Review Report

July 16, 2019
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg
Non-proprietary Name	Daratumumab (Genetical Recombination) (JAN*)
Applicant	Janssen Pharmaceutical K.K.
Date of application	December 14, 2018
Dosage Form/Strength	Solution for injection containing 100 or 400 mg of Daratumumab (Genetical Recombination) per vial (5 or 20 mL)
Application Classification	Prescription drug; (4) Drug with a new indication; and (6) Drug with new dosages
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 409 [*30 yaku*], PSEHB/PED Notification No. 0222-1, dated February 22, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour, and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of untreated multiple myeloma 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 and dosage and administration shown below, with the following conditions.

Indication

~~Relapsed or refractory m~~Multiple myeloma

(Strikethrough denotes deletions.)

Dosage and Administration

The usual adult dose is 16 mg/kg of Daratumumab (Genetical Recombination) administered as an intravenous drip infusion according to the following dosing schedule:

In combination with bortezomib, melphalan, and prednisolone,
Weekly (Weeks 1-6), every 3 weeks (Weeks 7-54), and every 4 weeks (Week 55 onwards)

In combination with lenalidomide and dexamethasone (for relapsed or refractory multiple myeloma only),
Weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards)

In combination with bortezomib and dexamethasone (for relapsed or refractory multiple myeloma only),
Weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards)

(Underline denotes additions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

June 6, 2019

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

Brand Name	Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg
Non-proprietary Name	Daratumumab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 14, 2018
Dosage Form/Strength	Solution for injection containing 100 or 400 mg of Daratumumab (Genetical Recombination) per vial (5 or 20 mL)

Proposed Indication ~~Relapsed or refractory~~ M~~m~~ultiple myeloma

(Strikethrough denotes deletions.)

Proposed Dosage and Administration The usual adult dose is 16 mg/kg of Daratumumab (Genetical Recombination) administered as an intravenous drip infusion according to the following dosing schedule:

In combination with bortezomib, melphalan, and prednisolone,
Weekly (Weeks 1-6), every 3 weeks (Weeks 7-54), and every 4 weeks (Week 55 onwards)

In combination with lenalidomide and dexamethasone,
Weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards)

In combination with bortezomib and dexamethasone,
Weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards)

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Summary of product submitted for approval

Daratumumab (INN, daratumumab), developed by Genmab (Denmark), is an immunoglobulin G1 (IgG1) subclass of a human monoclonal antibody to human CD38.

Daratumumab binds to CD38 expressed on the multiple myeloma (MM) cell membrane and induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cell-mediated cytotoxicity (ADCC) to MM cells. Daratumumab is, thereby, expected to inhibit the growth of tumor cells.

In Japan, daratumumab was approved for the indication of "relapsed or refractory multiple myeloma" in September 2017.

1.2 Development history etc.

The clinical development of daratumumab for untreated MM began abroad, with a phase I study (Study 1001) in patients with MM started by the US Janssen Research & Development in March 2014. A global phase III study (Study 3007) started in patients with untreated MM in February 2015.

In the US and EU, an application for marketing authorization of daratumumab for the indication of untreated MM was submitted with pivotal clinical data from Study 3007 in November 2017. In the US, the marketing authorization was granted in May 2018, for which indication was defined as "DARZALEX is a CD38-directed cytolytic antibody indicated in combination with bortezomib, melphalan, and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant." In the EU, the marketing authorization was granted in August 2018, for which indication was defined as "DARZALEX is indicated in combination with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant."

As of March 2019, daratumumab has been approved for the indication of untreated MM in 50 countries or regions.

In Japan, Janssen Pharmaceutical K.K. started to enroll patients in Study 3007 in June 2015.

Recently, an application for partial change was filed with a pivotal study data from Study 3007 for the additional indication of daratumumab, untreated MM, and the new dosage regimen for it.

Daratumumab was designated as an orphan drug with the proposed indication of "untreated multiple myeloma" in February 2018 (Orphan Drug Designation No. 409 [*30 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The present application was filed for a new indication and new dosages, no quality-related data were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The present application was filed for a new indication and new dosages, and non-clinical pharmacology data were evaluated for the initial approval. Accordingly, no new study data were submitted.

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

The present application was filed for a new indication and new dosages, and non-clinical pharmacokinetic data were evaluated for the initial approval. Accordingly, no new study data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application was filed for a new indication and new dosages, no toxicity data were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Analytical methods

6.1.1.1 Measurement of anti-daratumumab antibodies

Anti-daratumumab antibodies in human serum samples were determined with electrochemiluminescence (ECL) assay with solid-phase streptavidin, biotinylated daratumumab, and ruthenium-labeled daratumumab (detection sensitivity, 0.391 ng/mL).

The applicant's explanation about the effect of daratumumab in samples on the determination of anti-daratumumab antibodies:

With the assay, the upper limit of daratumumab concentrations in samples that did not affect the measurement of anti-daratumumab antibodies was 870 μg/mL. The maximum serum daratumumab concentration at the time points anti-daratumumab antibodies were measured in Studies 3007 and 1001, in which the above-mentioned assay was used, was 830.3 μg/mL. This suggests that anti-daratumumab antibodies were able to be determined without being affected by daratumumab in these studies.

6.2 Clinical pharmacology

The pharmacokinetics (PK) of daratumumab in cancer patients were evaluated based on daratumumab administered in combination with melphalan, prednisolone or prednisone, and bortezomib (MPB) (daratumumab/MPB).

6.2.1 Global phase III study (CTD 5.3.5.1.1-1: Study 3007 [Ongoing since February 2015 (data cutoff on June 12, 2017)])

An open-label, randomized study was conducted to evaluate the efficacy and safety of daratumumab/MPB in 680 patients with MM ineligible for autologous stem cell transplantation (ASCT) (329 patients included in the PK analysis set).

Each treatment cycle from Cycles 1 to 9 consisted of 42 days. Daratumumab was intravenously administered at 16 mg/kg in combination with MPB,[1)] QW in Cycle 1 and Q3W in Cycles 2 to 9. In Cycle 10 onwards, each consisting 28 days, daratumumab was intravenously administered at 16 mg/kg Q4W. Serum daratumumab concentrations were evaluated.

Daratumumab concentration (mean ± standard deviation) was 267 ± 87.8 µg/mL after the first dose, 274 ± 155 µg/mL before the dose on Day 1 of Cycle 3, 596 ± 205 µg/mL after the dose on Day 1 of Cycle 3, 296 ± 145 µg/mL before the dose on Day 1 of Cycle 6, and 636 ± 217 µg/mL after the dose on Day 1 of Cycle 6.

No anti-daratumumab antibodies were detected after the administration of daratumumab in 107 patients who had undergone the antibody evaluation.

6.2.2 Relationship between exposure and efficacy or safety

Based on the data from Study 3007, exposure-efficacy or -safety relationship of daratumumab was assessed. The daratumumab exposure was estimated by a population pharmacokinetics (PPK) analysis.[2)]

6.2.2.1 Exposure-efficacy relationship

Relationship between daratumumab exposure (C_{max} and a trough level at the initial infusion) and progression-free survival (PFS) was assessed with a stratified Cox regression model. PFS tended to be prolonged with increasing daratumumab exposure.

6.2.2.2 Exposure-safety relationship

Relationship between daratumumab exposure (C_{max} at the initial infusion) and the occurrence of infusion reactions was assessed. Relationship between daratumumab exposure (C_{max} at the end of infusion) and the occurrence of thrombocytopenia, anemia, neutropenia, lymphopenia, or infections was also assessed. No evident association was observed between daratumumab exposure and the occurrence of these adverse events.

6.R Outline of the review conducted by PMDA

Based on the data submitted, the applicant's explanation about the clinical pharmacological profile of daratumumab is acceptable.

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

Data from 1 global phase III study was submitted for the efficacy and safety evaluation, and the results of 1 foreign phase Ib study was submitted as reference data (Table 1).

[1)] In 42-day cycles, BTZ 1.3 mg/m^2 was administered subcutaneously (or intravenously for patients who could not tolerate subcutaneous administration) on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycle 1 and Days 1, 8, 22, and 29 of Cycles 2 to 9. Melphalan 9 mg/m^2 and prednisolone or prednisone (not approved in Japan) 60 mg/m^2 were orally administered on Days 1 to 4 of each cycle. However, in the daratumumab/MPB group, steroid was administered prophylactically for an infusion reactions against daratumumab (DEX 20 mg or equivalent steroid in Study 3007 and methylprednisolone 100 mg or equivalent steroid in Study 1001) on Day 1 of each cycle, prednisolone or prednisone (not approved in Japan) was not given on these days.

[2)] The PPK analysis was performed with a non-linear mixed effect model on the basis of the PK data (339 patients, 1,587 points) for daratumumab available from the global study (Study 3007) and the foreign clinical study (Study 1001) by using a software application of NONMEM Version 7.2.

Table 1. List of clinical studies evaluating the efficacy and safety

Data category	Region	Study ID	Phase	Subjects	Number enrolled	Outline of dosing regimens	Primary endpoints
Evaluation	Global	Study 3007	III	Patients with untreated MM ineligible for ASCT	680 (a) 337 (b) 343	(a) Daratumumab was intravenously administered at 16 mg/kg in combination with MPB[1)] in Cycles 1 to 9 (42-day cycles) QW in Cycle 1 and Q3W in Cycles 2 to 9. In Cycle 10 onwards (28-day cycles), daratumumab was intravenously administered at 16 mg/kg Q4W. (b) MPB[1)] was administered for up to 9 cycles.	Efficacy Safety
Reference	Foreign	Study 1001	Ib	Patients with MM	133 (a) 6 (b) 12 (c) 12 (d) 103	(a) Daratumumab was intravenously administered at 16 mg/kg in combination with Bd QW in Cycles 1 and 2 (21-day cycles) and Q3W in Cycle 3 onwards (21-day cycles). (b) Daratumumab was intravenously administered at 16 mg/kg in combination with BTZ, thalidomide, and DEX (BTd) QW in Cycles 1 and 2 (21-day cycles) and Q3W in Cycle 3 onwards (21-day cycles). (c) Daratumumab was intravenously administered at 16 mg/kg in combination with MPB[1)] QW in Cycle 1 and Q3W in Cycle 2 onwards (42-day cycles). (d) Daratumumab was intravenously administered at 16 mg/kg in combination with Pd QW in Cycles 1 and 2 (28-day cycles), Q2W in Cycles 3 to 6 (28-day cycles), and Q4W in Cycle 7 onwards (28-day cycles).	Safety PK

The clinical studies are summarized below:

Major adverse events other than deaths observed in the clinical studies are summarized in Section "7.2 Adverse events observed in clinical studies," and study data PK from the studies are summarized in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology." Data from Study 1001 were submitted for the initial approval application (see the Review Report for Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg, dated August 30, 2017) and are thus omitted in this report.

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase III study (CTD 5.3.5.1.1-1: Study 3007 [February 2015 to ongoing (data cutoff on June 12, 2017)])

An open-label, randomized, controlled study was conducted in patients with untreated MM ineligible for ASCT (target sample size, 700 patients) at 162 sites in 25 countries and regions including Japan to compare the efficacy and safety of daratumumab/MPB with those of MPB alone.

Daratumumab was intravenously administered at 16 mg/kg in combination with MPB[1)] in Cycles 1 to 9 (42-day cycles), QW in Cycle 1 and Q3W in Cycles 2 to 9. In Cycle 10 onwards (28-day cycles), daratumumab was intravenously administered at 16 mg/kg Q4W. In the MPB group, patients received MPB[1)] for up to 9 cycles. In both the daratumumab/MPB and MPB groups, treatment was continued until disease progression or any discontinuation criterion met.

A total of 706 patients (350 in the daratumumab/MPB group and 356 in the MPB group) were enrolled and randomized. Of these, 26 patients[3)] were excluded because of case deletion, and the remaining 680 patients (337 in the daratumumab/MPB group and 343 in the MPB group) were included in the intention-to-treat (ITT) population (Japanese patients, 11 in the daratumumab/MPB group and 13 in the MPB group) and were also included in the efficacy analysis set. A total of 674 patients who received the study drug (333 in the daratumumab/MPB group and 341 in the MPB group) in the ITT population were included in the safety analysis set (Japanese patients, 11 in the daratumumab/MPB group and 13 in the MPB group).

The primary endpoint of the study was centrally-assessed PFS based on the International Myeloma Working Group (IMWG) response criteria (*Leukemia.* 2006;20:1467-73). An interim analysis for efficacy was planned to be performed at the time point when the cumulative number of events reached approximately 216 (60% of the target number of events of 360). The O'Brien-Fleming alpha spending function with the Lan-DeMets method was used to adjust the Type I error rate associated with the implementation of the interim analysis.

The interim analysis results (data cutoff on June 12, 2017) of centrally-assessed PFS based on the IMWG criteria and Kaplan-Meier curves are shown in Table 2 and Figure 1, respectively. The superiority of daratumumab/MPB to MPB was verified.[4)]

Table 2. Results of PFS analysis (ITT population, centrally assessed, data cutoff on June 12, 2017)

	Daratumumab/MPB	MPB
Number of subjects	337	343
Number of death or exacerbation (%)	87 (25.8)	141 (41.1)
Median [95% CI] (months)	NE [NE, NE]	17.91 [16.13, 19.81]
Hazard ratio [*1] [95% CI]	0.51 [0.39, 0.67]	
p value (two-sided)[*2]	<0.0001	

*1 Calculated based on a stratified Cox proportional-hazards model with stratifying factors including disease stage at screening according to the international staging system (ISS) (I, II, and III), region (Europe and other), age (<75 years and ≥75 years); *2 A stratified log-rank test (with stratifying factors same as those used for the Cox proportional-hazards model), with a two-sided significance level of 0.0097.

[3)] All were Japanese patients. They were excluded from the ITT population because of unidentified batch number of BTZ used for them in the study [see Sections 8.1 and 8.2]. The comparison in in efficacy and safety between the population before and after the case deletion showed no obvious difference.

[4)] Given the PFS results in the population before the case deletion (hazard ratio [95% CI], 0.50 [0.38, 0.65]; a p-value [two-sided], <0.0001; two-sided significance level, 0.0103), the independent data monitoring committee (IDMC) proposed early termination of the study.

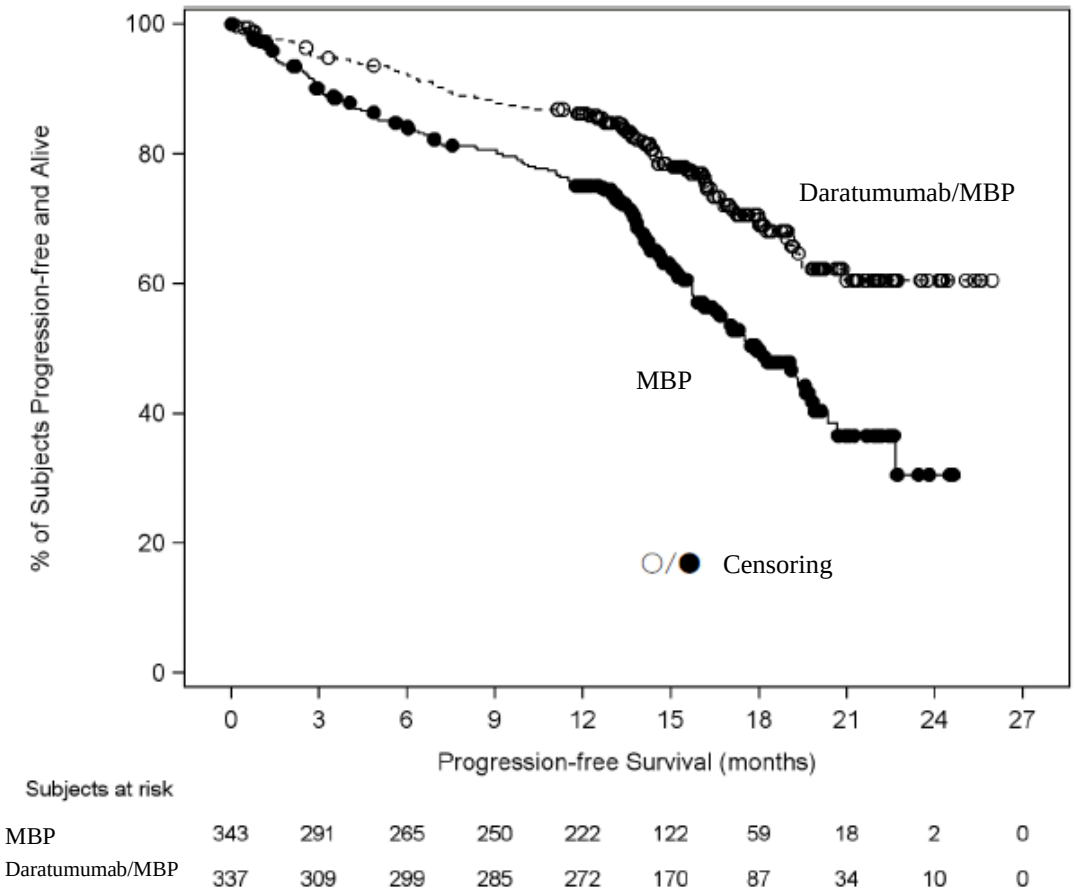

Figure 1. Kaplan-Meier curves for PFS (ITT population, centrally assessed, data cutoff on June 12, 2017)

The safety analysis revealed deaths occurring during the study treatment period or within 30 days after the last dose in 14 of 333 patients (4.2%) in the daratumumab/MPB group and 16 of 341 patients (4.7%) in the MPB group. Causes of death other than disease progression (2 patients in the daratumumab/MPB group and 0 in the MPB group) were; in the daratumumab/MPB group, death in 2 patients, pneumonia, acute myocardial infarction, cardiac arrest, acute cardiac failure, intracranial haemorrhage, ischaemic stroke, septic shock, tumor lysis syndrome (TLS), upper respiratory tract infection, and intestinal ischaemia in 1 patient each; in the MPB group, cardiac arrest and death in 2 patients each, septic shock, TLS, acute kidney injury, anuria, candida sepsis, cardiac failure, cardio-respiratory arrest, cerebral infarction, obstructive airways disorder, pulmonary embolism, sepsis, and traumatic shock in 1 patient each. A causal relationship to the study drug was not ruled out for pneumonia, acute myocardial infarction, and TLS in 1 patient each in the daratumumab/MPB group and pulmonary embolism in 1 patient in the MPB group (In the Japanese subgroup, 1 patient in the MPB group died of traumatic shock, for which a causal relationship to the study drug was ruled out).

7.R Outline of the review conducted by PMDA

7.R.1 Approach

Considering that, among the data submitted, the global phase III study (Study 3007) in patients with untreated MM ineligible for ASCT was the pivotal study to evaluate the efficacy and safety of daratumumab, PMDA decided that the evaluation should center on Study 3007. PMDA further decided the efficacy evaluation in Japanese patients should base on the viewpoint of consistency between the entire study population and the

Japanese subgroup in Study 3007, in accordance with the Basic Principles on Global Clinical Trials (PFSB/ELD Notification No. 0928010, dated September 28, 2007) and the Basic Principles on Global Clinical Trials (Reference Cases) (Administrative Notice, dated September 5, 2012).

7.R.2 Efficacy

As a result of the following review, PMDA concluded that the efficacy of treatment with daratumumab/MPB was demonstrated in patients with untreated MM ineligible for ASCT.

7.R.2.1 Control group

The applicant's explanation about the rationale for having the control group in Study 3007:

When Study 3007 began in 2014, the NCCN guidelines (v.2.2014) recommended the use of MPB for the treatment of patients meeting the eligibility criteria for the study, based on data from foreign clinical studies (*N Engl J Med.* 2008;359:906-17). Therefore, MPB was selected as the control treatment in Study 3007. However, for the reasons itemized below, the approved dosage regimen[5)] of bortezomib (BTZ) in the MPB treatment was partially modified. More specifically, BTZ was administered, in 42-day cycles, twice weekly in Cycle 1 (Days 1, 4, 8, 11, 22, 25, 29, and 32) and once weekly in Cycle 2 onwards (Days 1, 8, 22, and 29).

- A foreign clinical study of MPB treatment was conducted in patients with untreated MM ineligible for ASCT (Study GEM2005MAS65). In the study, BTZ was administered twice weekly in Cycle 1 (42-day cycle) and once weekly in Cycle 2 onwards (35-day cycles). The results demonstrated no clear difference in efficacy from the previously approved dosage regimen[5)] while indicating improved peripheral neuropathy (*Lancet Oncol*. 2010;11:934-41).
- The Japanese guidelines (e.g., the Practical guidelines for hematological malignancies in 2013 edited by the Japanese Society of Hematology) recommend to administer BTZ once weekly in MPB treatment as a standard treatment for patients with untreated MM ineligible for ASCT.
- A foreign textbook (*Wintrobe's Clinical Hematology, 13th Edition* [Lippincott Williams & Wilkins, 2013 USA]) mentions that, based on data from studies in elderly patients, changing the BTZ regimen from twice weekly to once weekly in the MPB treatment improves not only the feasibility and efficacy of BTZ treatment but also alleviates peripheral neuropathy.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the reason for selecting PFS as the primary endpoint of Study 3007:

MM is a refractory disease that can recur multiple times and hardly be cured by existing treatment. Although the treatment of MM is aimed to extend the patient's life, PFS prolongation is expected to contribute to delaying the disease progression and the start of the next therapy. PFS was thus selected as the primary endpoint of Study 3007 (*Leukemia.* 2006;20:1467-73).

[5)] BTZ was administered subcutaneously or intravenously on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycles 1 to 4, and Days 1, 8, 22, and 29 of Cycles 5 to 9 (42-day cycles).

PMDA's view:

The applicant's explanation is understandable. However, given that the treatment of MM is aimed to extend the patient's life, overall survival (OS) is also important. Therefore, PMDA will review the efficacy of daratumumab mainly focusing on centrally-assessed PFS based on the IMWG criteria, the primary endpoint, and will check OS as well.

7.R.2.3 Results of efficacy evaluation

In Study 3007, daratumumab/MPB was proven to be superior to MPB in the primary endpoint, centrally-assessed PFS based on the IMWG criteria [see Section 7.1.1.1].

Table 3 shows the results of a sensitivity analysis, i.e., investigator-assessed PFS based on the IMWG criteria.

Table 3. Results of PFS analysis (ITT population, investigator-assessed, data cutoff on June 12, 2017)

	Daratumumab/MPB	MPB
Number of subjects	337	343
Number of death or exacerbation (%)	87 (25.8)	135 (39.4)
Median [95% CI] (months)	NE [NE, NE]	19.12 [16.79, 20.37]
Hazard ratio *1 [95% CI]	0.55 [0.42, 0.72]	
p value (two-sided)*2	<0.0001	

*1 Calculated using a stratified Cox proportional-hazards model with stratifying factors including disease stage at the screening according to the ISS (I, II, and III), region (Europe and other), age (<75 years and ≥75 years). *2 A stratified log-rank test (with stratifying factors same as those used for the Cox proportional-hazards model)

In Study 3007, if any statistically significant difference was identified in the primary endpoint, stratified hypothesis tests were performed for the secondary endpoints of (a) the centrally-assessed rate of partial response (PR) or better, (b) the centrally-assessed rate of very good partial response (VGPR) or better, (c) the centrally-assessed rate of complete response (CR) or better, (d) minimal residual disease (MRD) negativity rate, and (e) OS in this order. Statistically significant differences were identified in (a) to (d),[6)] whereas there was no statistically significant difference in (e).[7)]

The results of the interim analysis (data cutoff on June 12, 2017) on OS, a secondary endpoint, are shown in Table 4 and Figure 2.

Table 4. Results of OS analysis (ITT population, data cutoff on June 12, 2017)

	Daratumumab/MPB	MPB
Number of subjects	337	343
Death (%)	45 (13.4)	47 (13.7)
Median [95% CI] (months)	NE [NE, NE]	NE [NE, NE]
Hazard ratio *1 [95% CI]	0.94 [0.62, 1.41]	
p value (two-sided)*2	0.7510	

*1 Calculated with a non-stratified Cox proportional-hazards model. *2 A non-stratified log-rank test, two-sided significance level of 0.0001

6) Based on the O'Brien-Fleming alpha spending function with the Lan-DeMets method, the significance level (two-sided) for a) to d) at the interim PFS analysis was specified to be 0.0244.

7) The significance level (two-sided) for OS at the interim PFS analysis was specified to be 0.0001.

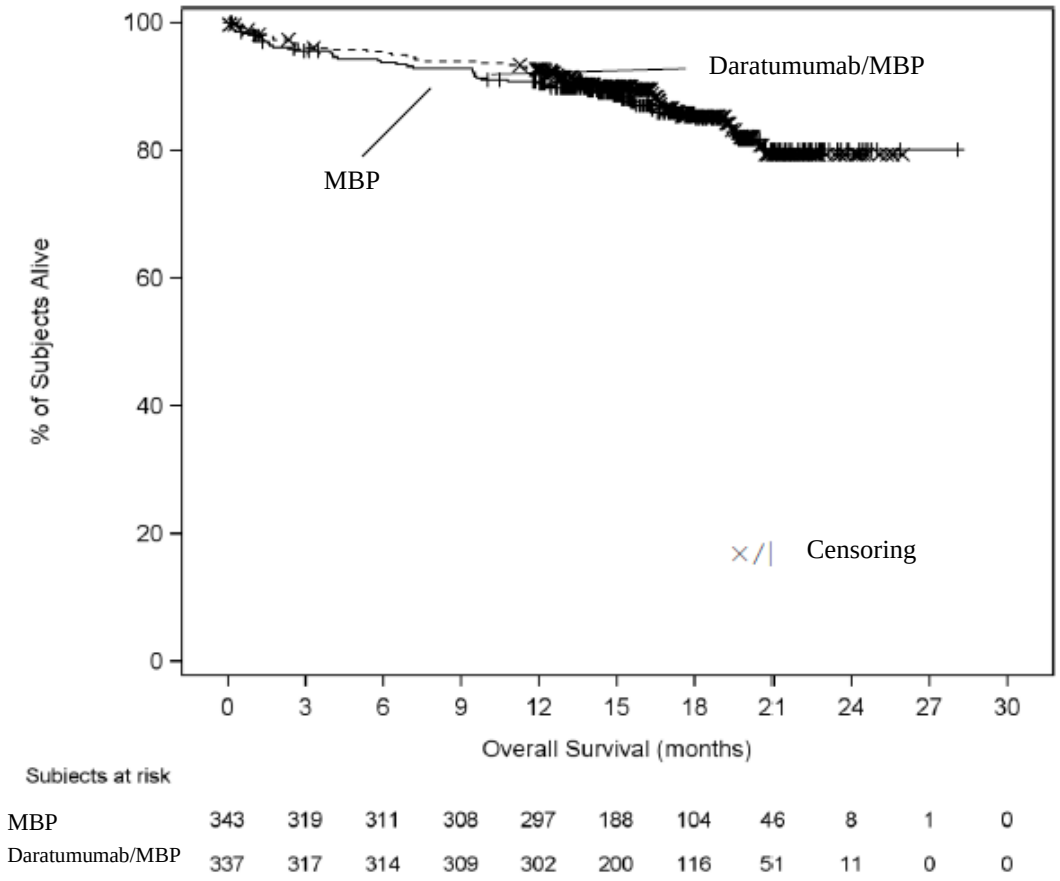

Figure 2. Kaplan-Meier curves for OS (ITT population, data cutoff on June 12, 2017)

The results of centrally-assessed PFS based on the IMWG criteria at the time of the interim analysis in Japanese subgroup in Study 3007and the Kaplan Meier curves are shown in Table 5 and Figure 3, respectively.

Table 5. Results of PFS analysis in Japanese subgroup (ITT population, centrally assessed, data cutoff on June 12, 2017)

	Daratumumab/MPB	MPB
Number of subjects	11	13
Number of death or exacerbation (%)	2 (18.2)	5 (38.5)
Median [95% CI] (months)	NE [16.72, NE]	20.67 [9.92, 20.67]
Hazard ratio * [95%CI]	0.39 [0.07, 1.99]	

* Calculated with a non-stratified Cox proportional-hazards model.

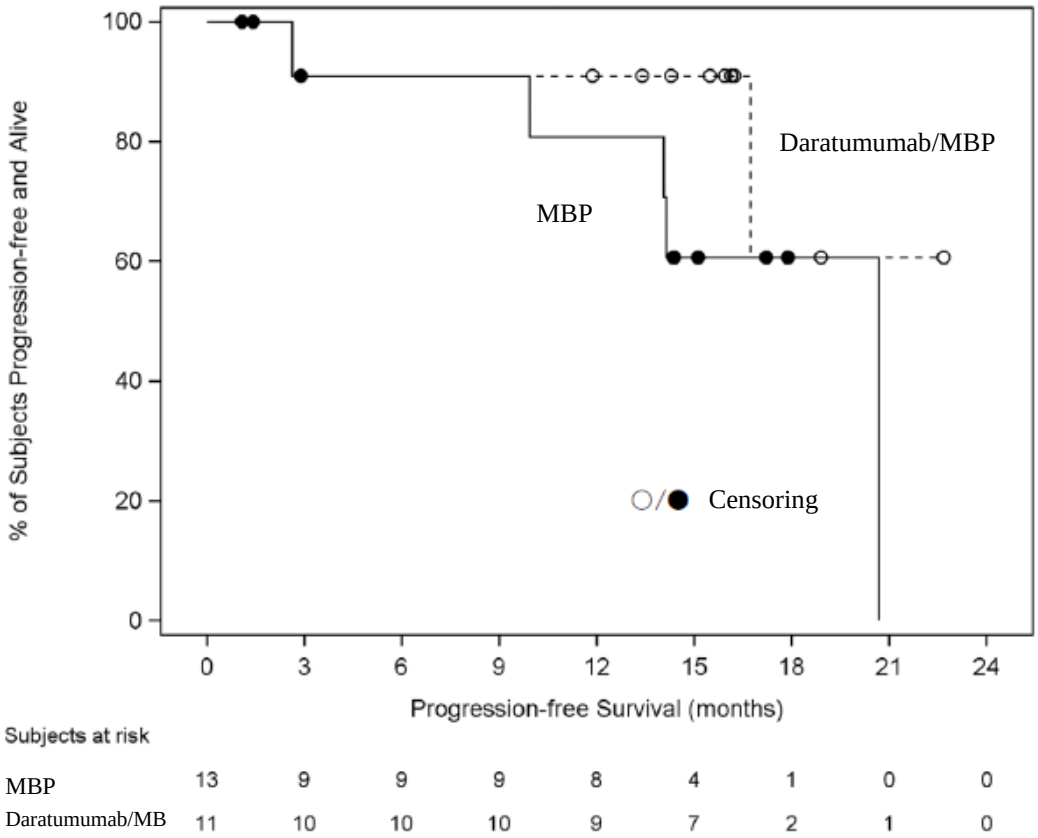

Figure 3. Kaplan-Meier curves for PFS in Japanese subgroup (ITT population, centrally assessed, data cutoff on June 12, 2017)

PMDA's view:

In light of the following, PMDA concluded that the efficacy of treatment with daratumumab/MPB was demonstrated in patients participated in Study 3007.

- The treatment with daratumumab/MPB was proven to be superior to MPB alone in the primary endpoint of centrally-assessed PFS based on the IMWG criteria, and the observed PFS prolongation effect is clinically meaningful.
- Daratumumab/MPB did not tend to obviously reduce OS, a secondary endpoint, as compared with MPB alone.
- Although the small number of Japanese patients in Study 3007 precluded precise evaluation, no markedly different tendency was observed in PFS between the Japanese subgroup and the entire study population in the study.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events observed in clinical studies"]

PMDA concluded that, based on reviews in the subsections below, the treatment with daratumumab/MPB in patients with untreated MM ineligible for ASCT requires attention to HBV reactivation, in addition to previously identified adverse events at the review for the approved indication (infusion reaction, bone marrow depression, infections, hemolysis, and TLS) (see the Review Report for Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg, dated August 30, 2017). Caution should be exercised against the onset of these adverse events in the use of daratumumab.

PMDA further concluded that, despite above mentioned possible adverse events that require attention, daratumumab is tolerable when adverse events are appropriately monitored and managed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

7.R.3.1 Safety profiles of daratumumab/MPB treatment and differences between Japanese and non-Japanese patients

The applicant's explanation about the safety profiles of the treatment with daratumumab/MPB and the differences between Japanese and non-Japanese patients, based on the safety data available from Study 3007 (data cutoff on June 12, 2017).

The safety in Study 3007 is summarized in Table 6.

Table 6. Safety summary (Study 3007)

	Number of subjects (%)					
	Entire study population		Japanese patients		Non-Japanese patients	
	Daratumumab/MPB n = 333	MPB n = 341	Daratumumab/MPB n = 11	MPB n = 13	Daratumumab/MPB n = 322	MPB n = 328
All adverse events	321 (96.4)	329 (96.5)	11 (100)	13 (100)	310 (96.3)	316 (96.3)
Grade ≥3 adverse events	260 (78.1)	264 (77.4)	11 (100)	13 (100)	249 (77.3)	251 (76.5)
Adverse events resulting in death	19 (5.7)	19 (5.6)	1 (9.1)	1 (7.7)	18 (5.6)	18 (5.5)
Serious adverse events	138 (41.4)	113 (33.1)	3 (27.3)	5 (38.5)	135 (41.9)	108 (32.9)
Adverse events leading to treatment discontinuation*1	17 (5.1)	30 (8.8)	2 (18.2)	3 (23.1)	15 (4.7)	27 (8.2)
Adverse events leading to treatment interruption*2	190 (57.1)	157 (46.0)	10 (90.9)	9 (69.2)	180 (55.9)	148 (45.1)
Adverse events leading to dose reduction*3	123 (36.9)	150 (44.0)	5 (45.5)	7 (53.8)	118 (36.6)	143 (43.6)

*1 Discontinuation of all study drugs including daratumumab; *2 Interruption of daratumumab or ≥1 concomitant drug; *3 Dose reduction of ≥1 concomitant drug. No dose reduction criterion was specified for daratumumab.

In Study 3007, adverse events with a ≥10% higher incidence in the daratumumab/MPB group than that in the MPB group were upper respiratory tract infection (89 patients [26.7%] in the daratumumab/MPB group, 49 patients [14.4%] in the MPB group), pneumonia (52 patients [15.6%] and 17 patients [5.0%]). The Grade ≥3 adverse event with a ≥5% higher incidence in the daratumumab/MPB group than that in the MPB group was pneumonia (39 patients [11.7%], 14 patients [4.1%]). A serious adverse event with a ≥2% higher incidence in the daratumumab/MPB group than that in the MPB group was pneumonia (34 patients [10.2%], 11 patients [3.2%]). Adverse events leading to the interruption of study treatment with a ≥2% higher incidence in the daratumumab/MPB group than that in the MPB group were thrombocytopenia (47 patients [14.1%], 30 patients [8.8%]), neutropenia (45 patients [13.5%], 34 patients [10.0%]), pneumonia (28 patients [8.4%], 5 patients [1.5%]), upper respiratory tract infection (24 patients [7.2%], 9 patients [2.6%]), bronchitis (14 patients [4.2%], 6 patients [1.8%]), neuralgia (12 patients [3.6%], 5 patients [1.5%]), and anaemia (11 patients [3.3%] and 3 patients [0.9%]). Among thoseadverse events with a ≥2% higher incidence in the daratumumab/MPB group than that in the MPB group, thrombocytopenia (39 patients [11.7%], 33 patients [9.7%]) led to the dose reduction of study drug. Among adverse events with a ≥2% higher incidence in the daratumumab/MPB group than that in the MPB group, none resulted in death or led to the discontinuation of study drug.

In the daratumumab/MPB group of Study 3007, adverse events with a ≥20% higher incidence in the Japanese patients than in non-Japanese patients were leukopenia (10 Japanese patients [90.9%] and 29 non-Japanese patients [9.0%]), thrombocytopenia (9 [81.8%] and 151 [46.9%]), neutropenia (8 [72.7%] and 157 [48.8%]), lymphopenia (8 [72.7%] and 22 [6.8%]), nausea (6 [54.5%] and 60 [18.6%]), injection site erythema (6 [54.5%] and 5 [1.6%]), diarrhoea (5 [45.5%] and 71 [22.0%]), oedema peripheral (5 [45.5%] and 56 [17.4%]), vomiting (4 [36.4%] and 50 [15.5%]), decreased appetite (4 [36.4%] and 32 [9.9%]), and insomnia (3 [27.3%] and 17 [5.3%]). Grade ≥3 adverse events with a ≥10% higher incidence in the Japanese patients than in non-Japanese patients were leukopenia (8 [72.7%] and 13 [4.0%]), lymphopenia (8 [72.7%] and 11 [3.4%]), neutropenia (7 [63.6%] and 124 [38.5%]), thrombocytopenia (7 [63.6%] and 105 [32.6%]), and diarrhoea (2 [18.2%] and 7 [2.2%]). Among adverse events with a ≥10% higher incidence in the Japanese patients than in non-Japanese patients, neutropenia (2 [18.2%] and 21 [6.5%]) and lymphopenia (2 [18.2%] and 0) led to the dose reduction of study drug. There were no adverse events with a ≥10% higher incidence in the Japanese patients than in non-Japanese patients resulting in death, leading to the discontinuation or interruption of study drug.

PMDA asked the applicant to explain differences in the safety profiles of daratumumab/MPB from the approved combination therapy with daratumumab/lenalidomide and dexamethasone (DEX) (Ld) or daratumumab/BTZ and DEX (Bd) in patients with relapsed or refractory MM.

The applicant's explanation:
The safety profiles of treatment in the daratumumab/MPB group of Study 3007, in the daratumumab/Ld group of the global phase III study (Study 3003) conducted in patients with relapsed or refractory MM,[8)] and in the daratumumab/Bd group of the foreign phase III study (Study 3004)[9)] are summarized in Table 7.

[8)] Each cycle consisted of 28 days. Daratumumab 16 mg/kg was intravenously administered QW in Cycles 1 and 2, Q2W in Cycles 3 to 6, and Q4W in Cycle 7 onwards, in combination with Ld (oral lenalidomide 25 mg QD on Days 1 to 21 and oral or intravenous DEX 40 mg on Days 1, 8, 15, and 22),

[9)] Daratumumab 16 mg/kg was intravenously administered QW in Cycles 1 to 3 (21 days/cycle) and Q3W in Cycles 4 to 8 (21 days/cycle) in combination with Bd (subcutaneous or intravenous BTZ 1.3mg/m^2 on Days 1, 4, 8, and 11 and oral or intravenous DEX 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12). In Cycle 9 onwards (28 days/cycle), daratumumab 16 mg/kg alone was intravenously administered Q4W.

Table 7. Safety summary in the daratumumab/MPB group of Study 3007, daratumumab/Ld group of Study 3003, and daratumumab/Bd group of Study 3004

	Number of subjects (%)		
	Study 3007	Study 3003	Study 3004
	Daratumumab/MPB n = 333	Daratumumab/Ld n = 283	Daratumumab/Bd n = 243
All adverse events	321 (96.4)	278 (98.2)	240 (98.8)
Grade ≥3 adverse events	260 (78.1)	229 (80.9)	185 (76.1)
Adverse events resulting in death	19 (5.7)	11 (3.9)	13 (5.3)
Serious adverse events	138 (41.4)	138 (48.8)	102 (42.0)
Adverse events leading to treatment discontinuation*1	17 (5.1)	19 (6.7)	18 (7.4)
Adverse events leading to treatment interruption*2	190 (57.1)	208 (73.5)	155 (63.8)
Adverse events leading to dose reduction*3	123 (36.9)	158 (55.8)	111 (45.7)

*1 Discontinuation of all study drugs including daratumumab. *2 Interruption of daratumumab or ≥1 concomitant drug; *3 Dose reduction of ≥1 concomitant drug. No dose reduction criterion was specified for daratumumab.

In the Study 3007 daratumumab/MPB group, there were no adverse events of any grade, Grade ≥3, or leading to the interruption or dose reduction of study drug, with a ≥10 percent higher incidence than in the Study 3003 daratumumab/Ld group [10)] or the Study 3004 daratumumab/Bd group.[10)] In the Study 3007 daratumumab/MPB group, there were no adverse events that were serious, led to the discontinuation of study drug, or resulted in death, with a ≥2% higher incidence than in the Study 3003 daratumumab/Ld group or the Study 3004 daratumumab/Bd group. Currently, available data from post-marketing surveillance (all-case surveillance) in patients with relapsed or refractory MM, the approved indication, show no newly identified adverse events requiring caution.

PMDA's view:

Adverse events occurring at a higher incidence in the daratumumab/MPB group than in the MPB group in Study 3007 deserve attention as they are more likely to occur following the daratumumab/MPB treatment. It is difficult to draw a definite conclusion on the differences in the safety profiles between Japanese and non-Japanese patients based on the results from Study 3007 because of the extremely limited number of Japanese participants. Nevertheless, caution should be exercised against Grade ≥3 adverse events occurring at a higher incidence in Japanese patients than in non-Japanese patients. Meanwhile, (a) the above-mentioned events were all known adverse events of daratumumab, and (b) no clear differences were identified in the safety profiles of daratumumab between the daratumumab/MPB regimen in patients with untreated MM and the approved dosage regimen for relapsed or refractory MM. Given these, daratumumab/MPB is tolerable when adverse events are appropriately monitored and managed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

In response to the applicant's report about several cases of HBV reactivation observed in the clinical studies underway and in the overseas post-marketing setting, PMDA's reviews focused on HBV reactivation.

[10)] Adverse events were termed and counted according to the MedDRA/J ver.20.0.

7.R.3.2 HBV Reactivation

PMDA asked the applicant to explain the occurrence of HBV reactivation in association with daratumumab treatment.

The applicant's explanation:
HBV reactivation-related adverse events were aggregated based on MedDRA PTs, namely, "acute hepatitis B," "hepatitis B," "hepatitis B reactivation," "chronic hepatitis B," "hepatitis B DNA assay positive," "hepatitis B DNA increased," and "hepatitis viral."

In the clinical studies conducted in and outside Japan[11] (data cutoff on June 29, 2018), HBV reactivation was reported from 6 (0.2%) of 3,293 patients receiving daratumumab. The reported events were hepatitis B reactivation in 3 patients (all non-serious), acute hepatitis B in 1 patient (resulting in death)[12], hepatitis B in 1 patient (non-serious), and positive HBV DNA, although which was not reported as an adverse event, in 1 patient. A causal relationship with daratumumab was not ruled out in all these cases except for positive HBV DNA.

In the overseas post-marketing setting (data cutoff on September 13, 2018), HBV reactivation was reported from 9 patients. The reported events were hepatitis B reactivation in 4 patients (all serious), hepatitis B in 4 patients (all serious), and acute hepatitis B/hepatitis B reactivation in 1 patient (resulting in death). A causal relationship with daratumumab was not ruled out for hepatitis B reactivation in 3 patients, hepatitis B in 2 patients, and acute hepatitis B/hepatitis B reactivation in 1 patient.

PMDA's view:
Serious HBV reactivation-related events occurred following daratumumab treatment in the clinical studies and post-marketing settings, including some with a fatal outcome. This indicates that caution should be exercised against HBV reactivation during the use of daratumumab. The occurrence of HBV reactivation in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. Furthermore, healthcare professionals should also be advised appropriately via the package insert that patients be checked for a history of HBV infection before starting daratumumab and be monitored for any sign of HBV reactivation through regular blood testing such as hepatic function test during daratumumab treatment.

7.R.4 Clinical positioning and indication

Treatment of "multiple myeloma" was proposed for the indication of daratumumab. The "Precautions Concerning Indication" section was proposed to present the following advice:

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[11] Studies 3003, 3004, 3007, MMY3006, MMY3008, LUC2001, 1001, MMY1002, MMY2002, GEN501, GEN503, MMY1004, MMY3012, SMM2001, NKT2001, LYM2001, AMY3001, MMY1005, MMY1006, MMY1008, MMY2040, MMY1003, MMY2012, and MMY2036.

[12] At hepatitis B virus (HBV) serology tests, the patient was tested positive for HBs antigen, anti-HBc IgG, and HBe antigen, and negative for anti-HBs antibody and anti-HBc IgM antibody. HBV DNA titer was 38,200,000 IU/mL. The patient did not undergo the HBV serology tests before starting the study drug, and the evaluation was performed retrospectively with blood samples collected before the administration of the study drug. The patient received no anti-HBV drugs before the start of the study drug treatment.

- Physicians should select appropriate patients after thoroughly understanding the details of the clinical study patients, including previous treatment history, described in the "Clinical Studies" section of the package insert and fully understanding the efficacy and safety profiles of daratumumab.

As a result of the discussions presented in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the flowing subsection, PMDA has concluded that daratumumab be approved for the proposed indication of treatment of "multiple myeloma" with the advice in the "Precautions Concerning Indications" section modified as below, and that the package insert note that Study 3007 was conducted in patients with untreated MM who were ineligible for ASCT.

- Physicians should select appropriate patients after thoroughly understanding the details described in the "Clinical Studies" section and fully understanding the efficacy and safety profiles of daratumumab.

7.R.4.1 Clinical positioning of daratumumab

The clinical practice guidelines in and outside Japan and major textbooks for hematology and clinical oncology describe daratumumab treatment for untreated MM.

Clinical practice guidelines

- NCCN guidelines (v2.2019): Daratumumab/MPB, the combination of BTZ and Ld (BLd), or Ld (Category 1[13)]) and the combination of BTZ, cyclophosphamide hydrate and DEX (BCd) (Category 2A[14)]) are recommended for the treatment of patients with untreated MM ineligible for ASCT.

Textbooks

- *Wintrobe's Clinical Hematology, 14th Edition* (Lippincott Williams & Wilkins, 2018 USA): Data including PFS following the daratumumab/MPB treatment in comparison with MPB treatment are provided as data from of the global phase III study (Study 3007) in patients with untreated MM ineligible for ASCT.

The applicant's explanation about the clinical positioning and the indication of daratumumab/MPB treatment: The textbook and clinical practice guidelines in and outside Japan[15)] recommend MPB and Ld as the standard therapies for patients with untreated MM ineligible for ASCT. In this context, Study 3007 demonstrated the clinical benefit of daratumumab/MPB in patients with untreated MM ineligible for ASCT [see Sections 7.R.2 and 7.R.3]. Thus, the daratumumab/MPB treatment can be recognized as a standard therapy for this patient population. Given no available clinical study data from patients with untreated MM comparing the efficacy and safety of daratumumab/MPB with those of Ld, it is difficult at present to draw a definite conclusion on the appropriate choice between daratumumab/MPB and Ld. Whichever is more appropriate should be chosen according to the general conditions and concurrent diseases, etc. of patients.

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13) Based upon high-level evidence with uniform NCCN consensus that the intervention is appropriate.
14) Based upon lower-level evidence with uniform NCCN consensus that the intervention is appropriate.
15) *Practical guidelines for hematological malignancies 2018* (edited by the Japanese Society of Hematology); *New Clinical Oncology, 5th Edition* (edited by the Japanese Society of Medical Oncology)

Patients with untreated MM eligible for ASCT were not enrolled in Study 3007, and there are no clinical study data on the efficacy and safety of the daratumumab/MPB treatment in this patient population. Therefore, the daratumumab/MPB treatment is not recommended for patients with untreated MM eligible for ASCT. However, (a) eligibility for ASCT depends on age, concurrent diseases, or other factors of each patient, and it is difficult to precisely define the eligibility in the indication. In addition, (b) because daratumumab is presumed to be prescribed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies, the drug can be indicated for the treatment of "multiple myeloma," presupposing that the "Clinical Studies" section of the package insert notes that Study 3007 targeted patients with untreated MM ineligible for ASCT and that the "Precautions Concerning Indications" section gives the following advice, which were also given for the approved indication.

- Physicians should select appropriate patients after thoroughly understanding the details of the clinical study patients, including previous treatment history, described in the "Clinical Studies" section of the package insert and fully understanding the efficacy and safety of daratumumab.

PMDA's view:

The applicant's explanation is generally acceptable. The description of the "Precautions Concerning Indications" section should be modified as below to provide precautions.

- Physicians should select appropriate patients after thoroughly understanding the details described in the "Clinical Studies" section and fully understanding the efficacy and safety profiles of daratumumab.

7.R.5 Dosage and administration

The proposed dosage and administration for daratumumab are as follows.

Dosage and Administration

The usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion according to the following dosing schedule:

In combination with bortezomib, melphalan, and prednisolone,

Weekly (Weeks 1-6), every 3 weeks (Weeks 7-54), and every 4 weeks (Week 55 onwards)

In combination with lenalidomide and dexamethasone,

Weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards)

In combination with bortezomib and dexamethasone,

Weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards)

The proposed "Precautions Concerning Dosage and Administration" section included advice on the consideration of the dose of concomitant corticosteroids administered before the start of daratumumab to reduce infusion reactions, in addition to the following cautionary advice given for the approved indication.

- The efficacy and safety of daratumumab as monotherapy have not been established.
- Physicians should carefully select the treatment interval of daratumumab and the nature and type of anticancer drugs to be used concomitantly with daratumumab after being familiar with information

described in the “Clinical Studies” section of the package insert. Physicians also should thoroughly and carefully read the package inserts of the concomitant drugs.

- Administration of corticosteroids, antipyretic analgesics, and antihistamines in order to reduce infusion reactions
- Dilution volume and infusion rate of daratumumab
- Actions to be taken in the event of infusion reaction

PMDA’s view:

In view of the discussions presented in Sections “7.R.2 Efficacy” and “7.R.3 Safety” and the sections below, the dosing regimen of daratumumab should be defined as below. There is not much necessity of the proposed additional cautionary advice on the dosage of corticosteroids in the “Precautions Concerning Dosage and Administration” section of the package insert because (a) similar advice has already been given through written materials for the approved indication and (b) daratumumab/MPB is presumed to be prescribed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

Dosage and Administration

The usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion according to the following dosing schedule:

In combination with bortezomib, melphalan, and prednisolone,

Weekly (Weeks 1-6), every 3 weeks (Weeks 7-54), and every 4 weeks (Week 55 onwards)

In combination with lenalidomide and dexamethasone (for relapsed or refractory multiple myeloma only),

Weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards)

In combination with bortezomib and dexamethasone (for relapsed or refractory multiple myeloma only),

Weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards)

7.R.5.1 Dosage and administration

The applicant’s explanation about the rationale for the proposed dosing regimen of daratumumab:

As with the clinical studies in patients with relapsed or refractory MM, the daratumumab 16 mg/kg was chosen in Study 3007 based on the observation that the level of CD38 expression in malignant plasma cells was consistent regardless of the stage of MM (*Clin Pathol.* 2004;121:482-8) (see the Review Report for Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg, dated August 30, 2017). The dosing schedule was specified as weekly (Weeks 1-6), every 3 weeks (Weeks 7-54), and every 4 weeks (Week 55 onwards), with the dosing schedule of concomitant MPB taken into consideration. Because Study 3007 data demonstrated the clinical efficacy of daratumumab in patients with untreated MM ineligible for ASCT [see Sections 7.R.2 and 7.R.3], the proposed dosing regimen of daratumumab was determined on the basis of the dosing regimen used in the study.

PMDA’s view:

The applicant’s explanation is generally acceptable. However, because of no available data of patients with untreated MM from the clinical studies, the approved daratumumab/Ld and daratumumab/Bd should be

prescribed only to patients with relapsed or refractory MM, and that should be clearly reminded in Dosage and Administration.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing safety information:

There is no need to conduct post-marketing surveillance immediately after approval to evaluate the safety of the daratumumab/MPB treatment in patients with untreated MM because of the following observations. Instead, safety information will be gathered through routine pharmacovigilance activities.

- No distinct differences were found in the safety profiles of daratumumab between Study 3007 and the approved indication, and the study identified no new safety issues deserving of investigation during the daratumumab/MPB treatment in patients with untreated MM.
- While the specified use-results survey is still underway in patients with relapsed or refractory MM, the approved indication (target sample size, 300 patients in the safety analysis set), a certain amount of clinical experience with daratumumab in Japanese patients[16)] has been gained. The currently available safety data of daratumumab from 150 Japanese patients[17)] have raised no new safety concerns.
- Overseas post-marketing data show no new safety concerns in daratumumab treatment.
- HBV reactivation was reported from the ongoing clinical studies and overseas post-marketing setting, which deserves caution. Nevertheless, findings on HBV reactivation in association with the use of daratumumab can be collected through the specified use-results survey, which includes "infections" in its safety specification.

PMDA accepted the applicant's explanation.

7.2 Adverse events observed in clinical studies

Deaths reported in the clinical study data which were submitted to evaluate the safety are described in Section "7.1 Evaluation data," and common adverse events other than death are summarized below.

7.2.1 Global phase III study (Study 3007)

Adverse events occurred in 321 of 333 patients (96.4%) in the daratumumab/MPB group and 329 of 341 patients (96.5%) in the MPB group. A causal relationship with the study drug could not be ruled out for adverse events in 294 of 333 patients (88.3%) in the daratumumab/MPB group and 290 of 341 patients (85.0%) in the MPB group. Adverse events with an incidence of ≥15% in either group are shown in Table 8.

Table 8. Adverse events with an incidence of ≥15% in either group

SOC PT (MedDRA/J ver.20.0)	Number of subjects (%)			
	Daratumumab/MPB n = 333		MPB n = 341	
	All grades	Grades ≥3	All grades	Grades ≥3
All adverse events	321 (96.4)	260 (78.1)	329 (96.5)	264 (77.4)
Blood and lymphatic system disorders				
Neutropenia	165 (49.5)	131 (39.3)	181 (53.1)	132 (38.7)

16) A total of 704 patients have been enrolled by November 15, 2018. Case reports are to be collected from 1,055 patients (patients who started to receive daratumumab before March 31, 2018).

17) Patients who were included in the safety analysis set among 150 whose case reports were finalized by November 15, 2018.

SOC PT (MedDRA/J ver.20.0)	Number of subjects (%)			
	Daratumumab/MPB n = 333		MPB n = 341	
	All grades	Grades ≥3	All grades	Grades ≥3
Thrombocytopenia	160 (48.0)	112 (33.6)	182 (53.4)	128 (37.5)
Anaemia	95 (28.5)	54 (16.2)	130 (38.1)	67 (19.6)
Leukopenia	39 (11.7)	21 (6.3)	51 (15.0)	28 (8.2)
Infections and infestations				
Upper respiratory tract infection	89 (26.7)	7 (2.1)	49 (14.4)	5 (1.5)
Pneumonia	52 (15.6)	39 (11.7)	17 (5.0)	14 (4.1)
General disorders and administration site conditions				
Pyrexia	73 (21.9)	2 (0.6)	65 (19.1)	1 (0.3)
Oedema peripheral	61 (18.3)	3 (0.9)	38 (11.1)	1 (0.3)
Gastrointestinal disorders				
Diarrhoea	76 (22.8)	9 (2.7)	83 (24.3)	11 (3.2)
Nausea	66 (19.8)	3 (0.9)	72 (21.1)	4 (1.2)
Constipation	60 (18.0)	3 (0.9)	62 (18.2)	1 (0.3)
Vomiting	54 (16.2)	5 (1.5)	53 (15.5)	6 (1.8)
Nervous system disorders				
Peripheral sensory neuropathy	95 (28.5)	5 (1.5)	118 (34.6)	14 (4.1)
Respiratory, thoracic and mediastinal disorders				
Cough	51 (15.3)	1 (0.3)	25 (7.3)	1 (0.3)

Serious adverse events occurred in 138 of 333 patients (41.4%) in the daratumumab/MPB group and 113 of 341 patients (33.1%) in the MPB group. The serious adverse events occurring in ≥7 patients were; in the daratumumab/MPB group, pneumonia in 34 patients (10.2%), bronchitis in 8 patients (2.4%), lower respiratory tract infection in 8 patients (2.4%), and upper respiratory tract infection in 7 patients (2.1%); in the MPB group, pneumonia in 11 patients (3.2%), anaemia in 9 patients (2.6%), febrile neutropenia in 7 patients (2.1%), and cardiac failure in 7 patients (2.1%). A causal relationship with the study drug was not ruled out for pneumonia in 10 patients, bronchitis in 3 patients, lower respiratory tract infection in 3 patients, and upper respiratory tract infection 2 patients in the daratumumab/MPB group and febrile neutropenia in 7 patients, pneumonia in 4 patients, anaemia in 4 patients, and cardiac failure in 2 patients in the MPB group.

Adverse events led to the discontinuation of study drug in 17 of 333 patients (5.1%) in the daratumumab/MPB group and 30 of 341 patients (8.8%) in the MPB group. None of the adverse events occurring in ≥ 7 patients in each group led to study drug discontinuation.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

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

The new drug application data were subjected to a document-based compliance 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. The inspection revealed missing information (e.g., batch number) which was supposed to be necessary for traceability that ensure the quality of BTZ administered to some patients in Study 3007 (CTD 5.3.5.1.1-1). For this reason, PMDA's review should be conducted after

any measures taken, e.g., the removal of the affected portions of study data from the application documents submitted.

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

The new drug application data (CTD 5.3.5.1.1-1) 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. The inspection revealed non-conformity with the GCP at the sponsor, which required appropriate measures, e.g., the removal of affected case data from the application documents submitted. Nevertheless, there are no obstacles to conducting its review based on the application documents other than the affected case data to be removed. The inspection also identified the following errors at the sponsor, although they had no significant impact on the overall assessment of the studies. The errors were notified to the sponsor to seek corrective actions.

Non-conformity with the GCP

Sponsor

- Some case reports had missing records such as the batch number of BTZ, which would be necessary for traceability to assure the quality of BTZ administered.

Findings requiring corrective action

Sponsor

- BTZ was not managed or handled as a study drug.
- The study protocol did not provide appropriate briefing on BTZ, even though which was a study drug focused in the clinical study.
- The investigator's brochure of BTZ was not provided to the heads of study sites.
- There was no documented procedure for the management for BTZ as a study drug.
- The annual report on the safety of BTZ was not appropriately provided to the investigators and the heads of study sites.
- Information including unexpected serious adverse reactions to BTZ was not appropriately provided to the investigators and the heads of study sites.

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

Based on the data submitted, PMDA has concluded that daratumumab has efficacy in the treatment of untreated MM and that daratumumab has acceptable safety in view of its benefits. Daratumumab is clinically meaningful because it offers a new treatment option for patients with untreated MM. PMDA considers that the indication and dosing regimen of daratumumab should be further discussed.

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

Review Report (2)

July 12, 2019

Product Submitted for Approval

Brand Name	Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg
Non-proprietary Name	Daratumumab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 14, 2018

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

As a result of its review in Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of treatment with daratumumab/MPB in patients with untreated MM ineligible for ASCT has been demonstrated, given the proven superiority of daratumumab/MPB to MPB alone in centrally-assessed PFS based on the IMWG criteria (the primary endpoint) in the global phase III study in patients with untreated MM ineligible for ASCT (Study 3007).

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

1.2 Safety

As a result of its review in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that the treatment with daratumumab/MPB in patients with untreated MM ineligible for ASCT requires particular attention to adverse events, namely, HBV reactivation, as well as the known events (infusion reaction, bone marrow depression, infections, hemolysis, and TLS) that were identified at the previous review of the application for the approved indication.

Furthermore, PMDA concluded that although attention is required for the above-mentioned adverse events, the treatment with daratumumab/MPB is tolerable when adverse events patients are appropriately monitored

and managed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

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

1.3 Clinical positioning and indication

As a result of its review in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), PMDA concluded that daratumumab should be indicated for the treatment of "multiple myeloma" as proposed by the applicant, with a note in the "Clinical Studies" section of the package insert that the participants in Study 3007 were patients with untreated MM who were ineligible for ASCT, and the following cautionary advice in the "Precautions Concerning Indications" section.

Precautions Concerning Indication

- Physicians should select appropriate patients after thoroughly understanding the details described in the "Clinical Studies" section and fully understanding the efficacy and safety profiles of daratumumab.

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

Based on the above, PMDA instructed the applicant to present the above advice in the "Indication" section and the "Precautions Concerning Indication" section. The applicant agreed.

1.4 Dosage and administration

As a result of its review in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the "Dosage and Administration" section and the "Precautions Concerning Dosage and Administration" section of the package insert should be described as follows:

Dosage and Administration

The usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous infusion according to the following dosing schedule:
In combination with bortezomib, melphalan, and prednisolone,
Weekly (Weeks 1-6), every 3 weeks (Weeks 7-54), and every 4 weeks (Week 55 onwards)
In combination with lenalidomide and dexamethasone (for relapsed or refractory multiple myeloma only),
Weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards)
In combination with bortezomib and dexamethasone (for relapsed or refractory multiple myeloma only),
Weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards)

Precautions Concerning Dosage and Administration

- The efficacy and safety of daratumumab as monotherapy have not been established.
- Physicians should carefully select the treatment interval of daratumumab and the nature and type of anticancer drugs to be used concomitantly with daratumumab after being familiar with information

described in the "Clinical Studies" section of the package insert. Physicians also should thoroughly and carefully read the package inserts of the concomitant drugs.

- The use of medications including corticosteroids, antipyretic analgesics, and antihistamines to reduce the risk of infusion reactions.
- Dilution volume and infusion rate of daratumumab.
- Measures taken in the event of infusion reactions.

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

Based on the above, PMDA instructed the applicant to provide the above advice in the "Dosage and Administration" section and the "Precautions Concerning Dosage and Administration" section. The applicant agreed.

1.5 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA considers that post-marketing surveillance is not necessarily conducted immediately after approval to evaluate the safety of the daratumumab/MPB treatment in patients with untreated MM, and accepts to collect safety information through routine pharmacovigilance activities.

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

In view of the discussion above, PMDA concluded that the risk management plan (draft) for daratumumab should include the safety and efficacy specifications presented in Table 9 and that the applicant should conduct additional pharmacovigilance activities, survey/study on efficacy, and risk minimization activities presented in Table 10.

Table 9. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infusion reactions • Interference with indirect Coombs test • Bone marrow depression • Infections • TLS	• Hemolysis	Not applicable
Efficacy specification		
• Efficacy in clinical settings		

No changes were made in this application for partial change.

Table10. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy Survey and studies	Additional risk minimization activities
• Specified use-results survey in patients with relapsed or refractory MM • Post-marketing clinical studies (Studies 1005 and 3003, and an extension study of Study 3007)	• Specified use-results survey in patients with relapsed or refractory MM • Post-marketing clinical studies (An extension study of Studies 1005 and 3003)	• Preparation and distribution of materials for healthcare professional (prescribing physician and those involved in blood transfusion) • Preparation and distribution of materials for patients

Underlined: Activities planned for the indication added in this application.

2. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the modified indication and dosing regimen shown below, with the following condition. The approval, however, presupposes appropriate cautionary advice given in the package insert, provision of information that promotes proper use of daratumumab in the post-marketing setting, as well as adherence to the proper use of daratumumab ensured under the supervision of physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies at medical institutions that are adequately capable of emergency care. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until September 26, 2027).

Indication (Strikethrough denotes deletions.)

~~Relapsed or refractory m~~Multiple myeloma

Dosage and Administration (Underline denotes additions.)

The usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion according to the following dosing schedule:

In combination with bortezomib, melphalan, and prednisolone,

Weekly (Weeks 1-6), every 3 weeks (Weeks 7-54), and every 4 weeks (Week 55 onwards)

In combination with lenalidomide and dexamethasone (for relapsed or refractory multiple myeloma only),

Weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards)

In combination with bortezomib and dexamethasone (for relapsed or refractory multiple myeloma only),

Weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warning (No change)

Daratumumab should be used only in patients who are considered appropriate to receive daratumumab under the supervision of physicians with adequate knowledge and experience in hematopoietic malignancies at medical institutions with adequate facilities for treatment of emergencies. Prior to the start of daratumumab, the patient or his/her family should be fully informed about the benefits and risks associated with the treatment. Daratumumab therapy should be started only after consent is obtained from the patient or his/her family.

Contraindications (No change)

Patients with a history of hypersensitivity to any of the ingredients of daratumumab.

Precautions Concerning Indications (Underline denotes additions, and strikethrough denotes deletions.)

~~1. Daratumumab should be used in patients with MM who failed to respond to at least one prior standard therapy or who had relapsed MM after the therapy.~~

~~2.~~ Physicians should select appropriate patients after thoroughly understanding the details ~~of the clinical study patients, including previous treatment history,~~ described in the "Clinical Studies" section of the package insert and fully understanding the efficacy and safety profiles of daratumumab.

Precautions Concerning Dosage and Administration (No change)

1. The efficacy and safety of daratumumab as monotherapy have not been established.
2. Physicians should carefully select the treatment interval of daratumumab and the nature and type of anticancer drugs to be used concomitantly with daratumumab after being familiar with information described in the "Clinical Studies" section of the package insert. Physicians also should thoroughly and carefully read the package inserts of the concomitant drugs.
3. Corticosteroids, antipyretic analgesics, and antihistamines should be administered 1 to 3 hours before the infusion of daratumumab to reduce infusion reactions. Corticosteroids or other proper drugs should be administered as needed after the infusion of daratumumab to reduce delayed infusion reactions. For patients with chronic obstructive pulmonary disease or bronchial asthma or patients with a history of chronic obstructive pulmonary disease or bronchial asthma, physicians should consider prescribing post-infusion medications such as bronchodilators and inhaled corticosteroids.
4. Daratumumab should be diluted with normal saline to the total volume of 1,000 mL and should be administered as an intravenous drip infusion at an initial rate of 50 mL/hour. When no infusion reactions occur, the total volume after dilution and infusion rate can be adjusted, as shown below, while the patient's status is monitored. The maximum infusion rate is 200 mL/hour.

Total volume after dilution and infusion rate for daratumumab administration

Timing of infusion	Total volume after dilution	Infusion rate after the start of administration (mL/h)			
		0- 1 h	1-2 h	2-3 h	≥3 h
First infusion	1,000 mL	50	100	150	200
Second infusion	500 mL[*1]				
Third and subsequent infusions	500 mL	100[*2]	150	200	

*1 In the absence of infusion reactions within 3 hours after the start of the first infusion, use dilution volume of 500 mL.
*2 In the absence of infusion reactions during the first and second infusions with the final infusion rate of ≥100 mL/h, the infusion rate can be started at 100 mL/h.

5. In the occurrence of infusion reactions, physicians should take appropriate measures, including interruption and discontinuation, or infusion rate modification of daratumumab, as outlined below. The grades are determined based on the criteria of the NCI-CTCAE v4.0.
   1) Grade 1 to 3: Interrupt daratumumab. Once infusion reaction symptoms resolve, daratumumab can be resumed at no more than half the rate at which the reaction occurred. If the patient does not experience additional infusion reaction, infusion rate can be modified [see the above table "Total volume after dilation and infusion rate for daratumumab administration"]. Daratumumab should be permanently discontinued upon the third occurrence of a Grade 3 infusion reaction.
   2) Grade 4: Permanently discontinue daratumumab.

Appendix

List of Abbreviations

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
Application for partial change	application for approval of partial changes to approved matters
ASCT	autologous stem cell transplantation
BCd	combination of BTZ, cyclophosphamide hydrate, and DEX
Bd	combination of BTZ and DEX
BLd	combination of BTZ and Ld
BTd	combination of BTZ, thalidomide, and DEX
BTZ	bortezomib
CDC	complement dependent cytotoxicity
CI	confidence interval
CR	complete response
daratumumab	daratumumab (genetical recombination)
daratumumab/Bd	combination of daratumumab and Bd
daratumumab/Ld	combination of daratumumab and Ld
daratumumab/MPB	combination of daratumumab and MPB
DEX	dexamethasone
DNA	deoxyribonucleic acid
ECL	electrochemiluminescence
HBV	hepatitis B virus
IDMC	independent data monitoring committee
Ig	immunoglobulin
IMWG	International Myeloma Working Group
IMWG criteria	evaluation criteria developed by the IMWG
ISS	international staging system
ITT	intent-to-treat
Ld	combination of lenalidomide and DEX
lenalidomide	lenalidomide hydrate
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MM	multiple myeloma
MPB	combination of melphalan, prednisolone or prednisone (not approved in Japan), and BTZ
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma
NE	not estimable
OS	overall survival
Pd	combination of pomalidomide and DEX
PFS	progression-free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PT	preferred term
QD	quaque die
QW	quaque 1 week
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
Q4W	quaque 4 weeks
SOC	system organ class

Study 1001	Study 54767414MMY1001
Study 1005	Study 54767414MMY1005
Study 3003	Study 54767414MMY3003
Study 3004	Study 54767414MMY3004
Study 3007	Study 54767414MMY3007
TLS	tumor lysis syndrome
VGPR	very good partial response