Progressed/Died, n (%)	112 (44.1)	62 (47.0)
Censored, n (%)	142 (55.9)	70 (53.0)
Median PFS2 (95% CI)[a], mo	20.0 (17.3, 24.0)	15.9 (11.8, 21.5)
Stratified HR (95% CI)[b]	0.744 (0.543, 1.021)	
Event-free rate % (SE)[d]		
6-month	85.1 (2.3)	84.4 (3.3)
12-month	72.1 (2.9)	57.8 (4.7)
MRD-negative status by NGS and ≥ CR, n (%)[j]	51 (20.1)	1 (0.8)
95% CI	(15.2, 25.0)	(0.0, 2.2)

Data Cut Off	28-Apr-2023
Analysis Population	The ITT population (N=386) includes all subjects in the screened population who are randomized to one of the two treatment arms. This is the primary analysis population for efficacy.

RESULTS AND ANALYSES

Summary of Efficacy

	Ide-cel Arm (N=254)	**Standard Regimens Arm (N=132)**
Primary Endpoint		
PFS per IRC, FDA Censoring Rules		
Events (Progressed/Died), n (%)	184 (72.4)	105 (79.5)
Median PFS (95% CI)[a], mo.	13.8 [11.8, 16.1]	4.4 [3.4, 5.8]
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]	0.49 [0.38, 0.63]	
Key Secondary Endpoint (Hierarchically Tested)		
ORR[e] per IRC		
N responders (%)	181 (71.3)	56 (42.4)
95% CI[f]	(65.7, 76.8)	(34.0, 50.9)
CR or better (sCR+CR)	111 (43.7)	7 (5.3)
sCR, n (%)	103 (40.6)	6 (4.5)

CR, n (%)	8 (3.1)	1 (0.8)
VGPR, n (%)	45 (17.7)	15 (11.4)
PR, n (%)	25 (9.8)	34 (25.8)
Other Secondary Endpoints		
DoR if best response is CR, n	111	7
Median DoR[i], mo, (95% CI)	15.7 [12.1, 22.1]	24.1 [4.6, NA]
DoR, if best response is PR, n	181	56
Median DoR[i], mo, (95% CI)	16.5 [12.0, 19.4]	9.7 [5.4, 15.5]
MRD-negative status by NGS and ≥ CR, n (%)[j]	57 (22.4)	1 (0.8)
95% CI	(17.3, 27.6)	(0.0, 2.2)

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 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).
d SE is based on Greenwood formula.
e Overall response rate is defined as the rate of subjects whose response is PR or better (i.e. sCR or CR or VGPR or PR); Complete response rate is defined as the rate of subjects whose response is CR or better (i.e. 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 Mantel-Haenszel 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.
h One-sided p-value from CMH test stratified by stratification factors.
i Median is based on the Kaplan-Meier estimation.
j Negative MRD values post randomization are considered. MRD negativity is determined by at least one negative MRD value within 3 months prior to achieving CR or above until time of progression/death (exclusive). ITT population is used as a denominator. The primary analysis for MRD negative response uses the sensitivity of 10^{-5}.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical study

The overall study design is considered adequate and in line with current European guidelines. The choice of an RCT is appropriate. Currently there is no single treatment algorithm for RRMM in third to fifth line per EHA-ESMO guidance, and the choice of treatment regimen depends on prior medicine exposure and responsiveness/refractoriness. Thus, the choice of the standard regimens in the comparator arm is appropriate, which is also in accordance with a recommendation from the EMA/Rapporteur during the PRIME kick-off meeting. The cross-over design will confound the OS data. However, for ethical reasons, as ide-cel is already approved for treatment of RRMM in 4th line, this is acceptable.

The inclusion and exclusion criteria are generally acceptable with minor remarks. The representativeness of the patient population to the real-world MM population is somewhat questionable since only patients with a performance status of 0-1 and no major co-morbidities or organ dysfunction were eligible. Considering the median age of the MM population, as well as the intended third and later line indication, one would expect that such strict inclusion criteria would exclude a rather large proportion of patients. While the exclusion of such patients is understood from a safety perspective, it reduces the external validity of the trial. Patients with previous allogeneic HSCT or treatment with any gene therapy-based therapeutic were excluded. This was mainly due to a potential risk of clinical manifestations of GVHD when treated with CAR-T cell therapy and is considered acceptable in a clinical trial setting.

The clinical dose range of ide-cel was 150 to 450 x 10^6 CAR+ T cells, which is the same as the dose range in the pivotal KarMMa study for the CMA. No change is proposed by the MAH to the approved target dose of 260 to 500 × 10^6 CAR+ viable T-cells in the SmPC.

Subjects in the comparator arm received study treatment with a standard regimen (DPd, DVd, IRd, Kd or EPd) that was selected by investigators based on the subject's most recent anti-myeloma treatment regimen, which is considered appropriate. The standard regimen was assigned to each subject by the investigator prior to randomization. In subjects randomized to arm A, the respective standard regimen was to be used as bridging therapy, if clinically indicated, which is considered acceptable.

The primary endpoint was PFS per IRC according to the IMWG response criteria, which is considered acceptable. The EMA Guideline recognizes PFS as an acceptable primary endpoint, as long as OS is reported as a secondary endpoint. The MAH has performed the primary analysis on PFS using FDA censoring rules, which is also prespecified in the SAP. PFS censored according to the EMA guideline has been provided as further analysis.

Key secondary endpoints were ORR per IRC and OS, tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate, which is considered acceptable. However, due to study design with possible crossover (comparator arm to ide-cel), the OS results will be of a limited value. Other secondary endpoints included CR rate, TTR, DoR, EFS, PFS2, time to next antimyeloma treatment, MRD negativity rates and PRO. The MAH defined the enrolled (ITT) population as the primary analysis population.

The sample size calculations are based on clinically relevant assumptions and the study is powered also for the key secondary endpoint ORR, which is endorsed. A stratified log-rank test was the primary analytic method to compare the treatment arms. The univariate Cox proportional hazards model stratified by stratification factors was used to compute the hazard rate (risk) ratio between treatment arms. The Kaplan-Meier (KM) product limit method was used to estimate the survival curves and the median (95% CI) was computed. The randomisation and stratification design are deemed acceptable. Statistical analyses were also stratified according to what was pre-specified.

The blinding procedures are acceptable given the study design and its logistical aspects.

Data were reported based on a primary data cut-off of 18-Apr-2022. For OS, updates based on a later data cut-off was also provided (03-Oct-2022). Updated data for PFS, ORR, DoR and OS from the final PFS analysis (DCO 28-Apr-2023) has been provided. As subjects from standard regimens arm had the possibility to receive ide-cel after disease progression, the following analyses were performed as sensitivity analyses: a 2-stage Weibull approach, also called 2-stage accelerated failure time model if data permitted it, and rank preserving structural failure time (RPSFT) method. Overall, the statistical design is satisfactory and the MAH has addressed during assessment a number of potential methodological issues ensuring that the conclusions regarding efficacy are sound.

The recruitment seems reasonable, including the distribution of regions. Overall, protocol amendments and deviations do not raise any concerns on the study conduct.

Efficacy data and additional analyses

At DCO 18 April 2022 a total of 254 subjects was assigned to the ide-cel arm and 158 (62.2%) of these subjects were still ongoing in the study. For the standard regimens arm, 132 patients were assigned and 81 (61.4%) of these subjects were still ongoing in the study, of which 52 after cross-over to ide-cel treatment post progression. The most common reason for study discontinuation in both arms was death. Out of the 132 patients randomized to the standard regimens arm, 60 (45.5%) received ide-cel infusion after disease progression. The extensive cross-over will confound the OS data. In regard to this, the

MAH was asked to provide baseline data on standard regimens arm patients who received and not received ide-cel after IRC confirmation of progression. Among patients in the standard regimens arm who received ide-cel after PD more patients had high tumor burden, whereas fewer patients had ECOG PS 1 and fewer patients had received 4 prior anti-myeloma regimens compared to those who did not receive ide-cel after PD. Otherwise, the baseline demographics and disease characteristics were similar for standard regimens arm patients who received ide-cel, or not, after PD. However, these results should be interpreted with caution due to the small number of patients in each subgroup.

Overall, the baseline demographic and disease characteristics in the study are considered representative of the intended patient population with RRMM in the third- and later lines setting, and generally balanced between the ide-cel and standard regimens arms. However, the proportion of subjects with missing/not reported baseline value is relatively high for some of the parameters, such as baseline cytogenetic abnormality and R-ISS stage at baseline. In the total study population, median age was 63 years, with median 4.1 years since initial diagnosis. The rate of high-risk cytogenetics was 43.5%. Approximately 30% of the patients had received 2, 3 or 4 prior antimyeloma regimens. Of total patients, 65.5% were triple-class refractory, elucidating the fact that patients were quite heavily pretreated, with 85% of the patients having received at least one prior ASCT. Overall, the baseline demographic and disease characteristics in the study were considered representative of the intended patient population with RRMM in the third- and later lines setting. The short median time to progression on the last prior regimen before study entry in both treatment arms (7.1 months in the ide-cel arm and 6.9 months in the standard regimens arm) is reflective of the hard-to-treat nature of myeloma in the study population.

The median received dose of ide-cel was 445.3 x 10^6 CAR+ T cells (min, max: 174.9, 529.0) for the 225 subjects who received ide-cel infusion in arm A. The median time from leukapheresis to ide-cel administration was 49 days. The majority of subjects (83.9%) received bridging therapy for myeloma control during the ide-cel manufacturing. The median treatment duration of bridging therapy was 22 days.

Progression free survival (PFS)

The MM-003 study met its primary endpoint, demonstrating a statistically significant difference in PFS in favour of ide-cel [stratified HR = 0.493 (95% CI: 0.377, 0.645, p < 0.0001), using FDA censoring rules]. The median PFS was 13.3 months (95% CI: 11.8, 16.1) for patients receiving ide-cel versus 4.4 months (95% CI: 3.4, 5.9) for patients receiving standard regimens. At the DCO (18-Apr-2022) of the current analysis, 149 patients (58.7%) in the ide-cel arm and 93 patients (70.5%) in the standard regimen arm had experienced a PFS event. Consistent results were shown in the final PFS analysis (DCO 28-Apr-2023); median PFS was 13.8 months for patients treated with ide-cel compared to 4.4 months for patients treated with standard regimens (HR: 0.493 [95% CI: 0.384, 0.634]). At the final PFS analysis, 184 patients (72.4%) in the ide-cel arm and 105 patients (79.5%) in the standard regimen arm had experienced a PFS event.

The MAH has provided PFS results (Kaplan-Meier plots) from patients in Arm A according to the standard regimen they would have received should they have been randomized to Arm B, as requested. The results appear similar regardless of what standard regimen the patient would have received had they been randomised to Arm B, which is reassuring. The only subgroup outperforming the other is patients for which the investigator indicated that bridging therapy was not required, as can be expected.

The MAH also provided PFS data claimed to be censored according to the EMA guideline, which were consistent with the primary analysis, however, the description of censoring rules provided by the MAH reveals that the EMA guideline was not strictly followed. PFS data by EMA censoring rules have only been presented as a supportive analysis and not as the primary analysis.

The statistically significant improvement in the primary endpoint was further supported by various sensitivity analyses. Moreover, an improvement in PFS in patients receiving ide-cel compared to standard regimens was consistently observed in all pre-specified subgroups, including patients that were double class refractory, triple class refractory, had high-risk cytogenetics, high tumour burden or extramedullary plasmacytoma, or had received 2-4 prior antimyeloma regimens. However, a numerically higher PFS HR for patients with R-ISS stage III (CI for HR crossed 1) compared to patients with R-ISS stage I or II was observed. This could indicate slightly less benefit of ide-cel compared to the standard regimens for R-ISS stage III patients, although the number of patients in this subgroup was low, and thus the result should be interpreted with caution.

Median PFS per IRC assessment across the ide-cel dose levels of 300 to 460 x 10^6 CAR+ T cells and > 460 to 540 x 10^6 CAR+ T cells was similar, and consistent to that of the overall ide-cel arm. Only 3 subjects were treated with dose level < 300 x 10^6 CAR+ T cells, thus these results are difficult to interpret.

Overall response rate (ORR)

The study met its key secondary endpoint (hierarchically tested), demonstrating statistically significant higher ORR per IRC after ide-cel treatment. ORR was 71.3% (95% CI: 65.7, 76.8) for the ide-cel arm compared to 41.7% (95% CI: 33.3, 50.1) for the comparator arm, with a common odds ratio at 3.54 (95% CI: 2.26, 5.54) and p-value < 0.0001 (Cochran-Mantel-Haenszel test) (DCO 18 April 2022). Furthermore, a higher ORR for ide-cel treated patients compared to patients treated with standard regimens was consistently observed in all pre-specified subgroups. ORR per investigator assessment was 65% (95% CI: 59.1, 70.8) for the ide-cel arm and 40.2% (95% CI: 31.8, 48.5) for the comparator arm, thus similar to ORR per IRC assessment in both arms. Moreover, the observed ORR for ide-cel is also comparable to the ORR reported in the single-arm KarMMa study (67.1%), which was the basis of the CMA. Consistent with data from the interim analysis, ORR per IRC at the updated DCO (28-Apr-2023) was 71.3% (95% CI: 65.7, 76.8) for the ide-cel arm compared to 42.4% (95% CI: 34.0, 50.9) for the comparator arm.

Overall Survival (OS)

The MAH has presented OS data from one pre-planned as well as one additional interim analysis. At the DCO (18-Apr-2022) for the pre-planned interim OS IA1 (from PFS IA2) analysis, with 49% of the events required for the final analysis (109 out of 222 events), the OS data presented with HR = 1.093 (95% CI: 0.727, 1.645), and one-sided p = 0.6657. The 95% CI for HR crossed 1 and the one-sided p-value for OS did not meet the significance boundaries for either superiority of efficacy (< 0.001) or futility (> 0.8).

At the second interim analysis, OS IA2 (DCO 3-Oct-2022), with 67.1% of the events required for the final analysis (149 out of 222 events), OS data presented with a HR = 0.891 (95% CI: 0.637, 1.246) and a p-value of 0.2494. Median OS was not reached for the ide-cel arm (95% CI: 29.4, NA), whereas median OS was 27.6 months (95% CI: 20.9, NA) for the comparator arm. These data are considered immature, with 63.8% of the patients censored in the ide-cel arm and 56.8% of the patients censored in the standard regimens arm. Furthermore, the 95% CI for the HR crossed 1 and the KM plot revealed crossing survival curves. During the first 12 months after randomization, OS rates were numerically higher in the standard regimens arm compared to the ide-cel arm. Thereafter, at the 18 to 24-month period, OS rates were numerically higher in the ide-cel compared to the standard regimens arm.

Updated OS data from DCO 28-Apr-2023 showed consistent results; median OS was 41.4 months (95% CI: 30.9, NA) for the ide-cel arm, versus 37.9 months (95% CI: 23.4, NA) for the comparator arm (HR = 1.012 [95% CI: 0.731, 1.400]). The 95% CI for the HR crossed 1, the p-value did not meet the significance boundary for superiority of efficacy (< 0.001), and the KM plot revealed crossing

survival curves and non-proportional hazards, questioning the appropriateness of the use of the Cox model and caution is therefore needed in the interpretation of the hazard ratio. The OS data were considered immature (74% maturity, 164 of the required 222 final events), with 58.3% and 56.1% of the patients censored in the ide-cel arm and the standard regimens arm, respectively. Most censoring occurred from 21 months onwards. The major reason for censoring after 14 months, 136/146 in Arm A and 56/69 in Arm B, is that the subjects are still in follow-up. Out of these subjects still in follow-up, 53 subjects in Arm A are still in PFS follow-up, while none in Arm B. About 4% of the subjects in both arms are off study. Importantly, 56.1% of patients in the standard regimens arm had received ide-cel infusion after disease progression at the DCO of the third OS interim analysis, thus OS data are confounded by extensive cross-over between the two treatment arms. The median time from randomization to ide-cel infusion for the SOC arm patients was 8.1 months (range 2.9 - 36.7). Considering that 103 patients in Arm B were alive at 12 months, a significant proportion of them had in fact already received ide-cel or received it soon thereafter. The MAH has committed to submit final OS data from MM-003 when available in the post approval setting. The final OS data should include subgroup analysis of relevant subgroups.

The crossing survival curves, immaturity of the data as well as extensive cross-over between the treatment arms, make OS data difficult to interpret. The KM curve for OS showed that patients in the ide-cel arm have an increased risk of early death, compared to patients in the standard therapy arm.

The interpretation of OS was hampered by the option of cross-over in the control arm to ide-cel upon progression. In order to better understand the course of the OS curves and to possibly identify patients who will not benefit from ide-cel, the MAH provided the inverse probability of censoring weighting (IPCW) method to adjust for cross-over (EMA/845963/2018) and updated OS results of the control group for patients who cross-over compared to those who do not cross over, as well as an assessment of the risk of early death in patients who receive ide-cel after progression. The available re-analysis of OS data did not provide further explanation. Due to methodological weaknesses, further data updates were not expected to provide more conclusive information. OS rates remain numerically higher in the standard regimens arm compared to the ide-cel arm for the first 12 months, and after 12 months a significant proportion of patients in the SOC arm have already crossed over to receive ide-cel. Available PFS2 data does not alleviate the concerns regarding the effect on OS: median PFS2 was longer (23.5 months versus 16.7 months) in the ide-cel arm compared with the standard regimens arm (HR = 0.790 [95% CI: 0.603, 1.035]), but it should be noted that for 62% of the subjects in the SOC arm the subsequent therapy was ide-cel.

Most of the deaths that occurred within 6 months after randomization in the ide-cel arm were attributed to myeloma disease progression and occurred among subjects who never received ide-cel treatment (11/13 during the first 3 months, or 17/30 during the first 6 months). Of the 132 subjects randomized to the standard regimens arm, only 9 subjects died within 6 months from randomization, thus, the results should be interpreted with caution. The crossing of the curves, as well as the provided baseline characteristics of patients with early death, indicated that this was due to a subgroup of patients with poor prognosis experiencing potential harm by being randomised to the ide-cel arm. Indeed, subgroup analysis and KM curves showed a negative trend in OS with ide-cel treatment for certain subgroups, especially for patients with presence of high-risk cytogenetic abnormalities, but possibly also for patients with R-ISS stage III, presence of extramedullary plasmacytoma or high tumor burden. Per request, a more explicit warning regarding the above-mentioned subgroups has been included in the SmPC.

Per protocol, bridging therapy was limited to 1 cycle and the last dose had to be administered ≥ 14 days prior to the initiation of LD chemotherapy. Median time from end of bridging therapy to ide-cel infusion was 24 days. This could be suboptimal and not sufficient to control the disease in the subjects with high-

risk factors as compared to the continuous treatment in the standard regimens arm. Thus, the early deaths did not seem to be associated with ide-cel treatment *per se* but more likely due to suboptimal bridging strategies. Therefore, the MAH should submit within a time period of two months a draft protocol and SAP for a prospective observational study assessing whether potentially suboptimal bridging therapy in high-risk patients observed in the KARMMa-3 study may be alleviated in a real-world setting. This draft should then be discussed with CAT/CHMP, so that a decision can be made on whether such a prospective study should be initiated, in its initial or amended form.

Other secondary endpoints

The benefit of ide-cel was supported by several secondary endpoints. A numerically higher proportion of patients had a BOR of sCR or CR in the ide-cel arm (38.6%) compared to the standard regimens arm (5.3%). The proportion of patients who had a BOR of CR or better in the ide-cel arm was comparable to the result from the KarMMa study (30.0%). In addition, the median DoR per IRC was longer for the ide-cel arm (13.9 months (95% CI: 11.2, 17.8)) compared to the comparator arm (9.2 months (95% CI: 4.9, 15.7)). The DoR estimate was based on 94 events (out of 181 responders) for the ide-cel arm and 37 events (out of 55 responders) for the comparator arm (DCO 18 April 2022). Updated data (DCO 28-Apr-2023) showed a median DoR of 16.5 months (95% CI: 12.0, 19.4) for the ide-cel arm versus 9.7 months (95% CI: 5.4, 15.5) for the comparator arm using EMA censoring rules. This estimate was based on 128 events (out of 181 responders) for the ide-cel arm and 47 events (out of 56 responders) for the comparator arm. For comparison, the median DoR in the KarMMa study was 10.6 months, thus slightly shorter than in the present MM-003 study.

More patients achieved MRD-negative status after ide-cel treatment compared to standard regimens. However, MRD negativity rate was only reported at a fixed point in time (defined as the proportion of subjects who achieved ≥ CR and MRD negative status at a sensitivity of 10^{-5} at any time point (assessed at screening, between leukapheresis and LD chemotherapy, and at months 2, 7, and 13) within 3 months prior to achieving at least CR until the time of PD/death) whereas sustained MRD negativity rate over a period of 6-12 months would have been considered of higher prognostic value. Nevertheless, 20% versus 0.8% is a rather large difference and thus, likely, a difference would have been observed also in sustained MRD negativity rate over 6-12 months. The MAH was asked to submit data on sustained MRD negativity rate over 6-12 months. However, the MRD sampling of the study was not planned to measure sustained MRD negativity rate over a period of 6-12 months. Nevertheless, the MAH has provided an acceptable approach to estimate this post hoc. By this approach, the rates of sustained MRD negativity were reported to be numerically higher in the ide-cel arm than in the standard regimens arm, although these results should be interpreted with caution.

Shorter time to subsequent antimyeloma treatment was observed for patients in the standard regimens arm (6.9 months) compared to the ide-cel arm (20.3 months). Furthermore, median PFS2 was numerically longer in the ide-cel arm (20.0 months (17.3, 24.0) compared with the standard regimens arm (15.9 months (11.8, 21.5)). However, these data are immature, with 55.9% and 53.0% of the patients censored in the ide-cel arm and standard regimens arm, respectively.

Time to response was numerically slightly longer with ide-cel vs standard regimens (median TTR per IRC was 2.9 vs 2.1 months), and longer than observed in the single-arm KarMMa study (1 month).

The ide-cel arm showed improvements with regards to mean change from baseline on EORTC QLQ-C30 domains (fatigue, pain, physical functioning, and global health status/QoL) compared with the standard regimens arm, which were stable or worsened over time. However, the open-label design reduces the interpretability of the PRO-data, limiting their value for the benefit-risk evaluation.

Additional expert consultation

On 9th January 2024 a SAG oncology has been organised to answer the following questions to which the relevant position of the experts is provided:

1. *For the MM-003 (KarMMA-3) study; given the robust effect on PFS, a possible early detrimental effect for OS and a lack of interpretable OS data overall, does the SAG consider that the available data overall supports that a clinically relevant benefit has been demonstrated in the targeted population?*

The SAG agreed that overall a benefit has been demonstrated in terms of PFS, the primary endpoint, and ORR, which was statistically significant and clinically convincing. The benefit is clear in the intended target population and is corroborated by consistent effect across subgroups and HRQoL. The benefit is also clear from a patient perspective, especially considering the treatment-free interval following CAR-T therapy compared to other treatments and the benefit in HRQoL. An improvement in OS in favour of Ide-cel (Abecma) has not been observed. Lack of an observed effect on OS may possibly also be due to treatment switch post-progression.

Some patients applying the bridging strategies in the MM-003 trial experienced an early death and this may be associated with high-risk patients with worse prognosis for OS. However, it is expected that bridging therapies according to current standards, including adapting the strategy according to prognosis, might be able to avoid the observed increase in early deaths.

Further data (e.g., observational) should be collected to confirm the benefit of optimising bridging therapy to avoid early deaths in high-risk patients.

2. Given the crossing of the OS KM-curves around 15 months and the possible early detrimental effect observed for ide-cel, please discuss for which patients with r/r Multiple Myeloma, matching study inclusion criteria, Abecma would be an appropriate treatment option. Please also consider if there are identifiable subpopulations where Abecma should be avoided."

The early deaths were not associated with Ide-cel (Abecma) but with suboptimal bridging strategies and failure to undergo CAR-T cell infusion.

Poor prognostic factors for progression may be associated with early death and this needs to be managed through more effective bridging therapy rather than patient exclusion. In any case, the choice of prognostic factors is not clear, including MRD, and risk classifications are evolving.

If patients have clinically rapidly progressive disease, the disease should be controlled so that CAR-T therapy becomes a possibility. If patients are not expected to be able to access infusion in due time, then CAR-T therapy should be avoided until this becomes feasible and/or patients should be referred to alternative therapeutic options. A general exclusion of high risk patients should be avoided.

The proposed text for 4.4 of the SmPC seems acceptable with small suggested modification to reflect the outcome of therapy to control rapidly progressive disease with a view to future CAR-T therapy: "Before selecting patients for Abecma treatment, physicians should consider patients with high-risk cytogenetic abnormalities, R-ISS stage III, presence of extramedullary plasmacytoma or high tumor burden, particularly those who have rapidly progressing disease that would impact the ability to receive CAR T infusion in due time."

2.5.3. Conclusions on the clinical efficacy

Treatment with ide-cel in adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, showed a statistically significant and clinically meaningful benefit over standard regimens in terms of PFS. The improvement in the primary endpoint was supported by various sensitivity analyses. In addition, subgroup analysis showed a consistent benefit of ide-cel on PFS in all pre-specified subgroups. Furthermore, ide-cel treatment showed increased ORR compared to standard regimens. The observed responses appeared to be durable and longer lasting compared to standard regimens, supporting the clinical benefit observed in terms of PFS. The benefit was further supported by outcomes of the secondary endpoints including EFS, PFS2 and MRD negativity rate. Benefit in terms of increased OS has not been demonstrated. The crossing survival curves, as well as extensive cross-over between the treatment arms, make OS data difficult to interpret. Importantly, the KM curve for OS showed that patients in the ide-cel arm were at increased risk of early death, compared to patients in the standard therapy arm. The provided baseline characteristics of patients with early death indicated that a subgroup of patients with poor prognosis may experience potential harm by being randomised to the ide-cel arm. Subgroup analysis and KM curves showed a negative trend in OS with ide-cel treatment for certain subgroups, especially for patients with presence of high-risk cytogenetic abnormalities, but possibly also for patients with R-ISS stage III, presence of extramedullary plasmacytoma or high tumour burden. This is now reflected in the product information. Notably, the early deaths did not seem to be associated with ide-cel treatment per se but more likely due to suboptimal bridging strategies and failure to undergo CAR-T cell infusion.

The sought extension of the indication to an earlier line of treatment for RRMM patients after **at least two prior therapies** is supported by the data from study MM-003.

The following measures are considered necessary to address issues related to efficacy (recommendation):

- The MAH should submit final OS data from MM-003 when available. The final OS data should include subgroup analyses of relevant subgroups.
- The MAH should submit, within a time period of two months, a draft protocol and SAP for a prospective observational study assessing whether potentially suboptimal bridging therapy in high-risk patients observed in the KARMMa-3 study may be alleviated in a real-world setting. This draft should then be discussed with CAT/CHMP, so that a decision can be made on whether such a prospective study should be initiated, in its initial or amended form.

The CHMP endorse the CAT conclusion on clinical efficacy as described above

2.6. Clinical safety

Introduction

The primary safety data presented in this variation application are from the pivotal study BB2121-MM-003 (MM-003). Safety summaries were conducted using the MM-003 Treated Population and the Safety Population as appropriate, unless otherwise specified. All subjects who received ide-cel continue to be monitored for long-term for survival, toxicity, and viral vector safety under a separate protocol (Study GC-LTFU-001) for up to 15 years from ide-cel infusion.

Data from study MM-003 are presented side-by-side with the pooled safety data from the supportive study CRB-401 (Phase I) and the pivotal study MM-001 (Phase III). Additionally, all 3 studies (MM-003, CRB-401, and MM-001) are pooled in support of the current SmPC and for the proposed label update.

Patient exposure

At the time of the MM-003 data cutoff (18-Apr-2022), which was the basis for the initial submission, the majority of randomized subjects were ongoing in the study (66.3%), with the median duration of follow-up being 17.0 months (from ide-cel infusion to data cutoff date). An overview of the safety analysis populations is presented in the table below.

Table 38. Safety Analysis Populations in Study MM-003

Population[a]	Ide-cel (N = 254) n (%)	Standard Regimens (N = 132) n (%)	Total (N = 386) n (%)
Intent-to-Treat[b]	254 (100.0)	132 (100.0)	386 (100.0)
Treated[c]	250 (98.4)	126 (95.5)	376 (97.4)
Safety[d]	225 (88.6)	126 (95.5)	351 (90.9)

Source: Table 5.2-1 of the MM-003 Primary CSR.[1]

[a] Percentages are based on the ITT Population.

[b] The ITT Population is defined as all subjects who are randomized to one of the two treatment groups.

[c] The Treated population is defined as all subjects in the ITT population who received leukapheresis, bridging 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.

[d] The Safety Population is defined as all subjects in the Treated Population who have 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.

Treatment for Ide-cel arm and control arm are as described in the efficacy section above.

Adverse events

Adverse events (AEs) were coded according to MedDRA version 24.1 and AEs were tabulated using the worst grade per the NCI-CTCAE v4.03 criteria by SOC and PT. Descriptive statistics of safety are presented using NCI-CTCAE v4.03 by treatment arm. An overall summary of safety in study MM-003 is presented in Table 42.

Table 39. Overall Summary of Safety - Study MM-003 (DCO 28-Apr-2023)

Safety Parameters, n (%)	No. of Subjects (%)	
	Ide-cel Arm	Standard Regimens Arm
ITT Population	**N=254**	**N=132**
Deaths	106 (41.7)	58 (43.9)
Primary Reason for Death		
Death from malignant disease under study, or complication due to malignant disease under study[a]	64 (25.2)	37 (28.0)
Death from adverse event[a]	17 (6.7)	8 (6.1)
Death from other cause[a]	23 (9.1)	12 (9.1)
Death from second primary malignant disease, or complication due to second primary malignant disease[a]	2 (0.8)	1 (0.8)
	Adverse Event by Grades	
Treated Population	**N=249**	**N=126**
SAEs[b]		
Any Grade	139 (55.8)	52 (41.3)
AEs[b]		
Any Grade	248 (99.6)	124 (98.4)
Grade 3 or 4[c]	234 (94.0)	97 (77.0)
Safety Population	**N=225**	**N=126**
SAEs[b]		
Any Grade	121 (53.8)	52 (41.3)
AEs[b]		
Any Grade	225 (100.0)	124 (98.4)
Grade 3 or 4[c]	214 (95.1)	97 (77.0)
Treatment-related SAEs[d]		
Any Grade	53 (23.6)	20 (15.9)
Treatment-related AE[d]		
Any Grade	225 (100.0)	106 (84.1)
Grade 3 or 4[c]	199 (88.4)	76 (60.3)

Safety Parameters, n (%)	No. of Subjects (%)	
	Ide-cel Arm	Standard Regimens Arm
Safety Population	**N=225**	**N=126**
AESIs (Number of subjects with ≥ 1 AESI/selected AE)[b]		
Any Grade	225 (100.0)	120 (95.2)
CRS		
Any Grade	197 (87.6)	0
NT - Focused 2.0 FDA		
Any Grade	171 (76.0)	89 (70.6)
Infections - Overall		
Any Grade	143 (63.6)	72 (57.1)
Cytopenia - Overall		
Any Grade	207 (92.0)	92 (73.0)
Cytopenia - Neutropenia		
Any Grade	193 (85.8)	60 (47.6)
Cytopenia - Thrombocytopenia		
Any Grade	127 (56.4)	38 (30.2)
Immunogenicity		
Any Grade	42 (18.7)	25 (19.8)
Hypogammaglobulinaemia		
Any Grade	24 (10.7)	3 (2.4)
New Malignancies		
Any Grade	18 (8.0)	5 (4.0)
MAS		
Any Grade	5 (2.2)	0
Tumour Lysis Syndrome		
Any Grade	4 (1.8)	1 (0.8)
Autoimmune Disorders		
Any Grade	1 (0.4)	0

Note: For Standard Regimens arm, all AEs are included for those subjects who did not receive leukapheresis, but only AEs before leukapheresis are included for those subjects who planned to receive ide-cel infusion.

[a] 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.

[b] Data presented reflect 'On/after randomization' for Arm A and Arm B (as done in Table 8.1-1 of the MM-003 Primary CSR).

[c] Graded using CTCAE version 5.0.

[d] Data presented reflect 'On/after infusion' for Arm A and 'On/after randomization' for Arm B (as done in Table 8.1.1 of the MM-003 Primary CSR).

Source: ITT Population - Table 14.3.2.41.1A (Deaths) of Appendix 23

Treated Population - Table 14.3.2.5.1 (SAEs); Table 14.3.2.1.1 (AEs); Table 14.3.2.7.1 (Grade 3/4 AEs) of Appendix 22B.

Safety Population - Table 14.3.2.1.1A (SAEs, AEs, related AEs, Grade 3/4 AEs, related Grade3/4 AEs) of Appendix 22B; Table 14.3.2.21.1A (AESIs) of Appendix 23

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

Table 4011. SAEs by SOC and PT, irrespective of ide-cel relationship, occurring in ≥2% of patients - Study MM-003 - Safety Population - Cutoff date: 28-Apr-2023

	Arm A (Ide cel) On/after randomization	Arm B (Standard Regimens) On/after randomization
System Organ Class Preferred Term [a]	Total (N=225) n (%)	Total (N=126) n (%)
Subjects with at least one Serious AE	121 (53.8)	52 (41.3)
Infections and infestations	63 (28.0)	27 (21.4)
Pneumonia	15 (6.7)	6 (4.8)
COVID-19	5 (2.2)	2 (1.6)
COVID-19 pneumonia	5 (2.2)	4 (3.2)
Influenza	5 (2.2)	3 (2.4)
Sepsis	5 (2.2)	1 (0.8)
Bacteraemia	2 (0.9)	0
Urinary tract infection bacterial	2 (0.9)	0
General disorders and administration site conditions	25 (11.1)	10 (7.9)
Pyrexia	11 (4.9)	1 (0.8)
General physical health deterioration	9 (4.0)	4 (3.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (10.7)	4 (3.2)
Myelodysplastic syndrome	4 (1.8)	0
Blood and lymphatic system disorders	18 (8.0)	4 (3.2)
Febrile neutropenia	9 (4.0)	2 (1.6)
Neutropenia	5 (2.2)	1 (0.8)
Nervous system disorders	18 (8.0)	5 (4.0)
Depressed level of consciousness	4 (1.8)	0
Syncope	3 (1.3)	0
Musculoskeletal and connective tissue disorders	14 (6.2)	6 (4.8)
Pathological fracture	5 (2.2)	0
Immune system disorders	12 (5.3)	0
Cytokine release syndrome	10 (4.4)	0
Haemophagocytic lymphohistiocytosis	5 (2.2)	0
Renal and urinary disorders	11 (4.9)	3 (2.4)
Acute kidney injury	6 (2.7)	2 (1.6)
Psychiatric disorders	10 (4.4)	2 (1.6)
Confusional state	6 (2.7)	1 (0.8)
Cardiac disorders	9 (4.0)	7 (5.6)
Atrial fibrillation	1 (0.4)	3 (2.4)

Note: For Standard Regimens Arm, all AEs are included for those subjects who did not receive leukapheresis, but only AEs before leukapheresis are included for those subjects who planned to receive ide-cel infusion.
Note: all PTs selected to reported in this table occurred at >=2% patients under the corresponding population (i.e., Arm A-aLVV, Arm A-sLVV, Arm A-Total, Arm B-Total)
[a] Coded using MedDRA version 26.0. A subject is counted only once for multiple events within preferred term (PT)/system organ class (SOC). AEs are sorted by descending frequency of SOCs and then by descending frequency of PTs within each SOC for the last column under Ide-cel Arm.
Program path:
/u02/projects/bb_2121/bb_2121_mm_003/deliverables/d056_pfsanalysis_jun2023/programs/requests/final/t_ae1_ser1_trt_lvv_ema.sas
Run Date: 09JAN2024 Data Extraction Date: 23JUN2023

Deaths

During the study so far (28-Apr-2023 CoD), 164 patients died. The majority of deaths were due to disease progression for both ide-cel (25.2%) and standard regimens arm (28.0%), while 6.7% vs 6.1% died from AEs, respectively.

Deaths attributed to 'other' causes were reported in 23 (9.1%) subjects in the ide-cel arm and 12 (9.1%) subjects in the standard regimens arm. The majority (18 out of 23 in the ide-cel arm and 9 out of 12 in the standard regimens arm) of 'death from other cause' in both study arms were reported verbatim as 'unknown' which was coded under the System Organ Class of "General Disorder and Administration Site Condition".

Adverse Events of Special Interest (AESIs)

An overview of adverse events of special interest (AESIs), cytokine release syndrome (CRS), investigator identified neurotoxicity (iiNT), cytopenia, malignancies, infections and macrophage activating syndrome (MAS), is presented in Table (COD 28-Apr-2023).

Cytokine release syndrome (CRS)

In the ide-cel arm, safety population, 197 (87.6%) subjects experienced at least one event of CRS. The median time to first onset of CRS was 1.0 day (range 1.0 to 14.0) and the median duration of CRS AEs was 4.0 days (range: 1.0 to 51.0). The majority of CRS events were of Grade 1 or 2 severity, while severe events were less frequent (Grade 3: 2.7%; Grade 4: 1.3%, and Grade 5: 0.9%).

Investigator identified neurotoxicity (iiNT)

In the ide-cel arm, safety population, 34 (15.1%) subjects experienced at least one event of iiNT. The median time to first onset of any iiNT AEs was 3.0 days (range 1.0, 317.0) and the median duration of iiNT AEs was 2.5 days (range: 1.0, 252).

The majority of iiNT AEs were of Grade 1 or 2 severity. Grade 3-4 iiNT was reported in 7 (3.1%) subjects, the most frequently reported symptoms of which were confusional state (1.3%) and depressed level of consciousness (1.3%). No Grade 5 iiNT events were reported.

Encephalopathy was reported in one subject 317 days after ide-cel infusion; considered by the investigator to be related to worsening pneumonia and C. difficile colitis.

Cytopenia

Most subjects in both the ide-cel arm and the standard arm had at least 1 cytopenia (overall) AE, 92.0% vs 73.0%, respectively, the majority of which were of Grade 3 or 4.

Malignancies

The most frequently reported second primary malignancy (SPM) PTs in the ide-cel arm were myelodysplastic syndrome (MDS) and squamous cell carcinoma. In MM-003, myelodysplastic syndrome and acute myeloid leukemia, which are hematologic malignancies of interest, occurred in 4 and 1, respectively, subjects in the ide-cel arm, and none in the standard regimens arm. Given the differences in duration of actual time at risk for subjects with SPMs ((adjusted incidence was 447.44 p-y in the ide-cel arm vs 121.49 p-y in the standard regimens arm, (DCO 28-Apr-2023)), these numerical differences should be interpreted with caution. Of note, no subjects treated with ide-cel were diagnosed with T cell malignancies.

Infections

In the ide-cel arm, safety population, 143 (63.6%) subjects had infections-overall (any grade) and 50 (22.2%) had Grade 3 or 4 infections-overall. In the standard regimens arm, safety population, 72 (57.1%) subjects had infections-overall (any grade) and 23 (18.3%) had Grade 3 or 4 infections-overall.

Macrophage activating syndrome (MAS)

In the ide-cel arm, safety population, 5 (2.2%) subjects had at least 1 MAS AE. All events were Grade 3/4, reported within the first 8 weeks after ide-cel infusion.

Laboratory findings

Overall, there were no unexpected or clinically significant changes in chemistry values over time following ide-cel infusion or treatment with standard regimens. Changes in clinical laboratory results in the ide-cel arm were consistent with those previously observed in studies with ide-cel treatment.

Changes in haematology laboratory results were consistent with the receipt of anticancer therapy for disease control and LDC prior to ide-cel treatment and were followed by the expected recovery from LDC. Changes in haematology laboratory results were consistent with the receipt of ide-cel treatment and were followed by the expected recovery post infusion.

Changes in clinical laboratory results in the standard regimens arm were consistent with subjects being on continuous therapy with anticancer medication.

Haematology

Mean levels of haematology laboratory results in the ide-cel arm, treated population, decreased with the receipt of LDC administration prior to ide-cel treatment and were followed by recovery. Mean neutrophil, platelet, and hemoglobin values decreased following ide-cel infusion and at 12 months, median values were similar to baseline and remained generally stable through months 12-24. This pattern is consistent with the receipt of LDC administration prior to ide-cel treatment, followed by the expected recovery from LDC. Mean lymphocyte counts were low at Day 1, followed by an increase over the next 2 weeks (concurrent with ide-cel expansion) and beyond.

In the standard regimens arm, treated population, mean neutrophil counts remained stable during the first 12 months after commencing therapy and then between 12 and 24 months after therapy decreased below baseline.

Clinical Chemistry

In the ide-cel arm, most changes in chemistry laboratory parameters occurred within 1 month after ide-cel infusion, and then remained stable over time.

For inflammatory markers, mean CRP levels in the ide-cel arm, treated population, were elevated at baseline evaluation (defined as the last non-missing value before or on the date of leukapheresis), continued to increase to Day 3 from infusion (consistent with the median time to onset for CRS), and then decreased steadily thereafter. Mean ferritin levels were elevated at baseline, continued to increase until Day 10, and then decreased steadily thereafter. The mean post-baseline maximum values within 1 month for the inflammatory markers CRP and ferritin were 88.5 mg/L and 3428 mg/L, respectively.

In the standard regimens arm, treated population, most changes in chemistry laboratory parameters occurred within 1 month after start of the first dose of the standard regimen, remained stable over time.

Vital signs, physical findings, and other observations related to safety

Vital signs, physical findings, and other observations related to safety in the ide-cel arm were consistent with that previously reported for ide-cel. For the ide-cel arm, safety population, replication-competent lentivirus (RCL) testing of all peripheral blood samples was reported as negative for RCL.

Subjects in the ide-cel safety population were monitored for persistent vector sequences (PVS), defined as detection of CAR vector sequences in more than 1% of cells in peripheral blood samples collected at

12 months or any time after 12 months post infusion of ide-cel. As of the primary data cut-off, 2 subjects in the ide-cel safety population were identified with PVS above the 1% threshold; follow-up insertion site analysis is underway and monitoring of transgene levels at subsequent visits will continue for these subjects.

Safety in special populations

According to the MAH, the frequencies of SAEs in the subgroups analyzed (age, sex, race, ethnicity, anti-CD38 monoclonal antibody refractory status, tumor burden at baseline, number of prior regimens, and ide-cel dose category [ide-cel arm only]) were generally similar to that of the overall treated population by arms.

Number of prior Antimyeloma Lines of Treatment

Table 41. Safety Summary by Prior Lines of Treatment - MM-003 (DCO 18- Apr-2022)

No. of Prior Lines	No. of Subjects, n (%)					
	2 Prior Lines		3 Prior Lines		4 Prior Lines	
Treatment Arm	Ide-cel	Standard regimens	Ide-cel	Standard regimens	Ide-cel	Standard regimens
Treated Population	**N = 75**	**N = 39**	**N = 95**	**N = 46**	**N = 80**	**N = 41**
SAEs	38 (50.7)	15 (38.5)	48 (50.5)	17 (37.0)	44 (55.0)	16 (39.0)
Grade 3/4 AE	72 (96.0)	30 (76.9)	88 (92.6)	34 (73.9)	73 (91.3)	30 (73.2)
Safety Population	**N = 71**	**N = 39**	**N = 85**	**N = 46**	**N = 69**	**N = 41**
AESIs (Number of subjects with ≥ 1 AESI/selected AE)	71 (100.0)	36 (92.3)	85 (100.0)	40 (87.0)	69 (100.0)	37 (90.2)
CRS	61 (85.9)	0	71 (83.5)	0	65 (94.2)	0
NT - Broad	45 (63.4)	22 (56.4)	62 (72.9)	25 (54.3)	52 (75.4)	30 (73.2)
NT - Focused	25 (35.2)	9 (23.1)	33 (38.8)	13 (28.3)	27 (39.1)	19 (46.3)
Infections	40 (56.3)	22 (56.4)	54 (63.5)	24 (52.2)	44 (63.8)	22 (53.7)
Cytopenia - Overall	65 (91.5)	28 (71.8)	77 (90.6)	34 (73.9)	64 (92.8)	29 (70.7)
Neutropenia	64 (90.1)	20 (51.3)	72 (84.7)	22 (47.8)	57 (82.6)	15 (36.6)
Thrombocytopenia	40 (56.3)	10 (25.6)	52 (61.2)	18 (39.1)	34 (49.3)	9 (22.0)
New Malignancies	4 (5.6)	1 (2.6)	3 (3.5)	2 (4.3)	8 (11.6)	2 (4.9)
MAS	2 (2.8)	0	3 (3.5)	0	-	-
Autoimmune Disorders	-	-	1 (1.2)	0	-	-

Source: Table 14.3.2.5.1.7, Table 14.3.2.7.1.7, and Table 14.3.2.21.1.7 in the MM-003 Primary CSR.[1]

Note: For Standard Regimens Arm, all AEs are included for those subjects who did not receive leukapheresis, but only AEs before leukapheresis are included for those subjects who planned to receive ide-cel infusion.

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

Ide-cel dose category (ide-cel arm only)

Table 42. Safety Summary by Ide-cel Dose Levels - MM-003 (Ide-cel Arm - Safety Population) (DCO 18- Apr-2022).

	< 300 x 10^6 CAR+ T Cells (N = 3) n (%)	300 - 460 x 10^6 CAR+ T Cells (N = 143) n (%)	> 460-540 x 10^6 CAR+ T Cells (N = 79) n (%)
SAEs	3 (100.0)	73 (51.0)	36 (45.6)
Grade 3/4 AE	3 (100.0)	135 (94.4)	75 (94.9)
AESIs (Number of subjects with ≥ 1 AESI/selected AE)	3 (100.0)	143 (100.0)	79 (100.0)
CRS	2 (66.7)	122 (85.3)	73 (92.4)
NT - Broad	3 (100.0)	106 (74.1)	50 (63.3)
NT - Focused	0	58 (40.6)	27 (34.2)
Infections	2 (66.7)	88 (61.5)	48 (60.8)
Cytopenia - Overall	3 (100.0)	130 (90.9)	73 (92.4)
Neutropenia	3 (100.0)	121 (84.6)	69 (87.3)
Thrombocytopenia	2 (66.7)	75 (52.4)	49 (62.0)
New Malignancies	2 (66.7)	7 (4.9)	6 (7.6)
MAS	0	2 (1.4)	3 (3.8)
Autoimmune Disorders	0	0	1 (1.3)

Source: Table 14.3.2.5.1.8, Table 14.3.2.7.1.8, and Table 14.3.2.21.1.8 in the MM-003 Primary CSR.[1]

Note: For Standard Regimens Arm, all AEs are included for those subjects who did not receive leukapheresis, but only AEs before leukapheresis are included for those subjects who planned to receive ide-cel infusion.

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

Cytokine Release Syndrome by Ide-cel Dose Levels

Table 4312. Summary of Cytokine Release Syndrome by Dose Levels - MM-003 (Ide-cel Arm - Safety Population) (DCO 18-Apr-2022)

Parameters	< 300 x 10^6 CAR+ T Cells (N = 3) n (%)	300 - 460 x 10^6 CAR+ T Cells (N = 143) n (%)	> 460-540 x 10^6 CAR+ T Cells (N = 79) n (%)
Grade 1	1 (33.3)	81 (56.6)	42 (53.2)
Grade 2	1 (33.3)	37 (25.9)	24 (30.4)
Grade 3	0	1 (0.7)	5 (6.3)
Grade 4	0	2 (1.4)	1 (1.3)
Grade 5	0	1 (0.7)	1 (1.3)
Time to first onset of any CRS (days)[a]			
n	2	122	73
Median (min, max)	7.5 (1.0, 14.0)	2.0 (1.0, 6.0)	1.0 (1.0, 4.0)
Total number of CRS events, n	2	126	81
Number of events by length of duration (days), n (%)			
1 - 5 days	1 (50.0)	93 (73.8)	61 (75.3)
6 - 10 days	1 (50.0)	26 (20.6)	17 (21.0)
> 10 days	0	6 (4.8)	3 (3.7)
Ongoing[b]	0	1 (0.8)	0
Duration of CRS (per event) descriptive statistics(days)[c]			
n	2	125	81
Median (min, max)	4.5 (2.0, 7.0)	4.0 (1.0, 40.0)	3.0 (1.0, 51.0)
Number of subjects who received tocilizumab for CRS, n (%)	2 (66.7)	96 (67.1)	63 (79.7)
1 Dose Tocilizumab	2 (66.7)	57 (39.9)	33 (41.8)
>1 Doses Tocilizumab	0	39 (27.3)	30 (38.0)
2 Doses Tocilizumab	0	28 (19.6)	17 (21.5)
>2 Doses Tocilizumab	0	11 (7.7)	13 (16.5)
Number of subjects who received steroids for CRS, n (%)	1 (33.3)	34 (23.8)	29 (36.7)

Source: Table 14.3.2.31.1.2 in the MM-003 Primary CSR.[1]

CRS is graded by Lee's Criteria.

[a] Time to first onset of CSR: first start date of CRS – infusion date + 1

[b] Ongoing CRS was excluded from calculation of duration of CRS.

[c] Algorithm for duration: if gap between two events ≤ 1 day, then these two events were considered as one event regardless of grade change, drug relationship change, or severity change.

Neurologic Toxicity by Ide-cel Dose Levels

Table 4413. Summary of Investigator Identified Neurotoxicity by Dose Levels - MM-003 (Ide-cel Arm - Safety Population) (DCO 18- Apr-2022).

Parameters	Ide-cel Arm		
	< 300 x 10^6 CAR+ T Cells (N = 3) n (%)	300 - 460 x 10^6 CAR+ T Cells (N = 143) n (%)	> 460-540 x 10^6 CAR+ T Cells (N = 79) n (%)
Number of Subjects with at Least one iiNT, n (%)	0	23 (16.1)	11 (13.9)
Maximum Reported iiNT Grade (NCI CTCAE V4.03), n (%)			
Grade 1	0	8 (5.6)	5 (6.3)
Grade 2	0	11 (7.7)	3 (3.8)
Grade 3	0	3 (2.1)	2 (2.5)
Grade 4	0	1 (0.7)	1 (1.3)
Grade 5	0	0	0
Time to first onset of any iiNT (days)[a]			
n	0	23	11
Median (min, max)	-	3.0 (1.0, 46.0)	3.0 (1.0, 317.0)[b]
Total number of iiNT events, n	0	28	12
Number of events by length of duration (days), n (%)			
1 - 5 days	0	20 (71.4)	7 (58.3)
6 - 10 days	0	4 (14.3)	1 (8.3)
> 10 days	0	2 (7.1)	1 (8.3)
Ongoing[c]	0	2 (7.1)	3 (25.0)
Duration of iiNT (per event) descriptive statistics (days)[d]			
n	0	26	9
Median (min, max)	-	3.0 (1.0, 37.0)	2.0 (1.0, 30.0)
Number of Subjects Who Received Steroids for iiNT - n (%)	0	10 (7.0)	5 (6.3)

Source: Table 14.3.2.32.1.2 in the MM-003 Primary CSR.[1]

Note: iiNT includes immune effector cell-associated neurotoxicity syndrome reported by investigator as a neurological toxicity AE.

[a] Time to first onset of iiNT: first start date of iiNT – infusion date + 1.

[b] Encephalopathy was reported in one subject 317 days after ide-cel infusion; considered by the investigator to be related to worsening pneumonia and C. difficile colitis.

[c] Ongoing iiNT was excluded from calculation of duration of iiNT.

Immunogenicity

In Study MM-003, ide-cel arm, safety population, (DCO 18-Apr-2022), the proportion of subjects with at least 1 CRS event was similar between post infusion anti-CAR antibody positive and negative subjects; 84.4% and 92%, respectively. The proportion of subjects with at least 1 iiNT event was also similar between post infusion anti-CAR antibody positive and negative subjects: 15.6% and 13.8%, respectively.

Safety related to drug-drug interactions and other interactions

Ide-cel is a cellular product that is not cleared by the usual mechanisms that apply to small molecules or antibodies. No drug-drug interaction studies have been performed.

HIV and the lentivirus used to make ide-cel have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received ide-cel.

Discontinuation due to adverse events

Among the safety population, 92 patients (32.0%) discontinued the study, none of them due to AEs.

Supportive Safety Information across studies and lines of therapy

Safety Analyses for the Individual and Pooled Studies

Safety data from the time of ide-cel infusion for the ide-cel arm in MM-003 (ie, ide-cel treated population, N = 225) are presented side-by-side with the pooled safety data from the supportive studies: CRB-401 and MM-001; and pooled with those from CRB-401 and MM-001.

Disposition, Demographics, and Baseline

Table 45. Subject Disposition – Individual and Pooled Studies – Leukapheresis Population (DCO 28-Apr-2023)

	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T cells	MM-003 Arm A	Total
Leukapheresis Population	**N = 201**	**N = 249**	**N = 450**
Discontinued after Leukapheresis and prior to LDC - n (%)[a]	13 (6.5)	22 (8.8)	35 (7.8)
Reason for discontinuation[a]			
Adverse event	2 (1.0)	2 (0.8)	4 (0.9)
Death	0	4 (1.6)	4 (0.9)
Failure to meet treatment criteria	0	6 (2.4)	6 (1.3)
Physician decision	5 (2.5)	7 (2.8)	12 (2.7)
Progressive disease	2 (1.0)	0	2 (0.4)
Study drug manufacturing failure	1 (0.5)	3 (1.2)	4 (0.9)
Withdrawal by subject	3 (1.5)	0	3 (0.7)
Discontinued after LDC and prior to ide-cel infusion - n (%)[a]	4 (2.0)	2 (0.8)	6 (1.3)
Reason for discontinuation[a]			
Adverse event	0	2 (0.8)	2 (0.4)
Death	2 (1.0)	0	2 (0.4)
Withdrawal by subject	2 (1.0)	0	2 (0.4)

	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T cells	MM-003 Arm A	Total
Safety Population	**N = 184**	**N = 225**	**N = 409**
Ongoing in study - n (%)[b]	68 (37.0)	153 (68.0)	221 (54.0)
Discontinued from study[b,c]	116 (63.0)	72 (32.0)	188 (46.0)
Reason for discontinuation[c]			
Death	50 (27.2)	56 (24.9)	106 (25.9)
Lost to follow-up	4 (2.2)	0	4 (1.0)
Other	1 (0.5)	0	1 (0.2)
Physician decision	0	1 (0.4)	1 (0.2)
Progressive disease	33 (17.9)	0	33 (8.1)
Withdrawal by subject	28 (15.2)	15 (6.7)	43 (10.5)
Subjects who entered long-term follow up study - n (%)[d]	35 (19.0)	0	35 (8.6)
Follow-up Duration for All Subjects Using Cut-off Date(Months)[e] - n	184	225	409
Median (Min, Max)	20.8 (15.0, 47.7)	17.0 (0.3, 34.3)	19.1 (0.3, 47.7)
Time Intervals from infusion n (%)			
<1 Month	0	1 (0.4)	1 (0.2)
1 to <3 Months	0	0	0
3 to <6 Months	0	1 (0.4)	1 (0.2)
6 to <9 Months	0	13 (5.8)	13 (3.2)
9 to <12 Months	0	39 (17.3)	39 (9.5)
12 to <15 Months	0	32 (14.2)	32 (7.8)
15 to <18 Months	47 (25.5)	38 (16.9)	85 (20.8)
18 to <24 Months	86 (46.7)	35 (15.6)	121 (29.6)
≥ 24 Months	51 (27.7)	66 (29.3)	117 (28.6)

Source: Appendix 2, Table 1.1

[a] Percentage is based on total number of subjects in the Leukapheresis Population.

[b] Percentage is based on total number of subjects in the Safety Population.

[c] In Study CRB-401, the reason for study discontinuation is reported directly in the CRF; subjects may discontinue the study by any of the reasons listed. In other studies, discontinuation from study occurs if subject discontinued last epoch due to death, withdrawal by subjects, physician decision or lost to follow up.

[d] In Study CRB-401, long-term follow-up study includes LTF-305 and GC-LTFU-001.

[e] (Cut-off date - ide-cel infusion date + 1)/30.4375.

Table 46. Demographics and Baseline Characteristics - Individual and Pooled Studies - Safety Population

	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Age (years)			
Median (Min, Max)	61.0 (33, 78)	63.0 (30, 81)	62.0 (30, 81)
Age Categories (years) - n (%)			
< 65	118 (64.1)	128 (56.9)	246 (60.1)
≥ 65	66 (35.9)	97 (43.1)	163 (39.9)
65 - 74	61 (33.2)	85 (37.8)	146 (35.7)
75 - 84	5 (2.7)	12 (5.3)	17 (4.2)
Sex - n (%)			
Male	112 (60.9)	141 (62.7)	253 (61.9)
Female	72 (39.1)	84 (37.3)	156 (38.1)
Race - n (%)			
American Indian or Alaska Native	0	1 (0.4)	1 (0.2)
Asian	4 (2.2)	6 (2.7)	10 (2.4)
Black or African American	10 (5.4)	17 (7.6)	27 (6.6)
White	153 (83.2)	155 (68.9)	308 (75.3)
Other	7 (3.8)	1 (0.4)	8 (2.0)
Unknown/Missing	10 (5.4)	45 (20.0)	55 (13.4)
Ethnicity - n (%)			
Hispanic or Latino	12 (6.5)	10 (4.4)	22 (5.4)
Not Hispanic or Latino	156 (84.8)	169 (75.1)	325 (79.5)
Not Reported	11 (6.0)	45 (20.0)	56 (13.7)
Unknown/Missing	5 (2.7)	1 (0.4)	6 (1.5)
Region - n (%)			
North America	151 (82.1)	131 (58.2)	282 (68.9)
Europe	33 (17.9)	90 (40.0)	123 (30.1)
Asia	0	4 (1.8)	4 (1.0)

Source: Appendix 2, Table 1.2.

BMI is calculated as weight (kg)/ ((height (m)^2).

	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
ECOG Performance Status - n (%)			
0	71 (38.6)	106 (47.1)	177 (43.3)
1	109 (59.2)	115 (51.1)	224 (54.8)
2	4 (2.2)	3 (1.3)	7 (1.7)
3	0	1 (0.4)	1 (0.2)
Revised International Staging System (Derived) - n (%)[a]			
Stage I	16 (8.7)	56 (24.9)	72 (17.6)
Stage II	128 (69.6)	119 (52.9)	247 (60.4)
Stage III	30 (16.3)	30 (13.3)	60 (14.7)
Unknown/Missing	10 (5.4)	20 (8.9)	30 (7.3)
Baseline Cytogenetic Abnormality - n (%)[b]			
High Risk	61 (33.2)	84 (37.3)	145 (35.5)
Not High Risk	93 (50.5)	109 (48.4)	202 (49.4)
Not Evaluable/Missing	30 (16.3)	32 (14.2)	62 (15.2)
Prior Stem Cell Transplant - n (%)			
Yes	171 (92.9)	189 (84.0)	360 (88.0)
1	113 (61.4)	149 (66.2)	262 (64.1)
>1	58 (31.5)	40 (17.8)	98 (24.0)
No	13 (7.1)	36 (16.0)	49 (12.0)
Number of Prior Antimyeloma Regimens			
n	184	225	409
Median (Min, Max)	6.0 (3, 18)	3.0 (2, 4)	4.0 (2, 18)
Distribution of Prior Antimyeloma Regimens - n (%)			
1	0	0	0
2	0	71 (31.6)	71 (17.4)
3	21 (11.4)	85 (37.8)	106 (25.9)
4	29 (15.8)	69 (30.7)	98 (24.0)
5	28 (15.2)	0	28 (6.8)
6	31 (16.8)	0	31 (7.6)
≥ 7	75 (40.8)	0	75 (18.3)
Number of Prior Anti-myeloma Regimens per Year Since Diagnosis			
n	184	223	407
Median (Min, Max)	1.04 (0.4, 5.1)	0.65 (0.1, 5.2)	0.82 (0.1, 5.2)
Refractory status to prior therapies - n (%)			
IMiD	178 (96.7)	197 (87.6)	375 (91.7)

	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
PI	164 (89.1)	161 (71.6)	325 (79.5)
Anti-CD38 antibodies	169 (91.8)	214 (95.1)	383 (93.6)
Double-class refractory - n (%)[c]			
Yes	161 (87.5)	143 (63.6)	304 (74.3)
No	23 (12.5)	82 (36.4)	105 (25.7)
Triple-class refractory - n (%)[c]			
Yes	150 (81.5)	139 (61.8)	289 (70.7)
No	34 (18.5)	86 (38.2)	120 (29.3)
Penta-drug refractory - n (%)[c]			
Yes	52 (28.3)	14 (6.2)	66 (16.1)
No	132 (71.7)	211 (93.8)	343 (83.9)
Refractory to last regimen - n (%)			
Yes	173 (94.0)	224 (99.6)	397 (97.1)
No	11 (6.0)	1 (0.4)	12 (2.9)
Presence of bone lesions - n (%)			
Yes	144 (78.3)	173 (76.9)	317 (77.5)
No	30 (16.3)	52 (23.1)	82 (20.0)
Missing	10 (5.4)	0	10 (2.4)
Presence of Extramedullary Plasmacytoma - n (%)			
Yes	70 (38.0)	55 (24.4)	125 (30.6)
Clinical	13 (7.1)	0	13 (3.2)
Radiological	68 (37.0)	7 (3.1)	75 (18.3)
Both Clinical and Radiological	11 (6.0)	48 (21.3)	59 (14.4)
Other	2 (1.1)	0	2 (0.5)
No	114 (62.0)	169 (75.1)	283 (69.2)
Missing	0	1 (0.4)	1 (0.2)
Bone Marrow Aspirate Plasma Cell (%)			
n	161	210	371
Median (Min, Max)	5.0 (0, 100)	4.0 (0, 99)	4.0 (0, 100)
Bone Marrow Biopsy CD138+ Plasma Cell (%)			
n	160	208	368
Median (Min, Max)	50.0 (0, 100)	20.0 (0, 95)	30.0 (0, 100)
Tumor Burden - n (%)[d]			
Low (plasma cells <50%)	88 (47.8)	153 (68.0)	241 (58.9)

	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
High (plasma cells ≥50%)	89 (48.4)	68 (30.2)	157 (38.4)
Missing	7 (3.8)	4 (1.8)	11 (2.7)
Renal Function (Cockcroft-Gault CrCl (ml/min)) - n (%)			
< 30	2 (1.1)	0	2 (0.5)
30 - < 45	9 (4.9)	4 (1.8)	13 (3.2)
45 - < 60	13 (7.1)	26 (11.6)	39 (9.5)
60 - < 80	57 (31.0)	63 (28.0)	120 (29.3)
≥ 80	103 (56.0)	132 (58.7)	235 (57.5)

Source: Appendix 2, Table 1.3.

Note: Baseline value is defined as the last value on or before the first dose date of LDC.

[a] Derived ISS is calculated using baseline values of Albumin and Beta-2-microglobulin.

[b] Cytogenetic risk 'High' is defined as positive in any of the following FISH probes: del17, t(14;16) or t(4;14); "Not High' risk is defined as negative in all of the above probes. The del17p13 probe is reflective of del17p.

[c] Double-class refractory is defined as refractory to at least one IMiD and one PI; Triple-class refractory is defined as refractory to at least one IMiD, one PI, and one anti-CD38 antibody; Penta-drug refractory for MM-003 is defined as refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and anti-CD38 antibodies. For all other studies, it is defined as refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (all five drugs).

[d] Tumor burden is determined by bone marrow biopsy CD138+ plasma cell for studies CRB-401 and MM-001, or determined by the higher value of bone marrow aspiration and biopsy CD138+ plasma cell for other studies. Low tumor burden: < 50%, High tumor burden: ≥ 50%.

Overall Extent of Exposure

Exposure data is presented in the tables below.

Table 4714. Lymphodepleting Chemotherapy Dosing Summary - Individual and Pooled Studies - Safety Population.

Parameter	MM-001 and CRB-401 Target Dose 150 - 450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Subjects with Any Dose of LDC Regimen - n (%)	183 (99.5)	225 (100)	408 (99.8)
Subjects with Adjusted LDC Regimen - n (%)[a]	41 (22.3)	36 (16.0)	77 (18.8)
Subjects with Adjusted Fludarabine - n (%)	41 (22.3)	36 (16.0)	77 (18.8)
Subjects with Adjusted Cyclophosphamide - n (%)	0	3 (1.3)	3 (0.7)
Fludarabine			
Number of Days Dosed (Days) - n	183	225	408
Mean (SD)	3.0 (0.00)	3.0 (0.28)	3.0 (0.21)
Median (Min, Max)	3.0 (3.0, 3.0)	3.0 (3.0, 6.0)	3.0 (3.0, 6.0)
Total Cumulative Dose (mg) - n	183	225	408
Mean (SD)	162.7 (30.10)	167.3 (31.16)	165.2 (30.74)
Median (Min, Max)	165.0 (82.0, 231.0)	172.5 (84.0, 279.0)	169.4 (82.0, 279.0)
Actual Daily Dose (mg/day) - n	183	225	408
Mean (SD)	54.2 (10.03)	55.4 (10.29)	54.9 (10.18)
Median (Min, Max)	55.0 (27.3, 77.0)	57.5 (26.3, 80.0)	56.4 (26.3, 80.0)
Actual Daily Dose by Body Surface Area (mg/m2/day), n	181	220	401
Mean (SD)	28.2 (3.14)	28.4 (3.38)	28.3 (3.27)
Median (Min, Max)	29.8 (17.8, 31.9)	29.8 (16.5, 32.4)	29.8 (16.5, 32.4)
Cyclophosphamide			
Number of Days Dosed (Days), n	184	225	409
Mean (SD)	3.0 (0.00)	3.0 (0.28)	3.0 (0.21)
Median (Min, Max)	3.0 (3.0, 3.0)	3.0 (3.0, 6.0)	3.0 (3.0, 6.0)
Total Cumulative Dose (mg), n	184	225	409
Mean (SD)	1715.9 (216.15)	1759.5 (255.59)	1739.9 (239.36)
Median (Min, Max)	1714.5 (1200.0, 2295.0)	1800.0 (1197.0, 3480.0)	1746.0 (1197.0, 3480.0)
Actual Daily Dose (mg/day), n	184	225	409
Mean (SD)	572.0 (72.05)	582.0 (74.17)	577.5 (73.30)
Median (Min, Max)	571.5 (400.0, 765.0)	598.0 (399.0, 795.0)	582.0 (399.0, 795.0)
Actual Daily Dose by Body Surface Area (mg/m2/day), n	182	220	402
Mean (SD)	298.5 (4.91)	299.2 (11.21)	298.9 (8.92)
Median (Min, Max)	300.0 (274.5, 318.9)	300.3 (240.6, 324.4)	300.0 (240.6, 324.4)

Source: Appendix 2, Table 1.8.1.

Note: For subjects in studies CRB-401 and MM-001 who received retreatment, only the initial lymphodepleting chemotherapy data are included.

Table 4815. Ide-cel Administration - Individual and Pooled Studies - Safety Population

	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Actual CAR+T cells infused (x 10^6 cells)			
Median (Min, Max)	323.8 (140.8, 518.4)	445.3 (174.9, 529.0)	442.1 (140.8, 529.0)

Source: Appendix 2, Table 2.1.

Note: For subjects in studies CRB-401 and MM-001 who received retreatment, only the initial infusion data are included.

Summary of Safety Results

Overall summary

Table 4916. Overall Summary of Safety - Individual and Pooled Studies (MM-003 DCO 28-Apr-2023)

Safety Parameter	MM-001 and CRB-401 Target Dose 150 - 450 10^6 CAR+T cells (N = 184) n (%)	MM-003 Arm A (N = 225) n (%)	Total (N = 409) n (%)
Overall number of deaths	64 (34.8)	56 (24.9)	120 (29.3)
Death from malignant disease under study, or complication due to malignant disease under study	42 (22.8)	29 (12.9)	71 (17.4)
Death from other cause	9 (4.9)	13 (5.8)	22 (5.4)
Death from adverse event (not otherwise specified)	13 (7.1)	12 (5.3)	25 (6.1)
Death from second primary malignant disease, or complication due to second primary malignant disease	0	2 (0.9)	2 (0.5)
All-causality			
SAEs	129 (70.1)	96 (42.7)	225 (55.0)
AEs	184 (100)	225 (100)	409 (100)
Grade 3-4 AEs	182 (98.9)	209 (92.9)	391 (95.6)
Treatment-related			
SAEs	63 (34.2)	37 (16.4)	100 (24.4)
AEs	175 (95.1)	217 (96.4)	392 (95.8)
Grade 3-4 AEs	121 (65.8)	155 (68.9)	276 (67.5)
AESI (Number of subjects with at least one AESI/Selected AEs)	184 (100)	225 (100)	409 (100)
CRS	149 (81.0)	197 (87.6)	346 (84.6)
NT - Focused	78 (42.4)	75 (33.3)	153 (37.4)
Infections - Overall	131 (71.2)	121 (53.8)	252 (61.6)
Cytopenia - Overall	176 (95.7)	203 (90.2)	379 (92.7)
Neutropenia	173 (94.0)	186 (82.7)	359 (87.8)
Thrombocytopenia	126 (68.5)	119 (52.9)	245 (59.9)
New Malignancies	16 (8.7)	15 (6.7)	31 (7.6)
MAS	4 (2.2)	5 (2.2)	9 (2.2)
Autoimmune Disorders	0	1 (0.4)	1 (0.2)

Source: Appendix 2, Table 3.4.1 (deaths), Table 3.1.1.1 (AEs), Table 3.1.2.1 (related AEs), Table 3.1.3.1 (Grade 3-4 AEs), Table 3.1.4.1 (related Grade 3-4 AEs), Table 3.1.5.1 (SAEs), Table 3.1.6.1 (related SAEs), Table 3.1.12.1 (AESIs)

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

Deaths

A summary of deaths is presented in the table below. In the pooled studies, 33% of subjects died > 8 weeks post ide-cel infusion, vs 23.7% in the MM-003 study (28-Apr-2022 CoD).

Table 5017. Summary of Deaths and Causes: On/After Initial ide-cel Infusion - Individual and Pooled Studies - Safety Population (COD 28-Apr-2022).

Primary Cause of Death[a]	MM-001 and CRB-401 Target Dose 150 - 450 x 10^6 CAR+T cells (N = 184) n (%)	MM-003 Arm A (N = 225) n (%)	Total (N = 409) n (%)
Overall number of deaths	64 (34.8)	56 (24.9)	120 (29.3)
Death from malignant disease under study, or complication due to malignant disease under study[b]	42 (22.8)	29 (12.9)	71 (17.4)
Death from other cause[b]	9 (4.9)	13 (5.8)	22 (5.4)
Death from adverse event (not otherwise specified)[b]	13 (7.1)	12 (5.3)	25 (6.1)
Death from second primary malignant disease, or complication due to second primary malignant disease[b]	0	2 (0.9)	2 (0.5)

Source: Appendix 2, Table 3.4.1.

[a] Coded using MedDRA version 24.1. All deaths after initial ide-cel infusion including deaths after retreatment are reported.

[b] Primary cause category selected from case report form except for CRB-401 death category was determined by clinical review.

Other Serious Adverse Events

An overall summary of the SAEs is presented in table 62 (MM-003 DCO 28-Apr-2023).

Adverse Events of Special Interest and Selected Adverse Events

- *Cytokine Release Syndrome (CRS)*

Table 5118. Summary of Cytokine Release Syndrome - Individual and Pooled Studies - Safety Population (MM-003 DCO 28-Apr-2023).

	MM-001 and CRB-401 Target Dose 150 - 450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Number of Subjects with at Least one CRS - n (%)	149 (81.0)	197 (87.6)	346 (84.6)
Maximum Reported CRS Grade (Lee Criteria) - n (%)			
1	84 (45.7)	124 (55.1)	208 (50.9)
2	55 (29.9)	62 (27.6)	117 (28.6)
3	8 (4.3)	6 (2.7)	14 (3.4)
4	1 (0.5)	3 (1.3)	4 (1.0)
5	1 (0.5)	2 (0.9)	3 (0.7)
Time to First Onset of Any CRS (days)[a]			
n	149	197	346
Median (Min, Max)	1.0 (1, 17)	1.0 (1, 14)	1.0 (1, 17)
Total Number of CRS Events - n	164	209	373
Number of Events by Length of Duration - n (%)			
1-5 days	87 (53.0)	155 (74.2)	242 (64.9)
6-10 days	55 (33.5)	44 (21.1)	99 (26.5)
>10 days	22 (13.4)	9 (4.3)	31 (8.3)
Ongoing[b]	0	1 (0.5)	1 (0.3)
Duration of CRS (per Event) Descriptive Statistics (days)[b,c]			
n	164	208	372
Median (Min, Max)	5.0 (1, 63)	3.5 (1, 51)	4.0 (1, 63)
Number of Subjects Received Tocilizumab for CRS - n (%)	83 (45.1)	161 (71.6)	244 (59.7)
1 Dose Tocilizumab	60 (32.6)	92 (40.9)	152 (37.2)
>1 Dose Tocilizumab	23 (12.5)	69 (30.7)	92 (22.5)
2 Doses Tocilizumab	22 (12.0)	45 (20.0)	67 (16.4)
>2 Doses Tocilizumab	1 (0.5)	24 (10.7)	25 (6.1)
Number of Subjects Received Siltuximab for CRS - n (%)	1 (0.5)	3 (1.3)	4 (1.0)
1 Dose Siltuximab	1 (0.5)	3 (1.3)	4 (1.0)
Number of Subjects Received Steroids for CRS - n (%)	29 (15.8)	64 (28.4)	93 (22.7)
Number of Subjects Received Anakinra for CRS - n (%)	2 (1.1)	8 (3.6)	10 (2.4)

	MM-001 and CRB-401 Target Dose 150 - 450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
1 Dose Anakinra	1 (0.5)	0	1 (0.2)
>1 Dose Anakinra	1 (0.5)	8 (3.6)	9 (2.2)
2 Doses Anakinra	1 (0.5)	0	1 (0.2)
>2 Doses Anakinra	0	8 (3.6)	8 (2.0)
Number of Subjects With CRS Symptoms Any Grade - n (%)	149 (81.0)	197 (87.6)	346 (84.6)
In ≥ 5% of Subjects			
ALT increased	10 (5.4)	11 (4.9)	21 (5.1)
AST increased	10 (5.4)	12 (5.3)	22 (5.4)
C-reactive protein increased	30 (16.3)	13 (5.8)	43 (10.5)
Chills	43 (23.4)	34 (15.1)	77 (18.8)
Fatigue	20 (10.9)	9 (4.0)	29 (7.1)
Headache	27 (14.7)	19 (8.4)	46 (11.2)
Hypotension	59 (32.1)	60 (26.7)	119 (29.1)
Hypoxia	30 (16.3)	35 (15.6)	65 (15.9)
Nausea	9 (4.9)	12 (5.3)	21 (5.1)
Pyrexia	144 (78.3)	194 (86.2)	338 (82.6)
Serum ferritin increased	8 (4.3)	12 (5.3)	20 (4.9)
Tachycardia	47 (25.5)	53 (23.6)	100 (24.4)
Tachypnoea	12 (6.5)	16 (7.1)	28 (6.8)
Number of Subjects with CRS Symptoms Grade 3 or 4 - n (%)	53 (28.8)	40 (17.8)	93 (22.7)
In ≥ 1% of Subjects			
ALT increased	0	5 (2.2)	5 (1.2)
AST increased	2 (1.1)	7 (3.1)	9 (2.2)
Blood bilirubin increased	2 (1.1)	0	2 (0.5)
C-reactive protein increased	2 (1.1)	0	2 (0.5)
Febrile neutropenia	6 (3.3)	5 (2.2)	11 (2.7)
Hypocalcaemia	2 (1.1)	0	2 (0.5)
Hypofibrinogenaemia	2 (1.1)	1 (0.4)	3 (0.7)
Hypotension	8 (4.3)	3 (1.3)	11 (2.7)
Hypoxia	9 (4.9)	9 (4.0)	18 (4.4)
Pyrexia	22 (12.0)	18 (8.0)	40 (9.8)
Tachycardia	2 (1.1)	0	2 (0.5)

	MM-001 and CRB-401 Target Dose 150 - 450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Tachypnoea	2 (1.1)	0	2 (0.5)

Source: Appendix 2, Table 3.2.1.
Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

[a] Time to first onset of CRS: first start date of CRS - infusion date + 1

[b] Ongoing CRS was excluded from calculation of duration of CRS.

[c] Algorithm for duration: if gap between two events ≤ 1 day, then these two events were considered as one event regardless of grade change, drug relationship change, or severity change.

- *Investigator Identified Neurotoxicity (iiNT)*

Of note, iiNT data were collected for Study CRB-401 and it is therefore excluded from the analysis.

Table 52. Summary of Investigator Identified Neurotoxicity - Individual and Pooled Studies - Safety Population (MM-003 DCO 28-Apr-2023).

	MM-001 (N = 128)	MM-003 Arm A (N = 225)	Total (N = 353)
Number of Subjects with at Least one iiNT - n (%)	23 (18.0)	34 (15.1)	57 (16.1)
Maximum Reported iiNT Grade (NCI CTCAE V4.03) - n (%)			
1	12 (9.4)	13 (5.8)	25 (7.1)
2	7 (5.5)	14 (6.2)	21 (5.9)
3	4 (3.1)	5 (2.2)	9 (2.5)
4	0	2 (0.9)	2 (0.6)
5	0	0	0
Time to First Onset of iiNT (days)[a]			
n	23	34	57
Median (Min, Max)	2.0 (1, 10)	3.0 (1,317)	3.0 (1,317)
Total Number of iiNT Events - n	24	40	64
Number of Events by Length of Duration - n (%)			
1-5 days	13 (54.2)	27 (67.5)	40 (62.5)
6-10 days	6 (25.0)	5 (12.5)	11 (17.2)
>10 days	4 (16.7)	3 (7.5)	7 (10.9)
Ongoing[b]	1 (4.2)	5 (12.5)	6 (9.4)
Duration of iiNT (per Event) Descriptive Statistics (days)[b,c]			
n	23	35	58
Median (Min, Max)	3.0 (1, 26)	2.0 (1, 37)	3.0 (1, 37)
Number of Subjects Received Tocilizumab for iiNT - n (%)	3 (2.3)	0	3 (0.8)
Number of Subjects Received Siltuximab for iiNT - n (%)	0	0	0
Number of Subjects Received Steroids for iiNT - n (%)	10 (7.8)	15 (6.7)	25 (7.1)
Number of Subjects Received Anakinra for iiNT - n (%)	1 (0.8)	0	1 (0.3)
Number of Subjects With iiNT Symptoms Any Grade - n (%)	23 (18.0)	34 (15.1)	57 (16.1)
In ≥ 1% of Subjects			
Aphasia	6 (4.7)	3 (1.3)	9 (2.5)
Asthenia	2 (1.6)	1 (0.4)	3 (0.8)
Cognitive disorder	3 (2.3)	1 (0.4)	4 (1.1)
Confusional state	12 (9.4)	18 (8.0)	30 (8.5)
Delirium	3 (2.3)	0	3 (0.8)

	MM-001 (N = 128)	MM-003 Arm A (N = 225)	Total (N = 353)
Depressed level of consciousness	0	6 (2.7)	6 (1.7)
Disorientation	1 (0.8)	3 (1.3)	4 (1.1)
Disturbance in attention	1 (0.8)	6 (2.7)	7 (2.0)
Dysgraphia	2 (1.6)	5 (2.2)	7 (2.0)
Encephalopathy	7 (5.5)	5 (2.2)	12 (3.4)
Hallucination	4 (3.1)	2 (0.9)	6 (1.7)
Headache	0	3 (1.3)	3 (0.8)
Hemiparesis	2 (1.6)	0	2 (0.6)
Lethargy	3 (2.3)	3 (1.3)	6 (1.7)
Memory impairment	1 (0.8)	5 (2.2)	6 (1.7)
Mental status changes	4 (3.1)	0	4 (1.1)
Somnolence	2 (1.6)	8 (3.6)	10 (2.8)
Tremor	3 (2.3)	5 (2.2)	8 (2.3)
Urinary incontinence	1 (0.8)	3 (1.3)	4 (1.1)
Number of Subjects with iiNT Symptoms Grade 3 or 4 - n (%)	5 (3.9)	7 (3.1)	12 (3.4)
In ≥ 1% of Subjects			
Confusional state	1 (0.8)	3 (1.3)	4 (1.1)
Depressed level of consciousness	0	3 (1.3)	3 (0.8)
Encephalopathy	3 (2.3)	0	3 (0.8)

Source: Appendix 2, Table 3.3.1

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

Note: For Study CRB-401, no iiNT data were collected and therefore it is excluded from the analysis.

For subjects who received retreatment, only the AEs started before retreatment lymphodepleting chemotherapy are included.

[a] Time to first onset of iiNT: first start date of iiNT - infusion date + 1.

[b] Ongoing iiNT was excluded from calculation of duration of iiNT.

[c] Algorithm for duration: if gap between two events ≤ 1 day, then these two events were considered as one event regardless of grade change, drug relationship change, or severity change.

Neurotoxicity - Focused

A numerically lower percentage of subjects experienced any grade NT-Focused events in the ide-cel arm in MM-003 versus the pooled studies (32.9% vs 41.3%, respectively), with a similar percentage of ≥ Grade 3 NT-Focused events. The median time to first onset of NT-Focused in the ide-cel arm in MM-003 was 3.5 days, compared to 5.0 days in the pooled studies.

- *Cytopenia and Prolonged Cytopenia*

Time to neutropenia and thrombocytopenia recovery from infusion is presented in the tables below respectively (MM-003 DCO 28-Apr-2023).

Table 5319. Time to Neutropenia Recovery from Infusion for Subjects with Last Lab within Month 1 of ide-cel Infusion Date Indicating Grade 3 or 4 Neutropenia - Individual and Pooled Studies - Safety Population. (MM-003 DCO 28-Apr-2023).

Parameter	MM-001 and CRB-401 Target Dose 150 - 450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Grade 3 or 4 Neutropenia within Month 1 of ide-cel Infusion Date - n (%)[a]	178 (96.7)	217 (96.4)	395 (96.6)
Last lab at Month 1 ≤G2 (Recover) - n (%)[b]	116 (65.2)	128 (59.0)	244 (61.8)
Last lab at Month 1 ≥G3 (Not Recover) - n (%)[b]	62 (34.8)	89 (41.0)	151 (38.2)
Recovery Status after Month 1[c]			
Recovery - n (%)	51 (82.3)	82 (92.1)	133 (88.1)
Censored - n (%)	11 (17.7)	7 (7.9)	18 (11.9)
Reasons for Censoring[d] - n (%)	11	7	18
Death	9 (81.8)	5 (71.4)	14 (77.8)
Lost to Follow Up	2 (18.2)	1 (14.3)	3 (16.7)
Ongoing Neutropenia	0	1 (14.3)	1 (5.6)
Physician Decision	0	0	0
Time to Recovery (Months)[e]			
Median (95% CI)	2.0 (1.9, 2.1)	1.7 (1.5, 1.9)	1.9 (1.9, 1.9)
Recovery Rate[e]			
1 month recovery %	0.0	0.0	0.0
2 months recovery %	56.7	69.0	63.9
3 months recovery %	76.7	87.4	83.0
4 months recovery %	81.7	92.0	87.8
5 months recovery %	83.3	93.1	89.1
6 months recovery %	85.0	94.3	90.5
Time to Recovery for Recovered Subjects[f] - n	51	82	133
Mean (SD)	2.1 (0.77)	1.9 (0.76)	2.0 (0.77)
Median (Min, Max)	1.9 (1.2, 5.6)	1.6 (1.1, 5.6)	1.9 (1.1, 5.6)

Source: Appendix 2, Table 4.1

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

[a] Percentage is calculated with the Safety population as the denominator.

[b] Percentage is calculated with subjects who had Grade 3 or 4 neutropenia at any timepoint on/before relative Day 33 after ide-cel infusion as the denominator, with the exception for MM-001 where relative Day 34 is used.

[c] Percentage is calculated with subjects who did not recover from Grade 3 or 4 neutropenia at the last assessment on or before Month 1 post infusion as the denominator.

[d] Percentage is calculated with censored subjects as the denominator.

[e] Time to recovery of Grade 3 or 4 neutropenia is defined as the time from ide-cel infusion date to the time when recovery was first met after Month 1 post infusion. The median and recovery rate are based on Kaplan-Meier estimate. Subjects who did not recover after Month 1 without death, including ongoing as cutoff date or lost to follow-up before recovery, are censored to last non-missing assessment date after Month 1, and subjects who died before recovery are censored to current data cut-off date.

[f] The summary statistics are univariate statistics without adjusting for censoring.

Table 54. Time to Thrombocytopenia Recovery from Infusion for Subjects with Last Lab within Month 1 of ide-cel Infusion Date Indicating Grade 3 or 4 Thrombocytopenia - Individual and Pooled Studies - Safety Population. (MM-003 DCO 28-Apr-2023).

Parameter	MM-001 and CRB-401 Target Dose 150 - 450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Grade 3 or 4 Thrombocytopenia within Month 1 of ide-cel Infusion Date - n (%)[a]	110 (59.8)	120 (53.3)	230 (56.2)
Last lab at Month 1 ≤G2 (Recover) - n (%)[b]	30 (27.3)	36 (30.0)	66 (28.7)
Last lab at Month 1 ≥G3 (Not Recover) - n (%)[b]	80 (72.7)	84 (70.0)	164 (71.3)
Recovery Status after Month 1[c]			
Recovery - n (%)	57 (71.3)	71 (84.5)	128 (78.0)
Censored - n (%)	23 (28.8)	13 (15.5)	36 (22.0)
Reasons for Censoring[d] - n (%)	23	13	36
Death	16 (69.6)	8 (61.5)	24 (66.7)
Lost to Follow Up	5 (21.7)	2 (15.4)	7 (19.4)
Ongoing Thrombocytopenia	2 (8.7)	3 (23.1)	5 (13.9)
Physician Decision	0	0	0
Time to Recovery (Months)[e]			
Median (95% CI)	3.0 (2.2, 4.7)	1.9 (1.5, 2.1)	2.2 (2.0, 2.8)
Recovery Rate[e]			
1 month recovery %	0.0	0.0	0.0
2 months recovery %	30.2	60.2	45.8
3 months recovery %	48.8	71.1	60.4
4 months recovery %	56.9	73.5	65.5
5 months recovery %	61.0	77.2	69.4
6 months recovery %	63.6	78.5	71.3
7 months recovery %	67.8	79.8	74.0
8 months recovery %	69.2	82.5	76.1
9 months recovery %	70.6	85.3	78.2
10 months recovery %	72.0	87.0	79.7

Parameter	MM-001 and CRB-401 Target Dose 150 - 450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
11 months recovery %	72.0	87.0	79.7
12 months recovery %	73.4	87.0	80.4
Time to Recovery for Recovered Subjects[f] - n	57	71	128
Mean (SD)	3.6 (2.88)	2.4 (1.87)	2.9 (2.43)
Median (Min, Max)	2.2 (1.1, 13.8)	1.7 (1.1, 9.2)	1.9 (1.1, 13.8)

Source: Appendix 2, Table 4.2

[a] Percentage is calculated with the Safety population as the denominator.

[b] Percentage is calculated with subjects who had Grade 3 or 4 thrombocytopenia at any timepoint on/before relative Day 33 after ide-cel infusion as the denominator, with the exception for MM-001 where relative Day 34 is used.

[c] Percentage is calculated with subjects who did not recover from Grade 3 or 4 thrombocytopenia at the last assessment on or before Month 1 post infusion as the denominator.

[d] Percentage is calculated with censored subjects as the denominator.

[e] Time to recovery of Grade 3 or 4 thrombocytopenia is defined as the time from ide-cel infusion date to the time when recovery was first met after Month 1 post infusion. The median and recovery rate are based on Kaplan-Meier estimate. Subjects who did not recover after Month 1 without death, including ongoing as cutoff date or lost to follow-up before recovery, are censored to last non-missing assessment date after Month 1, and subjects who died before recovery are censored to current data cut-off date.

[f] The summary statistics are univariate statistics without adjusting for censoring.

- *New Malignancies Including Second Primary Malignancies*

No subjects treated with ide-cel were diagnosed with acute myeloid leukemia.

Table 55. New Malignancy - Adverse Events of Special Interest (AESI)AESI (MM-003 DCO 28-Apr-2023).

AESI/Selected AEs Category [a] Preferred Term [b]	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T cells (N=184) n (%)	MM-003 Arm A (N=225) n (%)	Total (N=409) n (%)
New Malignancy	16 (8.7)	15 (6.7)	31 (7.6)
Basal cell carcinoma	6 (3.3)	2 (0.9)	8 (2.0)
Myelodysplastic syndrome	3 (1.6)	2 (0.9)	5 (1.2)
Squamous cell carcinoma	3 (1.6)	2 (0.9)	5 (1.2)
Breast cancer	1 (0.5)	2 (0.9)	3 (0.7)
Malignant melanoma	1 (0.5)	2 (0.9)	3 (0.7)
Anal cancer	1 (0.5)	0	1 (0.2)
Bladder cancer	1 (0.5)	0	1 (0.2)
Bowen's disease	0	1 (0.4)	1 (0.2)
Leukaemia	0	1 (0.4)	1 (0.2)
Lung adenocarcinoma	1 (0.5)	0	1 (0.2)
Metastases to central nervous system	0	1 (0.4)	1 (0.2)
Rectal adenocarcinoma	0	1 (0.4)	1 (0.2)
Renal cancer	0	1 (0.4)	1 (0.2)
Small intestine adenocarcinoma	0	1 (0.4)	1 (0.2)

- *Infections*

Serious infection is a known complication of CAR T therapy and of standard AMT and is a comorbidity of RRMM. The increased rates of cytopenias and hypogammaglobulinemia seen with CAR T products are additional risk factors for infection.

Table 56. Summary of Infections in ≥ 2% of Subjects the Total Population - Individual and Pooled Studies - Safety Population (MM-003 DCO 28-Apr-2023).

Parameter	MM-001 and CRB-401 Target Dose 150 - 450 x 10^6 CAR+T cells (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Infections-Overall	**131 (71.2)**	**121 (53.8)**	**252 (61.6)**
Upper respiratory tract infection	41 (22.3)	20 (8.9)	61 (14.9)
Pneumonia	23 (12.5)	19 (8.4)	42 (10.3)
Urinary tract infection	14 (7.6)	11 (4.9)	25 (6.1)
Influenza	13 (7.1)	4 (1.8)	17 (4.2)
Sinusitis	11 (6.0)	6 (2.7)	17 (4.2)
Bronchitis	6 (3.3)	10 (4.4)	16 (3.9)
Nasopharyngitis	9 (4.9)	7 (3.1)	16 (3.9)
Sepsis	8 (4.3)	5 (2.2)	13 (3.2)
Rhinovirus infection	7 (3.8)	5 (2.2)	12 (2.9)
Herpes zoster	5 (2.7)	6 (2.7)	11 (2.7)
COVID-19	1 (0.5)	9 (4.0)	10 (2.4)
Respiratory syncytial virus infection	9 (4.9)	1 (0.4)	10 (2.4)
Respiratory tract infection	6 (3.3)	3 (1.3)	9 (2.2)
Gastroenteritis	5 (2.7)	3 (1.3)	8 (2.0)

Source: Appendix 2, Table 3.1.12.1

Adverse Events

Table 5720. Grade 3 or 4 Adverse Events Related to Ide-cel by System Organ Class and Study - Individual and Pooled Studies - Safety Population (MM-003 DCO 28-Apr-2023).

System Organ Class	MM-001 and CRB-401 Target Dose 150-450 x 10^6 CAR+T cells (N = 184) n (%)	MM-003 Arm A (N = 225) n (%)	Total (N = 409) n (%)
Number of subjects with at least one Grade 3/4 AE	121 (65.8)	155 (68.9)	276 (67.5)
Blood and lymphatic system disorders	110(59.8)	144 (64.0)	254 (62.1)
Metabolism and nutrition disorders	13 (7.1)	27 (12.0)	40(9.8)
Infections and infestations	12 (6.5)	15 (6.7)	27 (6.6)
Immune system disorders	13 (7.1)	13 (5.8)	26 (6.4)
Investigations	8 (4.3)	8 (3.6)	16 (3.9)
Nervous system disorders	6 (3.3)	6 (2.7)	12 (2.9)
Psychiatric disorders	2 (1.1)	4 (1.8)	6 (1.5)
General disorders and administration site conditions	5 (2.7)	1 (0.4)	6 (1.5)
Gastrointestinal disorders	2 (1.1)	2 (0.9)	4 (1.0)
Vascular disorders	2 (1.1)	2 (0.9)	4 (1.0)
Renal and urinary disorders	1 (0.5)	2 (0.9)	3 (0.7)
Cardiac disorders	0	2 (0.9)	2 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	1 (0.4)	2 (0.5)
Respiratory, thoracic and mediastinal disorders	2 (1.1)	0	2 (0.5)
Hepatobiliary disorders	0	1 (0.4)	1 (0.2)
Musculoskeletal and connective tissue disorders	0	1 (0.4)	1 (0.2)

Source: Appendix 2, Table 3.1.4.1

Note: For subjects in studies CRB-401 and MM-001 who received retreatment, only the AEs started before retreatment lymphodepletion are included.

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

Clinical Laboratory Evaluations

According to the MAH, Hematology and chemistry laboratory parameters were similar in the ide-cel arm in MM-003 and the pooled studies.

Pooled Subgroup Analyses Including MM-003

Integrated safety data from the ide-cel arm in MM-003 and CRB-401 and MM-001 were used for subgroup analyses by the following categories: numbers of prior antimyeloma lines of treatment, age, sex, race, and ethnicity. Of note, in this section, referral to "the pooled studies" includes MM-003 (in contrast to above, where "the pooled studies" where referred to as only CRB-401 and MM-001).

Number of Prior Antimyeloma Lines of Treatment

Summary of Adverse Events

Table 58. Summary of Safety by Number of Prior Antimyeloma Lines of Treatment - Pooled Studies. (MM-003 DCO 28-Apr-2023).

System Organ Class	CRB-401, MM-001, and MM-003 Arm A On/After ide cel infusion		
	2 (N = 71) n (%)	≥ 3 (N = 338) n (%)	Total (N = 409) n (%)
All Causality			
SAEs	26 (36.6)	199 (58.9)	225 (55.0)
AEs	71 (100)	338 (100)	409 (100)
Grade 3-4 AEs	67 (94.4)	324 (95.9)	391 (95.6)
AESIs (Number of subjects with ≥ 1 AESI/selected AE)	71 (100)	338 (100)	409 (100)
CRS	61 (85.9)	285 (84.3)	346 (84.6)
NT - Focused	21 (29.6)	132 (39.1)	153 (37.4)
Infections - Overall	32 (45.1)	220 (65.1)	252 (61.6)
Cytopenia - Overall	65 (91.5)	314 (92.9)	379 (92.7)
Neutropenia	62 (87.3)	297 (87.9)	359 (87.8)
Thrombocytopenia	39 (54.9)	206 (60.9)	245 (59.9)
New Malignancies	4 (5.6)	27 (8.0)	31 (7.6)
MAS	2 (2.8)	7 (2.1)	9 (2.2)
Autoimmune Disorders	0	1 (0.3)	1 (0.2)

Source: Appendix 3, Table 3.1.1.1.5 (all causality AEs), Table 3.1.3.1.5 (Grade 3-4 all causality AEs), Table 3.1.5.1.5 (SAEs), Table 3.1.12.1.5 (AESIs).

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

Note: For subjects in studies CRB-401 and MM-001 who received retreatment, only the AEs started before retreatment lymphodepleting chemotherapy are included.

AESI/Selected AEs categories used either MedDRA version 24.1 SMQ or sub-SMQ or SOC or high level term or list of PTs.

CRS

Table 5921. Summary of Cytokine Release Syndrome by Number of Prior Antimyeloma Therapies - Pooled Studies - Safety Population. (MM-003 DCO 28-Apr-2023).

	Pooled Data from CRB-401, MM-001 and MM-003 Arm A		
	2 (N = 71)	≥ 3 (N = 338)	Total (N = 409)
Number of Subjects with at Least one CRS - n (%)	61 (85.9)	285 (84.3)	346 (84.6)
Maximum Reported CRS Grade (Lee Criteria) - n (%)			
1	44 (62.0)	164 (48.5)	208 (50.9)
2	15 (21.1)	102 (30.2)	117 (28.6)
3	0	14 (4.1)	14 (3.4)
4	1 (1.4)	3 (0.9)	4 (1.0)
5	1 (1.4)	2 (0.6)	3 (0.7)
Time to First Onset of Any CRS (days)[a] - n	61	285	346
Median (Min, Max)	2.0 (1, 6)	1.0 (1, 17)	1.0 (1, 17)
Total Number of CRS Events - n	62	311	373
Number of Events by Length of Duration - n (%)			
1-5 days	43 (69.4)	199 (64.0)	242 (64.9)
6-10 days	17 (27.4)	82 (26.4)	99 (26.5)
>10 days	2 (3.2)	29 (9.3)	31 (8.3)
Ongoing[b]	0	1 (0.3)	1 (0.3)
Duration of CRS (per Event) Descriptive Statistics (days)[b,c] - n	62	310	372
Median (Min, Max)	4.0 (1, 40)	4.0 (1, 63)	4.0 (1, 63)
Number of Subjects Received Tocilizumab for CRS - n (%)	50 (70.4)	194 (57.4)	244 (59.7)
1 Dose Tocilizumab	29 (40.8)	123 (36.4)	152 (37.2)
>1 Dose Tocilizumab	21 (29.6)	71 (21.0)	92 (22.5)
2 Doses Tocilizumab	14 (19.7)	53 (15.7)	67 (16.4)
>2 Doses Tocilizumab	7 (9.9)	18 (5.3)	25 (6.1)
Number of Subjects Received Siltuximab for CRS - n (%)	1 (1.4)	3 (0.9)	4 (1.0)
1 Dose Siltuximab	1 (1.4)	3 (0.9)	4 (1.0)
Number of Subjects Received Steroids for CRS - n (%)	18 (25.4)	75 (22.2)	93 (22.7)
Number of Subjects Received Anakinra for CRS - n (%)	4 (5.6)	6 (1.8)	10 (2.4)
1 Dose Anakinra	0	1 (0.3)	1 (0.2)
>1 Dose Anakinra	4 (5.6)	5 (1.5)	9 (2.2)
2 Doses Anakinra	0	1 (0.3)	1 (0.2)

	Pooled Data from CRB-401, MM-001 and MM-003 Arm A		
	2 (N = 71)	≥ 3 (N = 338)	Total (N = 409)
>2 Doses Anakinra	4 (5.6)	4 (1.2)	8 (2.0)
Number of Subjects With CRS Symptoms Any Grade - n (%)	61 (85.9)	285 (84.3)	346 (84.6)
In ≥ 5% of Subjects			
ALT increased	2 (2.8)	19 (5.6)	21 (5.1)
AST increased	2 (2.8)	20 (5.9)	22 (5.4)
C-reactive protein increased	5 (7.0)	38 (11.2)	43 (10.5)
Chills	16 (22.5)	61 (18.0)	77 (18.8)
Fatigue	2 (2.8)	27 (8.0)	29 (7.1)
Headache	6 (8.5)	40 (11.8)	46 (11.2)
Hypotension	16 (22.5)	103 (30.5)	119 (29.1)
Hypoxia	6 (8.5)	59 (17.5)	65 (15.9)
Nausea	5 (7.0)	16 (4.7)	21 (5.1)
Pyrexia	59 (83.1)	279 (82.5)	338 (82.6)
Serum ferritin increased	4 (5.6)	16 (4.7)	20 (4.9)
Tachycardia	16 (22.5)	84 (24.9)	100 (24.4)
Tachypnoea	3 (4.2)	25 (7.4)	28 (6.8)
Number of Subjects with CRS Symptoms Grade 3 or 4 - n (%)	12 (16.9)	81 (24.0)	93 (22.7)
In ≥ 1% of Subjects			
Acute kidney injury	2 (2.8)	0	2 (0.5)
ALT increased	1 (1.4)	4 (1.2)	5 (1.2)
AST increased	2 (2.8)	7 (2.1)	9 (2.2)
Atrial flutter	1 (1.4)	0	1 (0.2)
Blood lactate dehydrogenase increased	1 (1.4)	1 (0.3)	2 (0.5)
Chills	1 (1.4)	0	1 (0.2)
Dyspnoea	1 (1.4)	1 (0.3)	2 (0.5)
Febrile neutropenia	2 (2.8)	9 (2.7)	11 (2.7)
Hypofibrinogenaemia	1 (1.4)	2 (0.6)	3 (0.7)
Hypotension	2 (2.8)	9 (2.7)	11 (2.7)
Hypoxia	0	18 (5.3)	18 (4.4)
Pyrexia	8 (11.3)	32 (9.5)	40 (9.8)

Source: Appendix 3, Table 3.2.1.1

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

Note: For subjects who received retreatment, only the AEs started before retreatment lymphodepleting chemotherapy are included.

[a] Time to first onset of CRS: first start date of CRS - infusion date + 1

[b] Ongoing CRS was excluded from calculation of duration of CRS.

[c] Algorithm for duration: if gap between two events ≤ 1 day, then these two events were considered as one event regardless of grade change, drug relationship change, or severity change.

Investigator Identified Neurotoxicity

Table 6022. Summary of Investigator Identified Neurotoxicity by Number of Prior Antimyeloma Therapies - Pooled Studies - Safety Population. (MM-003 DCO 28-Apr-2023).

	MM-001 and MM-003 Arm A		
	2 (N = 71)	**≥ 3 (N = 282)**	**Total (N = 353)**
Number of Subjects with at Least one iiNT - n (%)	5 (7.0)	52 (18.4)	57 (16.1)
Maximum Reported iiNT Grade (NCI CTCAE V4.03) - n (%)			
1	4 (5.6)	21 (7.4)	25 (7.1)
2	0	21 (7.4)	21 (5.9)
3	0	9 (3.2)	9 (2.5)
4	1 (1.4)	1 (0.4)	2 (0.6)
5	0	0	0
Time to First Onset of iiNT (days)[a] - n	5	52	57
Median (Min, Max)	4.0 (1, 4)	3.0 (1,317)	3.0 (1,317)
Total Number of iiNT Events - n	5	59	64
Number of Events by Length of Duration - n (%)			
1-5 days	4 (80.0)	36 (61.0)	40 (62.5)
6-10 days	0	11 (18.6)	11 (17.2)
>10 days	1 (20.0)	6 (10.2)	7 (10.9)
Ongoing[b]	0	6 (10.2)	6 (9.4)
Duration of iiNT (per Event) Descriptive Statistics (days)[b,c] - n	5	53	58
Median (Min, Max)	3.0 (1, 37)	3.0 (1, 30)	3.0 (1, 37)
Number of Subjects Received Tocilizumab for iiNT - n (%)	0	3 (1.1)	3 (0.8)
1 Dose Tocilizumab	0	3 (1.1)	3 (0.8)
Number of Subjects Received Siltuximab for iiNT - n (%)	0	0	0
Number of Subjects Received Steroids for iiNT - n (%)	2 (2.8)	23 (8.2)	25 (7.1)
Number of Subjects Received Anakinra for iiNT[d] - n (%)	0	1 (0.4)	1 (0.3)
1 Dose Anakinra	0	0	0
>2 Doses Anakinra	0	1 (0.4)	1 (0.3)
Number of Subjects With iiNT Symptoms Any Grade - n (%)	5 (7.0)	52 (18.4)	57 (16.1)
In ≥ 1% of Subjects			
Aphasia	0	9 (3.2)	9 (2.5)
Asthenia	0	3 (1.1)	3 (0.8)
Cognitive disorder	0	4 (1.4)	4 (1.1)

	MM-001 and MM-003 Arm A		
	2 (N = 71)	≥ 3 (N = 282)	Total (N = 353)
Confusional state	3 (4.2)	27 (9.6)	30 (8.5)
Delirium	0	3 (1.1)	3 (0.8)
Depressed level of consciousness	2 (2.8)	4 (1.4)	6 (1.7)
Disorientation	1 (1.4)	3 (1.1)	4 (1.1)
Disturbance in attention	1 (1.4)	6 (2.1)	7 (2.0)
Dysarthria	0	3 (1.1)	3 (0.8)
Dysgraphia	1 (1.4)	6 (2.1)	7 (2.0)
Dysmetria	1 (1.4)	1 (0.4)	2 (0.6)
Encephalopathy	0	12 (4.3)	12 (3.4)
Hallucination	1 (1.4)	5 (1.8)	6 (1.7)
Headache	0	3 (1.1)	3 (0.8)
Lethargy	1 (1.4)	5 (1.8)	6 (1.7)
Memory impairment	0	6 (2.1)	6 (1.7)
Mental status changes	0	4 (1.4)	4 (1.1)
Slow speech	1 (1.4)	0	1 (0.3)
Somnolence	2 (2.8)	8 (2.8)	10 (2.8)
Tremor	0	8 (2.8)	8 (2.3)
Urinary incontinence	0	4 (1.4)	4 (1.1)
Number of Subjects with iiNT Symptoms Grade 3 or 4 - n (%)	1 (1.4)	11 (3.9)	12 (3.4)
In ≥ 1% of Subjects			
Confusional state	1 (1.4)	3 (1.1)	4 (1.1)
Depressed level of consciousness	1 (1.4)	2 (0.7)	3 (0.8)
Encephalopathy	0	3 (1.1)	3 (0.8)

Source: Appendix 3, Table 3.3.1.1

Coded using MedDRA version 24.1. Graded using CTCAE version 4.03.

Note: For Study CRB-401, no iiNT data were collected and therefore it is excluded from the analysis.

For subjects who received retreatment, only the AEs started before retreatment lymphodepleting chemotherapy are included.

[a] Time to first onset of iiNT: first start date of iiNT - infusion date + 1.

[b] Ongoing iiNT was excluded from calculation of duration of iiNT.

[c] Algorithm for duration: if gap between two events ≤ 1 day, then these two events were considered as one event regardless of grade change, drug relationship change or severity change.

Post marketing experience

The AEs observed with ide-cel are anticipated toxicities consistent with the mechanism of action of CAR T cell therapies and included CRS, neurotoxicity, cytopenias, and infections. These events were generally manageable across the dose range explored in clinical trials and were mitigated with clinical site training on recognition of these events and with protocol-specified toxicity management guidelines.

2.6.1. Discussion on clinical safety

Safety data from the pivotal study MM-003 are provided in support of the proposed indication of ide-cel.

MM-003 study safety data have been submitted either based on the first data cutoff (18-Apr-2022)), as well as the MAH provided during the procedure comprehensive more mature safety data with the same cut-off date as for the PFS final analysis efficacy data, DCO 28 April 2023, with a median duration of follow-up of 30.9 months. Overall, the updated safety data (28-Apr 2023 CoD; 23-Jun-2023 DBL) are consistent with the safety data from the previous cutoff (18- Apr-2022 CoD; 14-Jul-2022 DBL). No new safety issues were identified.

Data from the ide-cel arm of MM-003 are also presented side-by-side with the pooled safety data from the supportive study CRB-401 (Phase I) and study MM-001 (Phase II). Additionally, all 3 studies are pooled in support of the updated SmPC and for the proposed label update.

Overall, the safety data provided in the present application is consistent with the previously described safety profile of ide-cel.

Main analysis of Study MM-003

The safety analysis of study MM-003 is based on the safety populations (i.e., those who received the study medication of ide-cel or any standard regimen) consisting of 225 and 126 subjects for the ide-cel and standard regimens arms, respectively. Any grade AEs were reported in the majority of patients in both treatment arms, with Grade 3/4 AEs being more frequently reported in the ide-cel arm (100%; Grade 3/4: 95.1%) than in the standard regimens arm (98.4%; Grade 3/4: 77.0%).

The most common AEs observed in MM-003 are anticipated toxicities consistent with the known safety profile of ide-cel and CAR-T cell therapies in general.

Data from the later cutoff were consistent with the initially submitted data and the most common AEs are consistent with previously reported data. Overall, these high AE frequencies are expected taking into account the advanced stage of the disease and also the known safety profiles of the treatments administered.

In the original submission (18- Apr-2022 CoD), SAEs were more commonly reported in the ide-cel arm (52.9%) than in the standard regimens arm (38.1%). Even though there was a difference in the overall SAE frequency, related SAEs were reported at a similar frequency (16.4% for ide-cel vs. 15.1% for the standard regimens). The MAH has clarified that this was most likely due to different AE and SAE profiles between the study arms, and also due to different reporting periods for related SAEs. However, according to updated data, at least one SAE suspected to be treatment related was reported for 23.6% of subjects in the ide-cel arm and 15,9% of subjects in the standard regimens arm. For the ide-cel arm, the most frequently reported SAEs (by PT) reported were pneumonia (6.7%), pyrexia (4.9%), CRS (4.4%), general physical health deterioration and febrile neutropenia (4.0% each). For the standard regimens arm: pneumonia (4.8%), COVID-19 pneumonia and general physical health deterioration (3.2% each), and influenza and atrial fibrillation (2.4% each). These SAEs can be considered as expected.

During the study, 164 patients died (ITT population) so far, evenly distributed across the ide-cel (41.7%) and standard regimens (43.9%) arms, mainly caused by malignant disease or complication due to malignant disease in both arms (25.2% vs 28%%, respectively). The proportion of patients who died due to AEs was similar for the ide-cel (6.7%) and standard regimens arm (6.1 %).

Among the safety population, 92 patients (32.0%) in the ide-cel arm discontinued the study, none of them due to AEs.

AESIs (CRS, iiNT, cytopenias, malignancies, infections and macrophage activating syndrome (MAS)) were reported for 100% (Grade 3/4: 87.6%) of the subjects in the ide-cel arm, vs 95.2% (Grade 3/4: 67.5%) in the standard regimens arm. CRS was reported for 87.6% of subjects (Grade 3/4: 4.0%) in the ide-cel arm. The median time to first onset of CRS was 1.0 day (range 1.0 to 14.0 days) and the median duration of CRS AEs was 4.0 days (range: 1.0 to 51.0 days). The majority of CRS events were of Grade 1 or 2 severity. A small proportion of subjects had severe events (Grade 3: 2.7%; Grade 4: 1.3%, and Grade 5: 0.9%; 2 subjects). The reported frequency and severity of CRS events is in line with the current SmPC information.

In the ide-cel arm, 34 (15.1%) subjects experienced at least one event of iiNT. The median time to first onset of any iiNT AEs was 3.0 days (range 1.0, 317.0) and the median duration of iiNT AEs was 2.5 days (range: 1.0, 252). However, in the initially submitted data there were in total 5 patients with ongoing iiNT at the data cut-off date. Based on the DCO 28-Apr-2023 it can be summarised that for 3 subjects the iiNT was ongoing at the time of death, for one subject the iiNT was ongoing at the time of withdrawal of consent, and for one subject the iiNT eventually resolved. There were in total 7 subjects in whom the iiNT lasted for more than 10 days, and only for one subject that was very long-lasting In addition, the iiNT term dysmetria was reported by more than one patient and is now included in the SmPC, Section 4.8. Given the known neurological toxicity related to the ide-cel mode of action, The MAH has included information on the late onset iiNT in the SmPC, which is agreed. Adequate warnings and treatment guidelines concerning these iiNT events are provided in the SmPC.

As expected for this pre-treated patient population, cytopenia was reported in the majority of patients in both treatment arms, with a higher frequency and severity grade in the ide-cel (92.0%, Grade 3/4: 90.2%) vs the standard regimens arm (73.0%, Grade 3/4:62.7%). Even though the frequency of Grade 3/4 neutropenia in ide-cel arm was higher compared to that in the standard regimen arm, the frequency of Grade 3/4 infections was only modestly increased. No clear excess of bleeding event was seen despite higher frequencies of Grade 3/4 thrombocytopenia in the ide-cel arm compared to the standard regimen arm (44.4% vs. 18.3%).
The more profound cytopenia induced by ide-cel treatment was related to slightly higher infections and Grade 3/4 infections.

None of the ide-cel treated subjects in study MM-003 were diagnosed with secondary T cell malignancies. However, there is a numerical difference in the reporting of other new malignancies between the ide-cel arm (8.0%, n=18) and the standard regimens arm (4.0%, n=5) (DCO 28-Apr-2023). It is acknowledged that the total number of events is low, and data show that the duration of actual time at risk for patients with SPMs was higher for the ide-cel arm, resulting in a comparable incidence rate for secondary malignancies per 100 person years for both treatment arms (3.58 vs 4.12). None of the SPMs were of T-cell origin, which would be the most plausible malignancy type potentially related to ide-cel treatment. Secondary malignancies are a well-known risk in MM patients receiving chemotherapy treatment, and the frequency is usually higher with higher therapy lines. However, the follow-up is too short to evaluate, whether there is an increased risk for second primary malignancies among patients treated with ide-cel.

MAS was reported in 5 (2.2%, all of them Grade 3/4) patients in the ide-cel arm, which is consistent with previously reported data.

In addition, one autoimmune disease was reported. According to narrative data, this was G2 vasculitis on D25 after ide-cel infusions and considered to be related to ide-cel.

As expected for this patient population, the infection rate was high for both the ide-cel (63.6%, Grade 3/4: 22.2%) and the standard regimens arm (57.1%, Grade 3/4: 18.3%), being slightly more frequent in the ide-cel arm.

Apart from the haematological AESIs which were mainly of grade 3 or 4, the majority of AESIs were mild to moderate in severity and no new clinically important events were identified for ide-cel.

Changes in clinical laboratory results in the ide-cel arm were consistent with those previously observed in studies with ide-cel treatment. Overall, changes in haematology laboratory results were followed by the expected recovery post infusion. Further, changes in clinical laboratory results in the standard regimen arm were consistent with subjects being on anticancer medication.
With the DCO 28-Apr-2023 , four (4) subjects in the ide-cel arm were identified with persistence of vector sequence (PVS), defined as detection of CAR vector sequences in more than 1% of cells in peripheral blood samples collected at ≥12 months post infusion of ide-cel. No evidence of malignant transformation has been observed in these patients. Of note, one of these subjects was diagnosed with MDS about a year and a half post ide-cel infusion. By now there is no evidence from the peripheral blood testing suggesting an association between ide-cel transgene integration and the development of MDS. Monitoring of CAR-T cell frequency and kinetics and ISA testing for any PVS positive events will continue for all subjects through study completion, and after study end, monitoring will continue for up to 15 years in the context of the long-term follow-up study (GC-LTFU-001).

In Study MM-003 safety population, post-infusion anti-CAR antibody positivity did not appear to have an effect on safety of ide-cel. In the ide-cel arm, the proportion of subjects with at least one CRS or iiNT event was similar between post infusion anti-CAR antibody positive and negative subjects.

Finally, there were 60 patients, who received ide-cel in the standard regimen arm after disease progression. The MAH has confirmed that AEs after ide-cel infusion in the standard regimens arm subjects are not reported within the standard regimens arm safety results, but separately. The overall frequencies and types of SAEs, AEs, and AESIs observed in subjects who received ide-cel as subsequent therapy after progression in the standard regimens arm were consistent with those reported for ide-cel previously and no new safety concerns were observed.

Subgroup analyses of MM-003

Number of prior Antimyeloma Lines of Treatment

There are no noteworthy differences in the AE rates per SOC across the number of prior treatment lines subgroups and the safety profile of ide-cel versus standard regimens appears to be consistent across the number of prior lines of therapy, supporting the proposed indication of treatment for patients being exposed to 2 prior treatments. However, the subgroups are small, and data should be interpreted with caution.

Ide-cel dose category

Subgroup analyses were also performed by ide-cel dose levels (DCO 28-Apr-2022 The median dose of ide-cel in the MM-003 study was 445.3 x 10^6 CAR+ T cells (min, max: 174.9, 529.0); 79 (35.1%) subjects received ide-cel doses > 460 x 10^6 CAR+ T cells. The ide-cel dose was higher in the MM-003 study (445.3 x 10^6 CAR+ T cells, range: 174.9 – 529.9) compared to the pooled studies (323.8 x 10^6 CAR+ T cells, range: 140.8 – 518.4).

The proportion of subjects who experienced at least one event of CRS across the 2 ide-cel dose levels of 300 to 460 x 10^6 CAR+ T cells (85.3%) and > 460 to 540 x 10^6 CAR+ T cells (92.4%) was comparable to the overall ide-cel arm safety population (87.6%). Events of ≥Grade 3 level are numerically less frequent in the intermediate (2.8%, n=4) compared to the higher (8.9%, n=7) dose level, potentially reflecting the increased strength of T cell activation and a higher degree of T cell expansion in the high dose subgroup. Tocilizumab treatment was less frequently received by patients in the 300 to 460 x 10^6 CAR+ T cells group (67.1%) compared to the > 460 to 540 x 10^6 CAR+ T cells group (79.7%), and more patients received >2 doses in the latter. As for iiNT, the overall safety data

appears to be comparable for the dose levels of 300 to 460 x 10^6 CAR+ T cells and > 460 to 540 x 10^6 CAR+ T cells. The proportion of subjects experiencing at least one iiNT event across the two ide-cel dose levels of 300 to 460 x 10^6 CAR+ T cells (16.1%) and > 460 to 540 x 10^6 CAR+ T cells (13.9%) was comparable, and consistent to that of the overall ide-cel arm safety population. In addition, the time to the first onset of iiNT and the duration of iiNT events were consistent across ide-cel dose levels.

The overall safety profile of ide-cel appears to be consistent across the doses, apart for some numerical differences, however, data should be interpreted with caution due to the small subpopulations and low total number of events.

Supportive Safety Information across studies and lines of therapy

The MAH has presented safety data from the time of ide-cel infusion in MM-003 (i.e., ide-cel treated safety population, n = 225) (DCO 28-Apr-2022) side-by-side with the pooled safety data from the supportive studies CRB-401 and MM-001 (n=184). In addition, the MAH has presented pooled data including study MM-003 and the pooled CRB-401 and MM-001 studies (n=409). The subject disposition of the ide-cel arm in MM-003 was similar to that of the pooled studies. As expected, the proportion of subjects ongoing in the study is higher in the MM-003 (68%) vs the pooled studies (37%), in line with the lower proportion of study discontinuation in the former (32%) vs the latter (63%). The main reason for discontinuation is death in both MM-003 (24.9%) and the pooled studies (27.2%), and the higher proportion of discontinuation in the pooled studies compared to MM-003 is mainly driven by progressive disease and withdrawal by subject. Of note, discontinuation by manufacturing failure in the leukapheresis population was infrequent in both groups (n=3; 1.3% in MM-003 and n=1; 0.5% in the pooled studies). The median follow-up time for subjects in study MM-003 safety population for ide-cel arm (DCO 28-Apr-2022) was 17.0 months (0.3 – 34.3 months), whereas that for the pooled studies was longer, i.e., 20.8 months (15.0 – 47.7 months). These different follow-up times need to be considered when safety data are compared. For lymphodepleting chemotherapy, the data from the ide-cel arm in MM-003 is overall consistent with the pooled studies.

Regarding the demographics, the age distribution and sex ratio are comparable for the pooled studies and study-MM-003, with slightly more subjects over 75 years in the MM-003 study. There are slight differences in race, ethnicity, and regional distribution. Concerning race, majority of included patients where white (68.9% in MM-003 vs. 83.2% in the pooled studies). In the pooled studies, 82.1% of patients were included in North America vs. 17.9% in Europe, while for study MM-003, the distribution was 58.2% vs 40.0%, respectively.

Based on inclusion criteria, the number of previous antimyeloma regimens was higher in the pooled studies (median 6.0 vs. 3.0), as were also the percentage of double, triple and penta-refractory patients and those with extramedullary disease (38.0% vs. 24.4%). A higher number of subjects in the pooled studies had also received stem cell transplantation (92.9% vs. 84.0%), as well as more than one transplantation (31.5% vs. 17.8%). In addition, tumour burden was higher (plasma cells ≥ 50%) in the pooled studies (47.8%) compared to MM-003 (30.2%).

The patients in the pooled studies were thus more heavily pre-treated and had in general poorer prognostic factors compared to MM-003, as expected based on the applied inclusion and exclusion criteria. On the other hand, it also seems that pooled studies included highly selected patients who had maintained good performance status despite that e.g., >40% of patients had received ≥7 lines of treatment.

The baseline severity of disease is higher in the pooled studies (CRB-401 and MM-001) compared to MM-003, consistent with the median number of prior antimyeloma regimens being 6.0 vs 3.0 for the pooled studies and Study MM-003, respectively.

Overall, the nature and frequency of Grade 3 or 4 AEs (by SOC) related to ide-cel appears to be similar between the pooled studies and MM-003. The rate of SAEs is higher in the pooled studies compared to MM-003 (70.1% vs 42.7%), approximately half of the events being assessed as treatment-related (34.2% vs 16.4%).

The rate of CRS was comparable for the pooled studies (81.0%) vs MM-003 (87.6%), with a similar proportion of ≥ Grade 3 CRS events (5.4% vs 4.9%). The median time to first onset of CRS was identical (1.0 day), while the duration of CRS per event (days) was higher in the pooled studies (5.0; min, max 1,63) vs MM-003 (3.5; min, max 1,51). There were a higher number of long-lasting (>10 days) CRS in the pooled studies (13.4% vs. 4.9%). However, the severity grade of CRS symptoms was higher in the pooled studies (Grade 3-4: 28.8%) vs MM-003 (Grade 3-4: 17.8%), which might be a consequence of the markedly lower proportion of subjects treated with tocilizumab for CRS is in the pooled studies (45.1%) vs MM-003 (71.6%). In addition, patients in MM-003 study also received more often > 2 doses of tocilizumab. There was also an important difference in the use of steroids for treating CRS, 15.8% vs 28.4% in the pooled studies and MM-003, respectively. It has been confirmed that the currently used guidelines for CRS management advise earlier use of tocilizumab and earlier escalation to further CRS treatment lines (steroids). The currently proposed Abecma SmPC already contains the latest guidelines concerning tocilizumab use, and no update is required.

Overall, the iiNT data are comparable between MM-001 and MM-003. A similar proportion of subjects experienced any grade iiNT in MM-001 (18.0%) versus MM-003 (15.1%), with 3.1% of events in both studies being ≥ Grade 3 iiNT. The median time to first onset of iiNT was comparable for MM-001 (2.0 days) vs MM-003 (3.0 days), and the median duration of iiNT (per event) was comparable for both studies (3.0 vs 2.0, respectively). The use of steroids for iiNT was comparable for both studies, 7.8% vs 6.7%, for MM-001 and MM-003 respectively.

The frequency of Grade 3 or 4 neutropenia within the first month after ide-cel infusion was high and comparable for the pooled studies (96.7%) and MM-003 (96.4%). Thrombocytopenia was also reported with comparable frequencies of Grade 3 or 4 events in the pooled studies (59.8%) and MM-003 (53.3%). In both cases, with most patients recovering with similar rate for both data sets.

New malignancies were reported at a comparable frequency in pooled studies (8.7%) and study MM-003 (6.7%), with the most commonly reported secondary malignancies (>1%) being basal cell carcinoma, myelodysplastic syndrome, and squamous cell carcinoma. However, the follow-up is too short to evaluate, whether there is an increased risk for second primary malignancies among patients treated with ide-cel.

As expected with CAR T treatment and in this MM patient population, the infection rate was high, with more subjects experiencing infections in the pooled studies (71.2%) vs the MM-003 (53.8%), which might be related to the higher disease severity in the pooled studies.

There was a higher number of deaths in the pooled studies compared to the MM-003 study (34.8% vs. 24.9%). The main reasons for death were death from malignant disease under study, or complication due to malignant disease under study (22.8% vs. 12.9%). These findings are not unexpected, taking into account the more advanced disease state in the pooled studies (including higher number of treatments, refractory status etc.) and longer follow-up of patients in the pooled studies. Majority of the deaths also occurred > 8 weeks after ide-cel infusion.

Finally, the SmPC section 4.8 was updated based on the pooled data from all three studies (CRB-401, MM-001 and MM-003 (28-Apr-2023 CoD). As no major difference in safety was observed between these groups based on previous treatment, the pooled safety data (N=409) can be reliably used as basis for safety description in SmPC Section 4.8, as currently proposed. The overall safety profile of ide-cel remains unchanged, although some frequencies of the most common ADRs were notably

decreased in the updated SmPC vs the previous version; infections-pathogen unspecified (43.8% vs 53.8%), leucopenia (32.8% vs 48.4%) fatigue (29.8% vs 39.1%), upper respiratory tract infection (15.6% vs 21.7%), hypogammaglobulinaemia (13.7% vs 19.6%) and febrile neutropenia (11.2% vs 16.3%). Also, the frequencies of asthenia, and blood alkaline phosphatase increased were changed from "very common" to "common", hemiparesis was changed from "common" to "uncommon", while insomnia was changed from "common" to "very common". Another noteworthy difference in the updated SmPC is the serious ADR of CRS, being decreased to 10.3% vs previously 17.4%.

2.6.2. Conclusions on clinical safety

Overall, the MM-003 safety data reported for the sought indication are consistent with the known safety profile of ide-cel. The main safety concerns are, as previously reported, cytopenias, CRS, infections, and neurological toxicity, and no new safety concerns were identified.

The safety profile appears to be similar regardless of whether the patients have received 2, or ≥3 prior antimyeloma treatments, supporting the proposed indication. Data is consistent between the first and updated cutoff dates. Safety data has been provided for different subgroups and appear overall comparable across the analysis populations. No new safety concerns have been identified.

Altogether, from a clinical safety perspective, the sought indication is considered approvable.

The CHMP endorse the CAT conclusion on clinical safety as described above.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CAT received the following PRAC Advice on the submitted Risk Management Plan:

The MAH submitted an updated RMP version 3.2 with this application.

Rationale for submitting an updated RMP:

- Proposed indication for the treatment of adult patients with relapsed and refractory MM who have received at least two prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 monoclonal antibody and have demonstrated disease progression on the last therapy
- Removal of the specific obligation - Study BB2121-MM-003
- Update of post-authorisation exposure information

The main changes made to the RMP v.3.2 were related to the Phase 3 Efficacy and Safety Study (BB2121-MM-003). Safety specification was updated with the data from this study. The MAH has removed this PAES from the RMP Part IV.

No changes were made to important identified, important potential risks and missing information. Pharmacovigilance plan and risk minimisation measures remain unchanged. Additionally, several editorial changes were made, which are acceptable.

The removal of the specific obligation Study BB2121-MM-003 is acceptable in light of the final positive opinion for the extension of indication.

The PRAC considered that the risk management plan version 3.2 is acceptable.

The CAT and CHMP endorsed this advice without changes.

The CAT and CHMP endorsed the Risk Management Plan version 3.2 with the following content:

Safety concerns

Important identified risks	Cytokine release syndrome
	Neurologic toxicity
	Cytopenias
	Hypogammaglobulinaemia
	Infections
Important potential risks	Secondary malignancies
	Tumour lysis syndrome
	Aggravation of GVHD

Important identified risks	Cytokine release syndrome
	Neurologic toxicity
	Cytopenias
	Hypogammaglobulinaemia
	Infections
	Generation of replication competent lentivirus
	Immunogenicity
Missing information	Impact on pregnancy and lactation
	Long-term safety
	Safety in elderly patients (≥ 75 years)

Pharmacovigilance plan

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Noninterventional, postauthorisation, registry-based study (BB2121-MM-006) / Ongoing	**Primary Objective** To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with ide-cel in the postmarketing setting and to monitor for potential clinically important events that have not yet been identified as part of the ide-cel safety profile. **Secondary Objective** To assess survival in patients treated with ide-cel in the postmarketing setting.	Cytokine release syndrome Neurologic toxicity Cytopenias Hypogammaglobulinaemia Infections Secondary malignancies Tumour lysis syndrome Aggravation of graft versus host disease[a] Impact on pregnancy and lactation Long-term safety	1. Date of Final Registry Protocol Submission to EMA	Date of Initial Registry Protocol Submission to EMA as part of MAA: 30-Apr-2020
			2. Start of data collection	14-Feb-2022[b]
			3. Study progress updates	Per the PSUR cycle, according to the EURD list
			4. Safety Reports	Every 6 months (aligned with the reporting period of the PSUR).[c] Additional reports every 3 months if a new safety concern is identified
			5. Interim Reports	Year 5, 10, and 15 or when last patient is out of the registry-based study
			6. Date of Study Completion	Q1 2042
			7. Date of Final Report Submission to EMA	Q1 2043
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 3 - Required additional pharmacovigilance activities				
Long-term follow-up study (GC-LTFU-001) / Ongoing	**Primary Objectives:** • To assess the risk of delayed AEs following exposure to GM T cells. • To monitor for long-term persistence of GM T cells, including analysis of vector integration sites, as appropriate. • To monitor for generation of replication competent retroviruses.	Long-term safety	1. Patients to be followed up for up to 15 years	NA
			2. Start of data collection	Jul-2018
		Secondary malignancies Long-term safety	3. Interim Reports (5 and 10 years from first subject first visit in GC-LTFU-001 [Jul 2018])	Q3 2023 and Q3 2028
			4. Anticipated last subject last visit	Q1 2037[e]
		Secondary malignancies	5. Final database lock	Q2 2037
		Generation of replication competent lentivirus Long-term safety	6. Final report of completed GC-LTFU-001 follow-up of 4L+[d] multiple myeloma ide- cel treated subjects	Mar-2038
			7. Safety data will be included in PSURs	Submitted in accordance with EURD list
Transgene assay service testing of secondary malignancies with insertion site analysis as applicable	Tumour tissue sample testing from patients that develop a secondary malignancy of T cell origin.	Secondary malignancies from insertional oncogenesis	1. Safety data will be included in PSURs	Submitted in accordance with the EURD list
			2. Interim Reports	EC decision + 5 years (Q2 2026) EC decision + 10 years (Q2 2031) EC decision + 15 years (Q2 2036)

[a] Included under the category of Other AEs considered related to ide-cel treatment in Study BB2121-MM-006.

[b] Based on the EC decision and protocol approval timeline.

[c] 6-month safety reports will be provided with the PSUR submission (PSUR single assessment) as determined by the EURD list.

[d] 4L+ = Fourth line and beyond.

[e] Ide-cel-treated 4L+ multiple myeloma subjects enrolled in the GC-LTFU-001 trial.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Cytokine release syndrome	**Routine Risk Minimisation Activities:** SmPC Sections 4.2 and 4.4, PL Sections 2 and 3 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional Risk Minimisation Activities: • Educational programme for HCPs and patients • Controlled distribution programme	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Neurologic toxicity	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 and 4.7, PL Section 2– warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire
	Additional Risk Minimisation Activities: • Educational programme for HCPs and patients • Controlled distribution programme	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Cytopenias	**Routine Risk Minimisation Activities:** SmPC Section 4.4, PL Sections 2 and 4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Hypogammaglobulinaemia	**Routine Risk Minimisation Activities:** SmPC Sections 4.4 and 4.6 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Infections	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 and PL Sections 2, 3 and 4 – warnings, advice and management discussed SmPC Section 4.8 and PL	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Section 4 – listed as an ADR Ide-cel is administered by an HCP	
	Additional Risk Minimisation Activities: • Educational programme for HCPs (need to coordinate ide-cel thawing and its infusion) • Controlled distribution programme	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Important Potential Risks		
Secondary malignancies	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings, advice and management discussed Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable
Tumour lysis syndrome	**Routine Risk Minimisation Activities:** Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Aggravation of graft versus host disease	**Routine Risk Minimisation Activities:** SmPC Section 4.4 and PL Section 2 – warnings, advice and management discussed Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** Included under the category of Other AEs considered related to ide-cel treatment in PASS (BB2121-MM-006)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Generation of replication competent lentivirus	**Routine Risk Minimisation Activities:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001)
Immunogenicity	**Routine Risk Minimisation Activities:** SmPC Section 4.2 and PL Section 3 – premedication with paracetamol and diphenhydramine or another H1-antihistamine SmPC Section 4.8 – listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** None
Missing Information		
Impact on pregnancy and lactation	**Routine Risk Minimisation Activities:** SmPC Section 4.6 and PL Section 2 – warnings, advice and management discussed Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006) for pregnancy events
Long-term safety	**Routine Risk Minimisation Activities:** SmPC Annex II – long-term registry discussed Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001)
Safety in elderly patients (≥ 75 years)	**Routine Risk Minimisation Activities:** SmPC Section 4.2 – No dose adjustment necessary Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** None

2.8. Update of the Product information

As a consequence of this new indication, sections 2.1, 2.2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3, 6.4 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current ATMP product information template version 1.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section to delete the remaining SOB as it has been considered fulfilled by this extension of indication procedure.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: No major changes to the PL have been introduced, only minor text additions where done. The layout and design of the artwork has not been changed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The present variation application concerns an extension of the indication to include:

treatment of adult patients with relapsed and refractory multiple myeloma who have received at least ***two*** prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

3.1.2. Available therapies and unmet medical need

Current treatment options for MM includes glucocorticoids, chemotherapy, primarily alkylating agents, high-dose chemotherapy followed by ASCT, PIs (bortezomib, carfilzomib and ixazomib), IMiDs (thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs; daratumumab, isatuximab and elotuzumab), histone deacetylase inhibitors (panobinostat), XPO1 inhibitors (selinexor), antibody drug conjugates targeting BCMA (belantamab mafodotin) as well as BCMA-directed CAR-T cell products (ide-cel and cilta-cel), and finally the recently approved bispecifc antibody teclistamab targeting both CD3 and BCMA.

Factors influencing choice of therapy in the RRMM setting, include age; performance status; comorbidities; type, efficacy and tolerability of the prior AMT; number of prior treatment lines; available remaining treatment options; the interval since the last therapy; and the type of relapse (Moreau, 2017). For RRMM patients with second or subsequent relapses, EHA-ESMO recommended options are triplet regimens, however, no single treatment algorithm exist, and the choice of treatment regimen depends on prior drug exposure and responsiveness/refractoriness. In RRMM patients exposed to multiple prior AMTs, or refractory to major classes of AMT, the disease is associated with low response rates, short DoR, and poor survival. Thus, there is an unmet medical need for more treatment options capable of achieving deep and durable responses.

3.1.3. Main clinical studies

The pivotal data come from an ongoing, open-label, multicenter, randomized, controlled phase 3 study (MM-003) comparing the efficacy and safety of ide-cel vs standard regimens (ie, daratumumab, pomalidomide, and dexamethasone (DPd), daratumumab, bortezomib and dexamethasone (DVd), Ixazomib, lenalidomide and dexamethasone (IRd), carfilzomib and dexamethasone (Kd) or elotuzumab, pomalidomide, and dexamethasone (EPd)) in subjects with RRMM who had received 2 to 4 prior myeloma regimens, including daratumumab, an immunomodulatory agent, and PI and had documented disease progression during or within 60 days after the last therapy.

Patients were randomized 2:1 to arm A (lymphodepleting chemotherapy (LDC) followed by ide-cel infusion) or arm B (standard regimens: DPd, DVd, IRd, Kd, or EPd) and stratified by age (< 65 years vs ≥ 65 years), number of prior antimyeloma regimens (2 vs 3 or 4 prior antimyeloma regimens) and high-risk cytogenetic abnormalities (presence vs absence or unknown presence of t(4;14) or t(14;16) or del 17p).

The primary endpoint was PFS per IRC according to the IMWG response criteria. Key secondary endpoints were ORR per IRC and OS, which were tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate. Other secondary endpoints included CR rate, TTR, DoR, EFS, PFS2, time to next antimyeloma treatment, MRD negativity rate and PRO. The MAH defined the enrolled (ITT) population as the primary analysis population. Data were reported based on a data cut-off of 28-Apr-2023. The end of trial was defined as 5 years after the last subject has been randomized (08-Apr-2022).

3.2. Favourable effects

The data obtained from the controlled phase 3 study MM-003 (also known as KarMMa-3) add a superior level of certainty compared to the data derived from the pivotal single-arm phase 2 study MM-001 for the CMA of ide-cel when evaluating the favourable effects of the product in patients with RRMM.

The primary endpoint of the MM-003 study was met, showing a statistically significant improvement in PFS, based on the IMWG criteria per IRC assessment (p-value < 0.0001), for patients treated with ide-cel compared to standard regimens with a stratified HR = 0.493 (95% CI: 0.384, 0.634) in the ITT population using FDA censoring rules. The median PFS was 13.8 months (95% CI: 11.8, 16.1) for patients receiving ide-cel versus 4.4 months (95% CI: 3.4, 5.8) for patients receiving standard regimens.

PFS analysis using EMA censoring rules was comparable with that using FDA censoring rules and showed a stratified HR = 0.512 (95.0% CI: 0.404, 0.649), with a median PFS of 12.8 months (95% CI: 11.3, 15.7) for patients receiving ide-cel versus 4.8 months (95% CI: 3.7, 5.9) for patients receiving standard regimens.

These results were supported by several sensitivity analyses. In addition, an improvement in PFS in patients receiving ide-cel compared to standard regimens was consistently observed in all pre-specified subgroups.

The key secondary endpoint (hierarchically tested) of ORR per IRC was met. ORR was 71.3% (95% CI: 65.7, 76.8) for the ide-cel arm compared to 42.4% (95% CI: 34.0, 50.9) for the comparator arm, with a common odds ratio at 3.44 (95% CI: 2.20, 5.40) and p-value < 0.0001 (Cochran-Mantel-Haenszel test). Higher ORR for ide-cel treated patients as compared to patients treated with standard regimens was consistently observed in all pre-specified subgroups.

Median OS was 41.4 months (95% CI: 30.9, NA) for the ide-cel arm, versus 37.9 months (95% CI: 23.4, NA) for the comparator arm (HR = 1.012 [95% CI: 0.731, 1.400]).

The median DoR, based on IMWG criteria per IRC, was 16.5 months (95% CI: 12.0, 19.4) for the ide-cel arm versus 9.7 months (95% CI: 5.4, 15.5) for the comparator arm using EMA censoring rules.

CR was achieved by 43.7% (95% CI: 37.6, 49.8) of the ide-cel treated patients, whereas by 5.3% (95% CI: 1.5, 9.1) of the patients treated with standard regimens.

MRD negativity by NGS was achieved by 22.4% (95% CI: 17.3, 27.6) of ide-cel treated patients, whereas by 0.8% (95% CI: 0.0, 2.2) of patients treated with standard regimens.

3.3. Uncertainties and limitations about favourable effects

A limitation of the study is that duration of follow-up was relatively short, with a median follow-up at 30.9 months and a minimum follow-up at 12.7 months.

Importantly, 56.1% of patients in the standard regimens arm received ide-cel infusion after disease progression at the DCO of the third OS interim analysis (DCO 28-Apr-2023), thus OS data are confounded by extensive cross-over between the two treatment arms, and interpretation of OS data is difficult. At the third OS interim analysis, the OS data presented with HR = 1.012 (95% CI: 0.731, 1.400). The 95% CI for the HR crossed 1, the p-value did not meet the significance boundary for superiority of efficacy (< 0.001), and the KM plot revealed crossing survival curves at 15 months and non-proportional hazards. The KM curve for OS indicated that patients in the ide-cel arm were at increased risk of early death for the first 12 months after randomization, compared to patients in the standard therapy arm. The provided baseline characteristics of patients with early death indicated that this was due to a subgroup of patients with poor prognosis experiencing potential harm by being randomised to the ide-cel arm. Subgroup analysis and KM curves showed a negative trend in OS with ide-cel treatment for certain subgroups of patients, especially for patients with presence of high-risk cytogenetic abnormalities, but possibly also for patients with R-ISS stage III, presence of extramedullary plasmacytoma or high tumor burden. The OS data were considered immature at the DCO for the third interim analysis (74% maturity, 164 of the required 222 final events), with 58.3% and 56.1% of patients censored in the ide-cel arm and the standard regimens arm, respectively.

DoR data was also rather immature, and the estimate for the comparator arm was based on relatively few events (47 events out of 56 responders), versus 128 events (out of 181 responders) for the ide-cel arm.

MRD negativity rate was only reported at a fixed point in time (defined as the proportion of subjects who achieved ≥ CR and MRD negative status at a sensitivity of 10^{-5} at any time point (assessed at screening, between leukapheresis and LD chemotherapy, and at months 2, 7, and 13) within 3 months prior to achieving at least CR until the time of PD/death) whereas sustained MRD negativity rate over a period of 6-12 months would have been considered of higher prognostic value.

Contextualization of the effect is of some concern due to the selected patient population studied; only patients with a PS 0-1 and no major co-morbidities or organ dysfunction were eligible and on the other hand patients were relatively young (median age 63 years) and 85% of the patients had received at least one prior ASCT.

3.4. Unfavourable effects

In study MM-003 (28-Apr-2023 CoD), almost all patients experienced at least one AE following ide-cel infusion (100%) or standard treatment (98.4%), with the majority of events (95.1% vs 77.0%, respectively) suspected as being treatment-related. SAEs were reported in 53.8% vs 41.3% of patients in the ide-cel arm vs the standard regimens arm respectively, with 23.6% vs 15.9% being suspected as related to treatment.

Consistent with the known safety profile of ide-cel, reported main safety events are related to CRS, neurological toxicity, cytopenia and infections.

CRS was reported in 87.6% of patients (Grade 3/4: 4.0%), mostly occurring within the first days post infusion, with a median time to first onset of 1.0 day (1.0 to 14.0), and a median duration of CRS of 4.0 days (range: 1.0 to 51.0).

iiNT was reported in 15.1% of patients, with only few events being of Grade 3/4 (3.1%). The median time to first onset of any iiNT AEs was 3.0 days (range 1.0, 317.0) and the median duration of iiNT AEs was 2.5 days (range: 1.0, 252).

Most patients in both the ide-cel and standard regimens arm reported at least one event of cytopenia overall (92.0% vs 73.0%), the majority of which were Grade 3/4 (90.2% vs 62.7%, respectively).

Infections overall were reported in 63.6% vs 57.1% of patients in the ide-cel and standard regimens arms respectively, with 22.2% vs 18.3% of events being of grade 3/4.

New malignancies were reported for 8.0% of patients in the ide-cel arm, vs 4.0% in the standard regimens arm. None of the events were of T cell origin.

Overall, the safety profile of ide-cel appears to be consistent with what has previously been reported.

3.5. Uncertainties and limitations about unfavourable effects

The primary safety data presented in this variation are from the pivotal study MM-003, including 225 patients with RRMM, who received ide-cel (safety population) and who had previously received 2 to 4 prior treatment lines for their disease. Given the rarity of the disease, the size of the safety database is considered acceptable, although the patient population receiving ide-cel treatment is relatively small, indicating that only common AEs are captured.

Although the duration of follow-up in MM-003 was substantially increased as of the updated data cutoff (median 30.9 months) compared to the first data cutoff (median 17.0 months), long-term toxicities such as persistent cytopenias, long-lasting neurotoxicity, second primary malignancies and late onset infections may still not be detected.

The overall safety profile of the subgroups "number of prior treatments" and "LVV type" remains an uncertainty, as data should be interpreted with caution due to the small sample size, and since the LVV subgroups were not predefined. However, the provided data do not indicate any new safety issues.

LDC and bridging therapies are confounding factors, contributing to difficulties in separating AEs related to treatment.

Finally, patients in clinical studies with ide-cel are considered highly selected, having good performance status (PS 0-1), being relatively young (median 63 years) and having no major co-morbidities. They do not necessary represent patients receiving ide-cel treatment in clinical practise, who may be more prone to toxicities of treatment. Hence, careful follow-up of safety based on postmarketing surveillance is important.

3.6. Effects Table

Table 61. Effects Table for the indication extension of Abecma to include treatment of adult patients with relapsed and refractory multiple myeloma after at least two prior therapies (DCO: 28-Apr-2023)

Effect	Short description	Unit	Treatment Ide-cel (n=254)	Control Standard Regimens (n=132)	Uncertainties / Strength of evidence
Favourable Effects					
PFS by IRC	Time from randomization to first PD based on IMWG	Months (95% CI)	13.8 (11.8, 16.1)	4.4 (3.4, 5.8)	HR: 0.493 (95% CI: 0.384, 0.634) p < 0.0001

Effect	Short description	Unit	Treatment Ide-cel (n=254)	Control Standard Regimens (n=132)	Uncertainties / Strength of evidence
	response criteria by IRC or death due to any cause, whichever occurs first				Ide-cel: 27.6% censored, standard regimen: 20.5% censored
ORR	Percentage of subjects who achieved a PR or better according to IMWG response criteria by IRC	% (95% CI)	71.3 (65.7, 76.8)	42.4 (34.0, 50.9)	Odds ratio: 3.44 (95% CI: 2.20, 5.40); p < 0.0001
OS	Time from randomization to time of death due to any cause	Months (95% CI)	41.4 (30.9, NA)	37.9 (23.4, NA)	HR: 1.012 (95% CI: 0.731, 1.400); p=0.5287 Crossing survival curves, immature data and extensive cross-over between arms (56.1% of patients randomised to the standard regimens arm received ide-cel after PD)
DoR	Time from response (PR or better) to PD or death from any cause, whichever occurs first	Months (95% CI)	16.5 (12.0, 19.4)	9.7 (5.4, 15.5)	Immature data, based on relatively few events (128 out of 181 responders for ide-cel and 47 out of 56 responders for comparator arm)
MRD-negative status by NGS and ≥ CR	MRD negativity is determined by at least one negative MRD value within 3 months prior to achieving CR or above until time of progression/death	n (%) 95% CI (%)	57 (22.4) (17.3, 27.6)	1 (0.8) (0.0, 2.2)	only reported at a fixed point in time (3 month). Lack of progressive report on MRD negativity data over a period of 6-12 months
Unfavourable Effects					

Effect	Short description	Unit	Treatment Ide-cel (n=254)	Control Standard Regimens (n=132)	Uncertainties / Strength of evidence
CRS			87.6% Grade 3/4: 4.4%	0%	
Neurologic toxicity "focused" iiNT			76.0% Grade 3/4: 12.4% 15.1% Grade 3/4: 3.1%	70.6% Grade3/4: 16.7%	
Cytopenia-overall			92.0% Grade 3/4: 90.2%	73.0% Grade 3/4: 62.7%	
Infections - overall			63.6% Grade 3/4: 26.7%	57.1% Grade 3/4: 19.8%	
Secondary malignancies			8.0% Grade 3/4: 4.0%	4.0% Grade 3/4: 1.6%	
MAS			2.2% Grade 3/4: 2.2%	0%	

Abbreviations: Cytokine release syndrome (CRS), investigator identified neurotoxicity (iiNT), macrophage activating syndrome (MAS).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the MM-003 study, median PFS was significantly prolonged for patients treated with ide-cel (13.8 months) compared to patients treated with standard regimens (4.4 months), with a HR of 0.493. Considering the poor prognosis of RRMM in third and later lines of therapy, the observed magnitude of PFS difference is considered clinically meaningful.

The PFS benefit of ide-cel compared to standard regimens was consistently observed across all pre-specified subgroups, including patients that were double class refractory, triple class refractory, had high-risk cytogenetics, high tumour burden or extramedullary plasmacytoma, or had received 2-4 prior antimyeloma regimens. However, a numerically higher PFS HR for patients with R-ISS stage III (CI for HR crossed 1) compared to patients with R-ISS stage I or II was observed. This could indicate slightly less benefit of ide-cel compared to the standard regimens for R-ISS stage III patients, although the number of patients in this subgroup was low, and thus the result should be interpreted with caution. Relevant warning has been raised in the SmPC.

Ide-cel demonstrated a substantial anti-tumour activity in the studied patient population, with an ORR of 71.3%, which was significantly higher as compared to the ORR of 42.4% for standard regimens. A numerically higher proportion of patients achieved deeper response; 43.7% in the ide-cel arm achieved CR or better compared to 5.3% in the standard regimens arm. The observed responses

appeared to be durable (median DoR of 16.5 months for ide-cel) and longer-lasting compared to standard regimens (9.7 months), supporting the clinical benefit observed in terms of PFS.

The open-label design increases the risk of bias; although the evaluation of PFS, ORR and DoR was performed by a blinded IRC.

Benefit in terms of improved OS has not been demonstrated. The CI for HR crossed 1 and the one-sided p-value for OS did not meet the significance boundaries for either superiority of efficacy or futility. Due to the crossing survival curves and non-proportional hazards, immaturity of the data as well as extensive cross-over between the treatment arms, OS data are difficult to interpret. Importantly, the KM curve for OS showed that patients in the ide-cel arm were at increased risk of early death during the first 12 months after randomisation, compared to patients in the standard therapy arm. The crossing of the curves at 15 months, as well as the provided baseline characteristics of patients with early death, indicated that this was due to a subgroup of patients with poor prognosis experiencing potential harm by being randomised to the ide-cel arm. However, most of the early deaths in the ide-cel arm were due to myeloma disease progression and occurred mainly among subjects who never received ide-cel treatment. This might be explained by the time from end of bridging therapy to ide-cel infusion (median 24 days), which could be suboptimal and not sufficient to control the disease in the subjects with high-risk factors as compared to the continuous treatment in the standard regimens arm. Subgroup analysis and KM curves showed a negative trend in OS with ide-cel treatment for certain subgroups of patients, especially for patients with presence of high-risk cytogenetic abnormalities, but possibly also for patients with R-ISS stage III, presence of extramedullary plasmacytoma or high tumor burden. This finding is reflected in the product information.

MRD negativity was achieved by 22.4% of the ide-cel treated patients, versus 0.8% of patients treated with standard regimens. However, MRD negativity rate was only reported at a fixed point in time (defined as the proportion of subjects who achieved ≥ CR and MRD negative status at a sensitivity of 10^{-5} at any time point (assessed at screening, between leukapheresis and LD chemotherapy, and at months 2, 7, and 13) within 3 months prior to achieving at least CR until the time of PD/death) whereas sustained MRD negativity rate over a period of 6-12 months would have been considered of higher prognostic value. Nevertheless, 22% versus 0.8% is a rather large difference and thus, likely, a difference would have been observed also in sustained MRD negativity rate over 6-12 months.

Overall, the reported safety findings are anticipated toxicities consistent with the mechanism of action of CAR-T cell treatments and with the main known safety concerns being cytopenias, CRS, infections, and neurological events. All these are very common AEs, can be life-threatening and need timely diagnosis and treatment. However, they are usually manageable following detailed treatment guidelines, as currently described in the SmPC.

The main limitation for the safety assessment is the limited size of the safety database (n=225 for study MM-003 and n=409 for all pooled studies).

3.7.2. Balance of benefits and risks

The substantial delay of disease progression observed in the controlled phase 3 study MM-003, together with the improved ORR and a promising DoR, indicates a significant clinical benefit of ide-cel compared to standard regimens currently available for the treatment of RRMM patients in third and later lines of therapy. The observed responses seem to be durable. Benefit in terms of improved OS has not been demonstrated. Patients in the ide-cel arm were at increased risk of early death compared to patients in the standard therapy arm, indicating that for a subgroup of patients with poor prognosis ide-cel may not be an optimal treatment option. Notably, early deaths did not seem to be associated with ide-cel treatment *per se,* but rather the failure to receive CAR-T cell infusion. This in turn could be

due to suboptimal bridging as provided by the discussion with the experts Adverse events are consistent with previously reported data for ide-cel and are generally manageable by adequate risk mitigation measures based on detailed treatment guidelines in the SmPC.

Considering all favourable and unfavourable effects reported, the benefit-risk balance of ide-cel is considered positive for RRMM patients after at least two prior therapies.

3.7.3. Additional considerations on the benefit-risk balance

The initial CMA was based on clinical data from a single-arm study. The main uncertainties remaining at the time of the CMA were the lack of a comparator arm in the pivotal study MM-001 leading to uncertainties in determining the true effect size with respect to ORR, and particularly the lack of interpretable time-to-event endpoint data (PFS and OS). In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH was requested to provide the results of the Phase 3 study KarMMa-3 (MM-003) comparing the efficacy and safety of Abecma vs. standard regimens in subjects with relapsed and refractory multiple myeloma.

The primary analysis of the results of the MM-003 study demonstrated that main efficacy endpoints (PFS, ORR, CR, DoR and MRD) are in favour of a positive clinical outcome for the studied patients. Considering the poor prognosis in the RRMM clinical setting in third- and later lines of therapy, the observed magnitude of effect is considered clinically meaningful. Benefit in terms of improved OS has not been demonstrated mainly due to a subgroup of patients with poor prognosis as described above which may experience potential harm by being randomized to ide-cel. Notably, the early deaths did not seem to be associated with ide-cel treatment *per se* but more likely due to suboptimal bridging strategies and failure to undergo CAR-T cell infusion. Nevertheless, the crossing survival curves and non-proportional hazards, as well as extensive cross-over between the treatment arms, make OS data difficult to interpret.

Overall, the MM-003 study demonstrated superiority in PFS as compared to a relevant selection of standard treatment regimens, and addressed the main uncertainties identified at the time of the initial CMA. Therefore, the agreed SOB to the CMA is considered to be fulfilled, and the CMA can be converted to a full MA.

3.8. Conclusions

The overall benefit/risk balance of Abecma is considered positive for the applied extension of the indication.

The CHMP endorse the CAT conclusion on Benefit Risk balance as described above

4. Recommendations

Outcome

Based on the draft CHMP opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD-38 antibody and have demonstrated disease progression on the last therapy for Abecma (idecabtagene vicleucel, ide-cel), based on results from study BB2121-MM-003 (MM-003, KarMMa-3). This is a Phase 3, multicentre, randomised, open-label study to compare the efficacy and safety of ide-cel versus standard regimens in subjects with RRMM. As a consequence, sections 2.1, 2.2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.1, 6.3, 6.4 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 3.2 of the RMP has also been submitted. Furthermore, the PI is brought in line with the Guideline on core SmPC, Labelling and Package Leaflet for advanced therapy medicinal products (ATMPs) containing genetically modified cells.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that it is deleted from the Annex II:

Description	Due date
In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH should submit the results of the Phase 3 study KarMMa-3 (MM-003) comparing the efficacy and safety of Abecma vs. standard regimens in subjects with relapsed and refractory multiple myeloma.	January 2024

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information

being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Key elements:

Availability of tocilizumab and site qualification via the controlled distribution programme

The MAH will ensure that hospitals and their associated centres that dispense Abecma are qualified in accordance with the agreed controlled distribution programme by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Abecma infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- healthcare professionals (HCP) involved in the treatment of a patient have completed the educational programme.

Educational programme

Prior to the launch of Abecma in each Member State, the MAH must agree on the content and format of the educational materials with the National Competent Authority.

HCP educational programme

All HCPs who are expected to prescribe, dispense and administer Abecma shall be provided with a healthcare professional guide, which will contain information about:

- identification of CRS and serious neurologic adverse reactions;
- management of the CRS and serious neurologic adverse reactions;
- adequate monitoring of CRS and serious neurologic reactions;
- provision of all relevant information to patients;
- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Abecma infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on-site;
- contact details for tumour sample testing after development of a secondary malignancy of T cell origin;
- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study;
- ensure that adverse reactions are adequately and appropriately reported;
- ensure that detailed instructions about the thawing procedure are provided.

Patient educational programme

All patients who receive Abecma shall be provided with a patient card, which will contain the following key messages:

- the risks of CRS and serious neurologic adverse reactions associated with Abecma;
- the need to report the symptoms of suspected CRS and NT to their treating doctor immediately;
- the need to remain in the proximity of the location where Abecma was received for at least 4 weeks following Abecma infusion;
- the need to carry the patient card at all times;
- a reminder to patients to show the patient card to all HCPs, including in conditions of emergency and a message for HCPs that the patient is using Abecma;
- fields to record contact details of the prescriber and batch number.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Interim reports to be submitted in accordance with the RMP. Final report: Q1 2043

Similarity with authorised orphan medicinal products

The CAT by consensus is of the opinion that Abecma is not similar to Farydak, Kyprolis, Darzalex, Ninlaro, Blenrep, Carvykti and Talvey within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

The CHMP endorse the CAT conclusion on the similarity with authorised orphan medicinal products.

Additional market protection

Furthermore, the CAT reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

The CHMP endorse the CAT conclusion on the Additional market protection.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Abecma-H-C-4662-II-0031'