November 6, 2023
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Products
Non-proprietary Name	Idecabtagene vicleucel
Brand Name	Abecma Intravenous Infusion
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 14, 2023 (Application for partial change)

Results of Deliberation

In the meeting held on November 6, 2023, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until January 19, 2032).

The following approval conditions must be satisfied.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Review Report

October 20, 2023
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following regenerative medical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Abecma Intravenous Infusion
Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Products
Non-proprietary Name	Idecabtagene vicleucel
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 14, 2023

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product prepared from autologous peripheral blood mononuclear cells (PBMCs) isolated from the leukocyte apheresis product of the patient, to which a transgene encoding chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA) is introduced by using a recombinant lentiviral vector.

Application Classification (3) Regenerative medical product with a new indication

Items Warranting Special Mention

Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 12 of 2019 [*31 sai*]; PSEHB/MDED Notification No. 1125-2 dated November 25, 2019, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare [MHLW])

Reviewing Office Office of Cellular and Tissue-based Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of relapsed or refractory multiple myeloma with at least 2 prior lines of therapy, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication or performance as well as dosage and administration or method of use shown below, with the following approval conditions.

Indication or Performance

Relapsed or refractory multiple myeloma. Abecma should be used only in patients meeting all of the following criteria:

- Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy
- Patients who have received at least 2~~3~~ prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-cluster of differentiation (CD)38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy

(Underline denotes additions. Strikethrough denotes deletions.)

Dosage and Administration or Method of Use

Process from leukapheresis at a medical institution to transportation to a manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a refrigerated container maintained at 2°C to 8°C and transported to a manufacturing facility of Abecma.

Process from receipt at the medical institution to administration of Abecma

3. Receipt and storage of Abecma
   Abecma is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before Abecma administration
   The patient undergoes a blood test, etc., for condition checking and receives the following lymphodepleting chemotherapy from 5 days prior to Abecma administration.
   Administer cyclophosphamide (anhydrate) 300 mg/m^2 as an intravenous infusion once daily for 3 days and fludarabine phosphate 30 mg/m^2 as an intravenous infusion once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
5. Administration of Abecma
   Abecma is thawed immediately before infusion. The usual adult dosage is the target dose of 450 × 10^6 cells (range, 280 × 10^6-540 × 10^6 cells) of CAR-expressing T cells, irrespective of body weight, administered intravenously as a single dose at an infusion rate not exceeding 10 mL/min. Retreatment with Abecma is not allowed.

(No change)

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.

2. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Attachment

Review Report (1)

August 31, 2023

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

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Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product prepared from autologous peripheral blood mononuclear cells (PBMCs) isolated from the leukocyte apheresis product of the patient, to which a transgene encoding chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA) is introduced by using a recombinant lentiviral vector.

Proposed Indication or Performance

Relapsed or refractory multiple myeloma. Abecma should be used only in patients meeting all of the following criteria:

- Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy
- Patients who have received at least 2~~3~~ prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-cluster of differentiation (CD)38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy

(Underline denotes additions. Strikethrough denotes deletions.)

Proposed Dosage and Administration or Method of Use

Process from leukapheresis at a medical institution to transportation to a manufacturing facility

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   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material
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   Administer cyclophosphamide (anhydrate) 300 mg/m^2 as an intravenous infusion once daily for 3 days and fludarabine phosphate 30 mg/m^2 as an intravenous infusion once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
5. Administration of Abecma
   Abecma is thawed immediately before infusion. The usual adult dosage is the target dose of 450 × 10^6 cells (range, 280 × 10^6-540 × 10^6 cells) of CAR-expressing T cells, irrespective of body weight, administered intravenously as a single dose at an infusion rate not exceeding 10 mL/min. Retreatment with Abecma is not allowed.

(No change)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Idecabtagene vicleucel (hereinafter referred to as "Abecma") is a regenerative medical product consisting of a patient's own peripheral T cells that have been cultured and proliferated through transduction with genetically modified lentiviral vector containing chimeric antigen receptor (CAR) that specifically recognizes B cell maturation antigen (BCMA). Abecma is intravenously administered into the patient to obtain a therapeutic effect based on the pharmacological action, in the same manner as drugs.

The CAR that is transfected into Abecma is comprised of a murine single-chain variable fragment (scFv) specifically recognizing BCMA, a human cluster of differentiation (CD)8α hinge and transmembrane domain fused to the intracellular signaling domains of human 4-1BB and CD3ζ. When recognizing BCMA-expressing cells, Abecma induces the activation and proliferation of the genetically modified T cells, thereby obtaining effector functions such as a cytopathic effect. Through these actions, Abecma is expected to kill BCMA-positive tumor cells.

In Japan, Abecma was approved in January 2022 with the indication for "Relapsed or refractory multiple myeloma (MM) in patients who have received at least 3 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody."

Abecma was designated as an orphan regenerative medical product with the intended indication or performance for treatment of "relapsed or refractory multiple myeloma" on November 25, 2019 (Orphan Regenerative Medical Product Designation No. 12 of 2019 [*31 sai*]).

1.2 Development history etc.

With the aim of clinical development of Abecma against MM, the applicant initiated Study BB2121-MM-003 (Study MM-003) in April 2019, in patients with relapsed or refractory MM who have received 2 to 4 prior lines of treatment including immunomodulatory agent, proteasome inhibitor, and daratumumab (genetical recombination) (DARA), an anti-CD38 monoclonal antibody.

In the US, an application for marketing approval (application) for Abecma was submitted in [redacted] 2023 with Study MM-003 as the pivotal study, and undergoing the review process as of August 2023.

In Europe, an application for Abecma was submitted in [redacted] 2023 with Study MM-003 as the pivotal study, and undergoing the review process as of August 2023.

In Japan, patient enrollment in Study MM-003 was initiated in [redacted] 20[redacted].

Recently, a partial change application for Abecma has been submitted to change the indication or performance for treatment of "relapsed or refractory MM in patients who have received ≥2 prior lines of treatment including immunomodulatory agent, proteasome inhibitor, and anti-CD38 monoclonal antibody," based on the results of Study MM-003.

2. Quality and Outline of the Review Conducted by PMDA

This application relates to the new indication, and no data relating to quality are not submitted.

3. Primary Pharmacodynamics or Performance and Outline of the Review Conducted by PMDA

This application relates to the new indication, but no new data are submitted because the data relating to non-clinical pharmacology have been evaluated during the review process for the initial application.

4. Non-clinical Safety and Outline of the Review Conducted by PMDA

This application relates to the new indication, but no new data are submitted because the data relating to non-clinical safety have been evaluated during the review process for the initial application.

5. Biological Disposition and Outline of the Review Conducted by PMDA

The applicant submitted the data on the biological disposition of Abecma obtained in Study MM-003. However, the data were confirmed to be similar to those submitted for the initial application.

6. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data from 1 global phase III study shown in Table 1.

Table 1. Clinical study on efficacy and safety

Data category	Region	Study identifier	Phase	Study population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Global	MM-003	III	Patients with relapsed or refractory MM	(a) 254 (b) 132	(a) Abecma A single intravenous administration of anti-BCMA CAR-expressing T cells at the dose of 150×10^6-450×10^6 cells (b) Standard treatment One of the standard treatments (DPd, DVd, IRd, Kd, EPd) selected by the investigator based on the last prior lines of treatment	Efficacy Safety

The clinical study is summarized below. The main adverse events excluding deaths observed in the clinical study are presented in Section “8. Adverse Events Observed in Clinical Study”

6.1 Evaluation data

6.1.1 Global study

6.1.1.1 Global phase III study (CTD 5.3.5.1-1, Study MM-003, ongoing since April 2019 [data cut-off on April 18, 2022])

An open-label randomized controlled study was conducted to compare the efficacy and safety between Abecma and the standard treatment in patients with relapsed or refractory MM (target sample size,[1)] 381 subjects [254 in the Abecma group, 127 in the standard treatment group]) at 49 study sites in 12 countries including Japan. Table 2 shows the main inclusion/exclusion criteria.

Table 2. Main inclusion/exclusion criteria

Inclusion criteria
• Patients with relapsed or refractory MM who have had all of the following prior treatments:
  ➢ Patients who have received 2 to 4 prior MM treatment regimens (Each of induction therapy, hematopoietic stem cell transplant, and maintenance therapy is considered a single regimen.)
  ➢ Patients who have had prior treatments including immunomodulator, proteasome inhibitor, and DARA. They should have undergone ≥2 consecutive cycles of treatment for each regimen.
  ➢ Refractory to their last line of therapy (Refractory is defined as documented PD during or within 60 days of completing treatment)
  ➢ Some response (MR or better) to at least 1 of the prior treatments
• Patients who have measurable disease, including ≥1 of the criteria below:
  ➢ Serum M-protein ≥0.5 g/dL
  ➢ Urine M-protein ≥200 mg/24 h
  ➢ Serum FLC assay ≥10 mg/dL (100 mg/L) and provided serum FLC ratio is abnormal
• Patients with ECOG PS score of 0 or 1
 	
Exclusion criteria
• Patients with any of the following previous treatments: an allogeneic hematopoietic stem cell transplantation, any gene therapy-based therapeutic for cancer, cellular therapy for cancer, or BCMA targeted therapy
• Patients with known CNS involvement with myeloma
• Patients with past or current clinically significant CNS disease

Treatment-eligible patients were randomized to the Abecma group and the standard treatment group in a 2:1 ratio. Study MM-003 consisted of the following periods:

(a) Screening phase: Period until randomization of patients to the Abecma group or the standard treatment group

(b) Leukapheresis phase (the Abecma group only): Period from the randomization through leukapheresis and Abecma production up to the time before the start of lymphodepleting chemotherapy (LD chemotherapy)

(c) Treatment phase: Period from the start of LD chemotherapy to Abecma administration in the Abecma group; period from the start of the standard treatment regimen up to confirmation of progressive disease (PD), occurrence of unacceptable toxicity, or consent withdrawal in the standard treatment group

(d) Progression free survival (PFS) follow-up period: Period from Abecma administration up to PD confirmation or up to the visit for PFS follow-up discontinuation within 7 days after decision of study discontinuation for reason of consent withdrawal, etc. in the Abecma group; period up to PD confirmation if the standard treatment regimen was discontinued before PD confirmation in the standard treatment group

[1)] By assuming the median progression free survival (PFS), the primary endpoint, to be 14 months in the Abecma group and 9 months in the standard treatment group (hazard ratio of the Abecma group to the standard treatment group, 0.643), the number of events necessary to ensure 94% statistical power (one-sided significance level of 2.5%) was calculated to be 289. The target sample size was 381 (254 in the Abecma group, 127 in the standard treatment group) in order to achieve the target number of events.

(e) Survival status follow-up phase: Period from PD confirmation up to 5 years after the randomization of the last patient

In the Abecma group, a single dose of anti-BCMA CAR-expressing T cells (target dose, 150×10^6-450×10^6 cells[2)]) was administered intravenously. In order to facilitate the engraftment and growth of Abecma in the body, Abecma infusion was preceded by treatment with LD chemotherapy consisting of an intravenous infusion of cyclophosphamide hydrate (cyclophosphamide) 300 mg/m^2 and fludarabine phosphate (fludarabine) 30 mg/m^2 over 30 minutes once daily for 3 consecutive days, starting from 5 days before administration of Abecma. While Abecma was in the process of manufacture, the patient was allowed to receive a bridging therapy for disease control. The bridging therapy was to be conducted as up to 1 cycle of the chemotherapy regimen (coadministration of daratumumab [genetical recombination], pomalidomide, and dexamethasone [DPd],[3)] coadministration of daratumumab [genetical recombination], bortezomib, and dexamethasone [DVd],[4)] coadministration of ixazomib citrate, lenalidomide, and dexamethasone [IRd],[5)] coadministration of carfilzomib and dexamethasone [Kd],[6)] or coadministration of elotuzumab (genetical recombination), pomalidomide, and dexamethasone [EPd][7)]) of the standard treatment group at the discretion of the investigator based on the last prior therapy given to the patient.[8)] The bridging therapy was required to be completed ≤14 days before the start of LD chemotherapy.

Each subject in the standard treatment group received either of the following chemotherapy regimens from Day 1 after randomization at the discretion of the investigator based on the last prior therapy given to the patient: DPd, DVd, IRd, Kd, or EPd. The number of subjects receiving each standard therapy was 43 subjects in DPd therapy, 7 subjects in DVd therapy, 22 subjects in IRd therapy, 30 subjects in Kd therapy, and 30 subjects in EPd therapy.

Among the subjects in the standard treatment group, subjects who were documented to be PD by the Independent Response Committee (IRC) assessment and found to be eligible for receiving Abecma were allowed to receive cross-over administration from the standard treatment to Abecma upon the request of

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2) The acceptable upper limit of the actual dose was 540×10^6 cells which was within the range of +20% of 450×10^6.

3) In the treatment cycles of 28 days each, DARA 16 mg/kg was administered intravenously on Days 1, 8, 15, and 22 (in Cycle 1 and Cycle 2), on Days 1 and 15 (in Cycle 3 to Cycle 6), and on Day 1 (in Cycle 7 and thereafter). Pomalidomide (POM) 4 mg was administered orally on Days 1 through 21 of each cycle. Dexamethasone (DEX) 40 mg (20 mg in patients aged >75 years) was administered on Days 1, 8, 15, and 22 in each cycle.

4) DARA 16 mg/kg was administered intravenously on Days 1, 8, and 15 (in Cycle 1 to Cycle 3) and on Day 1 (in Cycle 4 to Cycle 8) in the treatment cycles of 21 days each, and on Day 1 (in Cycle 9 and thereafter) in the treatment cycles of 28 days each. Bortezomib (BTZ) 1.3 mg/m^2 was administered subcutaneously on Days 1, 4, 8, and 11 (in Cycle 1 to Cycle 8) and discontinued in Cycle 9 and thereafter. DEX 20 mg was administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 in Cycle 1 to Cycle 8 (20 mg/week in patients aged ≥75 years, patients with body mass index (BMI) <18.5 kg/m^2, diabetes mellitus, or intolerant to corticoid therapy) and discontinued in Cycle 9 and thereafter.

5) In the treatment cycles of 28 days each, ixazomib citrate (IXA) 4 mg was administered orally on Days 1, 8, and 15, lenalidomide (LEN) 25 mg was administered orally on Days 1 through 21, and DEX 40 mg was administered orally on Days 1, 8, 15, and 22.

6) In the treatment cycles of 28 days each, carfilzomib (CFZ) was administered intravenously at the dose of 20 mg/m^2 on Days 1 and 2 and at the dose of 56 mg/m^2 on Days 8, 9, 15, and 16 in Cycle 1, and CFZ 56 mg/m^2 was administered intravenously on Days 1, 2, 8, 9, 15, and 16 of each cycle in Cycle 2 and thereafter. DEX 20 mg was administered orally on Days 1, 2, 8, 9, 15, 16, 22, and 23 in each cycle.

7) In the treatment cycles of 28 days each, elotuzumab (genetical recombination) (ELO) was administered intravenously at the dose of 10 mg/kg on Days 1, 8, 15, and 22 in Cycle 1 and Cycle 2, and at the dose of 20 mg/kg on Day 1 in Cycle 3 and thereafter. POM 4 mg was administered orally on Days 1 through 21, and DEX 40 mg was administered orally on Days 1, 8, 15, and 22 in patients aged ≤75 years (20 mg weekly in patients aged >75 years). Only on the day of ELO administration, DEX was administered orally at the dose of 28 mg and intravenously at the dose of 8 mg.

8) Of 254 subjects in the Abecma group in the ITT population, 213 subjects received the bridging therapy. The main anti-myeloma drugs (administered to ≥25% of patients) administered in the bridging therapy were POM 48.4% (123 subjects), DARA 31.9% (81 subjects), and ELO 26.4% (67 subjects).

the investigator. Patients receiving the cross-over administration of Abecma were to be followed up until the end of Study MM-003.

The primary efficacy endpoint of the study was IRC-assessed PFS (period from randomization to the first documented PD or death of any cause, whichever occurred earlier) based on the criteria established by International Myeloma Working Group (IMWG) (IMWG criteria) (*Lancet Oncol.* 2016;17:e328-46).

According to the original study protocol, the interim analysis was to be conducted to decide early termination for efficacy when approximately 193 PFS events (approximately 67% of the PFS events required) were observed. However, in the protocol amendment to the version [redacted] on [redacted], 20[redacted], the timing of the interim study was changed to be conducted when approximately 232 PFS events (approximately 80% of the PFS events required) were observed in consideration of [redacted]. Subsequently, on [redacted], 20[redacted], the number of PFS events reached the specified number, and an interim analysis was conducted by the independent data monitoring committee, which confirmed the fulfillment of the criteria for the pre-defined primary endpoint. On the other hand, the study was continued to evaluate overall survival (OS), one of the secondary endpoints, under continued blinded conditions except for some of the unblinded personnel[9)] of the sponsor.

In the interim analysis (data cut-off on April 18, 2022), 386 subjects (254 in the Abecma group and 132 in the standard treatment group, including 4 and 5 Japanese subjects, respectively) were enrolled and randomized. In the Abecma group, 249 subjects received leukapheresis excluding 5 subjects who discontinued the study (adverse event in 1 subject, consent withdrawal in 2 subjects, and failure to meet the criteria for treatment in 2 subjects), and 227 subjects received LD chemotherapy excluding 18 subjects who discontinued the study (death in 15 subjects, investigator's discretion in 1 subject, consent withdrawal in 2 subjects) after leukapheresis and 4 subjects who had not received LD chemotherapy at the time of data cut-off. Abecma was administered to 225 subjects excluding 2 subjects (death in 1 subject and 1 subject before administration of Abecma at the time of data cut-off). In the standard treatment group, 126 of 132 randomized subjects received the standard chemotherapy excluding 6 subjects (consent withdrawal in 3 subjects, investigator's discretion in 2 subjects, disease progression in 1 subject). Among the subjects in the standard treatment group, 70 subjects were considered appropriate to receive the cross-over administration of Abecma, and 69 subjects excluding 1 subject (death) received leukapheresis, and 60 subjects received Abecma, and the remaining 9 subjects were excluded because of death (2 subjects), failure to meet the criteria for treatment (2 subjects), consent withdrawal (2 subjects), failure in Abecma preparation (1 subject), and before administration of Abecma at the time of data cut-off (2 subjects).

A total of 386 randomized subjects (254 in the Abecma group, 132 in the standard treatment group) were included in the ITT population which was handled as the primary efficacy analysis population. A total of 375 subjects, comprising 250 subjects in the Abecma group (249 who received leukapheresis and 1 who received a bridging therapy but not leukapheresis) and 126 subjects who received the standard

9) The persons responsible for preparing OS report and persons responsible for responding to inquiries from regulatory authorities

chemotherapy in the standard treatment group, were handled as the treatment population. A total of 351 subjects, comprising 225 subjects receiving Abecma in the Abecma group and 126 subjects receiving the standard chemotherapy in the standard treatment group, were included in the safety analysis population. In each of the ITT population, the treatment population, and the safety analysis population, the Abecma group and the standard treatment group included 4 and 5 Japanese subjects, respectively.

Table 3 and Figure 1 show the results of PFS, the primary efficacy endpoint, and the Kaplan-Meier curves at the interim analysis (data cut-off on April 18, 2022), demonstrating the superiority of Abecma over the standard treatment (one-sided *P* value <0.001, one-sided significance level of 0.014, stratified log-rank test).

Table 3. Results of interim analysis of PFS
(IRC assessment, ITT population, data cut-off on April 18, 2022)

	Abecma N = 254	Standard treatment N = 132
PFS events (%)	149 (58.7)	93 (70.5)
PD (%)	129 (50.8)	89 (67.4)
Death before documented PD (%)	20 (7.9)	4 (3.0)
Median [95% CI] (months)	13.3 [11.8, 16.1]	4.4 [3.4, 5.9]
Hazard ratio [97.2% CI]*1	0.493 [0.365, 0.666]	
One-sided *P* value*2, *3	<0.0001	

*1 Stratified Cox proportional hazard model with age (<65 years, ≥65 years), number of prior treatment regimens for MM (2, 3 or 4), and presence/absence of high-risk cytogenetic abnormalities (t[4;14], t[14;16], or del 17p) as the stratification factors

*2 Stratified log-rank test with age (<65 years, ≥65 years), number of prior treatment regimens for MM (2, 3 or 4), and presence/absence of high-risk cytogenetic abnormalities (t[4;14], t[14;16], or del 17p) as the stratification factors

*3 The one-sided significance level was 0.014, and the one-sided significance level for the entire study was 0.025, and the O'Brien-Fleming type α consumption function was used as a method for adjusting the multiplicity of hypothesis testing between the interim analysis and the final analysis.

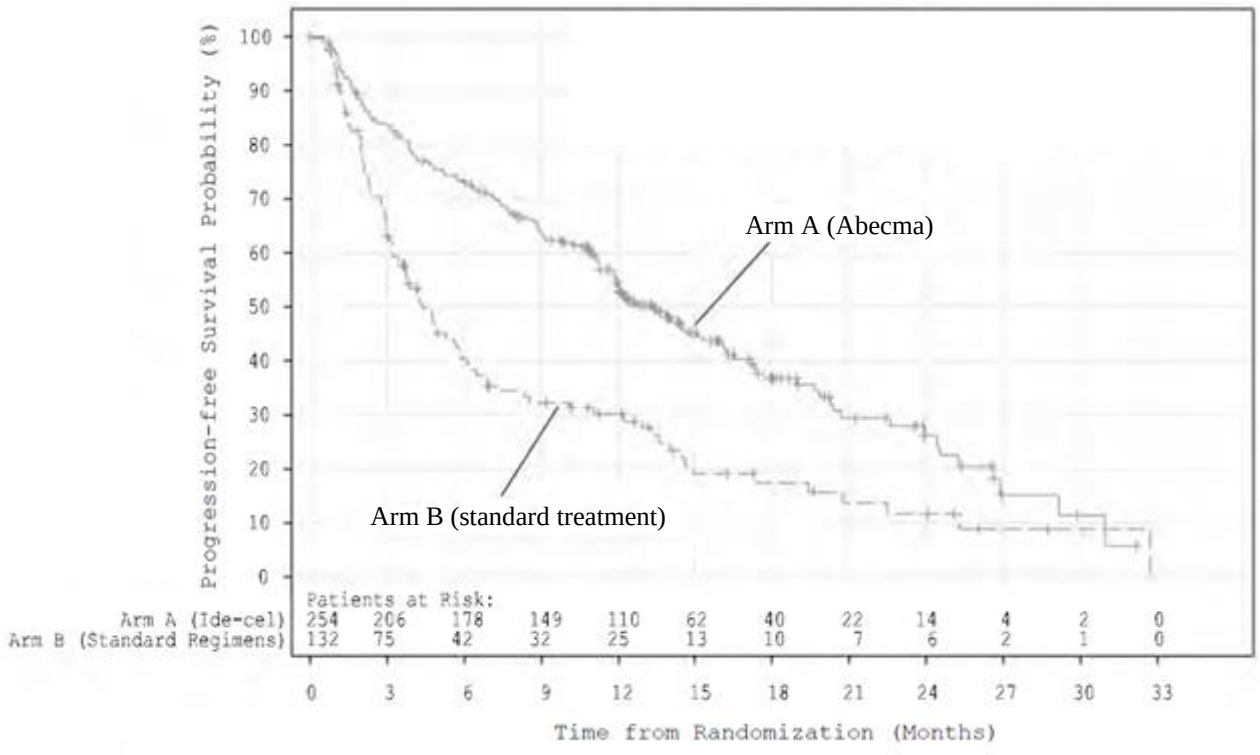

Figure 1. Kaplan-Meier curves of PFS in Study MM-003 (ITT population, data cut-off on April 18, 2022)

Death[10] was reported in 151 subjects (94 in the Abecma group, 57 in the standard treatment group) in the ITT population (data cut-off on October 3, 2022). The causes of deaths were as follows: (a) disease progression in 92 subjects (56 in the Abecma group, 36 in the standard treatment group); (b) adverse events in 23 subjects (15 in the Abecma group, sepsis in 3 subjects, septic shock in 2 subjects, COVID-19 in 2 subjects, cytokine release syndrome [CRS], amyotrophic lateral sclerosis, pulmonary sepsis, bronchopulmonary aspergillosis, candida sepsis, cytomegalovirus infection, pneumonia, and cerebrovascular accident in 1 subject each; 8 in the standard treatment group, COVID-19 in 2 subjects, sepsis in 2 subjects, neutropenic sepsis, Escherichia sepsis, multiple organ dysfunction syndrome, and respiratory failure in 1 subject each); (c) other causes in 32 subjects (20 in the Abecma group, death in 14 subjects, haemothorax, respiratory failure, cardiac failure, sepsis, cerebral haemorrhage, and shock in 1 subject each; 12 in the standard treatment group, death in 9 subjects, acute respiratory failure, CRS, and euthanasia in 1 subject each); (d) death due to secondary malignancy in 3 subjects (2 in the Abecma group, adenocarcinoma pancreas and leukaemia in 1 subject each; 1 in the standard treatment group, malignant neoplasm of unknown primary site); and (e) unknown cause in 1 subject (Abecma group). For adverse events leading to death, a causal relationship to the study treatment could not be ruled out in 6 subjects in the Abecma group (sepsis[11] in 2 subjects, CRS,[12] CRS/candida sepsis,[13] klebsiella sepsis,[14] and pulmonary sepsis[15] in 1 subject each) and in 1 subject in the standard treatment group (neutropenic sepsis[16]).

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[10] The major cause of death was recorded and classified at the discretion of the investigator into "death due to disease progression," "death due to adverse event," "death due to secondary malignancy," or "death from other causes."

[11] Subject No. 1: A 6[redacted]-year-old male with a prior treatment with 4 regimens. On Day 186, the patient visited an emergency room for pyrexia persisting from several days before, decreased appetite, altered state of consciousness, and shallow breathing. Hypotension, pyrexia, and tachycardia due to atrial fibrillation were observed, and the patient was diagnosed with sepsis. Treatment with antibiotics, artificial ventilation, etc., did not improve the symptoms, and the patient died on Day 187. Subject No. 2 (Japanese): A 5[redacted]-year-old male with a prior treatment with 4 regimens. The patient developed febrile neutropenia (Grade 3) and CRS (Grade 1) on the day of Abecma administration. On Day 2, CRS worsened to Grade 4, upon which he was admitted to intensive care unit (ICU) after receiving tocilizumab (genetical recombination) (tocilizumab). Supraventricular tachycardia (Grade 4), renal impairment (Grade 3), and tumor lysis syndrome (TLS) (Grade 3) were observed. On Day 3, ventricular tachycardia (Grade 4) was observed. On Day 8, neurotoxicity (Grade 1) occurred. CRS improved but neurotoxicity worsened, deteriorating to Grade 3 on Day 25. On Day 13, neutropenia worsened to Grade 4. The patient was diagnosed with bacteraemia on Day 23, fungal infection (Grade 3) on Day 24, and sepsis (Grade 4) on Day 36, and died on Day 39.

[12] A 5[redacted]-year-old female with a prior treatment with 2 regimens. The patient developed CRS (Grade 1) after receiving Abecma, on the same day and was treated with tocilizumab (2 doses) and DEX. On Day 3, CRS worsened to Grade 2, upon which she received the third dose of tocilizumab, followed by administration of anti-IL-1 antibody. On Day 5, she developed acute kidney injury (Grade 2). On Day 6, she developed non-ST elevation myocardial infarction, acute kidney injury, worsening of hypotension, and marked metabolic acidosis. She was treated with vasopressors, artificial ventilation, etc., but died on the same day due to aggravation of CRS.

[13] A 7[redacted]-year-old male with a prior treatment with 3 regimens. The patient experienced CRS (Grade 2) on the day of Abecma administration and neurotoxicity (Grade 2) on Day 2. Treatment with tocilizumab (2 doses), etc., was given. From Day 6, neurotoxicity worsened to Grade 3 while CRS improved to Grade 1, but treatment with tocilizumab (2 doses) was added. On Day 7, upon aggravation of CRS to Grade 2 and neurotoxicity to Grade 4, he was admitted to ICU. On Day 8, CRS aggravated to Grade 4, and hemophagocytic syndrome (Grade 4) and multi-organ failure (Grade 4) occurred, upon which hemodialysis was started. Treatment of CRS with tocilizumab was discontinued, and medications were changed to anti-IL-1 antibody, cyclophosphamide, and methylprednisolone. On Day 10, the patient showed a tendency of improvement in general conditions but developed candida sepsis (Grade 4) and enterococcal infection (Grade 3) on Day 15 and aspergillus infection (Grade 1) on Day 17. Grade 4 neutropenia and lymphopenia had persisted from Abecma administration up to Day 19, and the patient died of candida sepsis and CRS on Day 21. Autopsy showed multi-organ failure caused by candidiasis.

[14] A 6[redacted]-year-old female with a prior treatment with 4 regimens. On Day 177 after Abecma administration, the patient was hospitalized for klebsiella sepsis (Grade 4) and pyelonephritis (Grade 3). She also had disseminated intravascular coagulation (Grade 2), thrombocytopenia (Grade 3), etc., and was treated with antimicrobial agents, but experienced enterococcal sepsis (Grade 4) on Day 188. Treatment with vancomycin and other antimicrobial agents was given, but the patient died on Day 192.

[15] A 6[redacted]-year-old male with a prior treatment with 3 regimens. On Day 3 after Abecma administration, the patient developed neutropenia (Grade 3), which worsened to Grade 4 on Day 7. On Day 56, neutropenia improved to Grade 2, but the patient was in a susceptible state to infection with low IgG level and lymphocyte count. On Day 61, he experienced pulmonary sepsis (Grade 3), which became aggravated on Day 62, resulting in hospitalization. Cardiopulmonary resuscitation was attempted to restore shock and respiratory failure, but the patient died without recovery on the same day.

[16] A 6[redacted]-year-old male with a prior treatment with 4 regimens. On Day 380 after the start of the study treatment, the patient developed neutropenic sepsis (Grade 4) and was hospitalized. Pneumonia was found on X-ray, and *Escherichia coli* was detected in sputum. The patient was treated with antibiotics, etc., but died on Day 383 without improvement.

6.R Outline of the review conducted by PMDA

6.R.1 Efficacy

As a result of the following review, PMDA has concluded that Abecma was shown to have efficacy in patients with relapsed or refractory MM with 2 to 4 prior treatment regimens.

6.R.1.1 Control group

The applicant's explanation about the rationale for the control group used in Study MM-003:

The guidelines of Japan and foreign countries recommend selecting treatment regimens that include drugs that have not been used or have not been used at least for the past 6 months for the treatment of relapsed or refractory MM, and recommend treatment regimens such as DPd, DVd, IRd, Kd, and EPd in particular. In Study MM-003 in patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens, the treatment regimen for the control group was selected by the investigator from among DPd, DVd, IRd, Kd, and EPd, based on the most recent treatment given to each subject, taking account of the above recommendations.

PMDA accepted the applicant's explanation.

6.R.1.2 Efficacy endpoint

The applicant's explanation about the reason for using IRC-assessed PFS as the primary endpoint in Study MM-003:

PFS was defined as the period from randomization to the date of first documented PD or death due to any cause, whichever occurred first. MM is a refractory disease that is difficult to cure with conventional treatments, characterized by recurrent relapses, and the duration of efficacy decreases with the increase in the number of prior treatments for MM. PFS was selected as the primary endpoint because prolongation of PFS is expected to improve the symptoms, delay the disease progression, and prolong the period until the next treatment (*Leukemia.* 2006;20:1467-73), suggesting clinical significance.

PMDA's view:

The applicant's explanation is generally understandable. However, OS is also an important endpoint, given that the treatment of MM is conducted in expectation of prolongation of survival. In patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens, efficacy of Abecma was evaluated based not only on the primary endpoint, i.e., IRC-assessed PFS, but also on OS.

6.R.1.3 Results of efficacy evaluation

The applicant's explanation about the efficacy of Abecma in patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens:

Table 3 shows the results of IRC-assessed PFS at the interim analysis of efficacy (data cut-off on April 18, 2022). Results showed a statistically significant prolongation of PFS in the Abecma group compared with the standard treatment group [see Section 6.1.1.1].

Table 4 and Figure 2 show the results and Kaplan-Meier curve at the data cut-off point (April 28, 2023), respectively. A final analysis is planned to be performed when 222 OS events have occurred. The

analysis shown below was conducted when 74.0% of the planned number of events (164 of 222 events) were observed.

Table 4. Results of OS (Study MM-003, ITT population, data cut-off on April 28, 2023)

	Abecma N = 254	Standard treatment N = 132
Number of deaths (%)	106 (41.7)	58 (43.9)
Median [95% CI] (months)	41.4 [30.9, NE]	37.9 [23.4, NE]
Hazard ratio [95% CI]*	1.012 [0.731, 1.400]	

* Stratified Cox proportional hazard model with age (<65 years, ≥65 years), the number of prior treatment regimens (2, 3, or 4) for MM, and presence/absence of cytogenetic abnormality (t[4;14], t[14;16], or del 17p) as the stratification factors.

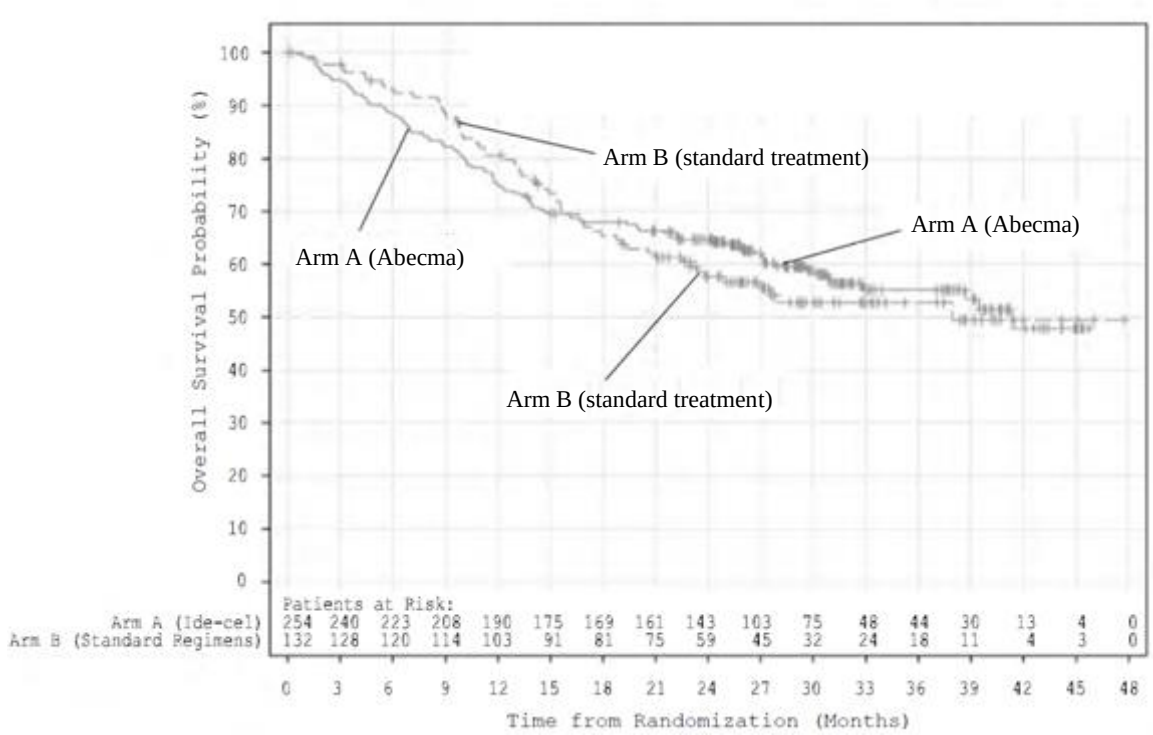

Figure 2. Kaplan-Meier curves of OS in Study MM-003 (ITT population, data cut-off on April 28, 2023)

In 76 of 132 subjects in the standard treatment group, Abecma was administered according to the cross-over design. As for the results of OS in the ITT population (data cut-off on April 28, 2023), when the effect of this cross-over treatment is taken into account, the hazard ratio [95% CI] calculated by the inverse probability of censoring weighted (IPCW) method[17] was 0.745 [0.509, 1.215], and Kaplan-Meier curves were as shown in Figure 3.

[17] In patients in the standard treatment group who received Abecma according to the cross-over design, OS was cut off, etc. on the day of leukapheresis for Abecma manufacture.

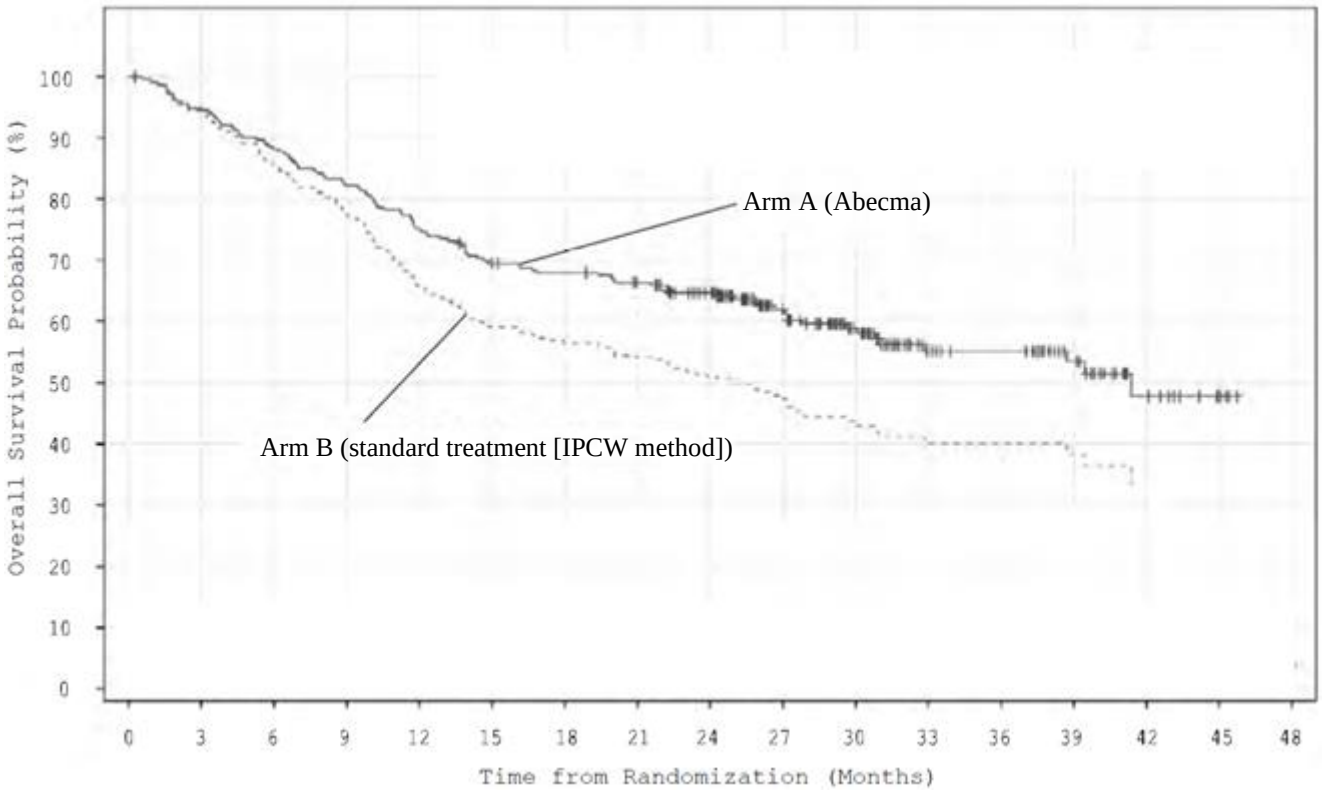

Figure 3. Kaplan-Meier curves of OS in Study MM-003 analyzed by IPCW method (ITT population, data cut-off on April 28, 2023)

Table 5 and Figure 4 show the results of OS and Kaplan-Meier curves, respectively, in the safety analysis population of 225 subjects who received Abecma in the Abecma group and 126 subjects who received the standard chemotherapy in the standard treatment group.

Table 5. Results of OS (Study MM-003, safety analysis population, data cut-off on April 28, 2023)

	Abecma N = 225	Standard treatment N = 126
Number of deaths (%)	81 (36.0)	54 (42.9)
Median [95% CI] (months)	NE [38.7, NE]	NE [23.8, NE]
Hazard ratio [95% CI]*	0.828 [0.584, 1.175]	

* Stratified Cox proportional hazard model with age (<65 years, ≥65 years), the number of prior treatment regimens (2, 3, or 4) for MM, and presence/absence of cytogenetic abnormality (t[4;14], t[14;16], or del 17p) as the stratification factors.

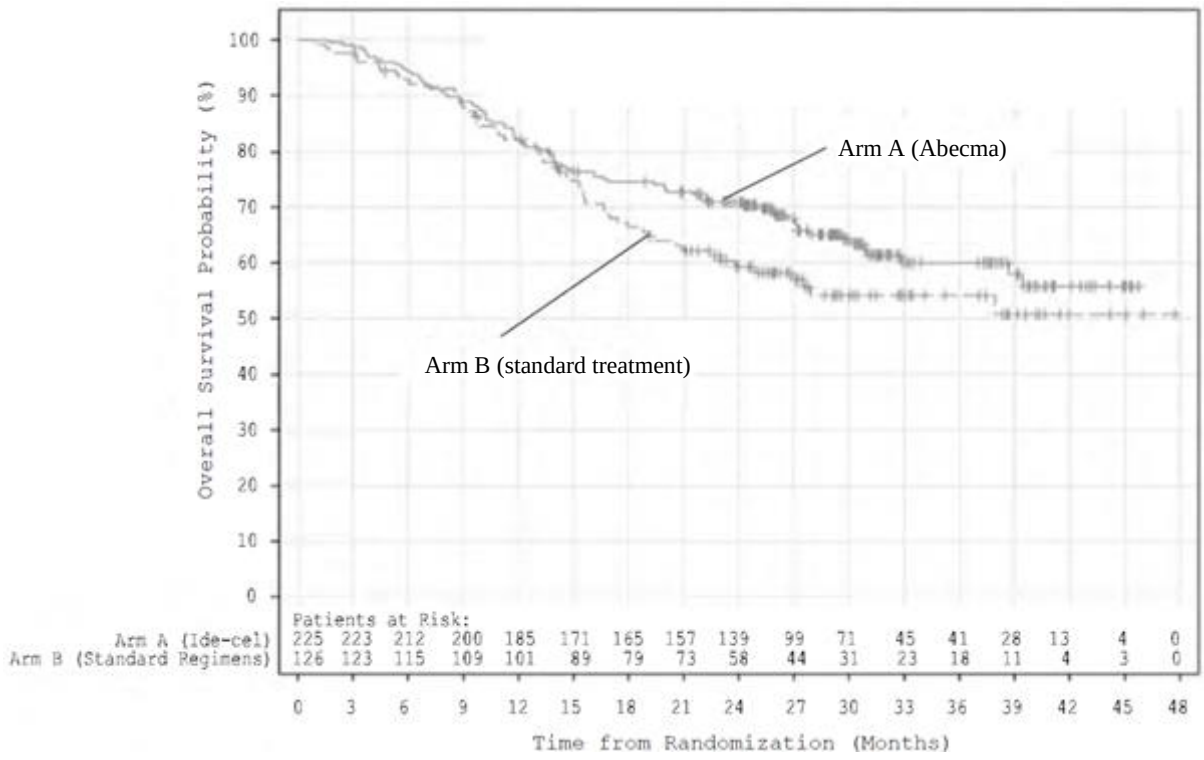

Figure 4. Kaplan-Meier curves of OS in Study MM-003 (safety analysis population, data cut-off on April 28, 2023)

The applicant's explanation about the tendency of the higher deaths observed during a certain period after randomization in the Abecma group than in the standard treatment group (Figure 2):

The incidence of early death tended to be higher in the Abecma group than in the standard treatment group. Details of deaths within 6 months after randomization were investigated to clarify the cause. Results showed that death within 6 months after randomization occurred in 30 subjects in the Abecma group (disease progression in 18 subjects, adverse events in 8 subjects, other reason in 4 subjects [18)]) and in 9 subjects in the standard treatment group (disease progression in 6 subjects, adverse events in 3 subjects). All fatal cases in the Abecma group had high-risk factor[19)] for MM progression, and 17 of them (disease progression in 13 subjects, adverse events in 3 subjects, other reason in 1 subject) died before Abecma administration. From the past experiences of clinical studies and Abecma manufacture, it was expected that implementing a bridging therapy period of 1 cycle (21 or 28 days) would cover the manufacturing timeline of formulation. Accordingly, only 1 cycle of the bridging therapy was allowed for disease control from randomization until Abecma administration. In addition, with consideration given to the recovery period from toxicity associated with the bridging therapy and to avoid interaction between the drugs and CART cells, a 14-day withdrawal period was introduced before the start of LD chemotherapy (*The European Society for Blood and Marrow Transplantation [EBMT] and European Hematology Association (EHA) CAR-T Cell Handbook.* Springer 2022; pp 127-9). In cases where subjects died from disease progression before Abecma administration, disease control may have been inadequate.

18) "Death" (preferred term) and "unknown" (reporter's term) in all 4 subjects

19) Patients with any of the following conditions (a) to (f) were regarded as patients with high risk for MM progression: (a) high-risk cytogenetic abnormality, (b) R-ISS stage III, (c) extramedullary disease/extramedullary plasmacytoma, (d) high tumor volume, (e) high baseline LDH level, and (f) high 3-class resistance.

The applicant's explanation:

As the observation period extended after 30 months post randomization, the difference of OS between the Abecma group and the standard treatment group tended to decrease. Crossover administration of Abecma in the standard treatment group may have influenced the OS, judging from the following finding: In the analysis where OS of patients who received crossover treatment with Abecma in the majority (76 of 132 patients) of the standard treatment group was adjusted (Figure 3), there was no observed trend of narrowing of the gap in OS between the Abecma group and the standard treatment group.

Table 6 shows the results of efficacy classified by the number of prior treatment regimens in Study MM-003.

Table 6. Efficacy by the number of prior treatment regimens (IRC assessment, Study MM-003, ITT population, data cut-off on April 18, 2022)

	2 regimens		3 regimens		4 regimens		Total	
	Abecma N = 78	Standard treatment N = 39	Abecma N = 95	Standard treatment N = 49	Abecma N = 81	Standard treatment N = 44	Abecma N = 254	Standard treatment N = 132
PFS events (%)	41 (52.6)	26 (66.7)	57 (60.0)	37 (75.5)	51 (63.0)	30 (68.2)	149 (58.7)	93 (70.5)
Median [95% CI] (months)	15.1 [12.7, 19.7]	4.8 [3.2, 13.3]	12.5 [10.8. 17.7]	3.2 [2.3, 5.7]	11.2 [7.4, 14.1]	4.9 [3.2, 6.9]	13.3 [11.8, 16.1]	4.4 [3.4, 5.9]
Hazard ratio [95% CI]	0.511 [0.311, 0.839]		0.445 [0.292, 0.678]		0.580 [0.364, 0.923]		0.493 [0.377, 0.645]	
Best response (number of subjects [%])								
sCR	29 (37.2)	5 (12.8)	30 (31.6)	0	31 (38.3)	1 (2.3)	90 (35.4)	6 (4.5)
CR	4 (5.1)	0	3 (3.2)	1 (2.0)	1 (1.2)	0	8 (3.1)	1 (0.8)
VGPR	18 (23.1)	6 (15.4)	23 (24.2)	3 (6.1)	14 (17.3)	4 (9.1)	55 (21.7)	13 (9.8)
PR	7 (9.0)	9 (23.1)	10 (10.5)	13 (26.5)	11 (13.6)	13 (29.5)	28 (11.0)	35 (26.5)
MR	2 (2.6)	0	1 (1.1)	6 (12.2)	1 (1.2)	3 (6.8)	4 (1.6)	9 (6.8)
SD	10 (12.8)	16 (41.0)	13 (13.7)	19 (38.8)	8 (9.9)	13 (29.5)	31 (12.2)	48 (36.4)
PD	3 (3.8)	2 (5.1)	11 (11.6)	3 (6.1)	10 (12.3)	5 (11.4)	24 (9.4)	10 (7.6)
NE	5 (6.4)	1 (2.6)	4 (4.2)	4 (8.2)	5 (6.2)	5 (11.4)	14 (5.5)	10 (7.6)
Response (sCR, CR, VGPR, or PR)	58	20	66	17	57	18	181	55
Overall response rate [95% CI] (%)	74.4 [64.7, 84.0]	51.3 [35.6, 67.0]	69.5 [60.2, 78.7]	34.7 [21.4, 48.0]	70.4 [60.4, 80.3]	40.9 [26.4, 55.4]	71.3 [65.7, 76.8]	41.7 [33.3, 50.1]

Table 7 shows the results of efficacy in the Japanese population. At the data cut-off on April 28, 2023, the median OS [95% CI] (months) was not evaluable (NE) [3.1, NE] in the Abecma group[20)] and NE [NE, NE] in the standard treatment group.[21)] Evaluation of consistency of IRC-assessed PFS, the primary endpoint, between the entire population and the Japanese population was difficult for the following reasons: (1) The number of Japanese patients was limited; and (2) the follow-up period was short (<3 months in 1 of 4 subjects in the Abecma group and in 3 of 5 subjects in the standard treatment group). Japanese patients who have received 2 prior treatment regimens were not enrolled in the Abecma group. However, considering no clear differences in efficacy between Japanese and non-Japanese patients, and taking into account the following factors, Abecma is expected to show efficacy in Japanese patients who have received 2 to 4 prior treatment regimens, as indicated by the results of Study MM-003.

20) The estimated overall survival rates based on the Kaplan-Meier method at 6, 12, 18, 24, 30, and 36 months after randomization were 75.0%, 50.0%, 50.0%, 50%, NE, and NE, respectively.

21) The estimated overall survival rates based on the Kaplan-Meier method at 6, 12, 18, 24, 30, and 36 months after randomization were all 100%.

- In Study BB2121-MM-001 (Study MM-001), which investigated the efficacy of Abecma for relapsed or refractory MM with ≥3 lines of prior treatment (the approved indication), there were no observed differences in the efficacy of Abecma between Japanese and non-Japanese patients.
- In Studies MM-003 and MM-001, no difference was observed in the cellular kinetics/pharmacokinetics of Abecma between Japanese and non-Japanese patients.
- The Japanese and foreign clinical practice guidelines are not significantly different in the diagnosis and treatment algorithm for relapsed or refractory MM.

Table 7. Comparison of efficacy between Japanese population and the entire population (Study MM-003, IRC assessment, ITT population, data cut-off on April 18, 2022)

	Japanese population		Entire population	
	Abecma N = 4*1	Standard treatment N = 5*2	Abecma N = 254	Standard treatment N = 132
PFS events (%)	2 (50.0)	1 (20.0)	149 (58.7)	93 (70.5)
Median [95% CI] (months)	NE [2.0, NE]	20.7 [NE, NE]	13.3 [11.8, 16.1]	4.4 [3.4,5.9]
Hazard ratio [95% CI]	5.21×10^7 [0.000, NE]		0.493 [0.377, 0.645]	
Best response (number of subjects [%])				
sCR	1 (25.0)	0	90 (35.4)	6 (4.5)
CR	0	0	8 (3.1)	1 (0.8)
VGPR	1 (25.0)	0	55 (21.7)	13 (9.8)
PR	0	2 (40.0)	28 (11.0)	35 (26.5)
MR	0	2 (40.0)	4 (1.6)	9 (6.8)
SD	1 (25.0)	0	31 (12.2)	48 (36.4)
PD	1 (25.0)*3	0	24 (9.4)	10 (7.6)
NE	0	1 (20.0)	14 (5.5)	10 (7.6)
Response (sCR, CR, VGPR, or PR)	2*4	2*5	181	55
Overall response rate [95% CI] (%)	50.0 [1.0, 99.0]	40.0 [0.0, 82.9]	71.3 [65.7, 76.8]	41.7 [33.3, 50.1]

*1 Two subjects with 3 prior treatment regimens and 2 subjects with 4 prior treatment regimens
*2 One subject with 2 prior treatment regimens, 2 subjects with 3 prior treatment regimens, and 2 subjects with 4 prior treatment regimens
*3 Diagnosed as PD before the start of LD chemotherapy (before Abecma administration)
*4 One subject (very good partial response [VGPR]) with 3 prior treatment regimens and 1 subject (stringent complete response [sCR]) with 4 prior treatment regimens
*5 One subject (partial response [PR]) with 2 prior treatment regimens and 1 subject (PR) with 3 prior treatment regimens

PMDA's view:
IRC-assessed PFS, the primary endpoint of Study MM-003, showed a statistically significant difference between the Abecma group and the standard treatment group, demonstrating the efficacy of Abecma.

The incidence of death tended to be higher in the Abecma group than in the standard treatment group over a certain period of time after randomization (Figure 2). Given the following points, however, there is no sufficient evidence to conclude that OS is shortened by Abecma:

- The deaths before Abecma administration in the Abecma group may have been attributable to inadequate bridging therapy, due to the following reasons: In Study MM-003, (a) only 1 cycle of bridging therapy was allowed to control the disease before Abecma administration; (b) ≥80% of patients enrolled in the study had high risk factor(s)[19] for MM progression; and (c) ≥50% of deaths within 6 months of randomization in the Abecma group occurred before Abecma administration.
- Post-randomization dropouts in the safety analysis population of the Abecma group diminish OS comparability, possibly causing bias in the between-group difference and thereby imposing limitations to the interpretation. Nevertheless, Kaplan-Meier curves of OS (Figure 4) do not show significant differences in the survival rate between the Abecma group and the standard treatment

group up to 12 month-time point after randomization and, after 12 months, the survival rate tended to be consistently higher in the Abecma group than in the standard treatment group.

Regarding the observation that the difference in OS between the Abecma group and the standard treatment group tended to diminish with the increase in the observation period after 30 months post randomization (Figure 2), the applicant's explanation that OS in the standard treatment group was influenced by cross-over administration of Abecma is understandable.

On the basis of the above, PMDA concluded that results of Study MM-003 demonstrated the efficacy of Abecma in patients with relapsed or refractory MM with 2 to 4 prior treatment regimens. The following are important pieces of information for deciding whether to treat patients with Abecma and should be appropriately provided to healthcare professionals through materials, along with the most recent results of OS:
(a) That in Study MM-003, death tended to occur more frequently in the Abecma group than the standard treatment group during a specific period following randomization.
(b) Details of characteristics of the fatal cases.

6.R.2 Safety [for adverse events, see Section "8. Adverse Events Observed in Clinical Study"]

As a result of the following reviews, PMDA concluded that adverse events requiring special attention when administering Abecma to patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens are similar to those[22)] determined to require attention at the time of approval for the approved indication. In the use of Abecma, caution should be exercised against these adverse events, as is the case with the approved indication.

In addition, PMDA concluded that Abecma is tolerable in patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens, as long as appropriate measures i.e., monitoring and management of adverse events are provided by a physician with sufficient knowledge and experience in the treatment of MM at a medical institution well-equipped for responding to the above adverse events.

6.R.2.1 Safety profile of Abecma

The applicant's explanation about the safety of Abecma in patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens:
Table 8 shows the summary of the safety[23)] in Study MM-003 (data cut-off on October 3, 2022).

22) CRS, haemophagocytic lymphohistiocytosis, neuropathy, infection, cytopenia, hypersensitivity, hypogammaglobulinaemia, and TLS.

23) From the time of obtaining informed consent up to at least 6 months after Abecma administration (Abecma group) or after the start of the standard treatment (standard treatment group), all adverse events, adverse events requiring special attention (CRS, neurotoxicity, cytopenia, infection, macrophage activation syndrome [MAS], autoimmune disorder, and secondary malignancies), and serious adverse events were recorded for both groups. In the subsequent period, Grade ≥3 adverse events, adverse events requiring special attention, and serious adverse events were recorded from 7 months after Abecma administration up to 28 days after study site visit for the last PFS follow-up in the Abecma group or from 7 months after the start of study treatment up to 28 days after study site visit for the last dose (or up to 28 days after study site visit for the last PFS follow-up in patients proceeding to PFS follow-up period) in the standard treatment group. In patients who were randomized to the standard treatment group and chose to receive Abecma after disease progression and eligibility were confirmed, all adverse events, adverse events requiring special attention, and serious adverse events were recorded from 28 days after study site visit for the last PFS follow-up of the standard treatment for at least 3 months after Abecma administration (up to Day 1 of the fourth month). All of the Grade ≥3 adverse events, serious adverse events, and adverse events requiring special attention for which a causal relationship to the study treatment was suspected were recorded from the start of survival status follow-up until the end of the study.

Table 8. Summary of safety (Study MM-003, safety analysis population, data cut-off on October 3, 2022).

	Abecma (entire period after randomization) N = 225	Standard treatment (entire period after randomization) N = 126	Cross-over from standard treatment (after Abecma administration) N = 69
All adverse events	225 (100)	124 (98.4)	69 (100)
Grade ≥3 adverse events	215 (95.6)	96 (76.2)	66 (95.7)
Serious adverse events	116 (51.6)	52 (41.3)	23 (33.3)
Adverse events leading to death	28 (12.4)	9 (7.1)	6 (8.7)
CRS*[1]	197 (87.6)	0	59 (85.5)
Grade ≥3 CRS	11 (4.9)	0	0
Nervous system events*[2]	162 (72.0)	78 (61.9)	39 (56.5)
Grade ≥3 nervous system events	31 (13.8)	16 (12.7)	6 (8.7)
CART-related neurotoxicity*[3]	34 (15.1)	0	14 (20.3)
Grade ≥3 CART-related neurotoxicity	7 (3.1)	0	2 (2.9)
Cytopenia*[4]	206 (91.6)	92 (73.0)	62 (89.9)
Grade ≥3 cytopenia	202 (89.8)	78 (61.9)	62 (89.9)
Infection*[5]	141 (62.7)	71 (56.3)	25 (36.2)
Grade ≥3 infection	58 (25.8)	26 (20.6)	10 (14.5)

*1 Adverse events corresponding to "cytokine release syndrome" in Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT)
*2 Adverse events corresponding to "nervous system disorders" or "psychiatric disorders" in MedDRA system organ class (SOC)
*3 Adverse events determined by investigator as neurotoxicity related to CART product
*4 Adverse events listed in Table 9
*5 Adverse events corresponding to "infections and infestations" in MedDRA SOC

Table 9. List of events included in cytopenia

Classification	MedDRA PT (MedDRA/J version 24.1)
Neutropenia	Neutropenia, leukopenia, febrile neutropenia, neutrophil count decreased, white blood cell count decreased, autoimmune neutropenia, agranulocytosis, cyclic neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, myelocyte count decreased, myelocyte percentage decreased, neutrophil percentage decreased, white blood cell analysis abnormal
Anaemia	Anaemia, anaemia macrocytic, anaemia megaloblastic, haematocrit decreased, haemoglobin decreased, hyperchromic anaemia, hypochromic anaemia, leukoerythroblastic anaemia, mean cell haemoglobin concentration decreased, mean cell haemoglobin decreased, mean cell volume decreased, microcytic anaemia, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia, proerythroblast count decreased, red blood cell count decreased, reticulocyte count decreased, reticulocyte percentage decreased, sideroblastic anaemia
Thrombocytopenia	Thrombocytopenia, platelet count decreased, acquired amegakaryocytic thrombocytopenia, amegakaryocytic thrombocytopenia, heparin-induced thrombocytopenia, heparin-induced thrombocytopenia test positive, non-immune heparin associated thrombocytopenia, platelet production decreased, severe fever with thrombocytopenia syndrome, thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Lymphopenia	Lymphopenia, CD4 lymphocytes decreased, B-lymphocyte abnormalities, B-lymphocyte count abnormal, B-lymphocyte count decreased, CD4 lymphocyte percentage decreased, CD4 lymphocytes abnormal, CD4/CD8 ratio decreased, CD8 lymphocyte percentage decreased, CD8 lymphocytes abnormal, CD8 lymphocytes decreased, lymphocyte count decreased, lymphocyte percentage decreased, natural killer T cell count decreased, plasma cells absent, plasma cells decreased, plasmablast count decreased, T-lymphocyte count decreased
Pancytopenia	Pancytopenia, autoimmune aplastic anaemia, autoimmune pancytopenia, aplasia pure red cell, aplastic anaemia, bicytopenia, bone marrow failure, cytopenia, erythroid maturation arrest, febrile bone marrow aplasia, granulocytes maturation arrest, hypoplastic anaemia, myeloid maturation arrest, panmyelopathy, platelet maturation arrest, pure white cell aplasia

In Study MM-003, adverse events with a ≥20% higher incidence in the Abecma group than in the standard treatment group (throughout the post-randomization period) were neutropenia (188 subjects [83.6%] in the Abecma group, 57 subjects [45.2%] in the standard treatment group), anaemia (151 subjects [67.1%], 46 subjects [36.5%]), thrombocytopenia (127 subjects [56.4%], 37 subjects [29.4%]), cytokine release syndrome (197 subjects [87.6%], 0 subjects [0%]), nausea (113 subjects [50.2%], 34 subjects [27.0%]), constipation (64 subjects [28.4%], 10 subjects [7.9%]), hypokalaemia (78 subjects [34.7%], 15 subjects [11.9%]), and hypophosphataemia (76 subjects [33.8%], 10 subjects [7.9%]).

Grade ≥3 adverse events with a ≥10% higher incidence in the Abecma group than in the standard treatment group were neutropenia (182 subjects [80.9%], 51 subjects [40.5%]), anaemia (114 subjects [50.7%], 24 subjects [19.0%]), thrombocytopenia (100 subjects [44.4%], 23 subjects [18.3%]), lymphopenia (69 subjects [30.7%], 24 subjects [19.0%]), leukopenia (69 subjects [30.7%], 13 subjects [10.3%]), and hypophosphataemia (49 subjects [21.8%], 3 subjects [2.4%]). Serious adverse events with a ≥3% higher incidence in the Abecma group than in the standard treatment group were pyrexia (11 subjects [4.9%], 1 subject [0.8%]), and cytokine release syndrome (10 subjects [4.4%], 0 subjects [0%]). Adverse events leading to death with a ≥1% higher incidence in the Abecma group than in the standard treatment group were general physical health deterioration (8 subjects [3.6%], 3 subjects [2.4%]) and sepsis (3 subjects [1.3%], 0 subjects [0%]).

The applicant's explanation about the difference in the safety of Abecma between Japanese and non-Japanese patients:
Table 10 shows a summary of safety in the Japanese and non-Japanese populations in Study MM-003.

Table 10. Summary of safety (Study MM-003, Japanese and non-Japanese populations, safety analysis population, data cut-off on October 3, 2022)

	Number of subjects (%)			
	Japanese		Non-Japanese	
	Abecma (entire period after randomization) N = 4	Standard treatment (entire period after randomization) N = 5	Abecma (entire period after randomization) N = 221	Standard treatment (entire period after randomization) N = 121
All adverse events	4 (100)	5 (100)	221 (100)	119 (98.3)
Grade ≥3 adverse events	4 (100)	4 (80.0)	211 (95.5)	92 (76.0)
Serious adverse events	1 (25.0)	0	115 (52.0)	52 (43.0)
Adverse events leading to death	1 (25.0)	0	27 (12.2)	9 (7.4)
CRS*1	4 (100)	0	193 (87.3)	0
Grade ≥3 CRS	1 (25.0)	0	10 (4.5)	0
Nervous system events*2	3 (75.0)	1 (20.0)	159 (71.9)	77 (63.6)
Grade ≥3 nervous system events	1 (25.0)	0	30 (13.6)	16 (13.2)
CART-related neurotoxicity*3	1 (25.0)	-	33 (14.9)	-
Grade ≥3 CART-related neurotoxicity	1 (25.0)	-	6 (2.7)	-
Cytopenia*4	4 (100)	3 (60.0)	202 (91.4)	89 (73.6)
Infection*5	1 (25.0)	3 (60.0)	140 (63.3)	68 (56.2)
Grade ≥3 infection	1 (25.0)	0	57 (25.8)	26 (21.5)

*1 Adverse events corresponding to "cytokine release syndrome" in MedDRA PT
*2 Adverse events corresponding to "nervous system disorders" or "psychiatric disorders" in MedDRA SOC
*3 Adverse events determined by investigator as neurotoxicity related to CART product
*4 Adverse events listed in Table 9
*5 Adverse events corresponding to "infections and infestations" in MedDRA SOC

In the Abecma group of Study MM-003, events that were observed both in ≥2 subjects and at ≥20% higher incidence in the Japanese population than in the non-Japanese population were lymphopenia, anaemia, leukopenia, thrombocytopenia, and febrile neutropenia. Adverse events leading to death or serious adverse events occurred in 1 Japanese patient[11)] in the Abecma group, which were cytokine release syndrome, depressed level of consciousness, fungal infection, sepsis, supraventricular tachycardia, tremor, and ventricular tachycardia.

Although there are limitations to the comparison between the Japanese population and the non-Japanese population due to the limited number of Japanese patients studied, Abecma administration to the

Japanese population raised no new safety concerns, suggesting that there is no difference in the safety profile that potentially impact the safety control.

The applicant's explanation about the difference in the safety profile of Abecma between patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens and the safety profile in the approved indication:
Table 11 shows the outline of safety in the Abecma group in Study MM-003 in patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens and in Study MM-001 in patients with relapsed or refractory MM who have received ≥3 prior treatment regimens. In Study MM-003, the safety profile in the entire Abecma group and the safety profile in the subpopulation with 2 prior treatment regimens were similar to that observed for the approved indication.

Table 11. Comparison with the study for approved indication (Study MM-003, *1 Study MM-001, *2 safety analysis population)

	Study MM-003		Study MM-001
	Subjects with 2 prior treatment regimens	Entire subject population	
	Abecma N = 71	Abecma N = 225	Abecma N = 137
All adverse events	71 (100.0)	225 (100)	137 (100)
Grade ≥3 adverse events	67 (94.4)	211 (93.8)	136 (99.3)
Serious adverse events	28 (39.4)	101 (44.9)	94 (68.6)
Adverse events leading to death	7 (9.9)	28 (12.4)	35 (25.5)
CRS*3	61 (85.9)	197 (87.6)	116 (84.7)
Grade ≥3 CRS	2 (2.8)	11 (4.9)	7 (5.1)
Nervous system events*4	37 (52.1)	132 (58.7)	91 (66.4)
Grade ≥3 nervous system events	8 (11.3)	26 (11.6)	18 (13.1)
CART-related neurotoxicity*5	5 (7.0)	34 (15.1)	24 (17.5)
Grade ≥3 CART-related neurotoxicity	1 (1.4)	7 (3.1)	5 (3.6)
Cytopenia*6	65 (91.5)	203 (90.2)	133 (97.1)
Grade ≥3 cytopenia	63 (88.7)	197 (87.6)	132 (96.4)
Infection*7	32 (45.1)	124 (55.1)	95 (69.3)
Grade ≥3 infection	10 (14.1)	48 (21.3)	35 (25.5)

*1 Data cut-off on October 3, 2022
*2 Data cut-off on December 21, 2020
*3 Adverse events corresponding to "cytokine release syndrome" in MedDRA PT
*4 Adverse events corresponding to "nervous system disorders" or "psychiatric disorders" in MedDRA SOC
*5 Adverse events determined by investigator as neurotoxicity related to CART product
*6 Adverse events listed in Table 9
*7 Adverse events corresponding to "infections and infestations" in MedDRA SOC

PMDA's view:
Caution is required against Grade ≥3 adverse events and serious adverse events that were observed at higher incidences in the Abecma group than in the standard treatment group in Study MM-003. Due to the limited use experience of Abecma in Japanese patients, there are limitations in precisely comparing the safety between Japanese patients and non-Japanese patients. Nevertheless, no clear difference was observed in the safety profile between the Japanese and non-Japanese population. The safety profile in the Abecma group of Study MM-003 showed no clear difference from the safety profile observed in Study MM-001 of the approved indication in patients with relapsed or refractory MM who have received ≥3 prior treatment regimens. In Study MM-003, serious adverse events such as CRS occurred frequently following Abecma administration. Patients should be monitored extremely closely, and adverse events, if any, should be resolved by a multidisciplinary approach.

On the other hand, given that all of the above adverse events are known adverse events of Abecma and that caution has already been raised in the package insert to regularly conduct blood tests, Abecma is tolerable also in patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens, as long as appropriate measures i.e., monitoring and management of adverse events are provided by a physician with sufficient knowledge and experience in the treatment of MM at a medical institution well-equipped for responding to these adverse events.

6.R.3 Indication or performance

The proposed "Indication or Performance" of Abecma was as follows:

Indication or Performance (The underlined word is added to, and the strikethrough word is deleted from, the approved text.)
Relapsed or refractory multiple myeloma. Abecma should be used only in patients meeting all of the following criteria:

- Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy
- Patients who have received at least 2~~3~~ prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy

The proposed "Precautions Concerning Indication or Performance" of Abecma was as follows:

Precautions Concerning Indication or Performance
Patients considered appropriate to receive Abecma must be selected by physicians who have fully understood the efficacy and safety of Abecma after being thoroughly familiar with prior treatment, etc. of patients enrolled in the clinical studies described in the "Clinical Studies" section.

PMDA's view:
On the basis of reviews in Sections "6.R.1 Efficacy," "6.R.2 Safety," and the review presented below, the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections should be specified as proposed.

6.R.3.1 Clinical positioning and target population of Abecma

Neither the Japanese nor foreign clinical practice guidelines included the description of Abecma as a treatment option for patients with relapsed or refractory MM who have received 2 prior treatment regimens.

The applicant's explanation about the clinical positioning and "Indication or Performance" of Abecma:
The OS of patients with MM has shown improvement with the introduction of recently approved therapeutic agents and their combination therapies. However, MM is a refractory disease that relapses repeatedly and is difficult to cure. Treatments with novel mechanisms of action are needed for patients who are resistant to conventional treatments (*Blood Cancer J.* 2020;10:94, *Lancet Oncol.* 2021;22:e105-18). In recent years, a variety of therapeutic agents have been approved for the treatment of recurrent or

refractory MM, expanding the range of treatment options. The recommended treatment options in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Multiple Myeloma (NCCN Guidelines) (v.3.2023) usually include combination of dexamethasone with 2 or more agents with various mechanisms of action (e.g., immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibody formulations). Notably, immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibody formulations are pivotal agents, and these 3 agents are increasingly used in the first or second regimen (*Lancet Oncol.* 2021;22:e105-18). On the other hand, treatment options for relapsed or refractory MM with a prior line of treatment of immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies are limited. The median PFS in conventional treatments for these patients ranges from 3.5 to 4.6 months, and the median OS is between 12.4 and 14.7 months (*Leukemia.* 2022;36:1371-6, *Clin Lymphoma Myeloma Leuk.* 2020;20:1-7, *Blood Cancer J.* 2022;12:98, etc.). Therefore, there exists an unmet medical need for relapsed or refractory MM with a prior line of treatment including immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies, necessitating the exploration of new therapeutic approaches.

Study MM-003 has confirmed the efficacy and safety of Abecma in patients with relapsed or refractory MM who have received ≥2 prior treatment regimens, including immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies [see Sections 6.R.1 and 6.R.2]. Abecma is thus considered as a new treatment option for such patients.

PMDA's view:
It is acceptable to specify "Indication or Performance" of Abecma based on the results of Study MM-003.

6.R.4 Dosage and administration or method of use

The proposed "Dosage and Administration or Method of Use" of Abecma in the present application was the same as approved.

The applicant's explanation about the rationale for the proposed "Dosage and Administration or Method of Use" of Abecma:
The dose of Abecma used in Study MM-003 was 150×10^6 to 450×10^6 anti-BCMA CAR-expressing T cells, which was different from the dose of 280×10^6 to 540×10^6 in the approved "Dosage and Administration or Method of Use." However, patients who received doses outside the approved range were limited to only 3 cases, with administered doses ranging from 174.9×10^6 to 183.8×10^6 cells, and most of the other patients in the Abecma group received Abecma within the range of the approved dose. Considering the above and based on the results of Study MM-003 which confirmed the efficacy and safety of Abecma, it was deemed appropriate to establish the same "Dosage and Administration or Method of Use" for relapsed or refractory MM with ≥2 prior lines of treatment as that for the approved indication.

PMDA's view:
The above explanation of the applicant is understandable. In consideration of the reviews in Sections "6.R.1 Efficacy" and "6.R.2 Safety," PMDA concluded that it is possible to establish the same "Dosage

and Administration or Method of Use" of Abecma for relapsed or refractory MM with ≥2 prior lines of treatment, as approved previously.

7. Risk Analysis and Outline of the Review Conducted by PMDA

The applicant's explanation:

On the basis of findings such as the safety profile of Abecma in patients with relapsed or refractory MM who have received ≥2 prior lines of treatment observed in Study MM-003 being comparable to the safety profile in the approved indication [see Section 6.R.2.1], subjects with relapsed or refractory MM who have received 2 prior lines of treatment will be included in the ongoing post-marketing database survey[24)] targeting all patients receiving Abecma under the approved indication.

PMDA's view:

Because of the extremely limited experiences of Abecma administration in Japanese patients with relapsed or refractory MM who have received ≥2 prior lines of treatment, the applicant should conduct the planned post-marketing database surveillance, collect information on safety, etc., and promptly provide the information thus collected to healthcare professionals.

Details of the post-marketing database surveillance will be finalized, taking account of comments from the Expert Discussion on the evaluation of the safety of Abecma.

8. Adverse Events Observed in Clinical Study

The following are the main adverse events observed in the clinical study data in the document submitted for safety evaluation.

8.1 Global phase III study (Study MM-003)

In the safety analysis population (data cut-off on October 3, 2022), adverse events of post-randomization onset were observed in 225 of 225 subjects (100%) in the Abecma group, in 124 of 126 subjects (98.4%) in the standard treatment group, and in 69 of 69 subjects (100%) after cross-over in the standard treatment group (after Abecma administration). Adverse events for which a causal relationship to the study treatment could not be ruled out were observed in 224 of 225 subjects (99.6%) in the Abecma group, in 105 of 126 subjects (83.3%) in the standard treatment group, and in 69 of 69 subjects (100%) after cross-over in the standard treatment group. Adverse events for which a causal relationship to Abecma could not be ruled out were observed in 217 of 225 subjects (96.4%) in the Abecma group and in 65 of 69 subjects (94.2%) after cross-over in the standard treatment group. Table 12 shows adverse events with an incidence of ≥10% in any group.

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24) Safety specifications
CRS, nervous system events, cytopenia, hypogammaglobulinaemia, infection, haemophagocytic lymphohistiocytosis, hypersensitivity, secondary malignancies (including oncogenesis due to insertional mutagenesis caused by lentiviral vector), TLS, impact on pregnancy and lactation, long-term safety, and safety in elderly patients

Table 12. Adverse events with an incidence of ≥10% in any group (Study MM-003, safety analysis population, data cut-off on October 3, 2022)

SOC PT (MedDRA ver.25.1)	Number of subjects (%)					
	Abecma (entire period after randomization) N = 225		Standard treatment (entire period after randomization) N = 126		Cross-over from standard treatment (after Abecma administration) N = 69	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	225 (100)	215 (95.6)	124 (98.4)	96 (76.2)	69 (100)	66 (95.7)
Blood and lymphatic system disorders						
Neutropenia	188 (83.6)	182 (80.9)	57 (45.2)	51 (40.5)	57 (82.6)	57 (82.6)
Anaemia	151 (67.1)	114 (50.7)	46 (36.5)	24 (19.0)	37 (53.6)	34 (49.3)
Thrombocytopenia	127 (56.4)	100 (44.4)	37 (29.4)	23 (18.3)	39 (56.5)	32 (46.4)
Lymphopenia	72 (32.0)	69 (30.7)	26 (20.6)	24 (19.0)	22 (31.9)	22 (31.9)
Leukopenia	70 (31.1)	69 (30.7)	17 (13.5)	13 (10.3)	26 (37.7)	25 (36.2)
Gastrointestinal disorders						
Nausea	113 (50.2)	3 (1.3)	34 (27.0)	0	16 (23.2)	0
Diarrhoea	79 (35.1)	4 (1.8)	31 (24.6)	4 (3.2)	19 (27.5)	0
Constipation	64 (28.4)	0	10 (7.9)	0	6 (8.7)	0
Vomiting	48 (21.3)	0	11 (8.7)	0	10 (14.5)	0
General disorders and administration site conditions						
Fatigue	65 (28.9)	3 (1.3)	44 (34.9)	3 (2.4)	12 (17.4)	1 (1.4)
Pyrexia	64 (28.4)	2 (0.9)	22 (17.5)	1 (0.8)	14 (20.3)	0
Oedema peripheral	35 (15.6)	0	20 (15.9)	4 (3.2)	9 (13.0)	0
Asthenia	27 (12.0)	1 (0.4)	13 (10.3)	1 (0.8)	4 (5.8)	0
Metabolism and nutrition disorders						
Hypokalaemia	78 (34.7)	12 (5.3)	15 (11.9)	1 (0.8)	20 (29.0)	2 (2.9)
Hypophosphataemia	76 (33.8)	49 (21.8)	10 (7.9)	3 (2.4)	20 (29.0)	9 (13.0)
Hypomagnesaemia	51 (22.7)	2 (0.9)	7 (5.6)	1 (0.8)	14 (20.3)	1 (1.4)
Decreased appetite	48 (21.3)	4 (1.8)	16 (12.7)	0	4 (5.8)	0
Hypocalcaemia	44 (19.6)	10 (4.4)	7 (5.6)	2 (1.6)	14 (20.3)	2 (2.9)
Hyponatraemia	24 (10.7)	11 (4.9)	4 (3.2)	1 (0.8)	5 (7.2)	2 (2.9)
Hypertriglyceridaemia	22 (9.8)	5 (2.2)	2 (1.6)	1 (0.8)	9 (13.0)	3 (4.3)
Nervous system disorders						
Headache	58 (25.8)	0	24 (19.0)	1 (0.8)	11 (15.9)	1 (1.4)
Dizziness	26 (11.6)	1 (0.4)	10 (7.9)	0	8 (11.6)	0
Peripheral sensory neuropathy	12 (5.3)	0	16 (12.7)	0	1 (1.4)	0
Tremor	9 (4.0)	0	5 (4.0)	0	7 (10.1)	1 (1.4)
Musculoskeletal and connective tissue disorders						
Arthralgia	51 (22.7)	2 (0.9)	19 (15.1)	2 (1.6)	7 (10.1)	0
Back pain	44 (19.6)	1 (0.4)	22 (17.5)	2 (1.6)	5 (7.2)	2 (2.9)
Pain in extremity	32 (14.2)	1 (0.4)	21 (16.7)	1 (0.8)	6 (8.7)	1 (1.4)
Muscle spasms	10 (4.4)	0	16 (12.7)	3 (2.4)	2 (2.9)	0
Infections and infestations						
Upper respiratory tract infection	30 (13.3)	4 (1.8)	9 (7.1)	0	4 (5.8)	1 (1.4)
Pneumonia	24 (10.7)	16 (7.1)	9 (7.1)	5 (4.0)	2 (2.9)	2 (2.9)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	39 (17.3)	3 (1.3)	28 (22.2)	2 (1.6)	11 (15.9)	0
Cough	39 (17.3)	0	17 (13.5)	0	7 (10.1)	0
Immune system disorders						
CRS	197 (87.6)	11 (4.9)	0	0	59 (85.5)	0
Vascular disorders						
Hypertension	39 (17.3)	21 (9.3)	14 (11.1)	4 (3.2)	11 (15.9)	7 (10.1)
Hypotension	34 (15.1)	3 (1.3)	9 (7.1)	1 (0.8)	8 (11.6)	0
Psychiatric disorders						
Insomnia	39 (17.3)	1 (0.4)	22 (17.5)	3 (2.4)	5 (7.2)	0
Confusional state	23 (10.2)	3 (1.3)	6 (4.8)	1 (0.8)	7 (10.1)	2 (2.9)
Cardiac disorders						
Tachycardia	23 (10.2)	0	3 (2.4)	0	5 (7.2)	0

Serious adverse events were observed in 116 of 225 subjects (51.6%) in the Abecma group, in 52 of 126 subjects (41.3%) in the standard treatment group, and in 23 of 69 subjects (33.3%) after cross-over in

the standard treatment group. Serious adverse events observed in ≥2 subjects in the Abecma group were pneumonia in 15 subjects; pyrexia in 11 subjects; CRS in 10 subjects; general physical health deterioration and febrile neutropenia in 9 subjects each; acute kidney injury and confusional state in 6 subjects each; neutropenia, haemophagocytic lymphohistiocytosis, COVID-19, sepsis, influenza, and pathological fracture in 5 subjects each, COVID-19 pneumonia, myelodysplastic syndrome, depressed level of consciousness, and hypercalcaemia in 4 subjects each; aphasia, encephalopathy, back pain, and deep vein thrombosis in 3 subjects each; and bacteraemia, bronchopulmonary aspergillosis, device related bacteraemia, herpes zoster, rhinovirus infection, streptococcal sepsis, upper respiratory tract infection, urinary tract infection bacterial, asthenia, basal cell carcinoma, breast cancer, malignant melanoma, plasma cell leukaemia, squamous cell carcinoma, thrombocytopenia, disturbance in attention, memory impairment, seizure, somnolence, spinal cord compression, syncope, arthralgia, bone pain, renal failure, dyspnoea, pleural effusion, respiratory failure, delirium, tumor lysis syndrome (TLS), nausea, and fall in 2 subjects each. A causal relationship to Abecma could not be ruled out for CRS in 10 subjects; haemophagocytic lymphohistiocytosis and confusional state in 5 subjects each; febrile neutropenia, neutropenia, and depressed level of consciousness in 4 subjects each; sepsis and aphasia in 3 subjects each; pneumonia, encephalopathy, memory impairment, somnolence, pyrexia, and myelodysplastic syndrome in 2 subjects each; and bronchopulmonary aspergillosis, COVID-19 pneumonia, influenza, rhinovirus infection, streptococcal sepsis, thrombocytopenia, disturbance in attention, seizure, syncope, asthenia, and TLS in 1 subject each.

Serious adverse events observed in ≥2 subjects in the standard treatment group were pneumonia in 6 subjects; COVID-19 pneumonia and general physical health deterioration in 4 subjects each; influenza and atrial fibrillation in 3 subjects each; and COVID-19, pneumonia legionella, oedema peripheral, febrile neutropenia, thrombocytopenia, spinal cord compression, back pain, arthralgia, pain in extremity, acute kidney injury, and diarrhoea in 2 subjects each. A causal relationship to the study treatment could not be ruled out for COVID-19 pneumonia, thrombocytopenia, and oedema peripheral in 2 subjects each; and influenza, febrile neutropenia, and diarrhoea in 1 subject each.

Serious adverse events observed in ≥2 subjects who underwent cross-over in the standard treatment group were sepsis and confusional state in 3 subjects each; and pneumonia, squamous cell carcinoma of skin, neutropenia, somnolence, and delirium in 2 subjects each. A causal relationship to the study treatment could not be ruled out for confusional state in 3 subjects; somnolence in 2 subjects; and sepsis, pneumonia, neutropenia, and delirium in 1 subject each.

9. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

9.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new regenerative medical product application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new regenerative medical product application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

10. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Abecma has a certain level of efficacy in the treatment of relapsed or refractory MM with ≥2 prior lines of treatment, and that Abecma has acceptable safety in view of its benefits. Accordingly, offering Abecma to clinical practice as a new therapeutic option for patients with relapsed or refractory MM who have received ≥2 prior lines of treatment has its significance.

PMDA has concluded that Abecma may be approved if Abecma is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

October 18, 2023

Product Submitted for Approval

Brand Name	Abecma Intravenous Infusion
Non-proprietary Name	Idecabtagene vicleucel
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 14, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

On the basis of review in Section "6.R.1 Efficacy" of the Review Report (1), a statistically significant difference was observed in the primary endpoint PFS between the Abecma group and the standard treatment group in Study MM-003 in patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens. PMDA, therefore, concluded that the efficacy of Abecma was demonstrated in patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the review in Section "6.R.2 Safety" of the Review Report (1), PMDA concluded that adverse events requiring special attention in Abecma treatment of patients with relapsed or refractory MM who have received 2 to 4 prior treatment regimens are the same as those identified as adverse events[25)] requiring caution at the approval of the established indication. Caution should be exercised against these adverse events in the use of Abecma as is the case with the use for the approved indication.

In addition, PMDA concluded that Abecma is tolerable, as long as appropriate measures i.e., monitoring and management of adverse events are provided by a physician with sufficient knowledge and

[25)] CRS, haemophagocytic lymphohistiocytosis, neuropathy, infection, cytopenia, hypersensitivity, hypogammaglobulinaemia, and TLS (Review report on Abecma Intravenous Infusion, dated November 17, 2021)

experience in the treatment of MM at a medical institution well-equipped for responding to these adverse events.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication or performance

As a result of the review in Section "6.R.3 Indication or performance" of the Review Report (1), PMDA concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections should be described as follows.

Indication or Performance

Relapsed or refractory multiple myeloma. Abecma should be used only in patients meeting all of the following criteria:

- Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy
- Patients who have received at least 2 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti- CD38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy

Precautions Concerning Indication or Performance

Patients considered appropriate to receive Abecma must be selected by physicians who have fully understood the efficacy and safety of Abecma after being thoroughly familiar with prior treatment, etc. of patients enrolled in the clinical studies described in the "Clinical Studies" section.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.4 Dosage and administration or method of use

As a result of the review in Section "6.R.4 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the "Dosage and Administration or Method of Use" section should be the same as that specified for the approved indication.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.5 Post-marketing surveillance plan (draft)

The applicant proposed the post-marketing surveillance plan (draft) shown in Table 13 for the reasons such as the safety profile of Abecma in patients with relapsed or refractory MM who have received ≥2 prior lines of treatment is the same as the safety profile in the approved indication. The applicant plans to expand the target patients for the post-marketing surveillance database surveillance planned at the initial approval of Abecma to all patients treated with Abecma, including patients with relapsed or refractory MM who have received ≥2 prior lines of treatment.

PMDA's view:

Data on the safety and efficacy of Abecma in patient with relapsed or refractory MM can be collected by setting the planned sample size for the surveillance at 200, including both patients with the approved indication and patients with the additional indication in the present application. On the basis of the review in Section "7. Risk Analysis and Outline of the Review Conducted by PMDA" in the Review Report (1), the post-marketing surveillance plan is acceptable.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Table 13. Outline of post-marketing surveillance plan

Objective	To evaluate the safety and the efficacy of Abecma in clinical use
Survey method	All-case surveillance The applicant will obtain data of the target population from the data accrued in the registry database (FormsNet) owned by the Center for International Blood and Marrow Transplant Research (CIBMTR) via the Japanese Data Center for Hematopoietic Cell Transplantation.
Population	Patients with relapsed or refractory MM
Observation period	Up to 8 years
Planned sample size	200 patients
Main survey items	Safety CRS, nervous system events, cytopenia, hypogammaglobulinaemia, infection, haemophagocytic lymphohistiocytosis, hypersensitivity, secondary malignancies (including oncogenesis due to insertional mutagenesis caused by lentiviral vector), TLS, impact on pregnancy and lactation, long-term safety, and safety in elderly patients Efficacy Best response, PFS, OS, and event-free survival (EFS) period

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication or performance as well as dosage and administration or method of use as described below, with the following approval conditions, based on the premise that appropriate cautions will be included in the package insert and information concerning the proper use of Abecma will be provided appropriately after the market launch. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until January 19, 2032).

Indication or Performance

Relapsed or refractory multiple myeloma. Abecma should be used only in patients meeting all of the following criteria:

- Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy
- Patients who have received at least 2~~3~~ prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy

(The underlined word is added to, and the strikethrough word is deleted from, the approved text.)

Dosage and Administration or Method of Use

Process from leukapheresis at a medical institution to transportation to a manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a refrigerated container maintained at 2°C to 8°C and transported to a manufacturing facility of Abecma.

Process from receipt at the medical institution to administration of Abecma

3. Receipt and storage of Abecma
   Abecma is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before Abecma administration
   The patient undergoes a blood test, etc., for condition checking and receives the following lymphodepleting chemotherapy from 5 days prior to Abecma administration.
   Administer cyclophosphamide (anhydrate) 300 mg/m^2 as an intravenous infusion once daily for 3 days and fludarabine phosphate 30 mg/m^2 as an intravenous infusion once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
5. Administration of Abecma
   Abecma is thawed immediately before infusion. The usual adult dosage is the target dose of 450 × 10^6 cells (range, 280 × 10^6-540 × 10^6 cells) of CAR-expressing T cells, irrespective of body weight, administered intravenously as a single dose at an infusion rate not exceeding 10 mL/min. Retreatment with Abecma is not allowed.

(No change)

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Appendix

List of Abbreviations

Abecma	Abecma Intravenous Infusion
Anti-BCMA CAR	anti-BCMA chimeric antigen receptor
Application	application for marketing approval
BCMA	B cell maturation antigen
BTZ	bortezomib
CAR	chimeric antigen receptor
CD	cluster of differentiation
CFZ	carfilzomib
Component cells	Cells constituting Abecma
CR	complete response
CRS	cytokine release syndrome
Cyclophosphamide	Cyclophosphamide Hydrate
DARA	Daratumumab (Genetical Recombination)
DEX	dexamethasone
DPd	coadministration of daratumumab (genetical recombination), pomalidomide, and dexamethasone
DVd	coadministration of daratumumab (genetical recombination), bortezomib, and dexamethasone
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EHA	European Hematology Association
ELO	Elotuzumab (Genetical Recombination)
EPd	coadministration of elotuzumab (genetical recombination), pomalidomide, and dexamethasone
FLC	free light chain
Fludarabine	Fludarabine Phosphate
ICU	intensive care unit
IMWG	International Myeloma Working Group
IMWG criteria	Criteria established by IMWG
IPCW	inverse probability of censoring weighted
IRC	Independent Response Committee
IRd	coadministration of ixazomib citrate, lenalidomide, and dexamethasone
IXA	Ixazomib citrate
Kd	coadministration of carfilzomib and dexamethasone
LD chemotherapy	lymphodepleting chemotherapy
LEN	Lenalidomide
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MM	multiple myeloma

MR	minimal response
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma
NE	not evaluable
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression free survival
PMDA	Pharmaceuticals and Medical Devices Agency
POM	pomalidomide
PR	partial response
PS	performance status
PT	preferred term
scFv	single-chain variable fragment
sCR	stringent complete response
SD	stable disease
SMQ	standardised MedDRA queries
SOC	system organ class
Study MM-001	Study BB2121-MM-001
Study MM-003	Study BB2121-MM-003
TLS	tumor lysis syndrome
Tocilizumab	Tocilizumab (Genetical Recombination)
VGPR	very good partial response