Report on the Deliberation Results

November 30, 2018
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Keytruda Injection 20 mg
	Keytruda Injection 100 mg
Non-proprietary Name	Pembrolizumab (genetical recombination) (JAN*)
Applicant	MSD K.K.
Date of Application	March 30, 2018

Results of Deliberation

In its meeting held on November 29, 2018, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the indication of "advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy" is 4 years. The re-examination period for the indication of "malignant melanoma" is the remainder of the ongoing re-examination period for the initial approval (until September 27, 2026).

Conditions of Approval

[Advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)]

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to provide healthcare professionals with the results of 2 ongoing phase II studies in patients with advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy, promptly after the studies are completed.
3. Since only limited data are available as to the efficacy of the product in the treatment of MSI-High solid tumors (except colorectal cancer), the applicant is required to conduct a drug use-results survey after the market launch to collect information on the characteristics of patients treated with the product, to promptly collect data on the efficacy and safety of the product, and to take necessary actions to ensure the proper use of the product.

[Malignant melanoma]

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

**Japanese Accepted Name (modified INN)*

Review Report

November 19, 2018
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	Keytruda Injection 20 mg Keytruda Injection 100 mg
Non-proprietary Name	Pembrolizumab (genetical recombination)
Applicant	MSD K.K.
Date of Application	March 30, 2018, May 10, 2018, and August 9, 2018[1)]
Dosage Form/Strength	Injection: Each 0.8 mL vial contains 20 mg of pembrolizumab (genetical recombination). Injection: Each 4 mL vial contains 100 mg of pembrolizumab (genetical recombination).
Application Classification	Prescription drug, (4) Drug with new indications, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 350 of 2014 [*26 yaku*]; PFSB/ELD Notification No. 0917-6 dated September 17, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) Drug for the conditional early approval system (PSEHB/PED Notification No. 0622-2 dated June 22, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) Priority review (PSEHB/PED Notification No. 0703-3 dated July 3, 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 for the following indications, and that the product has acceptable safety in view of its benefits (see Attachment). PMDA has also

1) Partial change approval applications for (a) a new indication for the treatment of MSI-High solid tumors and a modified dosage and administration for the treatment of unresectable malignant melanoma, (b) a new indication and a new dosage and administration for the adjuvant treatment of malignant melanoma, and (c) a modified indication for the treatment of NSCLC were filed on (a) March 30, 2018, (b) May 10, 2018, and (c) August 9, 2018, respectively.

concluded that the change in the dose of pembrolizumab (genetical recombination) from a body weight-based dose to a fixed-based dose for the treatment of unresectable malignant melanoma is acceptable.

- Pembrolizumab (genetical recombination) monotherapy for the adjuvant treatment of malignant melanoma
- Pembrolizumab (genetical recombination) in combination with platinum-based chemotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent non-small cell lung cancer
- Pembrolizumab (genetical recombination) monotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (Tumor Proportion Score [TPS][2)] ≥1%) non-small cell lung cancer
- Pembrolizumab (genetical recombination) monotherapy for the treatment of chemotherapy-treated patients with advanced or recurrent microsatellite instability-high (MSI-High) solid tumors, who have no other standard treatment options

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. The efficacy and safety of the product in the treatment of MSI-High solid tumors (except colorectal cancer) should be further investigated through post-marketing surveillance.

Indications

~~Unresectable~~ Malignant melanoma
Unresectable, advanced or recurrent ~~PD-L1 positive~~ non-small cell lung cancer
Relapsed or refractory classical Hodgkin lymphoma
Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy
Advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)

(Underline denotes additions. Strikethrough denotes deletions.)

Dosage and Administration

[~~Unresectable~~ Malignant melanoma]
The usual adult dosage is 200 mg ~~2 mg/kg body weight~~ of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks. For the adjuvant treatment of malignant melanoma, the maximum duration of treatment is 12 months.

[Unresectable, advanced or recurrent ~~PD-L1 positive~~ non-small cell lung cancer; relapsed or refractory classical Hodgkin lymphoma; radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy; or advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)]

2) Percentage of cells expressing PD-L1 in the tumor tissue

The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks.

(Underlines denote additions. Strikethrough denotes deletions.)

Conditions of Approval

[Malignant melanoma, or unresectable, advanced or recurrent non-small cell lung cancer]
The applicant is required to develop and appropriately implement a risk management plan.

[Advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)]

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to provide healthcare professionals with the results of 2 ongoing phase II studies in patients with advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy, promptly after the studies are completed.
3. Since only limited data are available as to the efficacy of the product in the treatment of MSI-High solid tumors (except colorectal cancer), the applicant is required to conduct a drug use-results survey after the market launch to collect information on the characteristics of patients treated with the product, to promptly collect data on the efficacy and safety of the product, and to take necessary actions to ensure the proper use of the product.

Attachment

Review Report (1)

October 12, 2018

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	Keytruda Injection 20 mg Keytruda Injection 100 mg
Non-proprietary Name	Pembrolizumab (genetical recombination)
Applicant	MSD K.K.
Date of Application	March 30, 2018, May 10, 2018, and August 9, 2018[1)]
Dosage Form/Strength	Injection: Each 0.8 mL vial contains 20 mg of pembrolizumab (genetical recombination). Injection: Each 4 mL vial contains 100 mg of pembrolizumab (genetical recombination).
Proposed Indications	~~Unresectable~~ Malignant melanoma Unresectable, advanced or recurrent ~~PD-L1 positive~~ non-small cell lung cancer Relapsed or refractory classical Hodgkin lymphoma Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy Locally advanced or metastatic microsatellite instability-high (MSI-High) cancers (Underline denotes additions. Strikethrough denotes deletions.)

Proposed Dosage and Administration

~~[Unresectable malignant melanoma]~~

~~The usual adult dosage is 2 mg/kg body weight of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks.~~

~~[Unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer; relapsed or refractory classical Hodgkin lymphoma; or radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy]~~

The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks.

(Strikethrough denotes deletions.)

1) Partial change applications for (a) a new indication for the treatment of MSI-High solid tumors and a modified dosage and administration for the treatment of unresectable malignant melanoma, (b) a new indication and a dosage and administration for the adjuvant treatment of malignant melanoma, and (c) a modified indication for the treatment of NSCLC were filed on (a) March 30, 2018, (b) May 10, 2018, and (c) August 9, 2018, respectively.

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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

CD279 (programmed cell death-1 [PD-1]) is a receptor belonging to the CD28 superfamily (a group of molecules that provide costimulatory signals involved in the control of T-cell activation) and is expressed on activated lymphocytes (including T cells, B cells, and natural killer T cells). PD-1 *in vivo* is thought to bind to PD-Ls (CD274 [PD-L1] and CD273 [PD-L2]) expressed on antigen-presenting cells to suppress the immune response (*Immunol Rev.* 2010;236:219-42). PD-L1 and PD-L2 are expressed on a wide range of tumor tissues (*Nat Rev Immunol.* 2008;8:467-77), suggesting that the PD-1/PD-L pathway is one of the mechanisms used by tumor cells to avoid attacks by antigen-specific T cells.

Pembrolizumab (genetical recombination) (hereinafter referred to as "pembrolizumab"), a humanized immunoglobulin (Ig) G4 monoclonal antibody against human PD-1, was discovered by the UK Medical Research Council. Pembrolizumab binds to the extracellular domain of PD-1 (PD ligand binding site) and blocks PD-1 binding to its ligands, PD-L1 and PD-L2. Pembrolizumab thereby enhances the activation of cancer antigen-specific T cells and cytotoxic activation against cancer cells, resulting in the suppression of tumor growth.

In Japan, pembrolizumab was approved for the treatment of "unresectable malignant melanoma" in September 2016, for the treatment of "unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer" in December 2016, for the treatment of "relapsed or refractory classical Hodgkin's lymphoma" in November 2017, and for the treatment of "radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy" in December 2017.

Recently, the applicant almost simultaneously submitted the following partial change approval applications (a) to (c) on different days in a short period. This review report summarizes the reviews of these applications. In this report, "MSI-High patients" are expressed as (a) "MSI-High (polymerase chain reaction [PCR]) patients," when the term refers to patients in whom a failure of the DNA mismatch repair system was detected by PCR (narrow term), or (b) "MSI-High patients," without specifying the assay method, when the term refers to patients in whom a deficiency of DNA mismatch repair (MMR) was detected by either IHC or PCR (broad term) [see Section 7.3.R.2.1 and other relevant sections].

(a) March 30, 2018
   (i) A new indication for the treatment of microsatellite instability-high (MSI-High) solid tumors
   (ii) A modified dosage and administration for the treatment of "unresectable malignant melanoma"

(b) May 10, 2018
   A new indication and a new dosage and administration for the adjuvant treatment of malignant melanoma

(c) August 9, 2018
   A modified indication for the treatment of "unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer"

1.2 Development history, the approval status in foreign countries, and other information

1.2.1 Malignant melanoma: (a) (ii) and (b) in Section 1.1. See Section 7.1 for outline of the review conducted by PMDA.

Pembrolizumab has been approved as a body weight-based dose (2 mg/kg every 3 weeks) therapy for "unresectable malignant melanoma," and as a fixed dose (200 mg every 3 weeks) therapy for the other approved indications. The applicant has filed a partial approval application to change the dosage and administration for the treatment of "unresectable malignant melanoma" from the approved body weight-based dose (2 mg/kg every 3 weeks) to a fixed dose (200 mg every 3 weeks), primarily based on the results of a PPK analysis.

Furthermore, the applicant started a global phase III study of pembrolizumab monotherapy in patients with resected malignant melanoma (Study 054) in [redacted] 20[redacted]. In Japan, patient enrollment in the study was started in [redacted] 20[redacted]. The applicant has filed a partial approval application for a new indication of the adjuvant treatment for malignant melanoma, based on the pivotal data from Study 054.

Pembrolizumab was designated as an orphan drug in September 2014 with the intended indication of "malignant melanoma" (Drug Designation No. 350 of 2014 [*26 yaku*]).

As of August 2018, the approval status of pembrolizumab outside Japan is as follows:

- Approval applications for the fixed-dose (200 mg every 3 weeks) treatment of unresectable malignant melanoma were filed primarily based on the results of a PPK analysis in the US in August 2016 and in the EU in April 2018, and approval was granted in May 2017 and August 2018, respectively. Pembrolizumab has been approved for the fixed-dose treatment of unresectable malignant melanoma in 56 countries and regions.
- Approval applications for the adjuvant treatment of malignant melanoma were filed in the US and EU in April 2018, based on the pivotal data from Study 054. The applications are currently under review. Pembrolizumab has not been approved for the adjuvant treatment of malignant melanoma in any country or region.

1.2.2 NSCLC: (c) in Section 1.1. See Section 7.2 for outline of the review conducted by PMDA.

Pembrolizumab has been approved for the treatment of "unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer," and has also been approved as a monotherapy for chemotherapy-naïve patients with PD-L1 positive (TPS ≥50%) NSCLC.

The applicant started the following 3 global phase III studies in patients with chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC in (a) February 2016, (b) August 2016, and (c) [redacted] 20[redacted], respectively, and in Japan, patient enrollment was started in (a) [redacted] 20[redacted], (b) [redacted] 20[redacted], and (c) [redacted] 20[redacted], respectively.

(a) A clinical study of pembrolizumab in combination with platinum-based chemotherapy in patients with nonsquamous NSCLC (NSQ-NSCLC) (Study 189)

(b) A clinical study of pembrolizumab in combination with platinum-based chemotherapy in patients with squamous NSCLC (SQ-NSCLC) (Study 407)
(c) A clinical study of pembrolizumab monotherapy in patients with PD-L1 positive (TPS ≥1%) NSCLC (Study 042)

The applicant has filed a partial application for the following modified indications for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC, based on the pivotal data from Studies 189, 407, and 042.

- Pembrolizumab in combination with platinum-based chemotherapy for the treatment of patients with NSCLC (i.e., the combined target patient populations of Studies 189 [NSQ-NSCLC] and 407 [SQ-NSCLC], regardless of PD-L1 expression status)
- Pembrolizumab monotherapy in patients with PD-L1 positive (TPS ≥1%) NSCLC

As of August 2018, the approval status of pembrolizumab outside Japan for the target patient populations of Study 189, 407, or 042 is as follows:

- Pembrolizumab in combination with other antineoplastic drugs for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC:
  Based on the pivotal data from Cohort G[2)] of Study 021, an approval application was filed in the US in November 2016, and pembrolizumab received accelerated approval for the following indication in May 2017: "KEYTRUDA, in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials."
  Approval applications were filed based on the pivotal data from Study 189 in the US and EU in March 2018, and pembrolizumab was approved for the following indication in the US in August 2018. The application is currently under review in the EU. Pembrolizumab, in combination with other antineoplastic drugs, has been approved for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC in 28 countries and regions.
  - KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- Pembrolizumab in combination with platinum-based chemotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC:
  Approval applications were filed based on the pivotal data from Study 407 in the US in April 2018, and in the EU in July 2018. The applications are currently under review. Pembrolizumab has not been approved for the treatment in any country or region.
- Pembrolizumab monotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC:

2) An open-label, randomized, comparative study to compare the efficacy and safety of pembrolizumab + CBDCA + PEM with those of CBDCA + PEM alone, in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC

Approval applications were filed based on the pivotal data from Study 042 in the US and EU in July 2018, and the applications are currently under review. Pembrolizumab has not been approved for the treatment of in any country or region.

1.2.3 MSI-High solid tumors: (a) (i) in Section 1.1. See Section 7.3 for outline of the review conducted by PMDA.

The applicant started a global phase II study of pembrolizumab monotherapy in patient with chemotherapy-treated patients with radically unresectable, advanced or recurrent mismatch repair deficient (dMMR) or MSI-High (PCR) colorectal cancer (Study 164) in [redacted] 20[redacted], and a global phase II study of pembrolizumab monotherapy in chemotherapy-treated patients with radically unresectable, advanced or recurrent solid tumors (Study 158) in [redacted] 20[redacted]. In Japan, patient enrollment in these studies was started in [redacted] 20[redacted] and [redacted] 20[redacted], respectively. The applicant has filed a partial change application for a new indication for the treatment of MSI-High solid tumors, based on the pivotal data from Studies 164 and 158.

Pembrolizumab was selected for review under the conditional early approval system for new drugs (PSEHB/PED Notification No. 0622-2 dated June 22, 2018).

As of August 2018, the approval status of pembrolizumab outside Japan is as follows:

- An approval application was filed based on the pivotal data from Studies 164 and 158 in the US in September 2016, and pembrolizumab received accelerated approval for the following indication in May 2017. Pembrolizumab has been approved for the treatment of MSI-High solid tumors in 14 countries and regions.
  - KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

Since the present application is for a new indication and a new dosage, no data relating to the quality of pembrolizumab were submitted.

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

Although the present application is for a new indication and a new dosage, no new study data on non-clinical pharmacology were submitted because the non-clinical pharmacology of pembrolizumab was evaluated during the review process for the initial approval.

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

Although the present application is for a new indication and a new dosage, no new study data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of pembrolizumab was evaluated during the review process for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is for a new indication and a new dosage, no data relating to the toxicity of pembrolizumab 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 procedures

In Studies 164 and 158, (a) dMMR and (b) MSI-High (PCR) were assessed using (a) an immunohistochemistry (IHC) assay and (b) a PCR assay, respectively. A PCR assay developed by FALCO Biosystems, the "MSI test kit (FALCO)" was approved on September 10, 2018 as an *in vitro* diagnostic to assist assessment of patient eligibility for pembrolizumab therapy.

6.2 Clinical pharmacology

6.2.1 Population pharmacokinetics (PPK) analyses

A PPK analysis was performed using a nonlinear mixed effects model, based on the pharmacokinetic data (21,457 time points in 3881 patients) from Japanese clinical studies (Studies 011, 025, and 041), foreign clinical studies (Studies 001, 002, 006, 037, 052, and 055), and global clinical studies (Studies 010, 024, 045, and 164) (NONMEM version 7.2.0). The results of the PPK analysis are described below.

- The $AUC_{ss,\ 6wk}$ (median [10 percentage point, 90 percentage point]) of pembrolizumab administered at 200 mg every 3 weeks (2.16 [1.45, 3.04] mg·day/mL) was similar to that at 2 mg/kg every 3 weeks (1.32 [0.722, 2.06] mg·day/mL), and lower than that at 10 mg/kg every 3 weeks (7.49 [4.32, 11.3] mg·day/mL).
- There were no clear differences in the $AUC_{ss,\ 6wk}$ (median [10 percentage point, 90 percentage point]) of pembrolizumab administered at 200 mg every 3 weeks between Japanese patients (2.15 [1.62, 3.75] mg·day/mL) and non-Japanese patients (1.79 [1.15, 2.67] mg·day/mL).

6.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA has concluded that the applicant's explanation about the clinical pharmacology and other relevant properties of pembrolizumab are acceptable.

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

7.1 Data on malignant melanoma and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of result data from a global phase III study (Table 1).

Table 1. Clinical studies on the efficacy and safety

Data type	Region	Study identifier	Phase	Subjects	No. of patients enrolled	Dosage regimen	Key endpoints
Evaluation data	Global	Study 054	III	Patients with resected malignant melanoma at high risk for recurrence	1019 (a) 514 (b) 505	(a) Intravenous pembrolizumab 200 mg every 3 weeks (b) Intravenous placebo every 3 weeks	Efficacy Safety

A summary of the clinical study is presented below. Common adverse events other than deaths reported in the study are detailed in Section "7.4.1 Adverse events reported in clinical studies in patients with malignant melanoma."

7.1.1 Evaluation data

7.1.1.1 Global clinical study

7.1.1.1.1 Global phase III study (CTD 5.3.5.1.1, Study 054, ongoing since [redacted] 20[redacted] [data cutoff date: October 2, 2017])

A double-blind, randomized, comparative study was conducted at 134 sites in 23 countries, including Japan, to evaluate the efficacy and safety of pembrolizumab versus placebo in patients with resected malignant melanoma[4] at high risk for recurrence[3] (target sample size, 900 patients).

Patients received pembrolizumab 200 mg or placebo intravenously, every 3 weeks, for a maximum of 12 months, or until the disease recurred or a withdrawal criterion was met.

All 1019 enrolled and randomized patients (514 in the pembrolizumab group and 505 in the placebo group, including 9 and 6 Japanese patients, respectively) were included in the intention-to-treat (ITT) population and used for the efficacy analyses. Of these 1019 patients, 8 (5 in the pembrolizumab group and 3 in the placebo group) did not receive the study drug. The remaining 1011 patients (509 in the pembrolizumab group and 502 in the placebo group, including 9 and 6 Japanese patients, respectively) were included in the safety analysis set.

The primary endpoint was recurrence-free survival (RFS)[5] as assessed by the investigator. At the start of the study, the primary analysis was planned to be conducted in the overall study population and the PD-L1 positive (melanoma [MEL] score ≥2) subpopulation when a total of 409 RFS events had occurred; however, [redacted] with respect to [redacted] in [redacted],[6] and it was considered that [redacted] based on [redacted], the study protocol was amended to perform an interim analysis on the overall study population to assess the superiority of pembrolizumab to placebo when a total of 330 RFS

4) Patients whose tumors were completely resected
3) Patients with (a) stage IIIA (>1 mm lymph node metastasis), (b) stage IIIB, or (c) stage IIIC melanoma were defined as being at a high risk for recurrence.
5) RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first.
6) [redacted]

events have occurred, and the final analysis when a total of 409 RFS events have occurred. In addition, if the primary RFS analysis showed a statistically significant result, each secondary endpoint was to be analyzed sequentially, starting with distant metastasis-free survival (DMFS), followed by overall survival (OS) (Protocol Amendment Version 2, dated October 2, 2017). To identify PD-L1 positive (MEL score ≥2) patients, PD-L1 levels in tumor tissue samples were determined using the "PD-L1 IHC 22C3 pharmDx 'Dako'," by Dako Japan Co., Ltd.

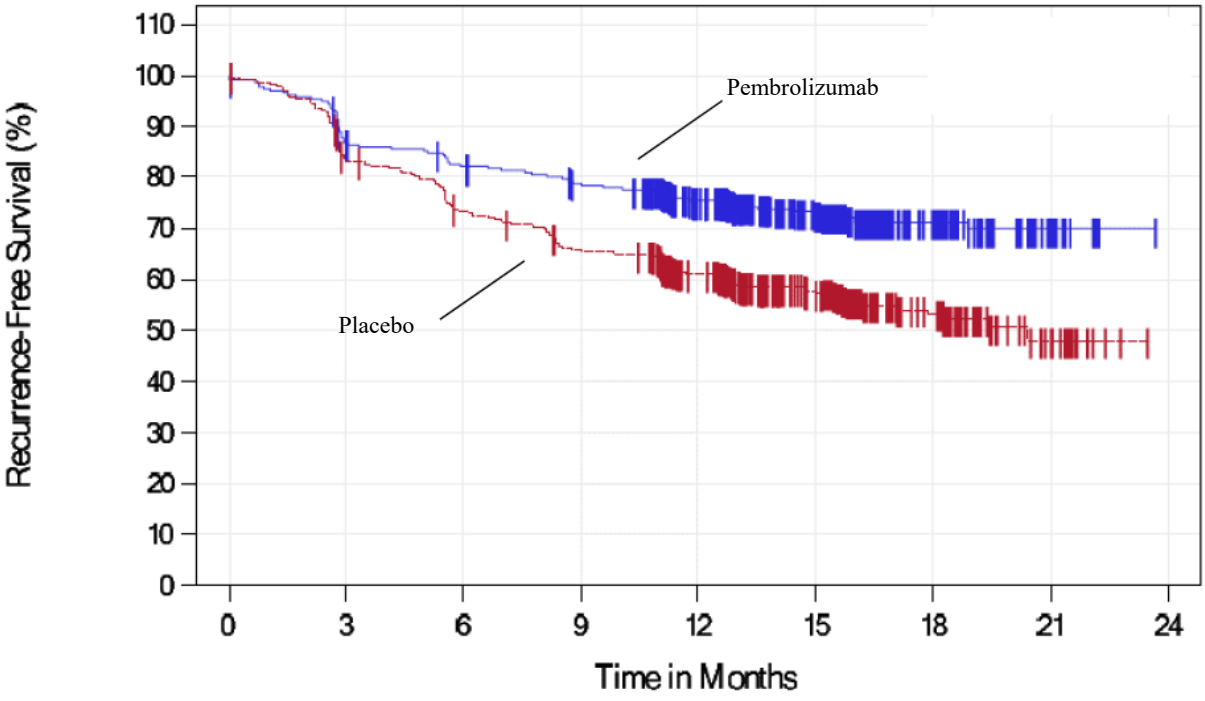
In the analysis of the overall study population, a one-sided significance level of 0.014 was used. In the analysis of the PD-L1 positive (MEL score ≥2) subpopulation, the one-sided significance level was determined by the method proposed by Spiessens and Debois (*Contemp Clin Trials* 2010;31:647-56). If a statistically significance was found in either the overall study population or the PD-L1 positive subpopulation, another population was analyzed at a one-sided significance level of 0.025. A Lan-DeMets α spending function of the O'Brien-Fleming type was used to control the probability of a type I error associated with the interim analysis.

The interim analysis (data cutoff date: October 2, 2017) was performed when a total of 351 RFS events had occurred. The results of the interim RFS analysis in the primary analysis sets (the overall study population and the PD-L1 positive [MEL score ≥2] subpopulation) (Table 2) and their Kaplan-Meier curves of RFS (Figures 1 and 2) are shown below.

Table 2. Interim RFS analysis (Investigator assessment [data cutoff date: October 2, 2017])

	Overall		PD-L1 positive (MEL score ≥2)	
	Pembrolizumab	Placebo	Pembrolizumab	Placebo
N	514	505	428	425
Number of events (%)	135 (26.3)	216 (42.8)	102 (23.8)	176 (41.4)
Median [95% CI] (months)	— [—, —]	20.4 [16.2, —]	—[—, —]	— [17.1, —]
Hazard ratio [CI]*1	0.57 [0.43, 0.74]*2		0.54 [0.42, 0.69]*3	
P value (one-sided)*4	<0.0001*5		<0.0001*6	

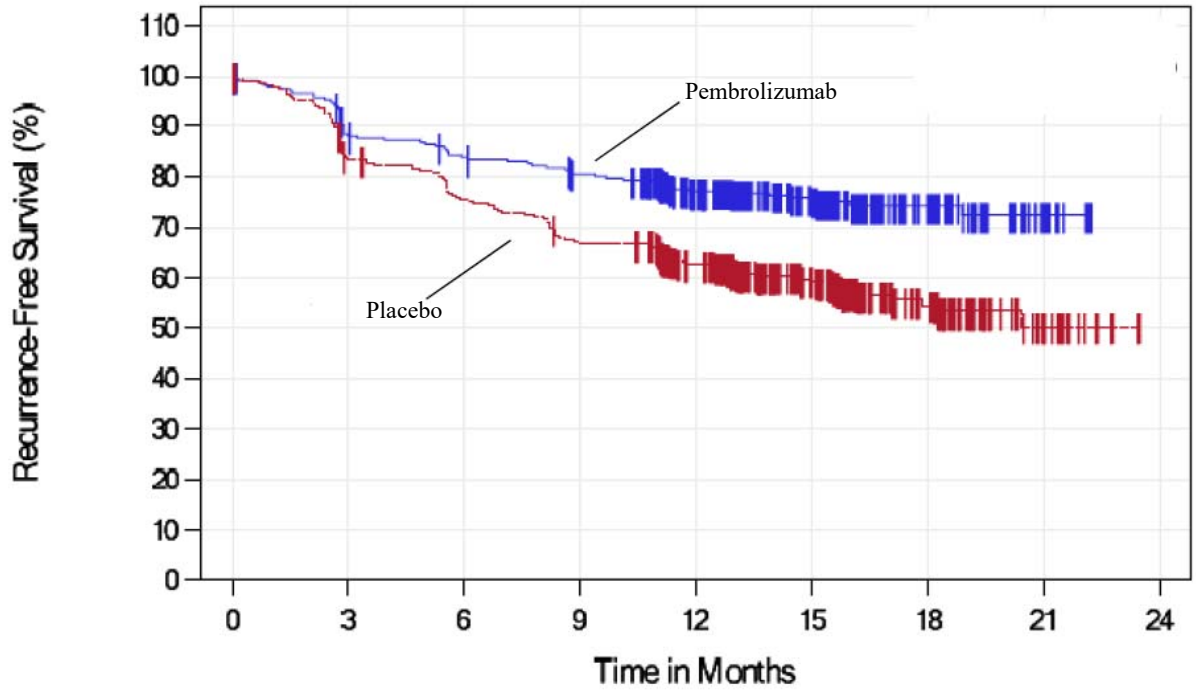
—, Not reached; *1, Cox regression stratified by disease stage (IIIA, IIIB, IIIC [1 to 3 lymph node metastases present], or IIIC [4 or more lymph node metastases present]); *2, 98.4% CI; *3, 95% CI; *4, Log-rank test stratified by disease stage (IIIA, IIIB, IIIC [1 to 3 lymph node metastases present], or IIIC [4 or more lymph node metastases present]); *5, One-sided significance level = 0.008; *6, One-sided significance level = 0.0155



n at risk

Pembrolizumab	514	438	413	392	313	182	73	15	0
Placebo	505	415	363	323	264	157	60	15	0

Figure 1. Kaplan Meier curves for the interim RFS analysis
(Investigator assessment, overall study population [data cutoff date: October 2, 2017])



n at risk

Pembrolizumab	428	370	350	333	266	156	61	13	0
Placebo	425	353	317	281	233	141	55	13	0

Figure 2. Kaplan Meier curves for the interim RFS analysis
(Investigator assessment, PD-L1 positive subpopulation [MEL score ≥2] [data cutoff date: October 2, 2017])

The safety analysis indicated that 1 of 509 patients (0.2%) died in the pembrolizumab group during the treatment period or within 90 days after the last dose. No Japanese patients died. The cause of death was a drug reaction with eosinophilia and systemic symptoms, for which a causal relationship to the study drug was denied.

7.1.R Outline of the review conducted by PMDA on malignant melanoma

7.1.R.1 Efficacy

PMDA evaluated the efficacy of pembrolizumab in Japanese patients, in terms of the consistency between the overall study population and the Japanese subpopulation of Study 054, according to "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated September 5, 2012).

Based on the discussion presented below, PMDA concluded that the efficacy of pembrolizumab was demonstrated in patients with resected malignant melanoma at high risk for recurrence.

7.1.R.1.1 Selection of control group

When Study 054 was planned, the National Comprehensive Cancer Network Clinical Practice Guidelines (NCCN guidelines) (malignant melanoma) (v.3.2015) recommended no standard treatment regimen for the target patient population of the study; therefore, placebo was selected as a control.

PMDA accepted the applicant's explanation.

7.1.R.1.2 Efficacy endpoints

The applicant's rationale for the selection of RFS as the primary endpoint in Study 054:
In Study 054, an RFS event was defined as either: (a) a local recurrence, a regional lymph node metastasis, or a distant metastasis; or, (b) death. The prolongation of RFS, which includes (a) and (b) as defined above, is clinically meaningful in patients with malignant melanoma who have undergone resection, because delayed recurrence would lead to the long-term maintenance of patient physical functions and quality of life. Therefore, the selection of RFS as the primary endpoint in Study 054 is appropriate.

PMDA's view:
The primary endpoint in Study 054 should have been OS, because treatment for patients with resected malignant melanoma is usually intended to prolong their survival. However, the applicant's explanation that prolonged RFS is clinically meaningful in such patients is understandable. In view of the applicant's explanation, and for other reasons, PMDA has concluded that evaluating the efficacy of pembrolizumab based on RFS data is acceptable.

7.1.R.1.3 Efficacy evaluation results

The primary analysis in Study 054 demonstrated the superiority of pembrolizumab to placebo in investigator-assessed RFS (the primary endpoint) [see Section 7.2.1.1.1]. The superiority of pembrolizumab to placebo was

also demonstrated in the PD-L1 positive (MEL score ≥2) subpopulation [see Section 7.1.1.1.1]. Table 3 compares the results of investigator-assessed RFS between the PD-L1 positive (MEL score ≥2) and negative (MEL score ≤1) subpopulations, and Figure 3 shows the Kaplan-Meier curves of RFS in the PD-L1 negative (MEL score ≤1) subpopulation.

Table 3. Efficacy by MEL score in tumor tissue samples (Study 054)

PD-L1 expression	Treatment	N	RFS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P* value for interaction
MEL score ≤1	Pembrolizumab	59	— [15.8, —]	0.47 [0.26, 0.85]	0.1028
	Placebo	57	19.4 [5.7, —]		
MEL score ≥2	Pembrolizumab	428	— [—, —]	0.54 [0.42, 0.69]	
	Placebo	425	— [17.1, —]		

—, Not reached; *, Cox regression stratified by disease stage (IIIA, IIIB, IIIC [1 to 3 lymph node metastases present], or IIIC [4 or more lymph node metastases present])

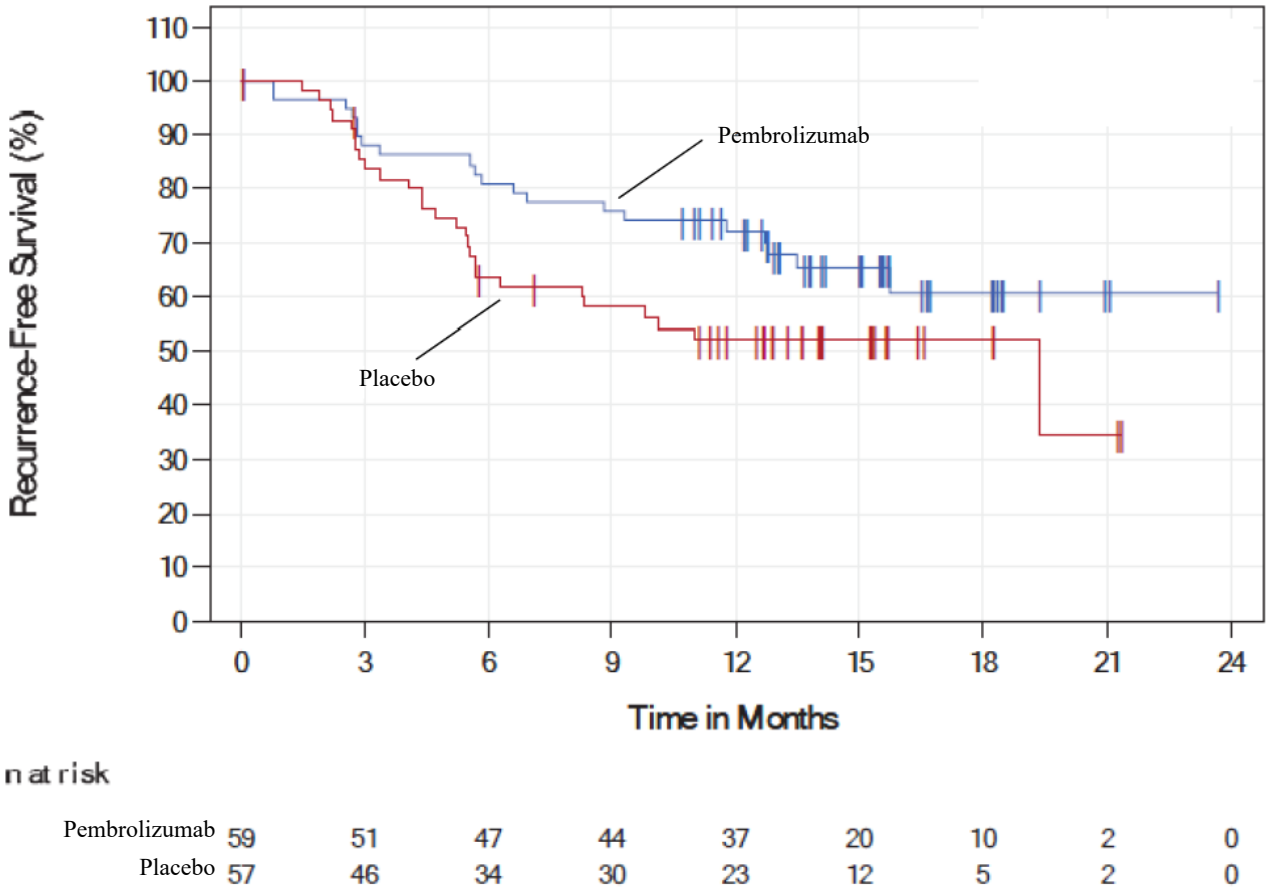


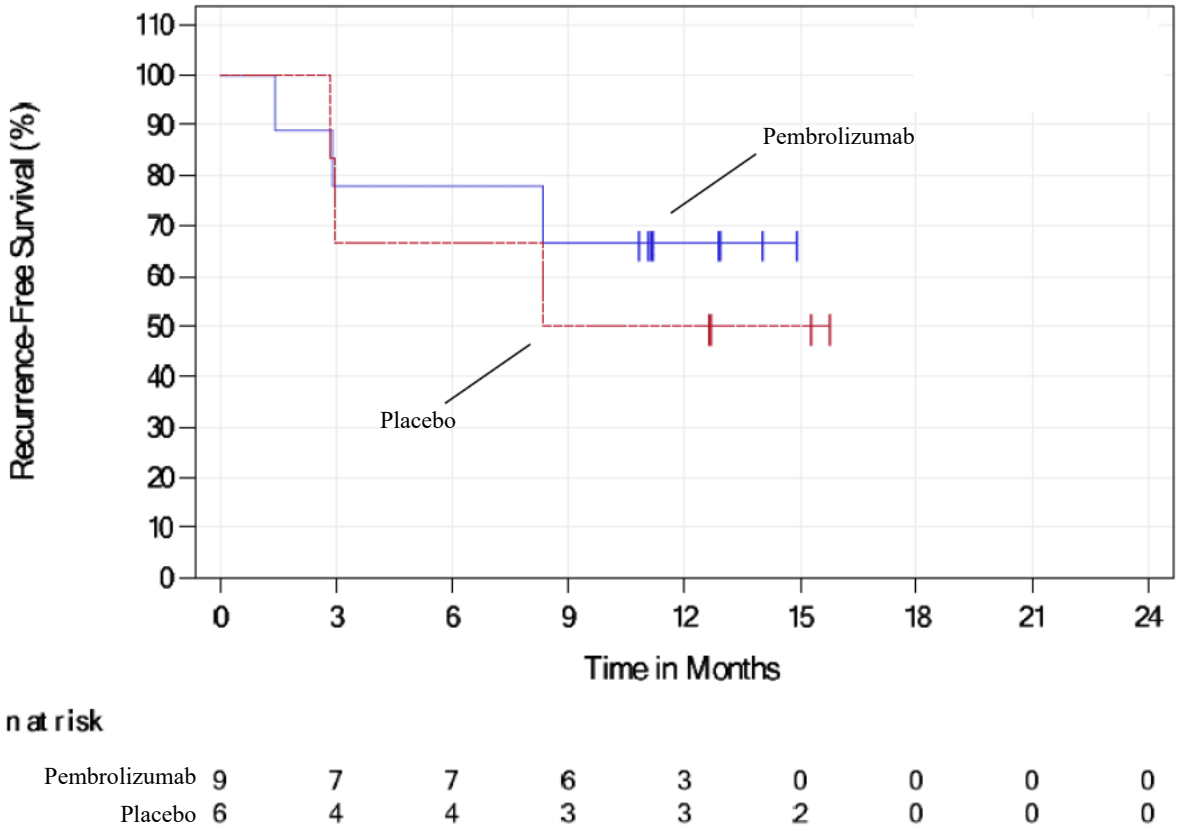
Figure 3. Kaplan-Meier curves for the interim RFS analysis in the PD-L1 negative (MEL score ≤1) subpopulation (data cutoff date: October 2, 2017)

Table 4 shows the results of the interim RFS analysis in Japanese patients in the primary analysis sets (the overall study population and the PD-L1 positive [MEL score ≥2] subpopulation) of Study 054, and Figures 4 and 5 show the corresponding Kaplan-Meier curves for RFS.

Table 4. Interim RFS analysis in Japanese patients
(Investigator assessment, primary analysis sets [data cutoff date: October 2, 2017])

	Overall		PD-L1 positive (MEL score ≥2)	
	Pembrolizumab	Placebo	Pembrolizumab	Placebo
N	9	6	9	3
Number of events (%)	3 (33.3)	3 (50.0)	3 (33.3)	2 (66.7)
Median [95% CI] (months)	— [1.4, —]	— [2.8,—]	— [1.4,—]	8.3 [2.8,—]
Hazard ratio [CI][*1]	0.64 [0.09, 4.59][*2]		0.44 [0.07, 2.63][*3]	
P value (one-sided)[*4]	0.29218		0.18294	

—, Not reached; *1, Non-stratified Cox regression; *2, 98.4% CI; *3, 95% CI; *4, Non-stratified log-rank test



n at risk

Pembrolizumab	9	7	7	6	3	0	0	0	0
Placebo	6	4	4	3	3	2	0	0	0

Figure 4. Kaplan-Meier curves for the interim RFS analysis in Japanese patients
(Investigator assessment, overall study population [data cutoff date: October 2, 2017])

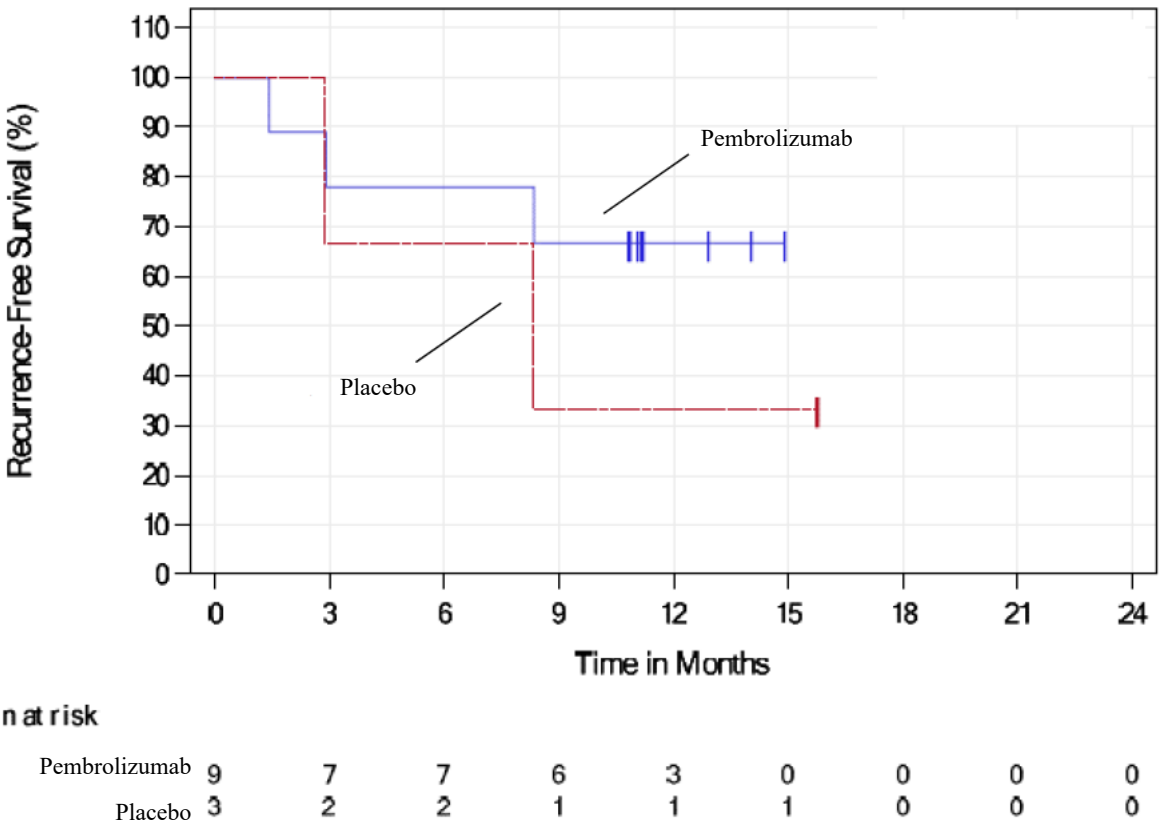


Figure 5. Kaplan-Meier curves for the interim RFS analysis in Japanese patients (Investigator assessment, PD-L1 positive (MEL score ≥2) subpopulation [data cutoff date: October 2, 2017])

PMDA's view:

Considering that pembrolizumab was demonstrated to prolong OS in an open-label, randomized, foreign phase III study in patients with unresectable malignant melanoma (Study 006) (see "Review Report for Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016"), PMDA has concluded that the efficacy of pembrolizumab has been demonstrated in patients with resected malignant melanoma at high risk for recurrence, in view of the following findings.

- In Study 054, pembrolizumab was superior to placebo in investigator-assessed RFS (the primary endpoint), and the observed RFS prolongation was clinically meaningful.
- Although the sample size of the Japanese subpopulation in Study 054 and the number of events occurring in the subpopulation were limited and not sufficient to appropriately evaluate the efficacy of pembrolizumab in Japanese patients, based on the results from the Japanese subpopulation, the RFS in the Japanese subpopulation did not tend to clearly differ from that in the overall study population.

7.1.R.2 Safety [For adverse events, see "7.4.1 Adverse events, etc. reported in clinical studies in patients with malignant melanoma."]

PMDA's view:

As a result of its review described in the section below, PMDA concluded that the adverse events that require special attention after the administration of pembrolizumab to patients with resected malignant melanoma are

those identified as requiring attention at the regulatory reviews for the approved indications[7)] and should also be closely monitored when administrating pembrolizumab.

PMDA's conclusion:
Although attention should be paid to the above events, pembrolizumab was concluded to be tolerable in patients with resected malignant melanoma, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis and patient management in anticipation of adverse reactions due to an excessive immune response, drug interruption, or other appropriate actions.

7.1.R.2.1 Differences in the safety profile between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of pembrolizumab in patients with resected malignant melanoma, based on the safety data from Study 054:

Table 5 shows a summary of the safety data from Study 054.

Table 5. Safety summary (Study 054)

	n (%)	
	Pembrolizumab N = 509	Placebo N = 502
All adverse events	475 (93.3)	453 (90.2)
Grade ≥3 adverse events	158 (31.0)	96 (19.1)
Serious adverse events	128 (25.1)	82 (16.3)
Adverse events leading to death	1 (0.2)	0
Adverse events leading to drug discontinuation	70 (13.8)	18 (3.6)
Adverse events leading to drug interruption	96 (18.9)	46 (9.2)

In Study 054, adverse events of any grade reported with a ≥5% higher incidence in the pembrolizumab group than in the placebo group were pruritus (19.4% [99 of 509 patients] in the pembrolizumab group, 11.6% [58 of 502 patients] in the placebo group), hypothyroidism (14.7% [75 of 509 patients], 2.8% [14 of 502 patients]), and hyperthyroidism (10.4% [53 of 509 patients], 1.2% [6 of 502 patients]). No Grade ≥3 adverse events, serious adverse events, adverse events leading to death, adverse events leading to drug discontinuation, or adverse events leading to drug interruption were reported with a ≥2% higher incidence in the pembrolizumab group than in the placebo group.

The incidences of adverse events of any grade by PD-L1 expression status in the pembrolizumab group were 89.8% in PD-L1 negative (MEL score ≤1) patients and 94.1% in PD-L1 positive (MEL score ≥2) patients, those of Grade ≥3 adverse events were 32.2% and 30.7%, and those of serious adverse events were 18.6% and

7) Gastrointestinal disorders, skin disorders, neurological disorders, hepatic function disorder, cholangitis sclerosing, eye disorders, endocrine disorders, renal impairment, interstitial lung disease (ILD), infusion-related reaction (IRR), pancreatitis, myositis, rhabdomyolysis, encephalitis and meningitis, myasthenia gravis, myocarditis, immune thrombocytopenic purpura, haemolytic anaemia, and aplasia pure red cell (see “Review Report for “Keytruda Injection 20 mg, Keytruda Injection 100 mg dated November 15, 2016”).

27.0%. These results suggested that pembrolizumab was tolerable, regardless of PD-L1 expression status, in patients with resected malignant melanoma.

The applicant's explanation about the differences in the safety profile of pembrolizumab between patients with resected malignant melanoma and those treated for the approved applications:

Table 6 shows a comparison of the incidences of adverse events in clinical studies (a) to (i) below.

(a) A global phase III study in resected malignant melanoma (Study 054)
(b) A foreign phase II study (Study 002) and a foreign phase III study (Study 006) in patients with unresectable malignant melanoma
(c) A global phase II/III study in platinum-based chemotherapy-treated patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC (Study 010), and a global phase III study in chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC (Study 024)
(d) A global phase III study in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC (Study 189)
(e) A global phase III study in chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC (Study 407)
(f) A global phase III study in chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC (Study 042)
(g) A global phase II study in MSI-High colorectal cancer (Study 164 [Cohort A])
(h) A global phase II study in patients with cHL (Study 087)
(i) A global phase III study in patients with radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy (Study 045)

Table 6. Safety summary by cancer type[*1]

	n (%)								
	(a) N = 509	(b) N = 912	(c) N = 836	(d) N = 405	(e) N = 278	(f) N = 636	(g) N = 61	(h) N = 210	(i) N = 266
All adverse events	475 (93.3)	891 (97.7)	809 (96.8)	404 (99.8)	273 (98.2)	610 (95.9)	60 (98.4)	202 (96.2)	248 (93.2)
Grade ≥3 adverse events	158 (31.0)	425 (46.6)	396 (47.4)	272 (67.2)	194 (69.8)	318 (50.0)	36 (59.0)	53 (25.2)	139 (52.3)
Adverse events leading to death	1 (0.2)	39 (4.3)	52 (6.2)	27 (6.7)	23 (8.3)	70 (11.0)	1 (1.6)	2 (1.0)	13 (4.9)
Serious adverse events	128 (25.1)	341 (37.4)	314 (37.6)	202 (49.9)	113 (40.6)	259 (40.7)	29 (47.5)	34 (16.2)	104 (39.1)
Adverse events leading to drug discontinuation*[2]	70 (13.8)	115 (12.6)	68 (8.1)	112 (27.7)	65 (23.4)	122 (19.2)	4 (6.6)	11 (5.2)	22 (8.3)
Adverse events leading to drug interruption*[3]	96 (18.9)	213 (23.4)	209 (25.0)	223 (55.1)	164 (59.0)	212 (33.3)	17 (27.9)	54 (25.7)	54 (20.3)

*1, Pembrolizumab was administered at: an intravenous dose of 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks, or 10 mg/kg every 3 weeks in patients with unresectable malignant melanoma; an intravenous dose of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, or 200 mg every 3 weeks in patients with PD-L1 positive NSCLC; or an intravenous dose of 200 mg every 3 weeks in other patients; *2, Adverse events that led to the discontinuation of pembrolizumab or the concomitant chemotherapy in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC or SQ-NSCLC; or adverse events that led to the discontinuation of pembrolizumab in other patients; *3, Adverse events that led to the interruption of pembrolizumab or the concomitant chemotherapy

in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC or SQ-NSCLC; or adverse events that led to the interruption of pembrolizumab in other patients

Adverse events of any grade reported with a ≥5% higher incidence in patients with resected malignant melanoma than in those with any other type of cancer were hypertension (14.5% in patients with resected malignant melanoma, 3.9% in patients with unresectable malignant melanoma, 3.7% in patients with PD-L1 positive NSCLC, 1.9% in patients with cHL, 4.1% in patients with radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy), weight increased (12.4%, 2.2%, 1.1%, 3.8%, 0.8%), aplasia influenza like illness (10.8%, 5.5%, 2.5%, 1.9%, 3.4%), and hyperthyroidism (10.4%, 4.2%, 5.3%, 2.9%, 3.8%). The Grade ≥3 adverse event reported with a ≥2% higher incidence in patients with resected malignant melanoma than in those with any other type of cancer was hypertension (5.5%, 1.4%, 1.4%, 0.5%, 2.3%). The serious adverse event reported with a ≥2% higher incidence in patients with resected malignant melanoma than in those with any other type of cancer was basal cell carcinoma (3.3%, 0.9%, 0.1%, 0%, 0%). No adverse events led to death, drug discontinuation, or interruption, with a ≥2% higher incidence in patients with resected malignant melanoma than in those with any other type of cancer.

Adverse events of any grade, which did not occur in patients treated with pembrolizumab for the approved indications but reported in ≥3 patients in the pembrolizumab group of Study 054 were anal haemorrhage, oral lichen planus, tenderness, and sensation of pharynx strangled in 3 patients each. There were no Grade ≥3 adverse events, serious adverse events, or adverse events leading to death, drug discontinuation, or interruption, which did not occur in patients treated for the approved indications but were reported in ≥2 patients in the pembrolizumab group of Study 054.

As was described above, some adverse events were more frequently reported in patients with resected malignant melanoma than in patients treated for the approved indications, or identified newly in patients with resected malignant melanoma. However, no clear differences were noticed in the incidences of serious adverse events and other notable adverse events between these patient populations. Therefore, the safety of pembrolizumab is comparable in patients with resected malignant melanoma and those treated for the approved indications.

The applicant's explanation about the differences in the safety of pembrolizumab between Japanese patients and non-Japanese patients, based on the safety data from Study 054:
In Study 054, adverse events of any grade reported in ≥2 Japanese patients were diarrhoea (4 Japanese patients [44.4%], 137 non-Japanese patients [27.4%]), rash (3 patients [33.3%], 64 patients [12.8%]), nasopharyngitis (2 patients [22.2%], 42 patients [8.4%]), upper respiratory tract infection (2 patients [22.2%], 37 patients [7.4%]), ALT increased (2 patients [22.2%], 35 patients [7.0%]), decreased appetite (2 patients [22.2%], 34 patients [6.8%]), AST increased (2 patients [22.2%], 25 patients [5.0%]), abdominal pain upper (2 patients [22.2%], 21 patients [4.2%]), and eczema (2 patients [22.2%], 18 patients [3.6%]). Serious adverse events reported in Japanese patients were diarrhoea (1 patient [11.1%], 4 patients [0.8%]), pyrexia (1 patient [11.1%], 3 patients [0.6%]), type 1 diabetes mellitus (1 patient [11.1%], 2 patients [0.4%]), decreased appetite (1 patient [11.1%], 1 patient [0.2%]), and rash (1 patient [11.1%], 0 patients). Grade ≥3 adverse events reported in

Japanese patients were type 1 diabetes mellitus (1 patient [11.1%], 4 patients [0.8%]) and rash (1 patient [11.1%], 0 patients). The adverse events that led to drug discontinuation in Japanese patients was diarrhoea (1 patient [11.1%], 4 patients [0.8%], and adverse events that led to drug interruption in Japanese patients were diarrhoea (1 patient [11.1%], 11 patient [2.2%]), AST increased (1 patient [11.1%], 6 patients [1.2%]), pyrexia (1 patient [11.1%], 1 patient [0.2%]), type 1 diabetes mellitus (1 patient [11.1%], 1 patient [0.2%]), cough (1 patient [11.1%], 3 patients [0.6%]), and rash (1 patient [11.1%], 0 patients). No Japanese patients died due to adverse events.

As only limited clinical experience with pembrolizumab is available in Japanese patients with resected malignant melanoma, it is difficult to assess the differences in the safety of pembrolizumab between Japanese and non-Japanese patients based on the results of Study 054. Nevertheless, no adverse events would require special attention in Japanese patients, because no serious adverse events were reported in ≥2 Japanese patients in Study 054, and due to other findings.

PMDA's view:
Although several adverse events were reported with a higher incidence in patients with resected malignant melanoma than in those treated for the approved indications, or were newly identified in patients with resected malignant melanoma, most of these adverse events were of Grade ≤2. PMDA has therefore concluded that pembrolizumab would be tolerable in patients with resected malignant melanoma, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis, and patient management in anticipation of adverse reactions caused by an excessive immune response, drug interruption, or other appropriate actions.

PMDA has also concluded that the currently available data indicate no adverse events requiring special attention in Japanese patients with resected malignant melanoma, although clinical experience with pembrolizumab in Japanese patients is limited.

7.1.R.3 Clinical positioning and indications

In the present partial change application, the applicant has proposed to change the approved indication of "unresectable malignant melanoma" to "malignant melanoma," and to delete the following precautionary statement included in the approved "Precautions for Indications" section of the package insert: "The efficacy and safety of pembrolizumab in adjuvant chemotherapy have not been established."

As a result of its review described in Sections "7.1.R.1 Efficacy," "7.1.R.2 Safety," and the section below, PMDA concluded that the indication of pembrolizumab should be "malignant melanoma," as proposed by the applicant, provided that the disease stage and other characteristics of the patients enrolled in Study 054 are detailed in the "Clinical Studies" section of the package insert, and that the following statement is included in the "Precautions for Indications" section.

- Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after thoroughly understanding the "Clinical Studies" section.

7.1.R.3.1 Clinical positioning and indication of pembrolizumab

In clinical practice guidelines or representative textbooks for clinical oncology in and outside Japan, pembrolizumab therapy for resected malignant melanoma is currently described as follows:

[Clinical practice guidelines]

- US National Cancer Institute Physician Data Query (NCI-PDQ) (version dated July 19, 2018):
  The results of Study 054 demonstrated the efficacy of pembrolizumab in the treatment of resected malignant melanoma.

PMDA asked the applicant to explain about the clinical positioning and indication of pembrolizumab in the treatment of resected malignant melanoma.

The applicant's explanation:

Since the results of Study 054 indicated that pembrolizumab can be positioned as an adjuvant chemotherapy option for patients with resected malignant melanoma at high risk for recurrence, the approved indication of "unresectable malignant melanoma" should be changed to "malignant melanoma." In addition, the following precautionary statement that was included in the "Precautions for Indications" section of the package insert at the previous approval should be deleted: "The efficacy and safety of pembrolizumab in adjuvant chemotherapy have not been established."

Administration of pembrolizumab to patients with different stages of malignant melanoma who were ineligible for entry in Study 054 should not be recommended because no clinical data is available as to the clinical benefit of pembrolizumab in such patients. However, in view of the fact that pembrolizumab is intended to be used by physicians with sufficient knowledge and experience in cancer chemotherapy, there is little necessity to specify the intended disease stage in the "Indications" section; thus, the disease stages of the patients enrolled in Study 054 will be stated in the "Clinical Studies" section.

The applicant's explanation about the choice between pembrolizumab and conventional antineoplastic drugs in the treatment of resected malignant melanoma:

Pembrolizumab and conventional antineoplastic drugs should be chosen according to *BRAF* mutation status as described below.

- *BRAF* mutation-negative malignant melanoma (conventional antineoplastic drug: nivolumab):
  There have been no clinical data comparing the efficacy and safety of pembrolizumab with those of nivolumab; therefore, it is unclear which drug should be chosen first.
- *BRAF* mutation-positive malignant melanoma (conventional antineoplastic drugs: dabrafenib and trametinib):
  There have been no clinical data comparing the efficacy and safety of pembrolizumab with those of dabrafenib or trametinib; therefore, it is unclear which drug should be chosen first.

PMDA's view:

PMDA accepted the applicant's explanation in general and has concluded that the indication of pembrolizumab should be “malignant melanoma,” as proposed by the applicant. However, since there have been no clinical data demonstrating the clinical benefit of pembrolizumab in patients with different stages of malignant melanoma who were ineligible for entry in Study 054, and for other reasons, the following precautionary statement should be included in the “Precautions for Indications” section of the package insert, provided that the disease stages of the patients enrolled in Study 054 are detailed in the “Clinical Studies” section.

- Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the “Clinical Studies” section.

7.1.R.4 Dosage and administration

The approved dosage and administration for the approved indication of “unresectable malignant melanoma” is a body weight-based dose (2 mg/kg every 3 weeks), while a fixed-based dose (200 mg every 3 weeks) has been approved for other approved indications.

The present partial change application has proposed the following dosage and administration for both indications of malignant melanoma (treatment of unresectable malignant melanoma and the adjuvant treatment of malignant melanoma): “The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks,” as well as the following statements to be included in the “Precautions for Dosage and Administration” section of the package insert (unchanged from the previous approval).

- The efficacy and safety of pembrolizumab in combination with other antineoplastic drugs have not been established.
- Criteria for interruption and discontinuation of pembrolizumab in case of adverse reactions

As a result of its review described in Sections “7.1.R.1 Efficacy,” “7.1.R.2 Safety,” and the section below, PMDA concluded that the dosage and administration of pembrolizumab for malignant melanoma should be “The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks. For the adjuvant treatment of malignant melanoma, the maximum duration of treatment should be 12 months.” provided that the statements proposed by the applicant (unchanged from the approved statements) are included in the “Precautions for Dosage and Administration” section of the package insert.

7.1.R.4.1 Dosage for the treatment of unresectable malignant melanoma

The applicant's explanation:

The dosage and administration of pembrolizumab for the treatment of unresectable malignant melanoma can be changed from the approved body weight-based dose (2 mg/kg every 3 weeks) to a fixed-based dose (200 mg every 3 weeks), based on the following findings, as well as the results of a PPK analysis [see Section 6.2.1].

- The pharmacokinetics of pembrolizumab was suggested to show similar inter-individual variability with the body weight-based dose and the fixed-based dose (*J Immunother Cancer* 2017;5:43).

- The results of foreign clinical studies (Studies 001, 002, and 006) showed no clear association between the $AUC_{ss,6wk}$ of pembrolizumab and its efficacy or safety, over the investigated dosage range (2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks, and 10 mg/kg every 3 weeks) (see "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016"). Based on the above, and other findings, the change of dosage and administration from 2 mg/kg every 3 weeks to 200 mg every 3 weeks is unlikely to result in the reduced efficacy of pembrolizumab.
- No clear differences were found in the safety of pembrolizumab administered at 2 mg/kg every 3 weeks among cancer types [see Sections 7.1.R.2, 7.2.R.2, and 7.3.R.1]. Likewise, pembrolizumab administered at a dose of 200 mg every 3 weeks is unlikely to cause clear differences in the incidence of adverse events among cancer types.

PMDA accepted the applicant's explanation.

7.1.R.4.2 Dosage and administration of pembrolizumab for the adjuvant treatment of malignant melanoma

The applicant's explanation about the dosage and administration of pembrolizumab for the adjuvant treatment of malignant melanoma:

In Study 054, based on the results of PK/PD analyses (see "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg, dated August 30, 2016" and "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg, dated November 15, 2016") and other findings, a fixed-based dose of 200 mg every 3 weeks, rather than a body weight-based dose, was selected as the dosage and administration of pembrolizumab. As a result, the study demonstrated the clinically significant efficacy [see Section 7.1.R.1] and acceptable tolerability [see Section 7.1.R.2] of pembrolizumab. Therefore, the dosage and administration of pembrolizumab for the adjuvant treatment of malignant melanoma has been proposed as, "The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks."

In Study 054, the maximum duration of treatment with pembrolizumab was 12 months. PMDA asked the applicant to explain the necessity of specifying the duration of pembrolizumab therapy for resected malignant melanoma.

The applicant's explanation:
No clinical data are available in patients who have been treated with pembrolizumab for resected malignant melanoma beyond 12 months. However, the treatment duration of pembrolizumab of up to 12 months in Study 054 will be stated in the "Clinical Studies" section of the package insert; therefore, the duration of pembrolizumab therapy does not have to be limited to 12 months in the "Dosage and Administration" section.

PMDA's view:

PMDA accepted the applicant's explanation in general. However, the duration of adjuvant treatment with pembrolizumab for malignant melanoma should be specified in the “Dosage and Administration” section of the package insert, in view of the following facts.

- In Study 054, which involved patients with resected malignant melanoma, the maximum duration of treatment with pembrolizumab was 12 months; therefore, no clinical data are available as to the clinical benefit of pembrolizumab administered beyond 12 months.
- The patients enrolled in Study 054 underwent surgery intended for complete cure. Administration of pembrolizumab without careful consideration should be avoided in patients who have completed a 12-month adjuvant treatment with pembrolizumab.

7.1.R.5 Post-marketing investigations

Post-marketing investigations in patients with malignant melanoma will be described in Section 7.3.R.4, together with those in patients with NSCLC or MSI-High solid tumors.

7.2 Data on NSCLC and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of result data from 1 Japanese phase I study, 3 global phase III studies, and 1 foreign phase I/II study (5 studies in total) (Table 7).

Table 7. Clinical studies on efficacy and safety

Data type	Region	Study identifier	Phase	Subjects	No. of patients enrolled	Brief description of dosage regimen*	Endpoints
Evaluation data	Japan	Study 011	I	Chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC Part B: Patients with NSQ-NSCLC Part C: Patients with SQ-NSCLC	Part B Cohort 1: 6 Cohort 2: 6 Part C Cohort 1: 8 Cohort 2: 6	Part B Cohort 1: Intravenous pembrolizumab 200 mg in combination with CDDP + PEM for 4 cycles, followed by intravenous pembrolizumab and PEM Cohort 2: Intravenous pembrolizumab 200 mg in combination with CBDCA + PEM for 4 cycles, followed by intravenous pembrolizumab and PEM Part C Cohort 1: Intravenous pembrolizumab 200 mg in combination with CBDCA + PTX for 4 cycles, followed by intravenous pembrolizumab Cohort 2: Intravenous pembrolizumab 200 mg in combination with CBDCA + nab-PTX for 4 cycles, followed by intravenous pembrolizumab	Safety Tolerability PK
	Global	Study 189	III	Chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC	616 (a) 410 (b) 206	In combination with CDDP/PEM or CBDCA/PEM, (a) Intravenous pembrolizumab 200 mg for 4 cycles, followed by intravenous pembrolizumab and PEM (b) Intravenous placebo for 4 cycles, followed by intravenous placebo and PEM	Efficacy Safety
		Study 407	III	Chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC	559 (a) 278 (b) 281	In combination with CBDCA + PTX or CBDCA + nab-PTX, (a) Intravenous pembrolizumab 200 mg for 4 cycles, followed by intravenous pembrolizumab (b) Intravenous placebo for 4 doses, followed by intravenous placebo	Efficacy Safety
		Study 042	III	Chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC	1275 (a) 638 (b) 637	(a) Intravenous pembrolizumab 200 mg (b) Intravenous CBDCA + PEM or CBDCA + PTX for 6 cycles, followed by intravenous PEM	Efficacy Safety
	Foreign	Study 021	I/II	Phase I part Cohort A: Chemotherapy-naïve patients with advanced or recurrent NSCLC Cohort C: Chemotherapy-naïve patients with advanced or recurrent NSQ-NSCLC Phase II part Cohort G: Chemotherapy-naïve patients with advanced or recurrent NSQ-NSCLC	Phase I part Cohort A: 25 Cohort C: 24 Phase II part Cohort G: (a) 60 (b) 63	Phase I part Cohort A: Intravenous pembrolizumab 2 or 10 mg/kg in combination with CBDCA + PTX for 4 cycles, followed by intravenous pembrolizumab Cohort C: Intravenous pembrolizumab 2 or 10 mg/kg in combination with CBDCA + PEM for 4 cycles, followed by intravenous pembrolizumab and PEM Phase II part Cohort G: (a) Intravenous pembrolizumab 200 mg in combination with CBDCA + PEM for 4 cycles, followed by intravenous pembrolizumab and PEM (b) Intravenous CBDCA + PEM for 4 cycles, followed by intravenous PEM	Efficacy Safety

* CBDCA was administered intravenously on Day 1 of each 3-week cycle: at a dose producing AUC of 5 mg·min/mL in Part B of Study 011, Cohorts C and G of Study 021, and Study 189; at a dose producing AUC of 6 mg·min/mL in Part C of Study 011, Cohort A of Study 021, and Study 407; or, at a dose producing AUC of 5 or 6 mg·min/mL in Study 042. CDDP was administered intravenously at a dose of 75 mg/m^2, PEM at a dose of 500 mg/m^2, PTX at a dose of 175 or 200 mg/m^2, and nab-PTX at 100 mg/m^2.

A summary of the clinical studies is shown below. Major adverse events, excluding deaths, were reported in the studies are detailed in Section "7.4.2 Adverse events reported in clinical studies in patients with NSCLC."

7.2.1 Evaluation data

7.2.1.1 Japanese clinical study

7.2.1.1.1 Japanese phase I study (CTD 5.3.5.2.1 and 5.3.5.2.2, Study 011, Parts B and C, ongoing since [redacted] 20[redacted] [data cutoff date: Part B, [redacted], 20[redacted]; Part C, [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 4 sites in Japan to evaluate the safety, tolerability, and other aspects of pembrolizumab in combination with platinum-based chemotherapy, in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC (Part B; target sample size, 12 to 18 patients) or SQ-NSCLC (Part C; target sample size, 12 to 18 patients).

As described below, the treatment was continued until disease progression was observed or a withdrawal criterion was met.

- Part B:
  - Cohort 1: Patients received an intravenous dose of pembrolizumab 200 mg in combination with CDDP 75 mg/m^2 and PEM 500 mg/m^2 on Day 1 of each 3-week cycle for 4 cycles, followed by an intravenous dose of pembrolizumab in combination with PEM for a total of 24 months.
  - Cohort 2: Patients received an intravenous dose of pembrolizumab 200 mg in combination with CBDCA (AUC 5 mg·mL/min) and PEM 500 mg/m^2 on Day 1 of each 3-week cycle for 4 cycles, followed by an intravenous dose of pembrolizumab in combination with PEM for a total of 24 months.
- Part C:
  - Cohort 1: Patients received an intravenous dose of pembrolizumab 200 mg in combination with CBDCA (AUC 6 mg·mL/min) and PTX 200 mg/m^2 on Day 1 of each 3-week cycle for 4 cycles, followed by an intravenous dose of pembrolizumab for a total of 24 months.
  - Cohort 2: Patients received an intravenous dose of pembrolizumab 200 mg in combination with CBDCA (AUC 6 mg·mL/min) and nab-PTX 100 mg/m^2 on Day 1 of each 3-week cycle for 4 cycles, followed by an intravenous dose of pembrolizumab for a total of 24 months.

All 26 enrolled patients (Part B [6 in Cohort 1 and 6 in Cohort 2], Part C [8 in Cohort 1 and 6 in Cohort 2]) were treated with the study drug and included in the safety analysis set.

During the first 21 days after the start of treatment with the study drug, dose limiting toxicities (DLTs) were evaluated. Although DLTs were found in 1 of 6 patients in Cohort 1 of Part B (Grade 4 hyponatraemia) and 2 of 6 patients in Cohort 1 of Part C (Grade 3 febrile neutropenia in both patients), pembrolizumab administered in combination with platinum-based chemotherapy was tolerable.

The safety analysis indicated that 2 of 12 patients (16.7%) in Part B (2 of 6 patients [33.3%] in Cohort 2) and 1 of 14 patients (7.1%) in Part C (1 of 6 patients [16.7%] in Cohort 2) died during the treatment period or within 90 days after the last dose. The causes of death were ILD and pneumonitis in 1 patient each in Part B, and lung infection in 1 patient in Part C. A causal relationship to the study drug was not ruled out for the ILD and pneumonitis in 1 patient each in Part B.

7.2.1.2 Global clinical study

7.2.1.2.1 Global phase III study (CTD 5.3.5.1.1, Study 189, ongoing since February 2016 [data cutoff date: November 8, 2017])

A double-blind, randomized, comparative study was conducted at 143 sites in 16 countries and regions, including Japan, to evaluate the efficacy and safety of pembrolizumab versus placebo, in combination with a platinum + PEM in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC (target sample size, 570 subjects).

Patients received an intravenous dose of pembrolizumab 200 mg or placebo in combination with a platinum (either of CDDP 75 mg/m^2 or CBDCA [AUC 5 mg·mL/min]) + PEM 500 mg/m^2 on Day 1 of each 3-week cycle for 4 cycles, followed by an intravenous dose of pembrolizumab 200 mg or placebo and PEM 500 mg/m^2 intravenously every 3 weeks. The treatment was continued for a total of 35 cycles, or until disease progression was observed or a withdrawal criterion was met.

All 616 enrolled and randomized patients (410 in the pembrolizumab group and 206 in the placebo group, including 4 and 6 Japanese patients, respectively) were included in the intention-to-treat (ITT) population and used for the efficacy analyses. Of these 616 patients, 9 (5 in the pembrolizumab group and 4 in the placebo group) did not receive the study drug, and the remaining 607 (405 in the pembrolizumab group and 202 in the placebo group, including 4 and 6 Japanese patients, respectively) were included in the safety analysis set.

When the study was planned, the single primary endpoint was progression-free survival (PFS) as assessed centrally using the Response Evaluation Criteria in Solid Carcinomas (RECIST) Ver. 1.1, and an interim PFS analysis was planned when 50% of the target number of PFS events (373 events) had occurred. However, since [redacted] was observed in [redacted] of [redacted], the study protocol was amended to add OS, which had been set as a secondary endpoint when the study was planned, as another primary endpoint, and to conduct the interim PFS analysis and the first interim OS analysis when a total of 370 PFS events have occurred, the final PFS analysis and the second OS interim analysis when a total of 468 PFS events have occurred, and the final OS analysis when a total of 416 OS events have occurred (Protocol Amendment Version 7 [dated November 6, 2017]).

In the PFS and OS analyses, the prespecified overall one-sided α level was allocated to the composite primary endpoints (i.e., either 0.95% or 2.5% for PFS, and either 1.55% or 2.5% for OS), based on the results of the PFS or OS analysis, according to the graphical approach of Maurer and Bretz (*Stat Biopharm Res* 2013;5:311-20). A Lan-DeMets α spending function of the O'Brien-Fleming type was used to control the probability of a type I error associated with the interim analysis.

The first interim analysis of OS, one of the primary efficacy endpoints, was performed (data cutoff date: November 8, 2017). The results of the first interim OS analysis (Table 8) and the Kaplan-Meier curves of OS (Figure 6) are shown below.

Table 8. First interim OS analysis (ITT population [data cutoff date: November 8, 2017])

	Pembrolizumab		Placebo
N	410		206
Number of events (%)	127 (31.0)		108 (52.4)
Median [95% CI] (months)	— [—, —]		11.3 [8.7, 15.1]
Hazard ratio [95% CI][*1]		0.49 [0.38, 0.64]	
P value (one-sided)[*2]		<0.00001	

—, Not reached; *1, Cox regression stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a platinum (CDDP, CBDCA), and smoking history (yes, no); *2, Log-rank test stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a platinum (CDDP, CBDCA), and smoking history (yes, no), with a one-sided significance level of 0.00128

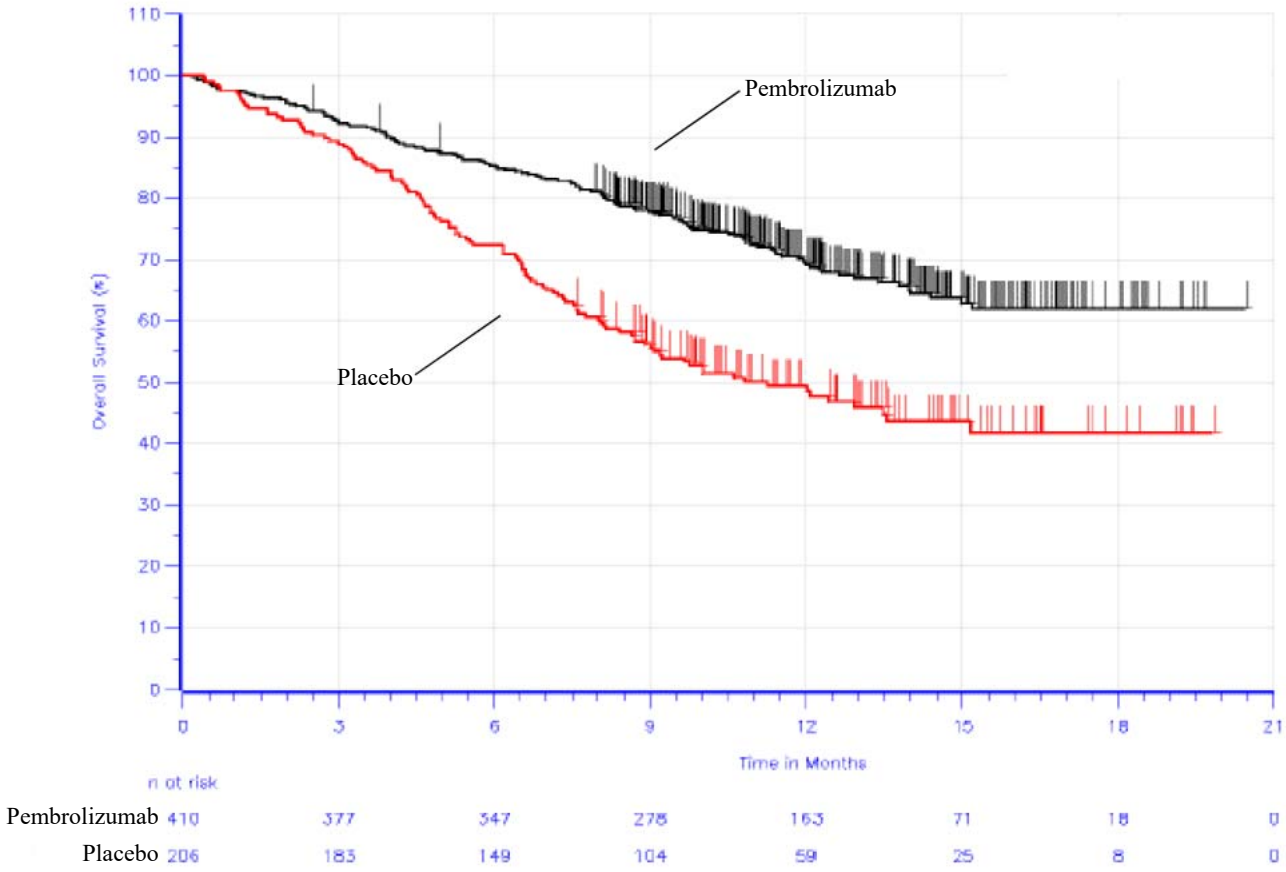


Figure 6. Kaplan-Meier curves for the first interim OS analysis (ITT population [data cutoff date: November 8, 2017])

Table 9 shows the results of the interim analysis of PFS, another primary endpoint (data cutoff date: November 8, 2017).

Table 9. Interim PFS analysis (RECIST Ver. 1.1, central assessment, ITT population [data cutoff date: November 8, 2017])

	Pembrolizumab	Placebo
N	410	206
Number of events (%)	244 (59.5)	166 (80.6)
Median [95% CI] (months)	8.8 [7.6, 9.2]	4.9 [4.7, 5.5]
Hazard ratio [95% CI][*1]	0.52 [0.43, 0.64]	
P value (one-sided)[*2]	<0.00001	

—, Not reached; *1, Cox regression stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a platinum (CDDP, CBDCA), and smoking history (yes, no); *2, Log-rank test stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a platinum (CDDP, CBDCA), and smoking history (yes, no), with a one-sided significance level of 0.00559

The safety analysis indicated that 27 of 405 patients (6.7%) in the pembrolizumab group and 12 of 202 patients (5.9%) in the placebo group died during the treatment period or within 90 days after the last dose (no Japanese patients died). The causes of death in the pembrolizumab group were death and pneumonitis in 3 patients each, intestinal ischaemia in 2 patients, and cardiac arrest/respiratory failure, cardiac arrest, acute kidney injury/neutropenic sepsis, acute kidney injury, neutropenic sepsis, cardiac failure, cardiopulmonary failure, cerebral infarction, chronic obstructive pulmonary disease, encephalopathy, haemoptysis, ischaemic stroke, lung infection, mesenteric artery embolism, myocardial infarction, peritonitis, pneumocystis jirovecii pneumonia, pneumonia, and septic shock in 1 patient each. The causes of death in the placebo group were pneumonia/respiratory failure, hypokalaemia/supraventricular tachycardia, pneumonia, respiratory failure, cerebral haemorrhage, death, disseminated intravascular coagulation, haemoptysis, haemorrhage intracranial, multiple organ dysfunction syndrome, renal failure, and septic shock in 1 patient each. A causal relationship to study drug could not be ruled out for the pneumonitis in 3 patients, acute kidney injury in 2 patients, and death, encephalopathy, neutropenic sepsis, and pneumonia in 1 patient each in the pembrolizumab group, and the pneumonia and septic shock in 1 patient each in the placebo group.

7.2.1.2.2 Global phase III study (CTD 5.3.5.1.4 and 5.3.5.1.5, Study 407, ongoing since August 2016 [data cutoff date: April 3, 2018])

A double-blind, randomized, comparative study was conducted at 125 sites in 17 countries and regions, including Japan, to evaluate the efficacy and safety of pembrolizumab versus placebo, in combination with platinum-based chemotherapy (CBDCA/PTX or CBDCA/nab-PTX) in chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC (target sample size, 560 subjects).

Patients received an intravenous dose of pembrolizumab 200 mg or placebo in combination with platinum-based chemotherapy (CBDCA [AUC 6 mg·mL/min] and either of PTX 200 mg/m^2 or nab-PTX 100 mg/m^2) on Day 1 of each 3-week cycle for 4 cycles, followed by an intravenous dose of pembrolizumab 200 mg or placebo every 3 weeks. The treatment was continued for a total of 35 cycles, or until disease progression was observed or a withdrawal criterion was met.

All 559 enrolled and randomized patients (278 in the pembrolizumab group and 281 in the placebo group, including 22 and 28 Japanese patients, respectively) were included in the ITT population and used for the efficacy analyses. Of the 559 patients, 1 patient in the placebo group did not receive the study drug, and the

remaining 558 (278 in the pembrolizumab group and 280 in the placebo group, including 22 and 28 Japanese patients, respectively) were included in the safety analysis set.

When the study was planned, the composite primary endpoints were PFS as assessed centrally using RECIST Ver. 1.1, and OS, while the response rate was a secondary endpoint. An interim analysis for efficacy was planned. The final response rate analysis was to be conducted when the 200th enrolled and randomized patient had been followed up for 28 weeks, the final PFS analysis and the interim OS analysis when a total of 331 PFS events had occurred, and the final OS analysis when a total of 334 OS events had occurred. However, since [redacted] was observed in [redacted] of [redacted], the study protocol was amended to change the prespecified allocation of the significance level for PFS and OS analyses, and to conduct the final response rate analysis when the 200th enrolled and randomized patient has been followed up for 28 weeks, the interim PFS analysis and the first interim OS analysis when a total of 332 PFS events have occurred, the final PFS analysis and the second interim OS analysis when a total of 415 PFS events have occurred, and the final OS analysis when a total of 361 OS events have occurred (Protocol Amendment Version 2 [dated October 26, 2017]).

In the PFS and OS analyses, the prespecified overall one-sided α level was allocated to the composite primary endpoints (i.e., 0.5% or 2.5% for the response rate, 1.0%, 1.5%, 2.0%, or 2.5% for PFS, and 1.0%, 2.0%, or 2.5% for OS) based on the results of the response rate, PFS, and OS analyses, according to the graphical approach of Maurer and Bretz (*Stat Biopharm Res* 2013;5:311-20). A Lan-DeMets α spending function of the O'Brien-Fleming type was used to control the probability of a type I error associated with the interim analysis.

The first interim analysis of OS, one of the primary efficacy endpoints, was performed (data cutoff date: April 3, 2018). The results of the first interim OS analysis (Table 10) and the Kaplan-Meier curves of OS (Figure 7) are shown below.

Table 10. First interim OS analysis (ITT population [data cutoff date: April 3, 2018])

	Pembrolizumab	Placebo
N	278	281
Number of events (%)	85 (30.6)	120 (42.7)
Median [95% CI] (months)	15.9 [13.2, —]	11.3 [9.5, 14.8]
Hazard ratio [95% CI]*1	0.64 [0.49, 0.85]	
P value (one-sided)*2	0.0008	

—, Not reached; *1, Cox regression stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a taxane-based chemotherapy (PTX, nab-PTX), and geographic region (East Asia, non-East Asia); *2, Log-rank test stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a taxane-based chemotherapy (PTX, nab-PTX), and geographic region (East Asia, non-East Asia), with a one-sided significance level of 0.0029

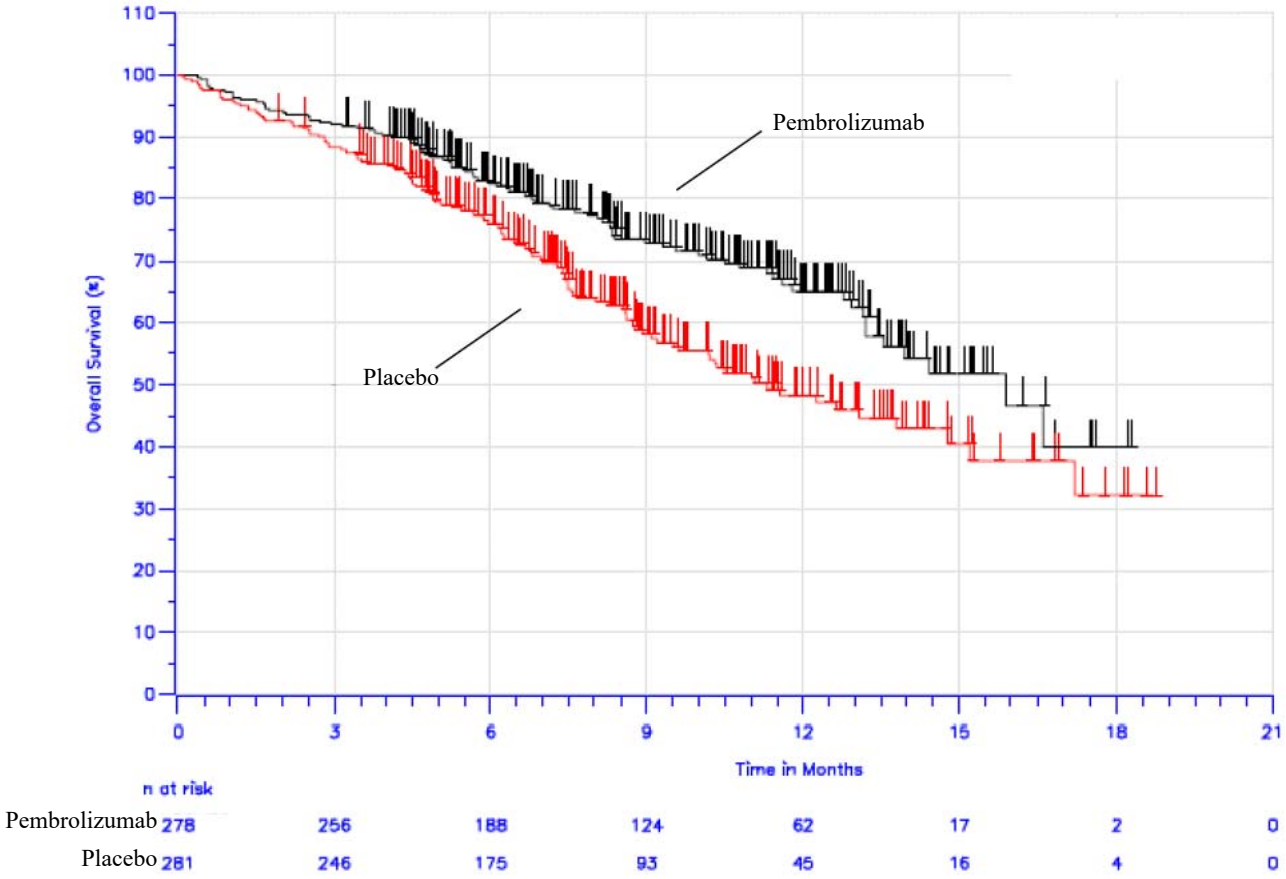


Figure 7. Kaplan-Meier curves for the first interim OS analysis (ITT population [data cutoff date: April 3, 2018])

Table 11 shows the results of the final analysis of PFS, another primary endpoint (data cutoff date: April 3, 2018).

Table 11. Interim PFS analysis (RECIST Ver. 1.1, central assessment, ITT population [data cutoff date: April 3, 2018])

	Pembrolizumab	Placebo
N	278	281
Number of events (%)	152 (54.7)	197 (70.1)
Median [95% CI] (months)	6.4 [6.2, 8.3]	4.8 [4.3, 5.7]
Hazard ratio [95% CI][*1]	0.56 [0.45, 0.70]	
P value (one-sided)[*2]	<0.0001	

—, Not reached; *1, Cox regression stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a taxane-based chemotherapy (PTX, nab-PTX), and geographic region (East Asia, non-East Asia); *2, Log-rank test stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a taxane-based chemotherapy (PTX, nab-PTX), and geographic region (East Asia, non-East Asia), with a one-sided significance level of 0.008

Table 12 shows the results of the final analysis of the response rate, which was the secondary endpoint as assessed centrally using RECIST Ver. 1.1, (data cutoff date: October 27, 2017).

Table 12. Best overall response and response rate
(RECIST Ver. 1.1, central assessment, ITT population [data cutoff date: October 27, 2017])

Best overall responses	n (%)	
	Pembrolizumab N = 101	Placebo N = 103
CR	0 (0)	2 (1.9)
PR	59 (58.4)	34 (33.0)
SD	26 (25.7)	36 (35.0)
PD	7 (6.9)	16 (15.5)
NE	9 (9.0)	15 (14.6)
Response (CR + PR) (Response rate [95% CI] [%])	59 (58.4 [48.2, 68.1])	36 (35.0 [25.8, 45.0])
Difference estimator [95% CI]*	23.6 [9.9, 36.4]	
P value (one-sided)*	0.0004	

*, Miettinen and Nurminen test, stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a taxane-based chemotherapy (PTX, nab-PTX), and geographic region (East Asia, non-East Asia), with a one-sided significance level of 0.005

The safety analysis indicated that 23 of 278 patients (8.3%, including 1 of 22 Japanese patients [4.5%]) in the pembrolizumab group, and 18 of 280 patients in the placebo group (6.4%, including 1 of 28 Japanese patients [3.6%]) died during the treatment period or within 90 days after the last dose. The causes of death in the pembrolizumab group were death in 4 patients, respiratory failure and sepsis in 3 patients each, cardiac arrest and pulmonary haemorrhage in 2 patients each, and cardiac failure, circulatory collapse, hepatic failure, intestinal perforation, lung abscess, necrotising fasciitis, pneumonia, pneumonitis, and pulmonary sepsis in 1 patient each. The causes of death in the placebo group were death and septic shock in 3 patients each, cardio-respiratory arrest in 2 patients, and acute kidney injury, cardiac arrest, haemothorax, multiple organ dysfunction syndrome, pleural effusion, pneumonia, pneumonitis, pulmonary haemorrhage, pulmonary mycosis, and sepsis in 1 patient each. A causal relationship to the study drug could not be ruled out for the sepsis in 3 patients, death in 2 patients, and hepatic failure, necrotising fasciitis, pneumonitis, pulmonary haemorrhage, and respiratory failure in 1 patient each in the pembrolizumab group, and the septic shock in 2 patients, and acute kidney injury, multiple organ dysfunction syndrome, pulmonary haemorrhage, and pneumonia in 1 patient each in the placebo group (The causes of death in 2 Japanese patients were pneumonitis in 1 patient in the pembrolizumab group and pulmonary haemorrhage in 1 patient in the placebo group, and a causal relationship to the study drug could not be ruled out for both the events.)

7.2.1.2.3 Global phase III study (CTD 5.3.5.1.6, Study 042, ongoing since [redacted] 20[redacted] [data cutoff date: February 26, 2018])

An open-label, randomized, comparative study was conducted at 196 sites in 32 countries and regions, including Japan, to evaluate the efficacy and safety of pembrolizumab versus the standard chemotherapy, in chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC (target sample size, 1240 patients).

Patients in the pembrolizumab group received an intravenous dose of pembrolizumab 200 mg on Day 1 of each 3-week cycle for up to 35 cycles. Patients in the chemotherapy group received CBDCA (AUC 5 or 6 mg·mL/min) and either of PEM 500 mg/m^2 or PTX 200 mg/m^2 intravenously for 6 cycles, followed by PEM

500 mg/m^2 intravenously.[8)] The treatment was continued until disease progression was observed or a withdrawal criterion was met.

All 1274 enrolled patients (637 in the pembrolizumab group and 637 in the chemotherapy group, including 47 and 46 Japanese patients, respectively) were included in the ITT population and used for the efficacy analyses. Of these 1274 patients, 23 patients (1 in the pembrolizumab group and 22 in the chemotherapy group) did not receive the study drug, and the remaining 1251 patients (636 in the pembrolizumab group and 615 in the chemotherapy group, including 47 and 44 Japanese patients, respectively) were included in the safety analysis set.

When the study was planned (dated [redacted], 20[redacted]), the primary endpoint was OS in PD-L1 positive (TPS ≥50%) patients, and both an interim analysis for futility in PD-L1 positive (TPS ≥1% and <50%) patients and 2 interim analyses for efficacy were planned. (For protocol amendments, as well as the types and timing of the analyses, see the table below.) However, since [redacted] was observed in [redacted] of [redacted], the study protocol was amended to cancel the interim analysis for futility in PD-L1 positive (TPS ≥1% and <50%) patients (Protocol Amendment Version 2 [dated [redacted], 20[redacted]]), to add a primary analysis set comprising PD-L1 positive (TPS ≥20%) patients, and to conduct a single interim analysis for efficacy when a total of 250 OS events have occurred in patients with PD-L1 positive (TPS ≥50%), and the last enrolled and randomized patient has been followed up for 6 months (Protocol Amendment Version 3 [dated [redacted], 20[redacted]]). Furthermore, since [redacted] for [redacted], the study protocol was amended to change the timing of the final OS analysis from the time when a total of 340 OS events have occurred in patients with PD-L1 positive (TPS ≥50%) to the time when the first enrolled and randomized patient has been followed up for 45 months, and to conduct the second interim analysis for efficacy when the first enrolled and randomized patient has been followed up for 38 months (Protocol Amendment Version 6 [dated [redacted], 20[redacted]]).

8) In patients with NSQ-NSCLC who were categorized as complete response (CR), partial response (PR), or stable disease (SD) by imaging-defined tumor assessment, according to the modified RECIST Ver. 1.1 performed after at least 4 cycles of CBDCA + PEM or CBDCA + PTX, PEM was administered thereafter.

Protocol	Type of analysis	Timing of analysis
Original version	Interim analysis (First)	When a total of 75 OS events have occurred in PD-L1 positive (TPS ≥1% and <50%) patients
	Interim analysis (Second)	When (a) a total of 315 PFS events have occurred in PD-L1 positive (TPS ≥50%) patients, (b) a total of 100 OS events have occurred in PD-L1 positive (TPS ≥50%) patients, and (c) patient enrollment has been completed
	Interim analysis (Third)	When a total of 283 OS events have occurred in PD-L1 positive (TPS ≥50%) patients
	Final analysis	When a total of 354 OS event have occurred in PD-L1 positive (TPS ≥50%) patients
Amendment Version 2 [dated ■■, 20■]	Interim analysis (First)	When a total of 187 OS events have occurred in PD-L1 positive (TPS ≥50%) patients and patient enrollment has been completed
	Interim analysis (Second)	When a total of 272 OS events have occurred in PD-L1 positive (TPS ≥50%) patients
	Final analysis	When a total of 340 OS events have occurred in PD-L1 positive (TPS ≥50%) patients
Amendment Version 3 [dated ■■, 20■]	Interim analysis	When a total of 250 OS events have occurred in PD-L1 positive (TPS ≥50%) patients, and the last enrolled and randomized patient has been followed up for 6 months
	Final analysis	When a total of 340 OS events have occurred in PD-L1 positive (TPS ≥50%) patients
Amendment Version 6 [dated ■■, 20■]	Interim analysis (First)	When a total of 250 OS events have occurred in PD-L1 positive (TPS ≥50%) patients, and the last enrolled and randomized patient has been followed up for 6 months
	Interim analysis (Second)	When the first enrolled and randomized patient has been followed up for 38 months
	Final analysis	When the first enrolled and randomized patient has been followed up for 45 months

To adjust for multiplicity concerns arising from 3 analysis populations, the analysis was performed sequentially, first in PD-L1 positive patients with TPS ≥50%, then in PD-L1 positive patients with TPS ≥20%, and finally in PD-L1 positive patients with TPS ≥1%. The type I error associated with the interim analyses was controlled through the use of a Lan-DeMets α spending function of the O'Brien-Fleming type for the first interim analysis, and through the use of a Hwang-Shih-DeCani α spending function (γ parameter, −0.9023[9)]) for the second interim analysis and the final analysis.

The results of the second interim OS analysis (Tables 13, 14, and 15) and the Kaplan-Meier curves of OS (Figures 8, 9, and 10) in the primary analysis sets are shown below.

Table 13. Second interim OS analysis (PD-L1 positive [TPS ≥50%] population [data cutoff date: February 26, 2018])

	Pembrolizumab	Chemotherapy
N	299	300
Number of events (%)	157 (52.5)	199 (66.3)
Median [95% CI] (months)	20.0 [15.4, 24.9]	12.2 [10.4, 14.2]
Hazard ratio [95% CI][*1]	0.69 [0.56, 0.85]	
P value (one-sided)[*2]	0.0003	

*1, Cox regression stratified by ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia); *2, Log-rank test stratified by ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia), with a one-sided significance level of 0.01220

9) With the addition of the second interim analysis and the change in the timing of the final analysis, the parameter was adjusted so that the α spent at the first interim analysis would not be affected.

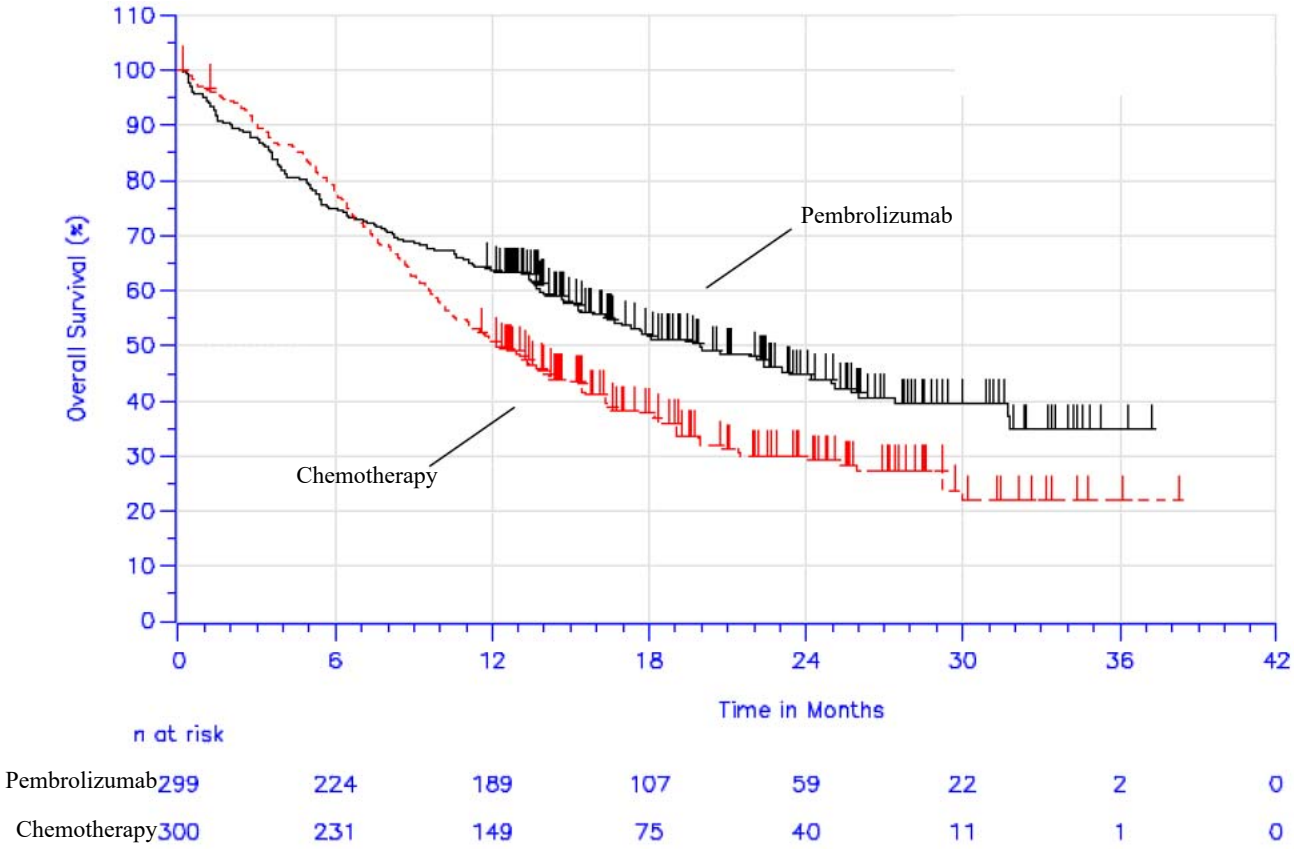


Figure 8. Kaplan-Meier curves for the second interim OS analysis (PD-L1 positive [TPS ≥50%] population [data cutoff date: February 26, 2018])

Table 14. Second interim OS analysis (PD-L1 positive [TPS ≥20%] population [data cutoff date: February 26, 2018])

	Pembrolizumab	Chemotherapy
N	413	405
Number of events (%)	230 (55.7)	266 (65.7)
Median [95% CI] (months)	17.7 [15.3, 22.1]	13.0 [11.6, 15.3]
Hazard ratio [95% CI][*1]	0.77 [0.64, 0.92]	
P value (one-sided)[*2]	0.0020	

*1, Cox regression stratified by PD-L1 expression status (TPS ≥50%, ≥1% and <50%), ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia); *2, Log-rank test stratified by PD-L1 expression status (TPS ≥50%, ≥1% and <50%), ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia), with a one-sided significance level of 0.01198

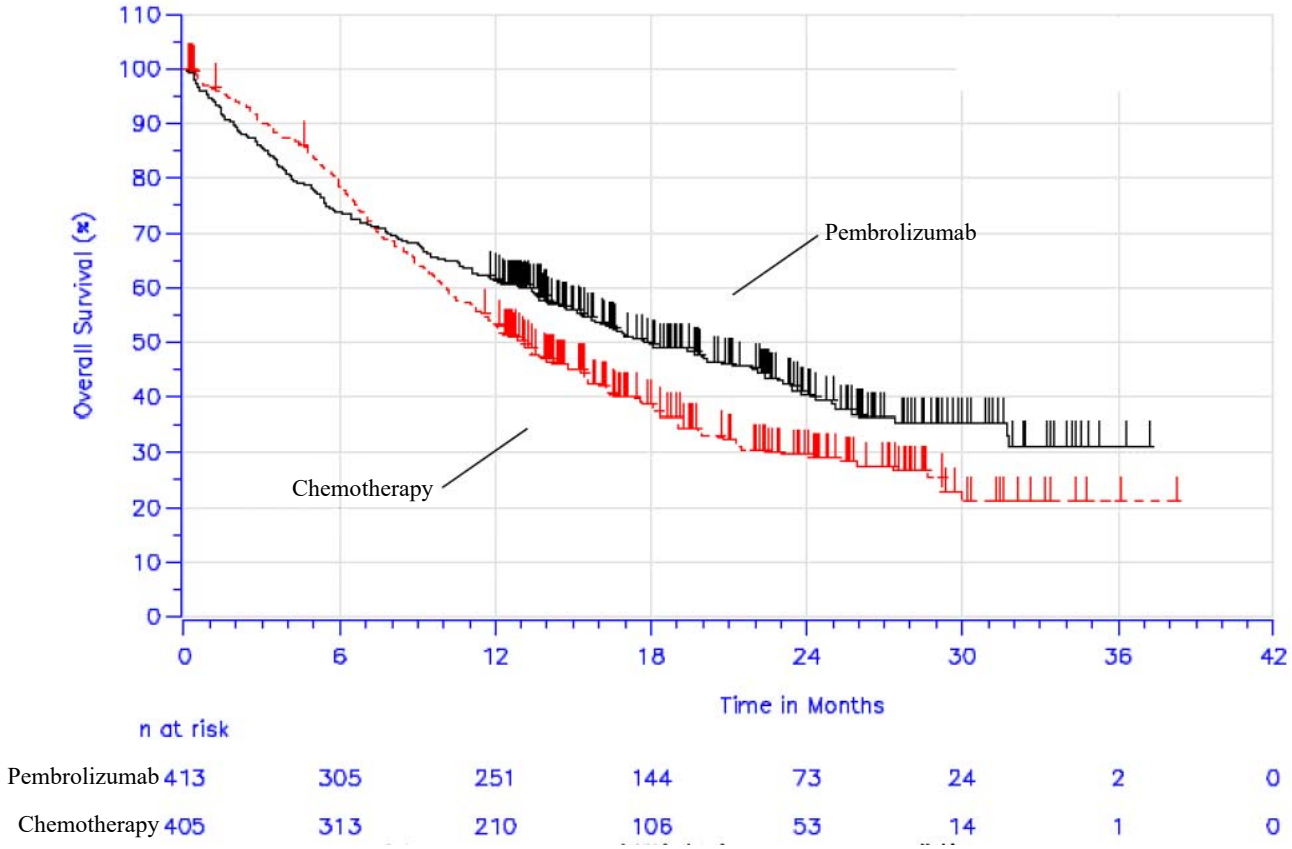


Figure 9. Kaplan-Meier curves for the second interim OS analysis (PD-L1 positive [TPS ≥20%] population [data cutoff date: February 26, 2018])

Table 15. Second interim OS analysis (PD-L1 positive [TPS ≥1%] population [data cutoff date: February 26, 2018])

	Pembrolizumab	Chemotherapy
N	637	637
Number of events (%)	371 (58.2)	438 (68.8)
Median [95% CI] (months)	16.7 [13.9, 19.7]	12.1 [11.3, 13.3]
Hazard ratio [95% CI][*1]	0.81 [0.71, 0.93]	
P value (one-sided)[*2]	0.0018	

*1, Cox regression stratified by PD-L1 expression status (TPS ≥50%, ≥1% and <50%), ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia); *2, Log-rank test stratified by PD-L1 expression status (TPS ≥50%, ≥1% and <50%), ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia), with a one-sided significance level of 0.01238

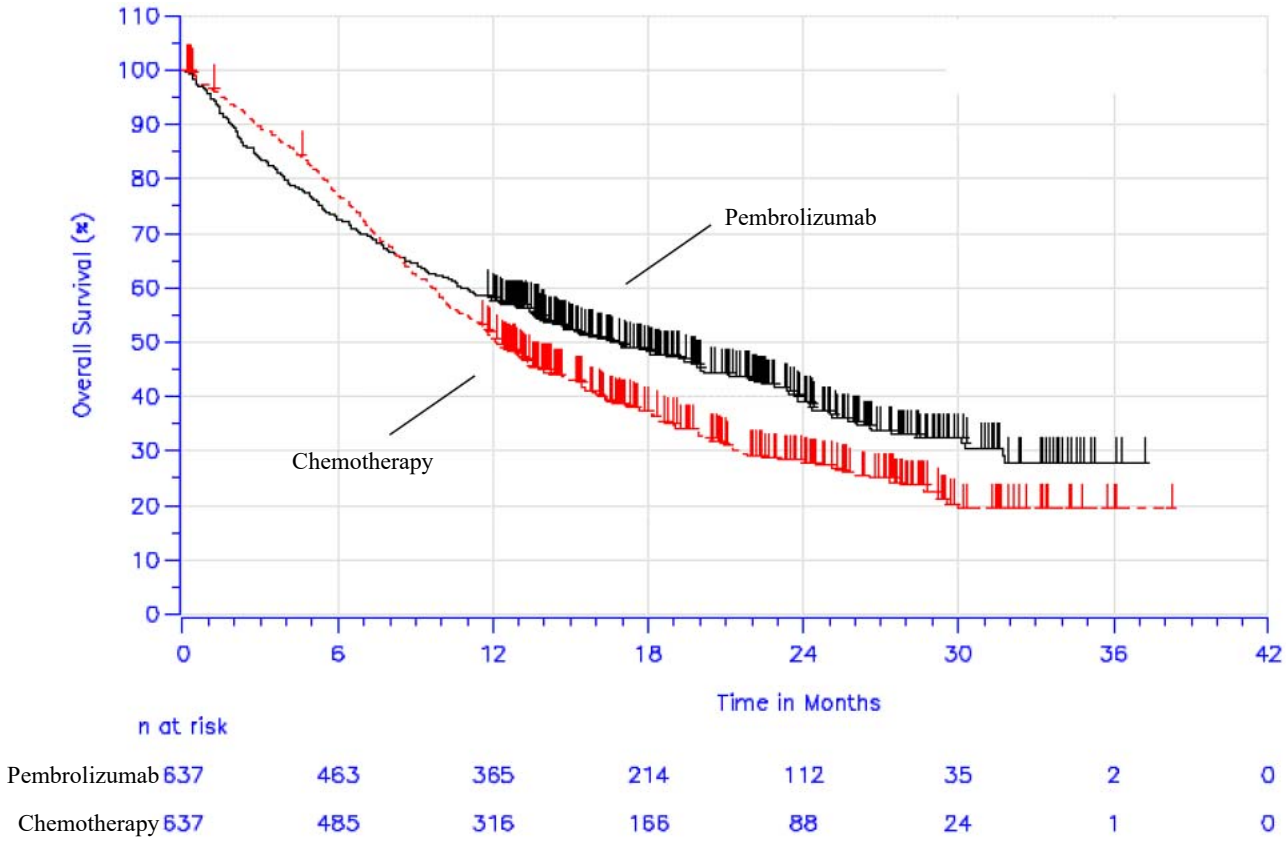


Figure 10. Kaplan-Meier curves for the second interim OS analysis (PD-L1 positive [TPS ≥1%] population [data cutoff date: February 26, 2018])

The safety analysis indicated that 70 of 636 patients (11.0%) in the pembrolizumab group and 46 of 615 patients (7.5%, including 1 of 44 Japanese patients [2.3%]) in the chemotherapy group died during the treatment period or within 90 days after the last dose. The causes of death in the pembrolizumab group were death in 10 patients, pneumonia in 8 patients, pulmonary embolism in 6 patients, pulmonary haemorrhage in 4 patients, respiratory failure in 3 patients, cardiac arrest, cardio-respiratory arrest, gastric ulcer haemorrhage, sepsis, and septic shock in 2 patients each, and malignant neoplasm progression, accidental death, acute respiratory failure, brain injury, cardiac failure, cardiac failure acute, cerebrovascular accident, chronic obstructive pulmonary disease, coma, diverticulitis, embolism, encephalopathy, febrile neutropenia, haemoptysis, hypercalcaemia of malignancy, hypovolaemic shock, ileus, intestinal ischaemia, ischaemic stroke, Klebsiella infection, lung infection, myocardial infarction, peripheral artery occlusion, pleural effusion, pneumonitis, pulmonary artery thrombosis, pulmonary sepsis, sudden death, and tumour embolism in 1 patient each. The causes of death in the chemotherapy group were pneumonia in 7 patients, death and pulmonary embolism in 5 patients each, respiratory failure in 3 patients, pulmonary haemorrhage, pulmonary oedema, and pulmonary sepsis in 2 patients each, abdominal sepsis, acute coronary syndrome, biliary sepsis, cardiac failure, cardio-respiratory arrest, cardiopulmonary failure, cerebral infarction, cerebrovascular accident, completed suicide, dyspnoea, haemoptysis, infection, ketoacidosis, neutropenic sepsis, pancytopenia, pleural effusion, respiratory distress, septic shock, sinus tachycardia, and sudden cardiac death in 1 patient each. A causal relationship to the study drug could not be ruled out for the death, pulmonary embolism, respiratory failure, sepsis, cardiac failure acute, encephalopathy, haemoptysis, hypovolaemic shock, ileus, Klebsiella infection, malignant neoplasm

progression, pneumonitis, and sudden death in 1 patient each in the pembrolizumab group, and the pneumonia in 4 patients, and cardiac failure, dyspnoea, infection, ketoacidosis, neutropenic sepsis, pancytopenia, pulmonary embolism, pulmonary sepsis, respiratory distress, and septic shock in 1 patient each in the chemotherapy group (A causal relationship to the study drug was denied for the death in the Japanese patient in the chemotherapy group).

7.2.1.3 Foreign clinical studies

7.2.1.3.1 Foreign phase I/II study (CTD 5.3.5.1.2, 5.3.5.1.3, and 5.3.5.1.7, Cohorts A, C, and G of Study 021, ongoing since [redacted] 20[redacted] [data cutoff date: November 7, 2016 for Cohort A, and [redacted], 20[redacted] for Cohorts C and G])

Cohorts A and C in Part I of Study 021 was an open-label, uncontrolled study conducted at 9 sites in 2 countries and regions outside Japan to evaluate the safety, tolerability, and other aspects of pembrolizumab in combination with CBDCA, etc. in chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC (Cohort A; target sample size, 24 patients) or in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC (Cohort C; target sample size, 24 patients). Cohort G in Part II of Study 021 was an open-label, randomized, comparative study conducted at 7 sites in the U.S. to evaluate the efficacy and safety of pembrolizumab in combination with CBDCA + PEM versus CBDCA + PEM alone in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC (Cohort G; target sample size, 108 patients).

In Part I, patients in Cohort A received an intravenous dose of pembrolizumab 2 or 10 mg/kg, in combination with CBDCA (AUC 6 mg·mL/min) + PTX 175 or 200 mg/m^2, on Day 1 of each 3-week cycle for 4 cycles, followed by pembrolizumab 2 or 10 mg/kg intravenously every 3 weeks. Patients in Cohort C received an intravenous dose of pembrolizumab 2 or 10 mg/kg, in combination with CBDCA (AUC 5 mg·mL/min) + PEM 500 mg/m^2, on Day 1 of each 3-week cycle for 4 cycles, followed by pembrolizumab 2 or 10 mg/kg and PEM 500 mg/m^2 intravenously every 3 weeks. In Part II, patients in Cohort G received CBDCA (AUC 5 mg·mL/min) + PEM 500 mg/m^2 intravenously, with or without an intravenous dose of pembrolizumab 200 mg, on Day 1 of each 3-week cycle for 4 cycles, followed by PEM 500 mg/m^2 intravenously, with or without of an intravenous dose of pembrolizumab 200 mg every 3 weeks. The treatment was continued for a total of 24 months, or until disease progression was observed or a withdrawal criterion was met.

In Part I, all 49 enrolled patients (Cohort A [13 in the 2 mg/kg group and 12 in the 10 mg/kg group], Cohort C [12 in the 2 mg/kg group and 12 in the 10 mg/kg group]) received the study drug and were included in the safety analysis set for Part I.

In Part II, all 123 patients enrolled in Cohort G (60 in the pembrolizumab + CBDCA + PEM group and 63 in the CBDCA + PEM group) were included in the ITT population, and used for the efficacy analyses. Of these 123 patients, 2 patients (1 in the pembrolizumab + CBDCA + PEM group and 1 in the CBDCA + PEM group) did not receive the study drug, and the remaining 121 (59 in the pembrolizumab + CBDCA + PEM group and 62 in the CBDCA + PEM group) were included in the safety analysis set.

The results for the response rate as assessed centrally using RECIST Ver. 1.1 (the primary endpoint in Part II) are shown in Table 16.

Table 16. Best overall response and response rate in Cohort G of Study 021 (RECIST Ver. 1.1, central assessment, ITT population [data cutoff date: [redacted], 20[redacted]])

Best overall responses	n (%)	
	Pembrolizumab + CBDCA + PEM N = 60	CBDCA + PEM N = 63
CR	1 (1.7)	1 (1.6)
PR	33 (55.0)	19 (30.2)
SD	19 (31.7)	24 (38.1)
PD	2 (3.3)	11 (17.5)
NE	5 (8.3)	8 (12.7)
Response (CR + PR) (Response rate [95% CI] [%])	34 (56.7 [43.2, 69.4])	20 (31.7 [20.6, 44.7])
Difference estimator [95% CI]*	24.8 [7.2, 40.9]	
P value (one-sided)	0.0029	

*, Miettinen and Nurminen test stratified by PD-L1 expression status (TPS ≥1%, <1%)

The safety analysis indicated that 5 of 170 patients (2.9%) (Cohort C, 2 of 24 patients [8.3%]; Cohort G, 3 of 121 patients [2.5%] [1 of 59 patients, 1.7% in the pembrolizumab + CBDCA + PEM group, 2 of 62 patients, 3.2% in the CBDCA + PEM group]) died during the treatment period or within 90 days after the last dose. The causes of death, other than disease progression, were: death in 2 patients in Cohort C; and, sepsis in 1 patient in the pembrolizumab + CBDCA + PEM group, and pancytopenia and sepsis in 1 patient each in the CBDCA + PEM group in Cohort G. A causal relationship to the study drug could not be ruled out for the sepsis in 1 patient in the pembrolizumab + CBDCA + PEM group, and the pancytopenia and sepsis in 1 patient each in the CBDCA + PEM group in Cohort G.

7.2.R Outline of the review conducted by PMDA for the treatment of NSCLC

7.2.R.1 Efficacy

Among the evaluation data submitted by the applicant, PMDA considered that the following 3 global phase III studies ((a) to (c)) were important, and decided that the efficacy and safety of pembrolizumab would be evaluated primarily based on the results of these studies.

PMDA also decided that the efficacy of pembrolizumab in Japanese patients would be evaluated in terms of the consistency between the overall study population and the Japanese subpopulation of each study, according to "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and "Basic Principles on Global Clinical Trials (Reference Cases)" (PFSB/ELD Administrative Notice, dated September 5, 2012).

(a) Study 189 to evaluate the efficacy and safety of pembrolizumab versus placebo, in combination with a platinum + PEM in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC
(b) Study 407 to evaluate the efficacy and safety of pembrolizumab versus placebo, in combination with CBDCA + PTX or CBDCA + nab-PTX in chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC

(c) Study 042 to evaluate the efficacy and safety of pembrolizumab versus chemotherapy in chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC

As a result of its review, summarized below, PMDA has concluded that the efficacy of pembrolizumab in the treatment of NSCLC has been demonstrated in the target patient populations of (a) Study 189, (b) Study 407, and (c) Study 042.

7.2.R.1.1 Selection of control group

The applicant's rationale for the control treatments selected in (a) Study 189, (b) Study 407, and (c) Study 042:

(a) When Study 189 was planned, the NCCN guidelines (v.3.2015), etc. recommended combination chemotherapy of a platinum + PEM, followed by maintenance therapy with PEM for the treatment of the target patient population of Study 189, based on reports that a platinum + PEM had been shown to be highly effective in such patient populations (*J Clin Oncol* 2008;26:3543-51, *J Clin Oncol* 2013;31:2895-902). A platinum + PEM (followed by maintenance therapy with PEM) was therefore selected as the control treatment.

(b) When Study 407 was planned, the NCCN guidelines (v.7.2015), etc. recommended CBDCA + PTX or CBDCA + nab-PTX for the treatment of the target patient population of Study 407, based on a report that these chemotherapy regimens had been shown to be highly effective in such patient populations (*J Clin Oncol* 2012;30:2055-62). CBDCA + PTX and CBDCA + nab-PTX were therefore selected as control treatments.

(c) When Study 042 was planned, the NCCN guidelines (v.3.2014), etc. recommended CBDCA + PEM or CBDCA + PTX, followed by maintenance therapy with PEM for the treatment of the target patient population of Study 042, based on reports that these chemotherapy regimens had been shown to be highly effective in such patient populations (e.g., *N Engl J Med* 2002;346:92-8, *Lancet Oncol* 2012;13:247-55). CBDCA + PEM and CBDCA + PTX (followed by maintenance therapy with PEM) were therefore selected as control treatments.

PMDA accepted the applicant's explanation.

7.2.R.1.2 Efficacy endpoints and evaluation results

(a) Study 189:

Study 189 demonstrated the superiority of pembrolizumab to placebo in OS (one of the primary endpoints) [see Section 7.2.1.2.1].

The results of the first interim OS analysis (Table 17) and the Kaplan-Meier curves of OS (Figure 11) in the Japanese subpopulation of Study 189 are shown below.

Table 17. First interim OS analysis in Japanese patients (ITT population [data cutoff date: November 8, 2017])

	Pembrolizumab		Placebo
N	4		6
Number of events (%)	1 (25.0)		2 (33.3)
Median [95% CI] (months)	— [4.1, —]		— [7.6, —]
Hazard ratio [95% CI][*1]		0.85 [0.08, 9.44]	
P value (one-sided)[*2]		0.46650	

—, Not reached; *1, Non-stratified Cox regression; *2, Non-stratified log-rank test

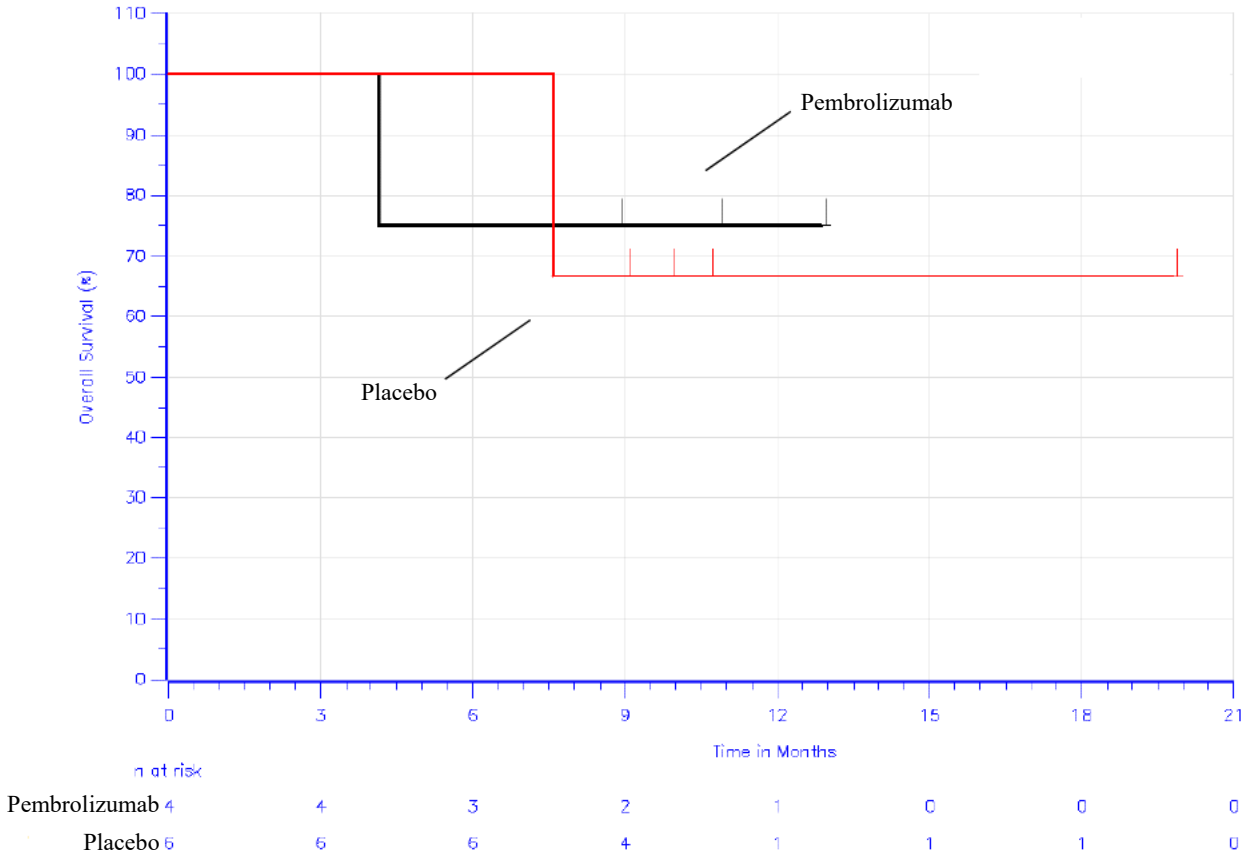


Figure 11. Kaplan-Meier curves for the first interim OS analysis in Japanese patients (ITT population [data cutoff date: November 8, 2017])

(b) Study 407:

Study 407 demonstrated the superiority of pembrolizumab to placebo in OS (one of the primary endpoints) [see Section 7.2.1.2.2].

The results of the first interim OS analysis (Table 18) and the Kaplan-Meier curves of OS (Figure 12) in the Japanese subpopulation of Study 407 are shown below.

Table 18. First interim OS analysis in Japanese patients (ITT population [data cutoff date: April 3, 2018])

	Pembrolizumab		Placebo
N	22		28
Number of events (%)	2 (9.1)		6 (21.4)
Median [95% CI] (months)	— [—, —]		— [7.5, —]
Hazard ratio [95% CI][*1]		0.33 [0.07, 1.66]	
P value (one-sided)[*2]		0.0788	

—, Not reached; *1, Non-stratified Cox regression; *2, Non-stratified log-rank test

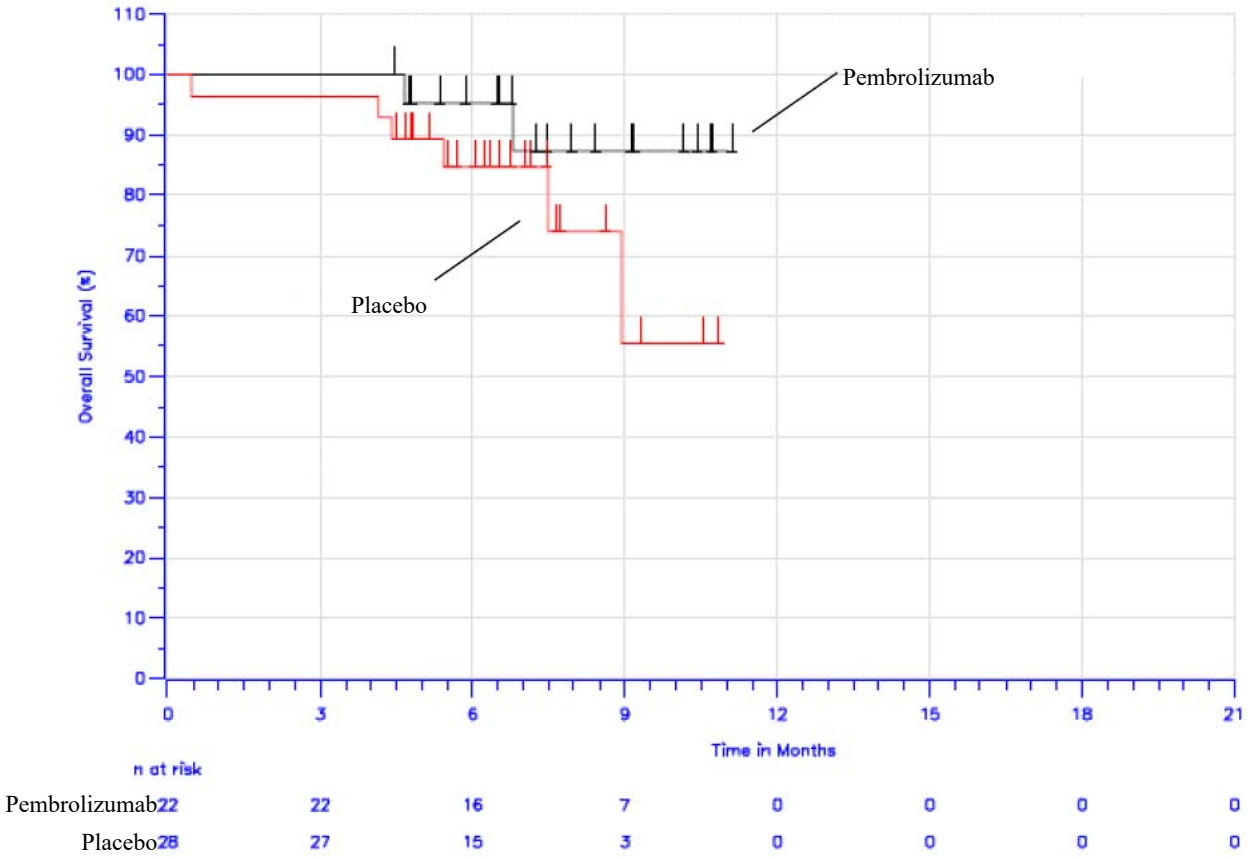


Figure 12. Kaplan-Meier curves for the first interim OS analysis in Japanese patients (ITT population [data cutoff date: April 3, 2018])

(c) Study 042:

Study 042 demonstrated the superiority of pembrolizumab to chemotherapy in OS (the primary endpoint) [see Section 7.2.1.2.3].

PMDA's view:

In Study 042, the addition of the second interim OS analysis, as well as changes in the timing of the final OS analysis and the method to control the increased probability of a type I error associated with the conduct of interim analyses were made after the first interim OS analysis. PMDA considered that the possible impacts of these changes on the interpretation of analytical results could not be excluded and asked the applicant to explain the results of the analysis performed based on the analytical plan before the changes (Protocol Amendment Version 2).

The applicant's response:

Table 19 shows the significance levels computed in the second interim OS analysis, accounting for the amount of α spent at the first interim analysis and using a Lan-DeMets α spending function of the O'Brien-Fleming type, based on the analysis plan specified in Protocol Amendment Version 2. The statistically significant superiority of pembrolizumab to the chemotherapy in OS was also found in the second interim analysis, performed based on the statistical plan before the changes.

Table 19. Second interim OS analysis based on the analysis plan specified in Protocol Amendment Version 5 (data cutoff date: February 26, 2018)

Population	Hazard ratio [95% CI]	*P* value (one-sided)	Significance level (one-sided)
PD-L1 positive (TPS ≥50%)	0.69 [0.56, 0.85][*1]	0.0003[*3]	0.00797
PD-L1 positive (TPS ≥20%)	0.77 [0.64, 0.92][*2]	0.0020[*4]	0.00777
PD-L1 positive (TPS ≥1%)	0.81 [0.71, 0.93][*2]	0.0018[*4]	0.00813

*1, Cox regression stratified by ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia); *2, Cox regression stratified by PD-L1 expression status (TPS ≥50%, ≥1% and <50%), ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia); *3, Log-rank test stratified by ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia); *4, Log-rank test stratified by PD-L1 expression status (TPS ≥50%, ≥1% and <50%), ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia)

The results of the second interim OS analysis (Tables 20, 21, and 22) and the Kaplan-Meier curves of OS (Figures 13, 14, and 15) in the Japanese subpopulation of Study 042 are shown below.

Table 20. Second interim OS analysis in Japanese patients (PD-L1 positive [TPS ≥50%] population [data cutoff date: February 26, 2018])

	Pembrolizumab	Chemotherapy
N	23	16
Number of events (%)	12 (52.2)	8 (50.0)
Median [95% CI] (months)	27.4 [13.4, —]	19.9 [5.0, —]
Hazard ratio [95% CI][*1]	0.87 [0.36, 2.14]	
P value (one-sided)[*2]	0.3833	

—, Not reached; *1, Non-stratified Cox regression; *2, Non-stratified log-rank test

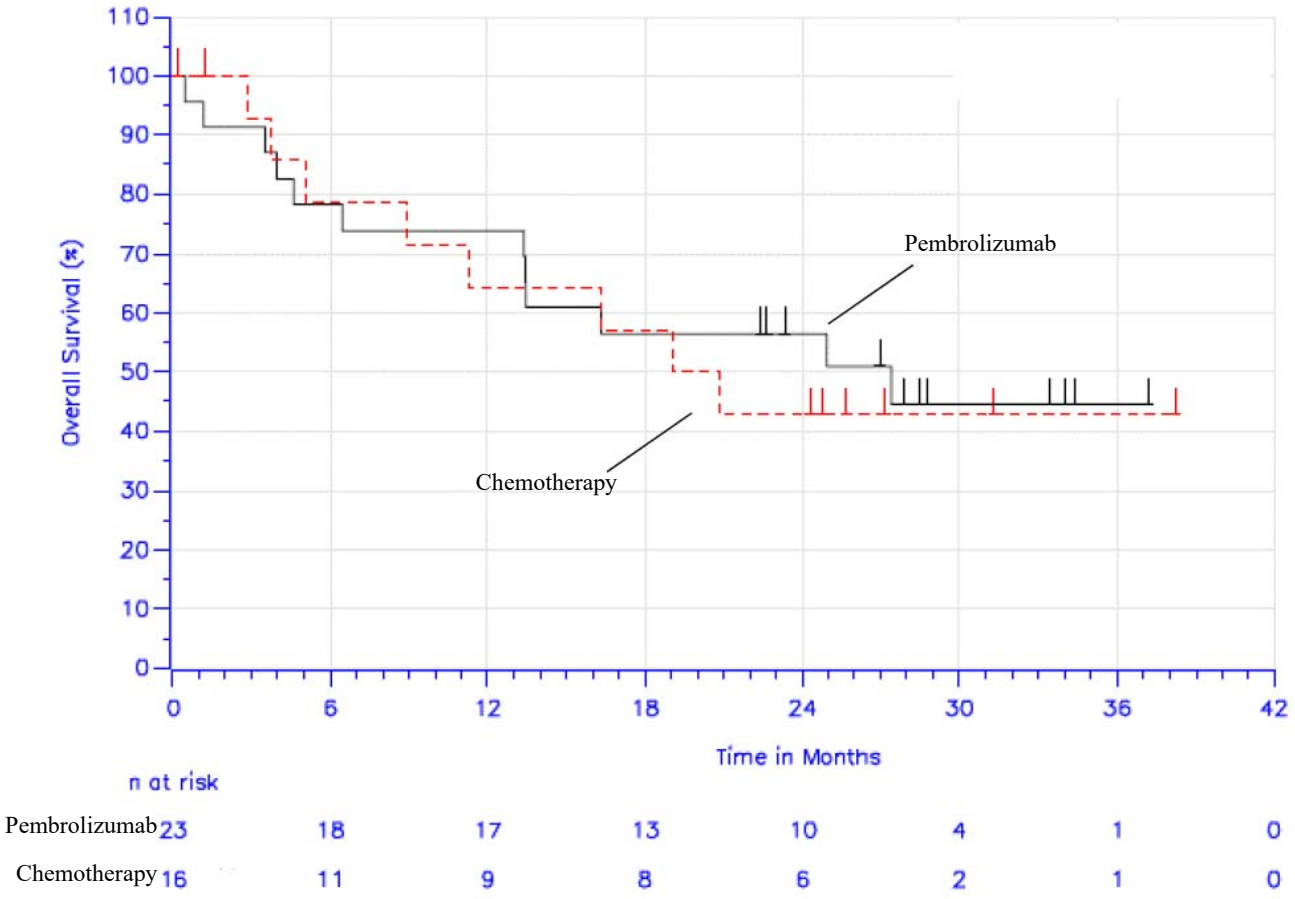


Figure 13. Kaplan-Meier curves for the second interim OS analysis (PD-L1 positive [TPS ≥50%] population [data cutoff date: February 26, 2018])

Table 21. Second interim OS analysis in Japanese patients (PD-L1 positive [TPS ≥20%] population [data cutoff date: February 26, 2018])

	Pembrolizumab	Chemotherapy
N	31	21
Number of events (%)	17 (54.8)	10 (47.6)
Median [95% CI] (months)	24.3 [13.4, —]	25.0 [11.3, —]
Hazard ratio [95% CI][*1]	1.00 [0.46, 2.20]	
P value (one-sided)[*2]	0.5045	

—, Not reached; *1, Non-stratified Cox regression; *2, Non-stratified log-rank test

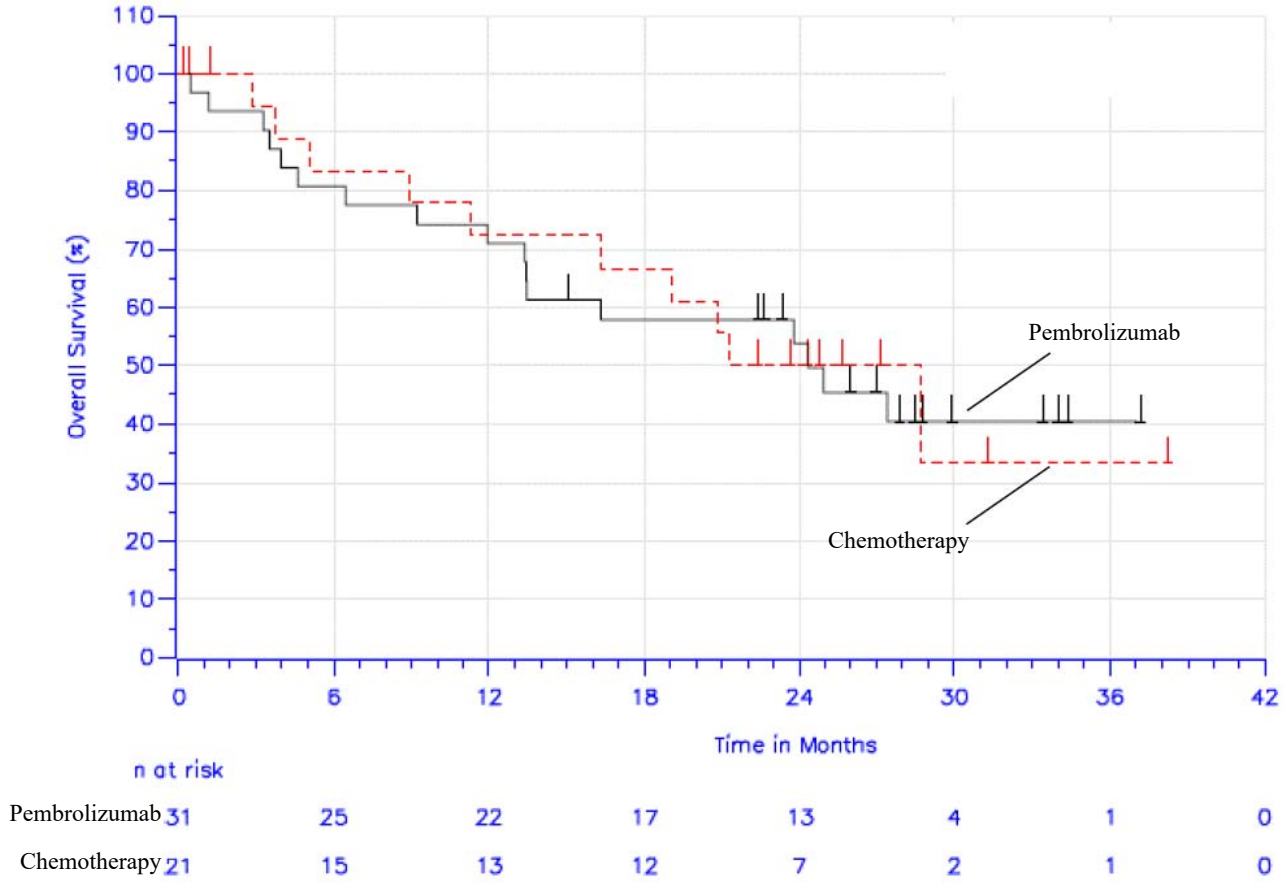


Figure 14. Kaplan-Meier curves for the second interim OS analysis in Japanese patients (PD-L1 positive [TPS ≥20%] population [data cutoff date: February 26, 2018])

Table 22. Second interim OS analysis in Japanese patients (PD-L1 positive [TPS ≥1%] population [data cutoff date: February 26, 2018])

	Pembrolizumab	Chemotherapy
N	47	46
Number of events (%)	24 (51.1)	24 (52.2)
Median [95% CI] (months)	24.9 [13.5, —]	25.5 [15.6, —]
Hazard ratio [95% CI][*1]	0.92 [0.52, 1.61]	
P value (one-sided)[*2]	0.3793	

—, Not reached; *1, Non-stratified Cox regression; *2, Non-stratified log-rank test

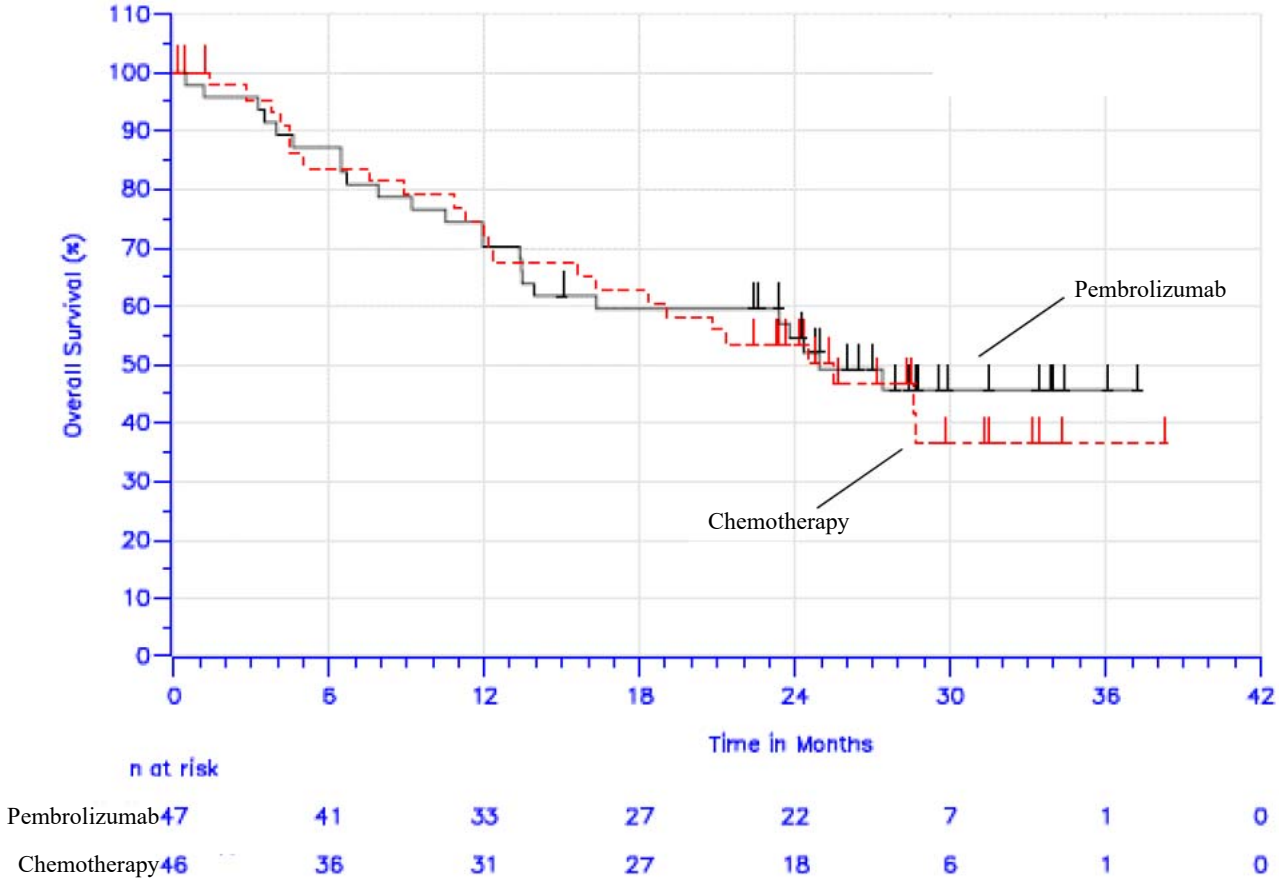


Figure 15. Kaplan-Meier curves for the second interim OS analysis in Japanese patients (PD-L1 positive [TPS ≥1%] population [data cutoff date: February 26, 2018])

PMDA's view:

PMDA has concluded that pembrolizumab has been demonstrated to be effective when administered in combination with chemotherapy, to chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC, and when administered as a monotherapy to chemotherapy-naïve patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC, in view of the following findings.

- In Study 189 in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC and in Study 407 in chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC, pembrolizumab was superior to placebo in OS (one of the primary endpoints).
- In Study 042 in chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC, pembrolizumab was superior to chemotherapy in OS (the primary endpoint).
- Although the sample size of the Japanese subpopulations in Studies 189, 407, and 042, and the numbers of events occurring in these subpopulations were insufficient to appropriately evaluate the efficacy of pembrolizumab in Japanese patients, based only on the results from the subpopulations, the results from the Japanese subpopulations did not tend to clearly differ from those from the overall study populations.

7.2.R.2 Safety [For adverse events, see "7.4.2 Adverse events reported in clinical studies in patients with NSCLC."]

PMDA's view:

As a result of its review described in the section below, PMDA considers that the adverse events that require special attention after the administration of pembrolizumab in combination with platinum-based chemotherapy to chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC, or as a monotherapy to chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC are those identified as requiring attention at the regulatory reviews for the approved indications[7)] and should also be closely monitored when pembrolizumab is administered.

PMDA's conclusion:

Although attention should be paid to the above events, pembrolizumab is also tolerable when administered in combination with platinum-based chemotherapy to chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC, or when administered as a monotherapy to chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis and patient management in anticipation of adverse reactions due to an excessive immune response, drug interruption, or other appropriate actions.

7.2.R.2.1 Differences in safety profile between Japanese and non-Japanese patients

The applicant's explanation about the safety of pembrolizumab, based on the safety data from Studies 189, 407, and 042:

Table 23 shows a summary of the safety data from Studies 189, 407, and 042.

Table 23. Safety summary (Studies 189, 407, and 042)

	n (%)					
	Study 189[*1]		Study 407[*1]		Study 042[*2]	
	Pembrolizumab N = 405	Placebo N = 202	Pembrolizumab N = 278	Placebo N = 280	Pembrolizumab N = 636	Chemotherapy N = 615
All adverse events	404 (99.8)	200 (99.0)	273 (98.2)	274 (97.9)	610 (95.9)	606 (98.5)
Grade ≥3 adverse events	272 (67.2)	133 (65.8)	194 (69.8)	191 (68.2)	318 (50.0)	351 (57.1)
Adverse events leading to death	27 (6.7)	12 (5.9)	23 (8.3)	18 (6.4)	70 (11.0)	46 (7.5)
Serious adverse events	202 (49.9)	95 (47.0)	113 (40.6)	107 (38.2)	259 (40.7)	187 (30.4)
Adverse events leading to drug discontinuation						
Pembrolizumab or placebo	82 (20.2)	21 (10.4)	48 (17.3)	22 (7.9)	122 (19.2)	—
Chemotherapy	96 (23.7)	26 (12.9)	44 (15.8)	29 (10.4)	—	89 (14.5)
Adverse events leading to drug interruption						
Pembrolizumab or placebo	213 (52.6)	92 (45.5)	141 (50.7)	107 (38.2)	212 (33.3)	—
Chemotherapy	199 (49.1)	91 (45.0)	132 (47.5)	131 (46.8)	—	225 (36.6)
Adverse events leading to dose reduction						
Chemotherapy	68 (16.8)	20 (9.9)	63 (22.7)	49 (17.5)	—	64 (10.4)

*1, Pembrolizumab or placebo was administered in combination with platinum-based chemotherapy; *2, Pembrolizumab monotherapy or platinum-based chemotherapy

In Study 189, adverse events of any grade reported with a ≥5% higher incidence in the pembrolizumab group than in the placebo group were rash (20.2% [82 of 405 patients] in the pembrolizumab group, 11.4% [23 of 202 patients] in the placebo group), oedema peripheral (19.3% [78 of 405 patients], 12.9% [26 of 202 patients]), and lacrimation increased (17.0% [69 of 405 patients], 10.9% [22 of 202 patients]). Grade ≥3 adverse events reported with a ≥2% higher incidence in the pembrolizumab group than in the placebo group were neutropenia (15.8% [64 of 405 patients], 11.9% [24 of 202 patients]), febrile neutropenia (6.7% [27 of 405 patients], 2.0% [4 of 202 patients]), asthenia (6.2% [25 of 405 patients], 3.5% [7 of 202 patients]), fatigue (5.7% [23 of 405 patients], 2.5% [5 of 202 patients]), diarrhoea (5.2% [21 of 405 patients], 3.0% [6 of 202 patients]), and acute kidney injury (2.0% [8 of 405 patients], 0%). Serious adverse events with a ≥2% higher incidence in the pembrolizumab group than in the placebo group were febrile neutropenia (5.7% [23 of 405 patients], 2.0% [4 of 202 patients]), neutropenia (2.5% [10 of 405 patients], 0.5% [1 of 202 patients]), and acute kidney injury (2.0% [8 of 405 patients], 0%). The adverse event that led to drug discontinuation with a ≥2% higher incidence in the pembrolizumab group than in the placebo group was acute kidney injury (2.0% [8 of 405 patients], 0%). Adverse events that led to drug interruption with a ≥2% higher incidence in the pembrolizumab group than in the placebo group were thrombocytopenia (4.7% [19 of 405 patients], 1.0% [2 of 202 patients]), diarrhoea (4.0% [16 of 405 patients], 1.0% [2 of 202 patients]), fatigue (3.5% [14 of 405 patients], 1.5% [3 of 202 patients]), and febrile neutropenia (2.2% [9 of 405 patients], 0%). No adverse events leading to death with a 2% higher incidence in the pembrolizumab group than in the placebo group.

In Study 407, adverse events of any grade reported with a ≥5% higher incidence in the pembrolizumab group than in the placebo group were alopecia (46.0% [128 of 278 patients] in the pembrolizumab group, 36.4% [102 of 280 patients] in the placebo group), thrombocytopenia (30.6% [85 of 278 patients], 23.2% [65 of 280 patients]), diarrhoea (29.9% [83 of 278 patients], 23.2% [65 of 280 patients]), arthralgia (20.5% [57 of 278

patients], 14.3% [40 of 280 patients]), pruritus (12.9% [36 of 278 patients], 7.5% [21 of 280 patients]), and taste abnormality (9.0% [25 of 278 patients], 3.9% [11 of 280 patients]). The Grade ≥3 adverse events reported with a ≥2% higher incidence in the pembrolizumab group than in the placebo group was pneumonitis (2.5% [7 of 278 patients], 0.4% [1 of 280 patients]). Adverse events that led to drug interruption with a ≥2% higher incidence in the pembrolizumab group than in the placebo group were thrombocytopenia (14.4% [40 of 278 patients], 8.9% [25 of 280 patients]), neutropenia (11.5% [32 of 278 patients], 8.6% [24 of 280 patients]), and pneumonitis (2.2% [6 of 278 patients], 0 %). No serious adverse events, adverse events leading to drug discontinuation or death were reported with a ≥2% higher incidence in the pembrolizumab group than in the placebo group.

In Study 042, adverse events of any grade reported with a ≥5% higher incidence in the pembrolizumab group than in the chemotherapy group were dyspnoea (16.5% [105 of 636 patients] in the pembrolizumab group, 11.4% [70 of 615 patients] in the chemotherapy group), cough (15.6% [99 of 636 patients], 10.6% [65 of 615 patients]), hypothyroidism (12.1% [77 of 636 patients], 1.5% [9 of 615 patients]), hyperthyroidism (6.1% [39 of 636 patients]), 0.7% [4 of 615 patients]), and pneumonitis (7.4% [47 of 636 patients]), 0.2% [1 of 615 patients]). The Grade ≥3 adverse events reported with a ≥2% higher incidence in the pembrolizumab group than in the chemotherapy group was pneumonitis (3.1% [20 of 636 patients]), 0%). Serious adverse events reported with a ≥2% higher incidence in the pembrolizumab group than in the chemotherapy group were pneumonia (7.4% [47 of 636 patients], 5.2% [32 of 615 patients]) and pneumonitis (3.9% [25 of 636 patients], 0.2% [1 of 615 patients]. The adverse event that led to drug discontinuation with a ≥2% higher incidence in the pembrolizumab group than in the chemotherapy group was pneumonitis (3.0% [19 of 636 patients], 0%). Adverse events that led to drug interruption with a ≥2% higher incidence in the pembrolizumab group than in the chemotherapy group were pneumonitis (3.1% [20 of 636 patients], 0.2% [1 of 615 patients] and hypothyroidism (2.2% [14 of 636 patients], 0%). No adverse events led to death with a ≥2% higher incidence in the pembrolizumab group than in the chemotherapy group.

The applicant's explanation about the differences in the safety profile of pembrolizumab between (a) chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC, (b) chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC, or (c) chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC, and patients treated for the approved indications was as follows:

The results of the comparisons of the incidences of adverse events between patients in the pembrolizumab group of Study 189, 407, or 042 and patients who were treated with pembrolizumab for the approved indications are shown in Table 6 [see Section 7.1.R.2.1].

(a) Study 189:

Adverse events of any grade reported with a ≥10% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent NSQ-NSCLC than in any of the other patient populations, treated for the approved indications, were nausea (chemotherapy-naïve, unresectable, advanced or recurrent NSQ-NSCLC,

55.6%; PD-L1 positive NSCLC, 20.2%, unresectable malignant melanoma, 25.3%; cHL, 13.3%; radically unresectable urothelial carcinoma, 20.7%), anaemia (46.2%, 10.3%, 12.5%, 9.0%, 17.3%), constipation (34.8%, 16.4%, 19.2%, 9.5%, 18.8%), neutropenia (27.2%, 0.6%, 0.5%, 6.2%, 0%), thrombocytopenia (18.0%, 1.1%, 2.1%, 5.2%, 0.4%), and lacrimation increased (17.0%, 0.5%, 0.7%, 1.9%, 1.1%). Grade ≥3 adverse events reported with a ≥5% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent NSQ-NSCLC than in any of the other patient populations were anaemia (16.3%, 2.8%, 3.7%, 3.8%, 8.3%), neutropenia (15.8%, 0%, 0.2%, 2.9%, 0%), thrombocytopenia (7.9%, 0.4%, 0.4%, 1.9%, 0%), febrile neutropenia (6.7%, 0.2%, 0%, 1.0%, 0%), and asthenia (6.2%, 1.2%, 1.2%, 0%, 0.8%). The serious adverse event reported with a ≥5% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent NSQ-NSCLC than in any of the other patient populations was febrile neutropenia (5.7%, 0.2%, 0%, 0%, 0%). Adverse events that led to drug (pembrolizumab or concomitant chemotherapy) interruption with a ≥5% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent NSQ-NSCLC than in any of the other patient populations were neutropenia (13.1%, 0%, 0.1%, 0%, 0%) and anaemia (7.4%, 0.8%, 0.8%, 0%, 0.4%). No adverse events led to death or drug (pembrolizumab or concomitant chemotherapy) discontinuation, with a ≥5% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent NSQ-NSCLC than in any of the other patient populations.

The above comparisons revealed no clear differences in the safety profile of pembrolizumab between chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC and patients treated for the approved indications, although some adverse events and serious adverse events, etc. occurred more frequently in chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC than in patients treated for the approved indications, however, all of these adverse events were known adverse events of CDDP, CBDCA, or PEM.

(b) Study 407:

Adverse events of any grade reported with a ≥10% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent SQ-NSCLC than in any of the other patient populations, treated for the approved indications, were anaemia (chemotherapy-naïve, unresectable, advanced or recurrent SQ-NSCLC, 53.2%; PD-L1 positive NSCLC, 10.3%; unresectable malignant melanoma, 12.5%; cHL, 9.0%; radically unresectable urothelial carcinoma, 17.3%), alopecia (46.0%, 1.3%, 2.1%, 2.4%, 0.8%), neutropenia (37.8%, 0.6%, 0.5%, 6.2%, 0%), nausea (35.6%, 20.2%, 25.3%, 13.3%, 20.7%), thrombocytopenia (30.6%, 1.1%, 2.1%, 5.2%, 0.4%), and neuropathy peripheral (20.5%, 1.9%, 1.8%, 3.8%, 0.4%). Grade ≥3 adverse events reported with a ≥5% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent SQ-NSCLC than in any of the other patient populations were neutropenia (22.7%, 0%, 0.2%, 2.9%, 0%), anaemia (15.5%, 2.8%, 3.7%, 3.8%, 8.3%), and neutrophil count decreased (6.1%, 0%, 0.1%, 0%, 0.4%). The serious adverse event reported with a ≥5% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent SQ-NSCLC than in any of the other patient populations was febrile neutropenia (5.4%, 0.2%, 0%, 0%, 0%). Adverse events that led to drug (pembrolizumab or concomitant chemotherapy) interruption with a ≥5% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent SQ-NSCLC than in any of the other patient populations were anaemia (12.9%, 0.8%, 0.8%, 0%, 0.4%), neutropenia (19.4%, 0%,

0.1%, 0%, 0%), and thrombocytopenia (18.0%, 0%, 0.2%, 0%, 0%). No adverse events led to death or drug (pembrolizumab or concomitant chemotherapy) discontinuation, with a ≥5% higher incidence in chemotherapy-naïve patients with unresected, advanced or recurrent SQ-NSCLC than in any of the other patient populations.

The above comparisons revealed no clear differences in the safety profile of pembrolizumab between chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC and patients treated for the approved indications, although some adverse events and serious adverse events, etc. occurred more frequently in chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC than in patients treated for the approved indications, however, all of these adverse events were known adverse events of CBDCA, PTX, or nab-PTX.

(c) Study 042:

Adverse events of any grade reported with a ≥5% higher incidence in chemotherapy-naïve patients with advanced or recurrent PD-L1 (TPS ≥1%) NSCLC than in any of the other patient populations, treated for the approved indications, was pneumonia (chemotherapy-naïve, advanced or recurrent PD-L1 positive [TPS ≥1%] NSCLC, 11.9%; PD-L1 positive NSCLC, 6.7%; unresectable malignant melanoma, 2.0%; cHL, 2.4%; radically unresectable urothelial carcinoma, 4.5%). The Grade ≥3 adverse events reported with a ≥2% higher incidence in chemotherapy-naïve patients with advanced or recurrent PD-L1 (TPS ≥1%) NSCLC than in any of the other patient populations was pneumonia (7.4%, 4.7%, 0.8%, 0.5%, 2.6%). The serious adverse event reported with a ≥2% higher incidence in chemotherapy-naïve patients with advanced or recurrent PD-L1 (TPS ≥1%) NSCLC than in any of the other patient populations was also pneumonia (7.4%, 4.7%, 1.1%, 1.4%, 3.4%). No adverse events led to death, drug interruption or discontinuation, with a ≥2% higher incidence in chemotherapy-naïve patients with advanced or recurrent PD-L1 (TPS ≥1%) NSCLC than in any of the other patient populations.

The above comparisons revealed no clear differences in the frequently noted adverse events and serious adverse events, etc. between chemotherapy-naïve patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC and patients treated for the approved indications, suggesting that the safety of pembrolizumab is similar for these patient populations.

The applicant's explanation about the safety of pembrolizumab between Japanese and non-Japanese patients, based on the safety data from patients receiving pembrolizumab in (a) Study 189, (b) Study 407, and (c) Study 042:

(a) Study 189:

Table 24 shows a summary of the safety data in Japanese patients (including the Japanese expanded cohort[10)]) and non-Japanese patients receiving pembrolizumab in Study 189.

10) In Part B of Study 011, 1 patient each died of ILD and pneumonitis, for which a causal relationship to the study drug could not be ruled out. Accordingly, the enrollment of Japanese patents in Study 189 was suspended, and an expanded cohort composed of

Table 24. Safety summary (Study 189)

	n (%)	
	Japanese N = 25	Non-Japanese N = 401
All adverse events	25 (100)	400 (99.8)
Grade ≥3 adverse events	13 (52.0)	270 (67.3)
Adverse events leading to death	0	27 (6.7)
Serious adverse events	5 (20.0)	200 (49.9)
Adverse events leading to drug discontinuation		
Pembrolizumab	3 (12.0)	81 (20.2)
Chemotherapy	3 (12.0)	96 (23.9)
Adverse events leading to drug interruption		
Pembrolizumab	16 (64.0)	211 (52.6)
Chemotherapy	15 (60.0)	198 (49.4)
Adverse events leading to dose reduction		
Pembrolizumab	—	—
Chemotherapy	3 (12.0)	67 (16.7)

In the pembrolizumab group of Study 189, adverse events of any grade reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients were nausea (Japanese, 72.0% [18 of 25 patients]; 55.6% [223 of 401 patients]), constipation (64.0% [16 of 25 patients], 34.4% [138 of 401 patients]), decreased appetite (56.0% [14 of 25 patients]), 27.9% [112 of 401 patients]), white blood cell count decreased (40.0% [10 of 25 patients], 6.2% [25 of 401 patients]), ALT increased (28.0% [7 of 25 patients], 11.5% [46 of 401 patients]), neutrophil count decreased (28.0% [7 of 25 patients], 2.7% [11 of 401 patients]), lymphocyte count decreased (28.0% [7 of 25 patients], 2.5% [10 of 401 patients]), hiccups (28.0% [7 of 25 patients], 4.7% [19 of 401 patients]), AST increased (24.0% [6 of 25 patients], 8.7% [35 of 401 patients]), stomatitis (24.0% [6 of 25 patients], 8.2% [33 of 401 patients]), dry skin (24.0% [6 of 25 patients], 4.2% [17 of 401 patients]), malaise (24.0% [6 of 25 patients], 0.5% [2 of 401 patients]), insomnia (20.0% [5 of 25 patients], 5.7% [23 of 401 patients]), alopecia (16.0% [4 of 25 patients], 5.0% [20 of 401 patients]), hepatic function abnormal (12.0% [3 of 25 patients], 0.2% [1 of 401 patients]), and diabetes mellitus (12.0% [3 of 25 patients], 0.2% [1 of 401 patients]). Grade ≥3 adverse events reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were neutrophil count decreased (20.0% [5 of 25 patients], 1.7% [7 of 401 patients]), lymphocyte count decreased (20.0% [5 of 25 patients], 0.5% [2 of 401 patients]), white blood cell count decreased (16.0% [4 of 25 patients]), 1.5% [6 of 401 patients]), and hyponatraemia (12.0% [3 of 25 patients]), 1.7% [7 of 401 patients]). Adverse events that led to drug interruption with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were white blood cell count decreased (20.0% [5 of 25 patients]), 1.7% [7 of 401 patients]), neutrophil count decreased (16.0% [4 of 25 patients], 0.5% [2 of 401 patients]), and lymphocyte count decreased (12.0% [3 of 25 patients], 0%). No adverse events leading to death, serious adverse events, or adverse events leading to drug discontinuation were reported, with a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

Japanese patients was to be added to enroll 40 Japanese patients (the target sample size for Japanese patients when Study 189 was planned), including the 10 Japanese patients who had been enrolled (Protocol Amendment Version 6 [dated [redacted]. 20[redacted]]).

In the placebo group of Study 189, adverse events of any grade reported in ≥2 Japanese patients and with a ≥10% higher incidence in Japanese patients than in non-Japanese patients were constipation (73.3% [11 patients], 30.6% [60 patients]), anaemia (66.7% [10 patients], 45.4% [89 patients]), decreased appetite (60.0% [9 patients], 29.1% [57 patients]), leukopenia (46.7% [7 patients], 5.1% [10 patients]), malaise (33.3% [5 patients], 1.5% [3 patients]), ALT increased (33.3% [5 patients], 8.2% [16 patients]), AST increased (33.3% [5 patients], 5.6% [11 patients]), taste abnormality (33.3% [5 patients], 9.2% [18 patients]), hiccups (33.3% [5 patients], 1.5% [3 patients]), thrombocytopenia (26.7% [4 patients], 13.8% [27 patients]), stomatitis (26.7% [4 patients], 7.7% [15 patients]), oedema peripheral (26.7% [4 patients], 12.2% [24 patients]), white blood cell count decreased (20.0% [3 patients], 5.6% [11 patients]), anxiety (20.0% [3 patients], 4.6% [9 patients]), neutrophil count decreased (13.3% [2 patients], 2.0% [4 patients]), platelet count decreased (13.3% [2 patients], 0.5% [1 patient]), tumour pain (13.3% [2 patients], 1.0% [2 patients]), peripheral sensory neuropathy (13.3% [2 patients]), 1.0% [2 patients]), and ILD (13.3% [2 patients], 0%). Grade ≥3 adverse events reported in ≥2 Japanese patients were anaemia (20.0% [3 patients], 14.3% [28 patients]) and neutropenia (13.3% [2 patients], 11.2% [22 patients]). The serious adverse event reported in ≥2 Japanese patients was ILD (13.3% [2 patients], 0%). No Japanese patient died due to adverse events.

(b) Study 407:

Table 25 shows a summary of the safety data from Japanese and non-Japanese patients receiving pembrolizumab in Study 407.

Table 25. Safety summary (Study 407)

	n (%)	
	Japanese N = 22	Non-Japanese N = 256
All adverse events	22 (100)	251 (98.0)
Grade ≥3 adverse events	19 (86.4)	175 (68.4)
Adverse events leading to death	1 (4.5)	22 (8.6)
Serious adverse events	13 (59.1)	100 (39.1)
Adverse events leading to drug discontinuation		
Pembrolizumab	7 (31.8)	41 (16.0)
Chemotherapy	8 (36.4)	36 (14.1)
Adverse events leading to drug interruption		
Pembrolizumab	20 (90.9)	121 (47.3)
Chemotherapy	15 (68.2)	117 (45.7)
Adverse events leading to dose reduction		
Chemotherapy	6 (27.3)	57 (22.3)

In the pembrolizumab group of Study 407, adverse events of any grade reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients were anaemia (Japanese, 86.4% [19 of 22 patients]; non-Japanese, 50.4% [129 of 256 patients]), alopecia (77.3% [17 of 22 patients], 43.4% [111 of 256 patients]), neutropenia (63.6% [14 of 22 patients], 35.5% [91 of 256 patients]), constipation (59.1% [13 of 22 patients], 19.9% [51 of 256 patients]), white blood cell count decreased (54.5% [12 of 22 patients], 7.4% [19 of 256 patients]), decreased appetite (50.0% [11 of 22 patients], 22.3% [57 of 256 patients]), malaise (40.9% [9 of 22 patients], 0.4% [1 of 256 patients]), platelet count decreased (40.9% [9 of 22 patients], 5.9% [15 of 256 patients]), peripheral sensory neuropathy (40.9% [9 of 22 patients], 9.0% [23 of 256 patients]), insomnia

(36.4% [8 of 22 patients], 7.8% [20 of 256 patients]), leukopenia (27.3% [6 of 22 patients], 7.0% [18 of 256 patients]), neutrophil count decreased (27.3% [6 of 22 patients], 7.0% [18 of 256 patients]), stomatitis (18.2% [4 of 22 patients], 2.3% [6 of 256 patients]), hyponatraemia (18.2% [4 of 22 patients], 3.9% [10 of 256 patients]), hiccups (18.2% [4 of 22 patients], 3.5% [9 of 256 patients]), and rash maculo-papular (18.2% [4 of 22 patients], 1.6% [4 of 256 patients]). Grade ≥3 adverse events reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were neutropenia (40.9% [9 of 22 patients], 21.1% [54 of 256 patients]), anaemia (36.4% [8 of 22 patients], 13.7% [35 of 256 patients]), leukopenia (22.7% [5 of 22 patients], 3.1% [8 of 256 patients]), neutrophil count decreased (18.2% [4 of 22 patients], 5.1% [13 of 256 patients]), white blood cell count decreased (18.2% [4 of 22 patients], 3.1% [8 of 256 patients]), hyponatraemia (18.2% [4 of 22 patients], 2.3% [6 of 256 patients]), diarrhoea (9.1% [2 of 22 patients], 3.5% [9 of 256 patients]), delirium (9.1% [2 of 22 patients], 0%), and pneumonitis(9.1% [2 of 22 patients], 2.0% [5 of 256 patients]). The serious adverse event reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients was pneumonitis (13.6% [3 of 22 patients], 1.6% [4 of 256 patients]). The adverse event that led to drug discontinuation with a ≥5% higher incidence in Japanese patients than in non-Japanese patients was also pneumonitis (9.1% [2 of 22 patients], 1.2% [3 of 256 patients]). Adverse events that led to drug interruption with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were anaemia (40.9% [9 of 22 patients], 5.9% [15 of 256 patients]), neutropenia (31.8% [7 of 22 patients], 9.8% [25 of 256 patients]), leukopenia (18.2% [4 of 22 patients], 1.2% [3 of 256 patients]), platelet count decreased (18.2% [4 of 22 patients], 1.6% [4 of 256 patients]), white blood cell count decreased (18.2% [4 of 22 patients], 0.4% [1 of 256 patients]), diarrhoea (9.1% [2 of 22 patients], 1.2% [3 of 256 patients]), rash (9.1% [2 of 22 patients], 0.4% [1 of 256 patients]), and decreased appetite (9.1% [2 of 22 patients], 0%). No adverse events led to death with a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

In the placebo group of Study 407, adverse events of any grade reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients were anaemia (Japanese, 64.3% [18 patients]; non-Japanese, 50.4% [127 patients]), decreased appetite (64.3% [18 patients], 25.4% [64 patients]), alopecia (60.7% [17 patients], 33.7% [85 patients]), constipation (57.1% [16 patients], 17.9% [45 patients]), white blood cell count decreased (46.4% [13 patients], 6.7% [17 patients]), peripheral sensory neuropathy (42.9% [12 patients], 9.5% [24 patients]), neutrophil count decreased (32.1% [9 patients], 7.5% [19 patients]), malaise (32.1% [9 patients], 1.6% [4 patients]), arthralgia (28.6% [8 patients], 12.7% [32 patients]), pyrexia (25.0% [7 patients], 11.9% [30 patients]), platelet count decreased (17.9% [5 patients], 6.0% [15 patients]), stomatitis (14.3% [4 patients], 4.0% [10 patients]), GGT increased (14.3% [4 patients], 1.6% [4 patients]), and gingivitis (10.7% [3 patients], 0%). Grade ≥3 adverse events reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were neutropenia (25.0% [7 patients], 6.7% [17 patients]), white blood cell count decreased (17.9% [5 patients], 2.4% [6 patients]), and lung infection (7.1% [2 patients], 0.4% [1 patient]). The serious adverse event reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients was lung infection (7.1% [2 patients], 0%). No adverse events led to death with a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

In the pembrolizumab group, the incidence of ILD-like events[11] was higher in Japanese patients (18.2% [4 of 22 patients]) than in non-Japanese patients (5.5% [14 of 256 patients]). However, the incidence of ILD-like events was also higher in the placebo group in Japanese patients (10.7% [3 of 28 patients] than in non-Japanese patients [1.2% [3 of 252 patients]). Of the 4 Japanese patients experiencing an ILD-like event in the pembrolizumab group, 1 died of the ILD-like event, for which a causal relationship to the study drug could not be ruled out. However, a blinded assessment by the ILD evaluation committee found that the patient had honeycomb lung at baseline, which was an exclusion criterion in Study 407, and that the ILD-like event that led to death might have been associated with the honeycomb lung. The ILD-like events in the remaining 3 patients were not resolving (Grade 3), resolved (Grade 2), and improved (Grade 2) in 1 patient each.

The above results indicated that pembrolizumab in combination with chemotherapy may cause ILD-like events more frequently than chemotherapy alone; therefore, attention should be paid to the risk of ILD-like events. However, these ILD-like events are known adverse events of both pembrolizumab and chemotherapy. Therefore, pembrolizumab in combination with platinum-based chemotherapy is also tolerable in Japanese patients, as long as the occurrence of ILD-like events is carefully monitored and managed appropriately.

(c) Study 042:

Table 26 shows a summary of the safety data from Japanese and non-Japanese patients receiving pembrolizumab in Study 042.

Table 26. Safety summary (Study 042)

	n (%)	
	Japanese N = 47	Non-Japanese N = 589
All adverse events	41 (87.2)	569 (96.6)
Grade ≥3 adverse events	19 (40.4)	299 (50.8)
Adverse events leading to death	0	70 (11.9)
Serious adverse events	17 (36.2)	242 (41.1)
Adverse events leading to drug discontinuation	8 (17.0)	114 (19.4)
Adverse events leading to drug interruption	13 (27.7)	199 (33.8)

In the pembrolizumab group of Study 042, adverse events of any grade reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients were constipation (Japanese, 23.4% [11 of 47 patients]; non-Japanese, 11.2% [66 of 589 patients]), insomnia (23.4% [11 of 47 patients], 3.7% [22 of 589 patients]), rash (23.4% [11 of 47 patients], 9.8% [58 of 589 patients]), malaise (19.1% [9 of 47 patients], 1.4% [8 of 589 patients]), back pain (19.1% [9 of 47 patients], 9.0% [53 of 589 patients]), pneumonitis (17.0% [8 of 47 patients], 6.6% [39 of 589 patients]), and renal impairment (10.6% [5 of 47 patients], 0.5% [3 of 589 patients]). The Grade ≥3 adverse event reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients was decreased appetite (6.4% [3 of 47 patients], 1.4% [8 of 589 patients]). The serious adverse event reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients was pneumonitis (10.6% [5 of 47 patients], 3.4% [20 of 589 patients]. The adverse event that led to drug interruption with a ≥5%

[11] Events coded as MedDRA preferred terms of “acute interstitial pneumonitis,” “ILD,” “pneumonitis,” “idiopathic pneumonia syndrome,” and “organising pneumonia” were counted.

higher incidence in Japanese patients than in non-Japanese patients was also pneumonitis (8.5% [4 of 47 patients], 2.7% [16 of 589 patients]). No adverse events led to death or drug discontinuation, with a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

In the pembrolizumab group, the incidence of ILD-like events[11)] was higher in Japanese patients (21.3% [10 of 47 patients]) than in non-Japanese patients (7.3% [43 of 589 patients]). Of the 10 Japanese patients experiencing ILD-like events in the pembrolizumab group, 3 had Grade ≥3 events (Grade 3 in all of these patients), and no patients died of ILD-like events. At the time of data cutoff, the ILD-like events occurring in 8 of the 10 patients, except those of Grade 1 and Grade 2 in 1 patient each, had improved or resolved. In view of these results, pembrolizumab is tolerable in Japanese patients as well as non-Japanese patients, although continuous attention should be paid to the risk of ILD-like events.

PMDA's view:
In Studies 189, 407, and 042, some adverse events were reported more frequently in the pembrolizumab group than in (a) the control group or (b) patients treated for the approved indications. However, all of these events were known adverse events of pembrolizumab or the concomitant chemotherapy. PMDA has therefore concluded that pembrolizumab is tolerable in the following treatments of patients with NSCLC, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis, and patient management in anticipation of adverse reactions caused by an excessive immune response, drug interruption, or other appropriate actions. In Studies 189 and 407, Grade 3 or serious febrile neutropenia were more frequently reported in the pembrolizumab group than in the placebo group. However, all of these events improved or resolved, and are known adverse events of the concomitant chemotherapy. Therefore, the inclusion of any specific precautions in the package insert is unnecessary, although information on the incidence of the adverse reactions should be provided to healthcare professionals, through the package insert or other materials.

- Pembrolizumab in combination with platinum-based chemotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC
- Pembrolizumab monotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC

All of the adverse events that were more frequently reported in Japanese patients than in non-Japanese patients are known adverse events of pembrolizumab. In addition, considering the incidences of Grade ≥3 adverse events, serious advance events, and other notable adverse events, PMDA has concluded that pembrolizumab is tolerable in Japanese patients with unresectable, advanced or recurrent NSCLC, as long as appropriate measures, such as drug interruption are taken.

7.2.R.3 Clinical positioning and indications

The present partial change application has been proposed to change the indication of pembrolizumab from the approved indication of “unresectable, advanced or recurrent PD-L1 positive NSCLC” to “unresectable,

advanced or recurrent NSCLC," and to include the following statements in the "Precautions for Indications" section of the package insert.

- The efficacy and safety of pembrolizumab in adjuvant chemotherapy have not been established (unchanged from the previous approval).
- The "Clinical Studies" section should be carefully read to understand the percentage of PD-L1-expressing tumor cells (TPS). PD-L1 testing should be performed by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic. When used as monotherapy, pembrolizumab should be administered to patients whose tumors have been demonstrated to express PD-L1.
- Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand the status of *EGFR* mutation or *ALK* fusion genes in patients enrolled in the clinical studies (unchanged from the previous approval).

As a result of its review described in Sections "7.2 R.1 Efficacy," "7.2.R.3 Safety," and the section below, PMDA concluded that the modified indication, "unresectable, advanced or recurrent NSCLC" proposed by the applicant is appropriate and that the following precautionary statements should be included in the "Precautions for Indications" section.

- The efficacy and safety of pembrolizumab in adjuvant chemotherapy have not been established (unchanged from the previous approval).
- When used as monotherapy, pembrolizumab should be administered to patients whose tumors have been demonstrated to express PD-L1. The "Clinical Studies" section should be carefully read to understand the percentage of PD-L1-expressing tumor cells (TPS). PD-L1 testing should be performed by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic.
- Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand the status of EGFR mutation or ALK fusion genes in patients enrolled in the clinical studies (unchanged from the previous approval).

7.2.R.3.1 Clinical positioning and indication of pembrolizumab

In representative clinical practice guidelines and representative textbooks for clinical oncology in and outside Japan, pembrolizumab therapy for NSCLC is currently described as follows:

[Clinical practice guidelines]

- NCCN guidelines (v. 6. 2018):
  - Pembrolizumab in combination with a platinum + PEM is strongly recommended as the first-line therapy for chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC.
  - Pembrolizumab in combination with CBDCA + PTX or CBDCA + nab-PTX is recommended as the first-line therapy for chemotherapy-naïve patients with unresectable, advanced or recurrent SQ-NSCLC.
  - Pembrolizumab monotherapy is strongly recommended as the first-line therapy for chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC.

- US National Cancer Institute Physician Data Query (NCI PDQ) (version dated August 6, 2018):
  - Pembrolizumab in combination with a platinum + PEM is recommended as the first-line therapy for chemotherapy-naïve patients with unresectable, advanced or recurrent NSQ-NSCLC.
  - Pembrolizumab monotherapy is recommended as the first-line therapy for chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 (TPS ≥50%) NSCLC.
- Japanese clinical practice guidelines (NSCLC):
  - Pembrolizumab monotherapy is strongly recommended as the first-line therapy for chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 (TPS ≥50%) NSCLC.

PMDA asked the applicant to explain about the clinical positioning and intended population of pembrolizumab in the treatment of unresectable, advanced or recurrent NSCLC.

The applicant's response:
Based on the results of Studies 189, 407, and 042, the combination of pembrolizumab and chemotherapy can be positioned as a therapeutic option for chemotherapy-naïve patients with advanced or recurrent NSCLC, and pembrolizumab monotherapy can be positioned as a therapeutic option for chemotherapy-naïve patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC. Furthermore, pembrolizumab in combination with chemotherapy was demonstrated to be effective and safe, regardless of PD-L1 expression status, in Studies 189 and 407; therefore, PD-L1 testing has little clinical significance in the combination therapy for NSCLC in clinical practice, while PD-L1 testing is necessary when pembrolizumab is administered alone.

In view of the above, the indication of pembrolizumab for NSCLC can be changed to “unresectable, advanced or recurrent NSCLC,” provided that the following precautionary statements are included in the “Precautions for Indications” section of the package insert.
- The efficacy and safety of pembrolizumab in adjuvant chemotherapy have not been established (unchanged from the previous approval).
- The “Clinical Studies” section should be carefully read to understand the percentage of PD-L1-expressing tumor cells (TPS). PD-L1 testing should be performed by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic. When used as monotherapy, pembrolizumab should be administered to patients whose tumors have been demonstrated to express PD-L1.
- Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the “Clinical Studies” section to understand the status of *EGFR* mutation or *ALK* fusion genes in patients enrolled in the clinical studies (unchanged from the previous approval).

PMDA asked the applicant to explain the choice between pembrolizumab monotherapy and pembrolizumab in combination with platinum-based chemotherapy in the treatment of chemotherapy-naïve patients with advanced or recurrent NSCLC.

The applicant's response:
Based on the results of Studies 189 and 407, pembrolizumab should be used in combination with other antineoplastic drugs, regardless of PD-L1 expression status, in the treatment of chemotherapy-naïve patients with advanced or recurrent NSCLC. In addition, the possibility of pembrolizumab monotherapy should also be considered in PD-L1 positive (TPS ≥1%) patients, in view of the results of Studies 024 and 042.

Although there have been no clinical data that compare the efficacy and safety of pembrolizumab monotherapy with those of combination therapy with pembrolizumab and platinum-based chemotherapy, the combination therapy, rather than the monotherapy, should be chosen in the treatment of PD-L1 positive (TPS ≥1%) patients, except the monotherapy should be considered for patients who are intolerant to combination therapy with pembrolizumab and platinum-based chemotherapy, and those who are unwilling to receive chemotherapy.

PMDA's view:
Considering that pembrolizumab is intended to be used by physicians with sufficient knowledge and experience in cancer chemotherapy, the indication of pembrolizumab for NSCLC can be changed as the applicant has proposed, provided that the PD-L1 expression status or other characteristics of the patients enrolled in Study 189, 407, or 042 are detailed in the "Clinical Studies" section of the package insert, and the following statements are included in the "Precautions for Indications" section.

- The efficacy and safety of pembrolizumab in adjuvant chemotherapy have not been established (unchanged from the previous approval).
- When used as monotherapy, pembrolizumab should be administered to patients whose tumors have been demonstrated to express PD-L1. The "Clinical Studies" section should be carefully read to understand the percentage of PD-L1-expressing tumor cells (TPS). PD-L1 testing should be performed by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic.
- Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand the status of *EGFR* mutation or *ALK* fusion genes in patients enrolled in the clinical studies (unchanged from the previous approval).

Since there have been no clinical data that compare the efficacy and safety of pembrolizumab monotherapy with those of combination therapy with pembrolizumab and platinum-based chemotherapy in the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC, differences in the use of pembrolizumab alone, versus that in combination with platinum-based chemotherapy are currently unclear, and an appropriate treatment regimen should be chosen according to individual patient conditions.

7.2.R.3.2 Efficacy and safety of pembrolizumab by PD-L1 expression status (TPS), and intended patient population

Pembrolizumab is an antibody against human PD-1. PMDA asked the applicant to explain the efficacy and safety of pembrolizumab according to the expression status of PD-L1, a ligand of PD-1, and to describe the intended patient population of pembrolizumab.

The applicant's explanation:

PD-L1 expression status in tumor tissue samples (TPS) were measured using "Clinical Trial Assay 'Dako' (Dako Japan Co., Ltd.)" in Study 189 or using "PD-L1 IHC 22C3 pharmDx assay 'Dako' (Dako Japan Co., Ltd.)" in Studies 407 and 042, to evaluate the efficacy and safety of pembrolizumab by TPS (cutoff values: 1% or 50% in Studies 189 and 407, and 20% or 50% in Study 042) in (a) Study 189, (b) Study 407, and (c) Study 042, as described below. The results indicated that pembrolizumab in combination with platinum-based chemotherapy can be recommended, regardless of PD-L1 expression status, for the treatment of chemotherapy-naïve patients with advanced or recurrent NSCLC, and that pembrolizumab monotherapy can be recommended, regardless of PD-L1 expression status, for the treatment of chemotherapy-naïve patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC.

(a) Study 189:

The efficacy of pembrolizumab was evaluated by TPS (cutoff value, 1% or 50%) in patients with NSQ-NSCLC with evaluable TPS data. Table 27 and Figure 16 show the OS in these patients by TPS (cutoff value, 1% or 50%) (data cutoff date: November 8, 2017).

In both the PD-L1 positive and negative subgroups, based on each cutoff value, patients receiving pembrolizumab showed a prolonged OS, compared with those receiving placebo. Pembrolizumab is thus expected to be effective, regardless of PD-L1 expression status, in patients with NSQ-NSCLC.

Table 27. Efficacy of pembrolizumab by TPS in tumor tissue samples (Study 189)

PD-L1 expression	Treatment	N	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P* value for interaction
TPS <1%	Pembrolizumab	127	15.2 [12.3, —]	0.59 [0.38, 0.92]	0.3274
	Placebo	63	12.0 [7.0, —]		
TPS ≥1%	Pembrolizumab	260	— [—,—]	0.47 [0.34, 0.66]	
	Placebo	128	11.3 [8.7, —]		
TPS <50%	Pembrolizumab	255	— [15.2, —]	0.57 [0.41, 0.79]	0.2294
	Placebo	121	12.1 [8.7, -]		
TPS ≥50%	Pembrolizumab	132	— [—,—]	0.42 [0.26, 0.68]	
	Placebo	70	10.0 [7.5, —]		

—, Not reached; *, Cox regression stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a platinum (CDDP, CBDCA), and smoking history (present, absent)

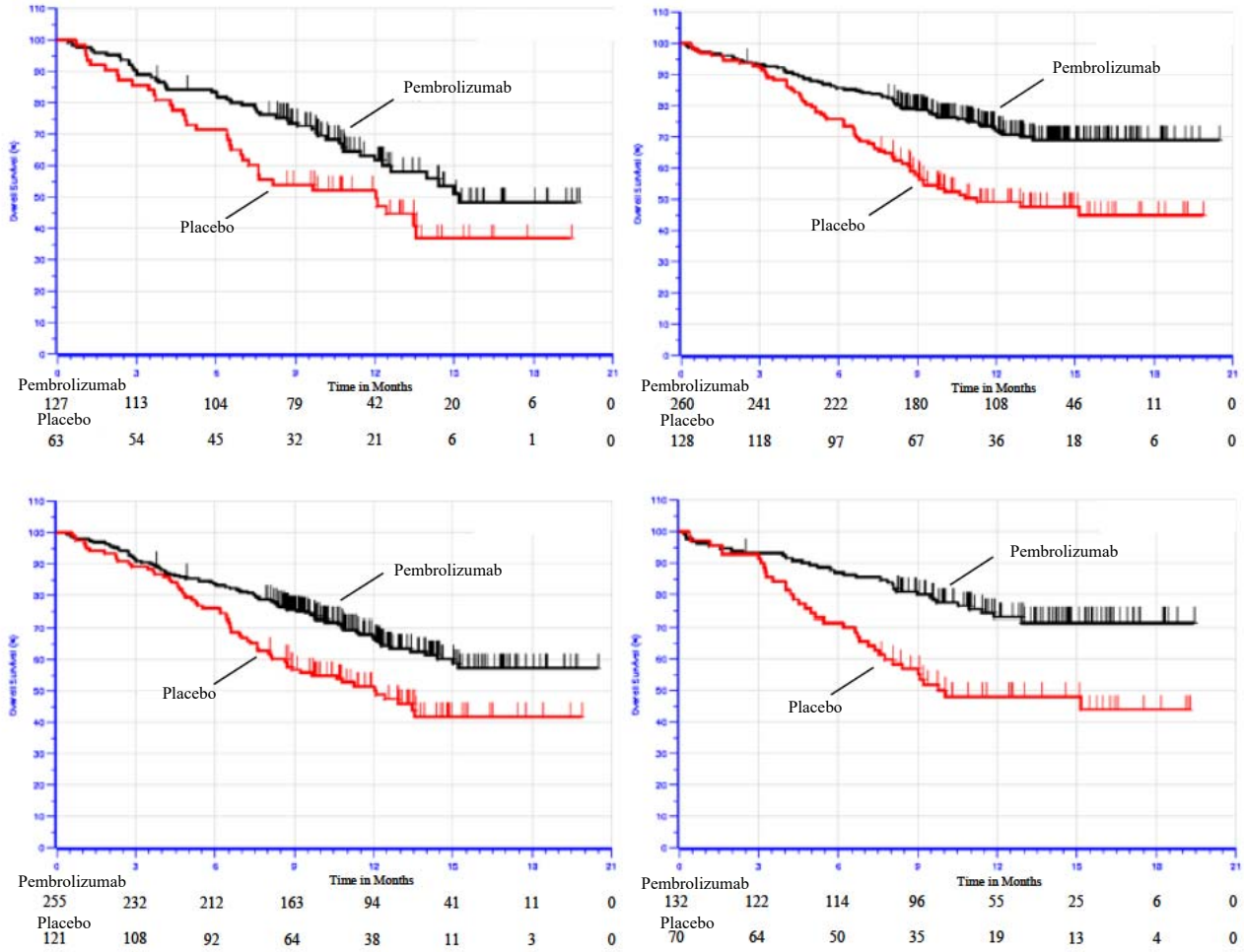


Figure 16. Kaplan-Meier curves of OS by TPS (data cutoff date: November 8, 2017)
(Top left, TPS <1%; top right, TPS ≥1%; bottom left, TPS <50%; bottom right, TPS ≥50%)

In the pembrolizumab group of Study 189, the incidences of adverse events of any grade were 100%, both in patients with TPS <1% and in those with TPS ≥1%. The incidences of Grade ≥3 adverse events were 58.7% in patients with TPS <1% and 71.5% in those with TPS ≥1%. The incidences of serious adverse events were 43.7% in patients with TPS <1% and 53.1% in those with TPS ≥1%. In addition, the incidences of adverse events of any grade were 100%, both in patients with TPS <50% and in those with TPS ≥50%. The incidences of Grade ≥3 adverse events were 62.8% in patients with TPS <50% and 76.0% in those with TPS ≥50%. The incidences of serious adverse events were 46.2% in patients with TPS <50% and 57.4% in those with TPS ≥50%. These results suggested no clear differences in the safety of pembrolizumab, according to PD-L1 expression status in patients with NSQ-NSCLC.

(b) Study 407:

The efficacy of pembrolizumab was evaluated by TPS (cutoff value, 1% or 50%) in patients with SQ-NSCLC with evaluable TPS data. Table 28 and Figure 17 show the OS in these patients by TPS (cutoff value, 1% or 50%) (data cutoff date: April 3, 2018).

In both the PD-L1 positive and negative subgroups, based on each cutoff value, patients receiving pembrolizumab showed a prolonged OS, compared with those receiving placebo. Pembrolizumab is thus expected to be effective, regardless of PD-L1 expression status, in patients with SQ-NSCLC.

Table 28. Efficacy of pembrolizumab by TPS in tumor tissue samples (Study 407)

PD-L1 expression	Treatment	N	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P* value for interaction
TPS <1%	Pembrolizumab	95	15.9 [13.1, —]	0.61 [0.38, 0.98]	0.9132
	Placebo	99	10.2 [8.6, 13.8]		
TPS ≥1%	Pembrolizumab	176	16.6 [13.2, —]	0.65 [0.45, 0.92]	
	Placebo	177	11.6 [8.9, -]		
TPS <50%	Pembrolizumab	198	15.9 [13.2, —]	0.59 [0.42, 0.82]	0.7466
	Placebo	203	11.1 [9.1, 13.8]		
TPS ≥50%	Pembrolizumab	73	— [11.3, —]	0.64 [0.37, 1.10]	
	Placebo	73	— [7.4, —]		

—, Not reached; *, Cox regression stratified by PD-L1 expression status (TPS ≥1%, <1%), choice of a taxane-based chemotherapy (PTX, nab-PTX), and geographic region (East Asia, non-East Asia)

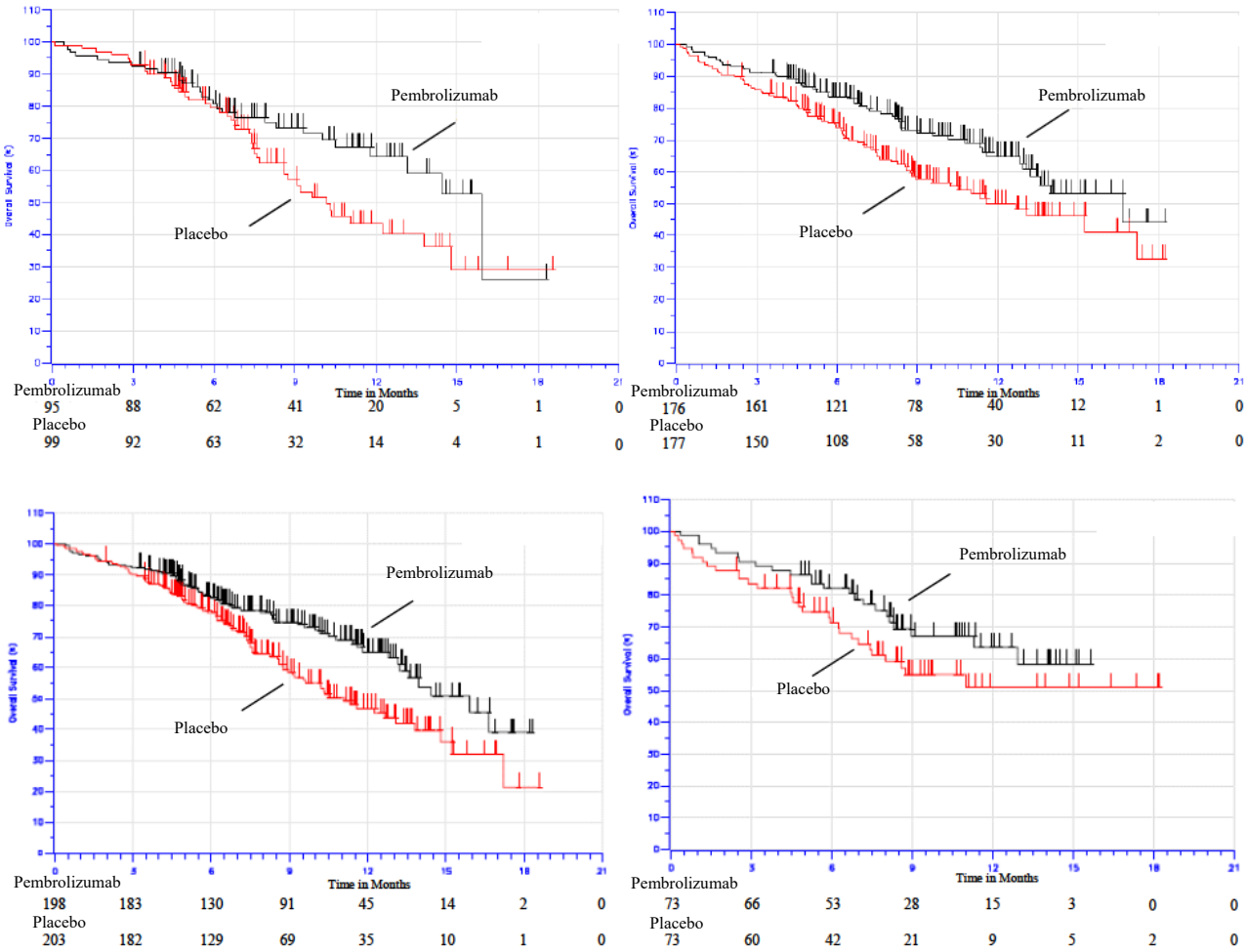


Figure 17. Kaplan-Meier curves of OS by TPS (data cutoff date: April 3, 2018)
(Top left, TPS <1%; top right, TPS ≥1%; bottom left, TPS <50%; bottom right, TPS ≥50%)

In the pembrolizumab group of Study 407, the incidences of adverse events of any grade were 97.9% in patients with TPS <1% and 98.3% in those with TPS ≥1%. The incidences of Grade ≥3 adverse events were 72.6% in

patients with TPS <1% and 67.0% in those with TPS ≥1%. The incidences of serious adverse events were 38.9% in patients with TPS <1% and 40.9% in those with TPS ≥1%. In addition, the incidences of adverse events of any grade were 97.5% in patients with TPS <50% and 100% in those with TPS ≥50%. The incidences of Grade ≥3 adverse events were 66.7% in patients with TPS <50% and 75.3% in those with TPS ≥50%. The incidences of serious adverse events were 39.4% in patients with TPS <50% and 42.5% in those with TPS ≥50%. These results suggested no clear differences in the safety of pembrolizumab, according to the degree of PD-L1 expression, also in patients with SQ-NSCLC.

(c) Study 042:

The efficacy of pembrolizumab was evaluated by TPS (cutoff value, 20% or 50%) in patients with NSCLC with evaluable TPS data. Table 29 and Figure 18 show the OS in these patients by TPS (cutoff value, 20% or 50%) (data cutoff date: February 26, 2018).

In the PD-L1 positive subgroups based on both cutoff values, patients receiving pembrolizumab showed a prolonged OS, compared with those receiving chemotherapy. Pembrolizumab is thus expected to be effective, regardless of the degree of PD-L1 expression, in patients with PD-L1 positive (TPS ≥1%) NSCLC.

Table 29. Efficacy of pembrolizumab by TPS in tumor tissue samples (Study 042)

PD-L1 expression	Treatment	N	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P* value for interaction
TPS ≥1% and <20%	Pembrolizumab	224	12.9 [9.7, 19.3]	0.89 [0.71, 1.12]	0.3318
	Chemotherapy	232	11.3 [9.7, 12.9]		
TPS ≥20%	Pembrolizumab	413	17.7 [15.3, 22.1]	0.77 [0.64, 0.92]	
	Chemotherapy	405	13.0 [11.6, 15.3]		
TPS ≥1% and <50%	Pembrolizumab	338	13.4 [10.7, 18.2]	0.92 [0.77, 1.11]	0.0410
	Chemotherapy	337	12.1 [11.0, 14.0]		
TPS ≥50%	Pembrolizumab	299	20.0 [15.4, 24.9]	0.69 [0.56, 0.85]	
	Chemotherapy	300	12.2 [10.4, 14.2]		

*, Cox regression stratified by ECOG PS (0, 1), tissue type (SQ, NSQ), and geographic region (East Asia, non-East Asia)

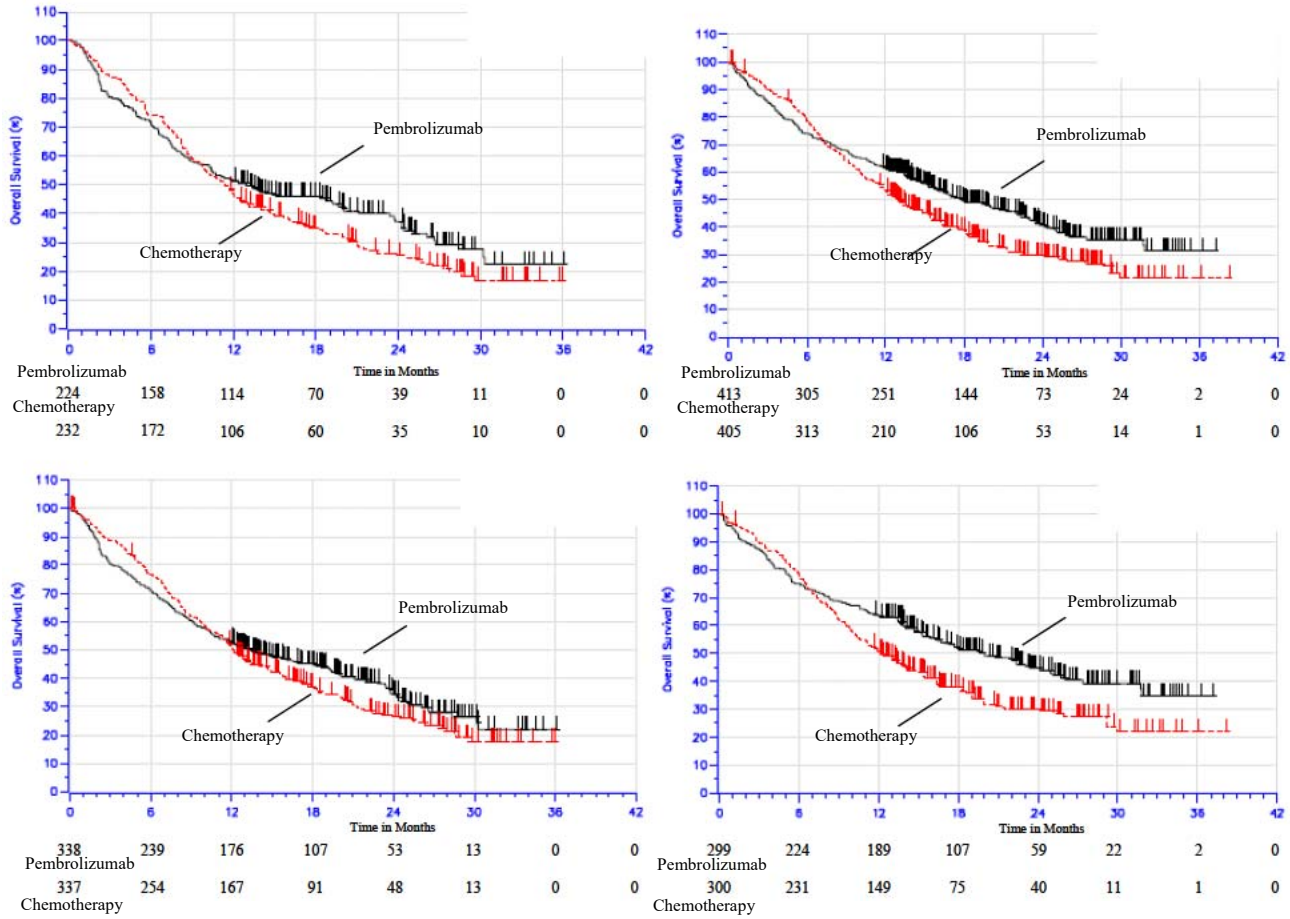


Figure 18. Kaplan-Meier curves of OS by TPS (data cutoff date: February 26, 2018)
(Top left, TPS ≥1% and <20%; top right, TPS ≥20%; bottom left, TPS ≥1% and <50%; bottom right, TPS ≥50%)

In the pembrolizumab group of Study 042, the incidences of adverse events of any grade were 96.0% in patients with TPS ≥1% and <20%, and 95.9% in those with TPS ≥20%. The incidences of Grade ≥3 adverse events were 47.8% in patients with TPS ≥1% and <20%, and 51.2% in those with TPS ≥20%. The incidences of serious adverse events were 39.7% in patients with TPS ≥1% and <20%, and 41.3% in those with TPS ≥20%. In addition, the incidences of adverse events of any grade were 95.6% in patients with TPS ≥1% and <50%, and 96.3% in those with TPS ≥50%. The incidences of Grade ≥3 adverse events were 50.0% in patients with TPS ≥1% and <50%, and 50.0% in those with TPS ≥50%. The incidences of serious adverse events were 40.2% in patients with TPS ≥1% and <50%, and 41.3% in those with TPS ≥50%. These results suggested no clear differences in the safety of pembrolizumab, according to the degree of PD-L1 expression, also in patients with PD-L1 positive (TPS ≥1%) NSCLC.

PMDA's view:

PMDA accepted the applicant's explanation in general. However, the applicant should continue to collect information on other possible predictors of response to pembrolizumab besides PD-L1 expression, and appropriately provide any new findings to healthcare professionals.

7.2.R.4 Dosage and administration

In the present partial change application, the proposed dosage regimen for the treatment of NSCLC was "The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks" (unchanged from the previous approval). The following precautionary statements were included in the proposed "Precautions for Dosage and Administration" section:

- When pembrolizumab is used with other antineoplastic drugs, the "Clinical Studies" section should be understood sufficiently before starting the combination therapy.
- When pembrolizumab is used with other antineoplastic drugs, pembrolizumab should be administered first. The package inserts of the concomitant antineoplastic drugs should be read thoroughly.
- Criteria for interruption and discontinuation of pembrolizumab in case of adverse reactions (unchanged from the previous approval)

As a result of its review described in Sections "7.2.R.1 Efficacy," "7.2.R.2 Safety," and the section below, PMDA concluded that the proposed dosage regimen is acceptable, provided that the following precautionary statements are included in the "Precautions for Dosage and Administration" section.

- When pembrolizumab is used with other antineoplastic drugs, the "Clinical Studies" section should be understood sufficiently before selecting concomitant antineoplastic drugs.
- Criteria for interruption and discontinuation of pembrolizumab in case of adverse reactions (unchanged from the previous approval)

7.2.R.4.1 Dosage and administration of pembrolizumab

The applicant's rationale for the dosage regimen of pembrolizumab for the treatment of NSCLC:

In Studies 189, 407, and 042, a fixed dose of 200 mg every 3 weeks, rather than a body weight-based dose, was selected based on data including the results of a PK/PD analysis (see "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016" and "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated November 15, 2016"). These studies demonstrated the clinically significant efficacy [see Section 7.2.R.1] and acceptable tolerability of pembrolizumab [see Section 7.2.R.2]. The dosage regimen of pembrolizumab for the treatment of NSCLC was therefore proposed to be "The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks."

However, no clinical data are available as to the combination therapy with pembrolizumab and antineoplastic drugs, except a platinum + PEM, in patients with NSQ-NSCLC, or as to the combination therapy, except CBDCA + PTX or CBDCA + nab-PTX, in patients with SQ-NSCLC. Therefore, the following precautionary statements are included in the "Precautions for Dosage and Administration" section, provided that information on the antineoplastic drugs used in combination with pembrolizumab in the clinical studies is provided in the "Clinical Studies" section.

- When pembrolizumab is used with other antineoplastic drugs, the "Clinical Studies" section should be understood sufficiently before starting the combination therapy.

- When pembrolizumab is used with other antineoplastic drugs, pembrolizumab should be administered first. The package inserts of all concomitant antineoplastic drugs should be read thoroughly.

PMDA's view:
The applicant's explanation is acceptable. However, the following proposed precautionary statements are general matters requiring no special caution, which are not necessary to include in the "Precautions for Dosage and Administration" section: "When pembrolizumab is used with other antineoplastic drugs, pembrolizumab should be administered first," and "The package inserts of all concomitant antineoplastic drugs should be read thoroughly."

7.2.R.5 Post-marketing investigations
Post-marketing investigations in patients with NSCLC will be described in Section 7.3.R.4, together with those in patients with malignant melanoma and those with MSI-High solid tumors.

7.3 Data on the treatment of MSI-High solid tumors and outline of the review conducted by PMDA
The applicant submitted efficacy and safety evaluation data, in the form of result data from 2 global phase II studies (Table 30).

Table 30. Clinical studies on efficacy and safety

Data type	Region	Study identifier	Phase	Subjects	No. of patients enrolled	Dosage regimen	Key endpoints
Evaluation data	Global	Study 164	II	Cohort A: Chemotherapy-treated patients with unresectable, advanced or recurrent dMMR or MSI-High (PCR) colorectal cancer	61	Intravenous pembrolizumab 200 mg every 3 weeks	Efficacy Safety
		Study 158	II	Chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High solid tumors (except colorectal cancer)	94	Intravenous pembrolizumab 200 mg every 3 weeks	Efficacy Safety

A summary of these clinical studies is presented below. Major adverse events other than deaths reported in the studies are detailed in Section "7.4.3 Adverse events reported in clinical studies in patients with MSI-High solid tumors."

7.3.1 Evaluation data
7.3.1.1 Global clinical study
7.3.1.1.1 Global phase II study (CTD 5.3.5.2.1, Study 164, ongoing since [redacted] 20[redacted] [data cutoff date: February 10, 2017])
An open-label, uncontrolled study was conducted at 21 sites in 9 countries, including Japan, to evaluate the efficacy and safety of pembrolizumab in chemotherapy-treated[12)] patients with unresectable, advanced or

12) When the study was planned, patients who had been treated with ≥2 chemotherapy regimens, including a fluoropyrimidine, oxaliplatin (L-OHP), or irinotecan hydrochloride hydrate (CPT-11) were to be eligible, assuming FOLFOX and FOLFIRI as commonly used standard therapies. However, the study protocol was later amended to enroll patients who had received

recurrent dMMR[13] or MSI-High[14] colorectal cancer. The study comprises Cohort A (target sample size, 60 patients) and Cohort B (target sample size, 60 patients).[15] The present review report describes only data from Cohort A.

Patients received an intravenous dose of pembrolizumab 200 mg every 3 weeks for a total of 35 cycles, or until disease progression was observed or a withdrawal criterion was met.

All 61 enrolled patients (including 7 Japanese patients) were treated with pembrolizumab and were included in both the efficacy analysis and safety analysis.

The primary endpoint was the response rate as assessed centrally using RECIST Ver. 1.1, with a threshold response rate set at 15%.[16] An interim analysis for efficacy was planned when the 40th patient enrolled had been followed up for 18 weeks, and the final analysis was planned when the last patient enrolled had been followed up for 6 months. A Lan-DeMets α spending function of the O'Brien-Fleming type was to be used to control the type I error associated with the interim analysis. However, because of [redacted], an interim analysis was performed when all of the enrolled patients had been followed up for ≥18 weeks (data cutoff date: June 3, 2016), with no multiplicity adjustment. The final analysis was performed (data cutoff date: August 3, 2016). However, [redacted], suggesting [redacted], the originally planned final analysis was regarded as a supportive analysis, and an additional analysis was newly planned (Protocol Amendment Version 4 [dated [redacted], 20[redacted]]).

The results of the response rate as assessed centrally using RECIST Ver. 1.1 (the primary endpoint) are shown in Table 31 (data cutoff date: February 10, 2017).

chemotherapy regimens including a fluoropyrimidine, L-OHP, and CPT-11, considering that FOLFOXIRI was used as a standard therapy containing a fluoropyrimidine, L-OHP, and CPT-11 (Protocol Amendment Version 2 [dated [redacted], 20[redacted]]).

13) A tumor tissue sample was classified as dMMR if the expression of ≥1 mismatch repair protein (MLH1, MSH2, MSH6, or PMS2) was absent by IHC assay.

14) A tumor tissue sample was classified as MSI-High, if the allelic size was changed in ≥2 microsatellite markers.

15) After the originally planned patient enrollment was completed, the study protocol was amended to add Cohort B, which comprised patients with radically unresectable, advanced, or recurrent, dMMR or MSI-High colorectal cancer, who had been treated with either (a) a fluoropyrimidine + L-OHP or (b) a fluoropyrimidine + CTP-11 (target sample size, 60 patients). The original cohort, from the time of the planning of the study, was termed Cohort A (Protocol Amendment Version 3 [dated [redacted], 20[redacted]]).

16) The threshold response rate of 15% was based on the results of a clinical study of regorafenib in patients with radically unresectable, advanced or recurrent colorectal cancer that had progressed after chemotherapies containing a fluoropyrimidine, L-OHP, CPT-11, and bevacizumab (with cetuximab or panitumumab, if *KRAS* wild-type) (*Lancet* 2013; 381:303-312).

Table 31. Best overall response and response rate
(RECIST Ver. 1.1, central assessment, efficacy analysis set [data cutoff date: February 10, 2017])

Best overall responses	n (%)	
	Overall N = 61	Japanese N = 7
CR	0	0
PR	17 (27.9)	2 (28.6)
SD	14 (23.0)	2 (28.6)
PD	28 (45.9)	3 (42.9)
NE	2 (3.3)	0
Response (CR + PR) (Response rate [95% CI*] [%])	17 (27.9 [17.1, 40.8])	2 (28.6 [3.7, 71.0])

*, Exact test

The safety analysis indicated that 1 (a non-Japanese patient) of 61 patients (1.6%) died during the treatment period or within 90 days after the last dose. The cause of death was aspiration, for which a causal relationship to the study drug was denied.

7.3.1.1.2 Global phase II study (CTD 5.3.5.2.2, Study 158, ongoing since [redacted] 20[redacted] [data cutoff date: April 28, 2017])

An open-label, uncontrolled study was conducted at 43 sites in 15 countries, including Japan, to evaluate the efficacy and safety of pembrolizumab in chemotherapy-treated[17] patients with unresectable, advanced or recurrent solid tumors.[18] The study comprised Groups A to K, divided according to cancer type (target sample size: approximately 200 to 1350 patients, in total).

Patients received an intravenous dose of pembrolizumab 200 mg every 3 weeks for a total of 35 cycles, or until disease progression was observed or a withdrawal criterion was met.

Of 1151 patients enrolled in the study (across Groups A to K), 94 patients (including 7 Japanese patients) with MSI-High solid tumors[19] (7 in Group D, 2 in Group E, 1 in Group H, 1 in Group J, and 83 in Group K) were treated with pembrolizumab and were included in both the efficacy analysis set and the safety analysis set.

The results for the response rate as assessed centrally using RECIST Ver. 1.1 (the primary endpoint) in Study 158 (Group K) are presented in Table 32 (data cutoff date: April 28, 2017).

17) When the study was planned, patients who were resistant or intolerant to standard therapies were to be eligible, irrespective of prior chemotherapies. However, as the medical history required for enrollment was not clearly defined, the study protocol was amended to enroll patients who were resistant or intolerant to chemotherapies recommended as standard first-line therapies, as well as to surgeries and radiotherapies routinely used in clinical practice (Protocol Amendment Version 1 [dated [redacted], 20[redacted]]).

18) The following patients were enrolled in each group: Group A, patients with anal cancer (squamous cell carcinoma); Group B, biliary carcinoma (adenocarcinoma of the gallbladder and bile duct), excluding tumors of the ampulla of Vater; Group C, patients with (well- or moderately-differentiated) neuroendocrine tumors derived from the lung, appendix, small intestine, colon, rectum, or pancreas; Group D, patients with endometrial cancer (excluding sarcoma and mesenchymal tumors); Group E, cervical cancer (squamous cell carcinoma); Group F, patients with vulvar carcinoma (squamous cell carcinoma); Group G; patients with small cell lung cancer; Group H, patients with mesothelioma; Group I, patients with thyroid cancer; Group J, patients with salivary gland cancer (excluding sarcoma and mesenchymal tumors); and Group K, advanced, MSI-High solid tumors (except colorectal cancer). Patients enrolled in Groups A to J had to have a PD-L1 level, a gene expression profile score by RNA analysis, and a tumor tissue sample which could be used for MSI biomarker analysis.

19) In patients enrolled in Groups A to J, MSI status (MSI-High) was assessed retrospectively.

Table 32. Best overall response and response rate (Group K)
(RECIST Ver. 1.1, central assessment, efficacy analysis set [data cutoff date: April 28, 2017])

Best overall responses	n (%)	
	Overall N = 83	Japanese N = 3
CR	4 (4.8)	0
PR	25 (30.1)	0
SD	20 (24.1)	2 (66.7)
PD	24 (28.9)	1 (33.3)
NE	10 (12.0)	0
Response (CR + PR) (Response rate [95% CI*] [%])	29 (34.9 [24.8, 46.2])	0

*, Exact test

Table 33 shows the results for the response rate as assessed centrally using RECIST Ver 1.1, by cancer type in patients with MSI-High solid tumors enrolled in the study (Groups A to K). The number of Japanese patients in each group and their best overall response were as follows: (a) endometrial cancer [Group D], 1 with PR; (b) cervical cancer [Group E], 1 with PD; (c) mesothelioma [Group H], 1 with PD; (d) salivary gland cancer [Group J], 1 with PR; (e) gastric cancer [Group K], 1 with SD and 1 with PD; and, (f) small intestine carcinoma [Group K], 1 with SD).

Table 33. Response rate by cancer type in patients with MSI-High solid tumors [Groups A to K]
(RECIST Ver. 1.1, central assessment, efficacy analysis set [data cutoff date: April 28, 2017])

Cancer type	n (%) N = 94	Responders (CR + PR) (Response rate [%])
Endometrial cancer	24 (25.5)	13 (54.2)
Gastric cancer	13 (13.8)	6 (46.2)
Small intestine carcinoma	13 (13.8)	4 (30.8)
Pancreatic carcinoma	10 (10.6)	1 (10.0)
Biliary carcinoma	9 (9.6)	2 (22.2)
Adrenocortical carcinoma	3 (3.2)	1 (33.3)
Mesothelioma	3 (3.2)	0
Small cell lung cancer	3 (3.2)	2 (66.7)
Cervical cancer	2 (2.1)	1 (50.0)
Neuroendocrine tumors	2 (2.1)	0
Thyroid cancer	2 (2.1)	0
Urothelial carcinoma	2 (2.1)	1 (50.0)
Brain tumor	1 (1.1)	0
Ovarian cancer	1 (1.1)	0
Prostate cancer	1 (1.1)	0
Retroperitoneal tumor	1 (1.1)	1 (100)
Salivary gland cancer	1 (1.1)	1 (100)
Sarcoma	1 (1.1)	1 (100)
Testicular tumor	1 (1.1)	0
Tonsil cancer	1 (1.1)	1 (100)

The safety analysis indicated that 6 (including no Japanese patients) of 94 patients (6.4%) died during the treatment period or within 90 days after the last dose. The causes of death were death in 2 patients, and acute respiratory failure, Cushing's syndrome, general physical health deterioration, and pneumonia in 1 patient each. A causal relationship to the study drug was denied for all of the events.

7.3.R Outline of the review conducted by PMDA for the treatment of MSI-High solid tumor

7.3.R.1 Safety [For adverse events, see Section "7.4.3 Adverse events reported in clinical studies in patients with MSI-High solid tumors."]

PMDA's view:

As a result of its review described in the section below, PMDA considers that the adverse events that require special attention after the administration of pembrolizumab are those identified as requiring attention at the regulatory reviews for the approved indications[7)] and should also be closely monitored when pembrolizumab is administered to chemotherapy-treated patients with MSI-High solid tumors.

Although attention should be paid to the above events, pembrolizumab is also tolerable when administered to chemotherapy-treated patients with MSI-High solid tumors, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis and patient management in anticipation of adverse reactions due to an excessive immune response, drug interruption, or other appropriate actions.

7.3.R.1.1 Differences in safety profile between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of pembrolizumab, based on the safety data from Studies 164 and 158:

Table 34 shows a summary of the safety data from Studies 164 and 158.

Table 34. Safety summary (Studies 164 and 158)

	n (%)	
	Study 164 N = 61	Study 158 N = 94
All adverse events	60 (98.4)	91 (96.8)
Grade ≥3 adverse events	36 (59.0)	41 (43.6)
Adverse events leading to death	1 (1.6)	6 (6.4)
Serious adverse events	29 (47.5)	32 (34.0)
Adverse events leading to drug discontinuation	4 (6.6)	13 (13.8)
Adverse events leading to drug interruption	17 (27.9)	27 (28.7)

In Study 164, adverse events of any grade reported with a ≥10% incidence were diarrhoea (34.4% [21 of 61 patients]), nausea (32.8% [20 of 61 patients]), abdominal pain (31.1% [19 of 61 patients]), fatigue (29.5% [18 of 61 patients]), vomiting (26.2% [16 of 61 patients]), pyrexia (24.6% [15 of 61 patients]), asthenia (23.0% [14 of 61 patients]), constipation, decreased appetite, and cough (19.7% [12 of 61 patients] each), anaemia and arthralgia (18.0% [11 of 61 patients] each), oedema peripheral and pruritus (14.8% [9 of 61 patients] each), and ALT increased, AST increased, back pain, headache, insomnia, and rash (11.5% [7 of 61 patients] each). Grade ≥3 adverse events reported with a ≥2% incidence were abdominal pain, ALT increased, anaemia, and ileus (6.6% [4 of 61 patients] each), AST increased, lipase increased, and pancreatitis (4.9% [3 of 61 patients] each), and asthenia, blood ALP increased, dehydration, fatigue, hypertension, hyponatraemia, pulmonary embolism, small intestinal obstruction, and urinary tract infection (3.3% [2 of 61 patients] each). Serious adverse events reported with a ≥2% incidence were ileus (6.6% [4 of 61 patients]), and abdominal pain, pulmonary embolism, pyrexia, small intestinal obstruction, and urinary tract infection (3.3% [2 of 61 patients]

each). Adverse events that led to drug interruption with a ≥2% incidence were ALT increased (6.6% [4 of 61 patients]), anaemia and AST increased (4.9% [3 of 61 patients] each), and blood ALP increased and pulmonary embolism (3.3% [2 of 61 patients] each). No adverse events led to death or led to drug discontinuation with a ≥2% incidence.

In Study 158, adverse events of any grade reported with a ≥10% incidence were diarrhoea (28.7% [27 of 94 patients]), fatigue (27.7% [26 of 94 patients]), nausea (25.5% [24 of 94 patients]), asthenia (18.1% [17 of 94 patients]), constipation (17.0% [16 of 94 patients]), vomiting and pyrexia (16.0% [15 of 94 patients] each), decreased appetite (14.9% [14 of 94 patients]), pruritus (13.8% [13 of 94 patients]), and anaemia (12.8% [12 of 94 patients]). Grade ≥3 adverse events reported with a ≥2% incidence were anaemia (6.4% [6 of 94 patients]), GGT increased (5.3% [5 of 94 patients]), blood ALP increased (4.3% [4 of 94 patients]), sepsis (3.2% [3 of 94 patients]), and ascites, death, diarrhoea, fatigue, hepatic enzyme increased, hyponatraemia, muscular weakness, pneumonia, urinary tract infection, and weight increased (2.1% [2 of 94 patients] each). Adverse event that led to death with a ≥2% incidence was death (2.1% [2 of 94 patients]). Serious adverse events reported with a ≥2% incidence were sepsis (3.2% [3 of 94 patients]), and death, pneumonia, and pneumonitis (2.1% [2 of 94 patients] each). Adverse events that led to drug discontinuation with a ≥2% incidence were blood ALP increased and death (2.1% [2 of 94 patients] each). Adverse events that led to drug interruption with a ≥2% incidence were ALT increased, blood creatinine increased, GGT increased, hypothyroidism, pneumonitis, sepsis, and thrombocytopenia (2.1% [2 of 94 patients] each).

The applicant's explanation about the differences in the safety profile of pembrolizumab between patients enrolled in Study 164 and patients treated for the approved indications:
Adverse events of any grade reported with a ≥5% higher incidence in patients enrolled in Study 164 than in all of the other patient populations were diarrhoea (MSI-High colorectal cancer, 34.4%; radically unresectable malignant melanoma, 26.2%; PD-L1 positive NSCLC, 15.2%, cHL, 17.1%; radically unresectable urothelial carcinoma, 16.2%), nausea (32.8%, 25.3%, 20.2%, 13.3%, 20.7%), abdominal pain (31.1%, 11.8%, 5.7%, 5.2%, 12.8%), vomiting (26.2%, 13.5%, 12.0%, 15.2%, 14.7%), asthenia (23.0%, 15.7%, 10.3%, 6.7%, 11.3%), oedema peripheral (14.8%, 8.9%, 8.3%, 4.8%, 9.8%), AST increased (11.5%, 6.4%, 5.3%, 2.9%, 5.3%), and ileus (8.2%, 0.4%, 0.1%, 0%, 0.4%). Grade ≥3 adverse events reported with a ≥2% higher incidence in patients enrolled in Study 164 than in any of the other patient populations were abdominal pain (6.6%, 1.3%, 0.5%, 0.5%, 1.1%), ALT increased (6.6%, 1.1%, 0.8%, 0.5%, 1.1%), ileus (6.6%, 0.3%, 0.1%, 0%, 0.4%), AST increased (4.9%, 0.8%, 0.8%, 0%, 2.3%), pancreatitis (4.9%, 0.2%, 0.2%, 0%, 0%), lipase increased (4.9%, 0.1%, 0%, 0.5%, 0.4%), asthenia (3.3%, 1.2%, 1.2%, 0%, 0.8%), blood ALP increased (3.3%, 0.7%, 0.8%, 0.5%, 1.1%), and small intestinal obstruction (3.3%, 0.1%, 0%, 0%, 0%). Serious adverse events reported with a ≥2% higher incidence in patients enrolled in Study 164 than in any of the other patient populations were ileus (6.6%, 0.4%, 0.1%, 0%, 0%), abdominal pain (3.3%, 1.0%, 0.4%, 0%, 0.8%), and small intestinal obstruction (3.3%, 0.2%, 0%, 0%, 0%). Adverse events that led to drug interruption with a ≥2% higher incidence in patients enrolled in Study 164 than in any of the other patient populations were ALT increased (6.6%, 1.0%, 1.1%, 0.5%, 0.8%), AST increased (4.9%, 1.0%, 1.2%, 1.0%, 0.8%), anaemia (4.9%, 0.8%, 0.8%, 0%, 0.4%), pulmonary embolism (3.3%, 0.4%, 0.4%, 0%, 0.4%), and blood ALP increased (3.3%, 0.1%, 0.4%, 0%, 0%).

No adverse events led to death or led to drug discontinuation, with a ≥2% higher incidence in patients enrolled in Study 164 than in any of the other patient populations.

The adverse event that had not been identified in patients treated for the approved indications but occurred in ≥2 patients in Study 164 was duodenal ulcer (2 patients). There were no adverse events leading to death, Grade ≥3 adverse events, serious adverse events, or adverse events leading to drug discontinuation or drug interruption, which had not been identified in patients treated for the approved indication but reported in ≥2 patients in Study 164.

The above comparisons revealed no clear differences in the incidences of clinically notable adverse events (e.g., serious adverse events) between patients enrolled in Study 164 and those treated for the approved indications, although some adverse events occurred more frequently or were newly identified in patients enrolled in Study 164. Thus, the safety of pembrolizumab does not clearly differ between patients enrolled in Study 164 and those treated for the approved indications.

The applicant's explanation about the differences in the safety of pembrolizumab between Japanese and non-Japanese patients, based on the safety data from Studies 164 and 158:
In Study 164, adverse events of any grade reported in ≥2 Japanese patients were anaemia in 3 patients, and vomiting, weight increased, cough, and rash in 2 patients each. Grade ≥3 adverse events reported in Japanese patients were anaemia, duodenal ulcer, gastrointestinal perforation, lower gastrointestinal haemorrhage, pancreatitis, oedema peripheral, amylase increased, lipase increased, and tumour pain in 1 patient each. Serious adverse events reported in Japanese patients were tumour pain and duodenal ulcer in 1 patient each. The adverse event that led to drug discontinuation in Japanese patients was pneumonitis in 1 patient. Adverse events that led to drug interruption in Japanese patients were anaemia, pancreatitis, amylase increased, and lipase increased in 1 patient each. No Japanese patient died due to adverse events.

In Study 158, adverse events of any grade reported in ≥2 Japanese patients were constipation and pruritus in 3 patients each, and anaemia, diarrhoea, nausea, fatigue, pyrexia, blood ALP increased, GGT increased, and rash in 2 patients each. Grade ≥3 adverse events reported in Japanese patients were anaemia and GGT increased in 2 patients each, and cataract, ascites, blood ALP increased, haemoglobin decreased, and fulminant type 1 diabetes mellitus in 1 patient each. Serious adverse events reported in Japanese patients were cataract, spinal fracture, and fulminant type 1 diabetes mellitus in 1 patient each. Adverse event that led to drug discontinuation in Japanese patients were blood ALP increased, GGT increased, and haemoglobin decreased in 1 patient each. Adverse event that led to drug interruption in Japanese patients were cataract, malaise, pain, spinal fracture, GGT increased, fulminant type 1 diabetes mellitus, hyperglycaemia, and tumour pain in 1 patient each. No Japanese patient died due to adverse events.

Only limited clinical experience with pembrolizumab is available in Japanese patients with MSI-High solid tumors, and there are limitations for an evaluation of the safety of pembrolizumab between Japanese and non-Japanese patients, based only on the data from Studies 164 and 158. Nevertheless, no adverse events requiring

special attention in Japanese patients were identified, in view of the absence of serious adverse events reported in ≥2 Japanese patients in both studies, as well as other findings.

PMDA's view:
Some adverse events occurred more frequently in patients enrolled in Study 164 than in patients treated for the approved indications; however, most of these events were known adverse events of pembrolizumab, and the adverse events that were newly identified in Study 164 were reported by only a limited number of patients. Therefore, PMDA has concluded that pembrolizumab is also tolerable in patients with MSI-High solid tumors, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis and patient management in anticipation of adverse reactions due to an excessive immune response, drug interruption, or other appropriate actions.

PMDA has also concluded that the currently available data indicate no adverse events requiring special attention in Japanese patients with MSI-High solid tumors, although clinical experience with pembrolizumab in Japanese patients is limited.

7.3.R.2 Clinical positioning, efficacy, and indication

The proposed indication was "locally advanced or metastatic MSI-High cancers," and the following statements were included in the proposed "Precautions for Indications" section:

- Pembrolizumab should be administered to patients who have been demonstrated to have an advanced MSI-High solid tumor by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic.
- The efficacy and safety of pembrolizumab as a first-line therapy have not been established.

As a result of its review described in Sections "7.3.R.1 Safety" and the sections below, PMDA has concluded that the appropriate indication of pembrolizumab should be "advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)," and that the characteristics (e.g., cancer type) and response to treatment (e.g., best overall response) of the patients enrolled in Study 158 should be detailed in the "Clinical Studies" section of the package insert, and the following precautionary statements should be included in the "Precautions for Indications" section.

- Pembrolizumab should be administered to patients who have been demonstrated to have an advanced MSI-High solid tumor by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic.
- In the treatment of colorectal cancer, the efficacy and safety of pembrolizumab have not been established in patients with no prior therapy with a fluoropyrimidine + L-OHP + CTP-11.
- In the treatment of solid tumors (except colorectal cancer), the efficacy and safety of pembrolizumab as a first-line therapy have not been established. In the second-line therapy for these solid tumors, standard treatments, if available, should be chosen before pembrolizumab.
- The efficacy and safety of pembrolizumab in adjuvant therapy have not been established.

- Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand particularly for the characteristics (e.g., cancer type) of patients enrolled in the clinical studies as well as a careful consideration of the choice of alternative therapies.

7.3.R.2.1 Clinical positioning and efficacy of pembrolizumab in the treatment of MSI-High solid tumors

In major clinical practice guidelines and textbooks for clinical oncology in and outside Japan, pembrolizumab therapy for MSI-High solid tumors is described as follows:

	Representative clinical practice guidelines and textbooks	Statements
Colon cancer	NCCN guidelines (Colon cancer) (v.3.2018)	Pembrolizumab is recommended as the second- or third-line therapy for patients with radically unresectable, advanced or recurrent dMMR or MSI-High (PCR) colon cancer.
	US NCI-PDQ (version dated April 6, 2018)	Results of Study 164, etc. demonstrated the efficacy of pembrolizumab in the treatment of radically unresectable, advanced or recurrent dMMR or MSI-High (PCR) colon cancer.
	Japanese clinical practice guidelines (Large intestine carcinoma)	Anti-PD-L1 antibodies have been reported to be effective in the treatment of radically unresectable, advanced or recurrent dMMR or MSI-High (PCR) colorectal cancer.
Rectal cancer	NCCN guidelines (Rectal cancer) (v.3.2018)	Pembrolizumab is recommended as the second- or third-line therapy for patients with radically unresectable, advanced or recurrent dMMR or MSI-High (PCR) rectal cancer.
	US NCI-PDQ (version dated June 7, 2018)	The results of Study 164, etc. demonstrated the efficacy of pembrolizumab in the treatment of dMMR or MSI-High (PCR) rectal cancer.
	Japanese clinical practice guidelines (Large intestine carcinoma)	Anti-PD-L1 antibodies have been reported to be effective in the treatment of radically unresectable, advanced or recurrent dMMR or MSI-High (PCR) colorectal cancer.
Gastric cancer	NCCN guidelines (Gastric cancer) (v.2.2018)	Pembrolizumab is a therapeutic option for the second-line therapy for patients with radically unresectable, advanced or recurrent dMMR or MSI-High (PCR) gastric cancer.
Esophageal and esophagogastric junction cancers	NCCN guidelines (Esophageal and esophagogastric junction cancers) (v.2.2018)	Pembrolizumab is a therapeutic option for the second-line or subsequent therapy for patients with recurrent or distant metastatic dMMR or MSI-High (PCR) esophageal and esophagogastric junction cancers.
Pancreatic carcinoma	NCCN guidelines (Pancreatic adenocarcinoma) (v.2.2018)	Pembrolizumab is recommended as the second-line therapy for patients with radically unresectable dMMR or MSI-High (PCR) pancreatic carcinoma.
Hepatobiliary cancer	NCCN guidelines (Hepatobiliary cancer) (v.3.2018)	Pembrolizumab is a therapeutic option for the second-line therapy for patients with dMMR or MSI-High (PCR) hepatobiliary cancer.
Uterine neoplasms	NCCN guidelines (Uterine neoplasms)(v.2.2018)	Pembrolizumab is a therapeutic option for patients with advanced or recurrent dMMR or MSI-High (PCR) endometrial cancer.
Cervical cancer	NCCN guidelines (Cervical cancer) (v.1.2019)	Pembrolizumab is a therapeutic option for patients with advanced or recurrent dMMR or MSI-High (PCR) cervical cancer.
Ovarian cancer	NCCN guidelines (Ovarian cancer) (v.2.2018)	Pembrolizumab is a therapeutic option for patients with recurrent dMMR or MSI-High (PCR) ovarian cancer.
Prostate cancer	NCCN guidelines (Prostate cancer) (v.4.2018)	Pembrolizumab is recommended as the second-line therapy for patients with distant metastatic, dMMR or MSI-High (PCR) prostate cancer.
Bone cancer	NCCN guidelines (Bone cancer) (v.1.2019)	Pembrolizumab is a therapeutic option for chemotherapy-treated patients with dMMR or MSI-High (PCR) osteosarcoma.

The applicant's explanation about the clinical positioning of pembrolizumab in the treatment of MSI-High solid tumors, taking account of the molecular pathogenesis of MSI-High solid tumors:

In general, (a) dMMR and (b) MSI status is determined or classified as follows:

(a) The expression of 4 mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) in a tumor tissue sample is observed by IHC assay. If any of the proteins are absent, the sample is classified as "dMMR."
(b) DNA is extracted from a tumor tissue sample, and 5 microsatellites (repeated sequences of 1 to several bases) from the DNA are amplified by PCR. If the number of base repeats is changed from that in normal tissues (non-tumor tissues) in ≥2 of the 5 microsatellites, the sample is classified as "MSI-High (PCR)."

Microsatellites are repetitive sequences located in the genome, and are often replicated incorrectly due to a failure of the DNA mismatch repair system during DNA replication (*Cell Res* 2008;18:85-98). The phenotype of MSI-High is closely associated with a loss of function of mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2). In MSI-High (PCR) solid tumors as compared with solid tumors with no MSI, somatic cell mutations are frequently detected, and a large burden of neoantigens, which can serve as the targets of cancer antigen-specific T cells, are formed. The microenvironment of MSI-High solid tumors is characterized by an abundance of activated cytotoxic T cells (*Cell Rep* 2016;15:857-65, etc.)

Furthermore, immunosuppressive signaling molecules (e.g., PD-1) are highly expressed by MSI-High solid tumors, making them resistant to tumor rejection (*Cancer Discov* 2015;5:43-51, etc.). In view of such findings, pembrolizumab, which is an immune checkpoint inhibitor, is expected to be effective in MSI-High solid tumors, regardless of cancer type.

The applicant's explanation about the efficacy of pembrolizumab, also taking the above view into account:
In chemotherapy-treated patients with radically unresectable, advanced or recurrent solid tumors, the achievement of response is expected to improve clinical symptoms associated with disease progression *(J Clin Oncol* 2008;26:2311-9, etc.). As achieving a response is thus clinically significant in chemotherapy-treated patients with unresectable, advanced or recurrent solid tumor, response rate was selected as the primary endpoint in Studies 164 and 158.

In Study 164, the response rate as assessed centrally using RECIST Ver. 1.1 (the primary endpoint) was 27.9 (95% confidence interval [CI], 17.1-40.8) (data cutoff date, February 10, 2017) [see Section 7.3.1.1.1]. In Study 158 (Group K), the response rate as assessed centrally using RECIST Ver. 1.1 (the primary endpoint) was 34.9 (95% CI, 24.8-46.2) (data cutoff date, April 28, 2017) [see Section 7.3.1.1.2]. Thus, pembrolizumab was shown to produce a clinically significant response rate in the target patient populations of Studies 164 and 158.

Pembrolizumab can be expected to be effective in chemotherapy-treated patients with advanced or recurrent dMMR or MSI-High (PCR) solid tumors, who have no other standard treatment options, also in view of the following findings.

- In a global phase III study to evaluate the efficacy and safety of regorafenib versus placebo in patients with radically unresectable, advanced or recurrent colorectal cancer that had progressed after ≥2 chemotherapies containing a fluoropyrimidine, L-OHP, CPT-11, and bevacizumab (with cetuximab or panitumumab, if *KRAS* wild-type), the response rate as assessed by the investigator was 1.0% in the regorafenib group (*Lancet* 2013;381:303-312).

- In a global phase III study to evaluate the efficacy and safety of the combination therapy with trifuridine + tipiracil hydrochloride versus placebo in patients with radically unresectable, advanced or recurrent colorectal cancer, who had received ≥2 prior chemotherapies and were unresponsive or intolerant to a fluoropyrimidine, L-OHP, CPT-11, and bevacizumab (as well as to cetuximab or panitumumab, if *KRAS* wild-type), the response rate as assessed by the investigator was 1.6% in the trifuridine + tipiracil hydrochloride group (*N Engl J Med* 2015;372:1909-19).

At the start of Study 164, as [redacted] was anticipated by referring to [redacted] and [redacted], the final analysis was planned when the last enrolled patient had been followed up for 6 months. However, [redacted] was observed at the data cutoff on August 3, 2016 (the time point of the originally planned final analysis), suggesting [redacted]. Thus the analysis was to be conducted [redacted], and the analysis as of the data cutoff of February 10, 2017 was retrospectively determined to be used as the final analysis.

The results for the response rate obtained at the time point of the originally planned final analysis (data cutoff date: August 3, 2016) are presented in Table 35. The lower bound of the 95% CI was lower than the pre-defined threshold response rate (15.0%).

Table 35. Best overall response and response rate in Study 164
(RECIST Ver. 1.1, central assessment, efficacy analysis set [data cutoff date: August 3, 2016])

Best overall responses	n (%)	
	Overall N = 61	Japanese N = 7
CR	0	0
PR	15 (24.6)	2 (28.6)
SD	16 (26.2)	2 (28.6)
PD	28 (45.9)	3 (42.9)
NE	2 (3.3)	0
Response (CR + PR) (Response rate [95% CI*] [%])	15 (24.6 [14.5, 37.3])	2 (28.6 [3.7, 71.0])

*, Exact test

PMDA's view:

The relationship between OS (the true endpoint) and the response rate has not been clarified in patients with radically unresectable, advanced or recurrent solid tumors, and it is difficult to evaluate the survival benefit of pembrolizumab in such patients, based on the results for the response rate (the primary endpoint) from Study 164 and Study 158 (Group K). In addition, the lower bound of the 95% CI for the response rate at the data cutoff of August 3, 2016 (the time point of the originally planned final analysis) was below the threshold response rate (15.0%) that had been prespecified. Therefore, the results of Studies 164 and 158 (Group K) should be interpreted carefully.

Nevertheless, the applicant's explanation about the efficacy of pembrolizumab is understandable. PMDA has concluded that the efficacy of pembrolizumab can be expected in chemotherapy-treated patients with advanced or recurrent MSI-High solid tumors, who have no other standard treatment options, including Japanese patients, based on the results for the response rate obtained at the time point of the originally planned final analysis (data cutoff date: August 3, 2016) in Study 164, and in view of the following facts.

- No clear differences were found in the pharmacokinetics of pembrolizumab administered alone between Japanese and non-Japanese patients (see "Review Report for Keytruda Injection 20 mg, Keytruda Injection 100 mg dated November 15, 2016").
- There are no clear differences in the diagnosis and treatment of unresectable, advanced or recurrent colorectal cancer between Japan and outside Japan.

7.3.R.2.2 Intended population and indication of pembrolizumab for the treatment of MSI-High solid tumors, and MSI-High testing

The applicant's explanation about the intended population of pembrolizumab, proposed based on the results of Studies 164 and 158 in the present partial change application:

The results of Study 164 [see Section 7.3.1.1.1] suggest that pembrolizumab can be positioned as a therapeutic option for dMMR or MSI-High (PCR) colorectal cancer that has progressed after the conventional standard chemotherapies. In addition, since Study 164 allowed the enrollment of patients who had received a first-line therapy with FOLFOXIRI containing 5-FU, L-OHP, and CPT-11, pembrolizumab can be recommended as a second-line or subsequent therapy option for patients with prior therapy with FOLFOXIRI. Currently, a global, open-label, randomized phase III study (Study 177) is ongoing to evaluate the efficacy and safety of pembrolizumab versus conventional standard chemotherapies in chemotherapy-naïve patients with unresectable, advanced or recurrent, dMMR or MSI-High (PCR) colorectal cancer (target sample size, 300 patients).

Based on the results of Study 158 [see Section 7.3.1.1.2] and considering that pembrolizumab is an immune checkpoint inhibitor and expected to be effective for MSI-High solid tumors, regardless of cancer type [see Section 7.3.R.2.1], pembrolizumab can be positioned as a therapeutic option for chemotherapy-treated patients with advanced or recurrent MSI-High solid tumors (except colorectal cancer) including cancer types that were not investigated in Study 158, who have no other standard treatment options. In addition, pembrolizumab can be positioned as a second-line therapy option for solid tumors (except colorectal cancer), that have progressed after standard chemotherapies, in view of the following findings.

- In Study 158, the response rate of pembrolizumab was 37.8% in patients with 1 prior chemotherapy, 34.6% in those with 2 prior chemotherapies, and 36.4% in those with 3 prior chemotherapies, indicating no significant differences in the response rate of pembrolizumab according to the number of prior chemotherapies.

- In Study 061,[20] the response rate in MSI-High patients (15 in the pembrolizumab group and 12 in the PTX group) was 46.7% in the pembrolizumab group and 16.7% in the PTX group, suggesting that pembrolizumab was highly effective as compared with PTX, which is a standard second-line therapy (*Lancet* 2018;392:123-133 suppl).

Based on the above, the proposed indication of pembrolizumab was "locally advanced or metastatic MSI-High cancers," and the following statement was included in the proposed "Precautions for Indications" section:

- The efficacy and safety of pembrolizumab as a first-line therapy have not been established.

Patients for pembrolizumab therapy should be selected using the "MSI test kit (FALCO)," and the use of the kit should be stated in the "Precautions for Indications" section, in view of the following.

- In Study 164, which demonstrated the clinical benefit of pembrolizumab, patients who were categorized as having dMMR by IHC assay, and those categorized as having MSI-High (PCR) by PCR were enrolled. Later, the equivalence between these assay methods and the "MSI test kit (FALCO)" was assessed, using samples from the patients enrolled in Study 164. The results showed a positive agreement rate of 100%, and suggested that the patient group that was categorized as having dMMR by IHC assay or categorized as MSI-High (PCR) by PCR was identical to the patient group that was classified as MSI-High by the "MSI test kit (FALCO)." Therefore, patients eligible for pembrolizumab therapy can also be selected by the use of the "MSI test kit (FALCO)," in the post-marketing setting.

PMDA's view:

PMDA accepted the applicant's explanation in general. However, the use of pembrolizumab before standard therapies such as a fluoropyrimidine, L-OHP, and CTP-11 cannot be recommended in chemotherapy-naïve patients with unresectable, advanced or recurrent dMMR or MSI-High (PCR) colorectal cancer, since no confirmatory clinical data have been obtained from patients treated with pembrolizumab for MSI-High colorectal cancer. Therefore, it should be clearly stated in the "Indications" section that pembrolizumab is indicated for the treatment of patients who are not candidates for standard treatments. In addition, a precautionary statement to the effect that the efficacy and safety of pembrolizumab have not been established in patients with no prior therapy with a fluoropyrimidine, L-OHP, and CPT-11 should be included in the "Precautions for Indications" section.

Similarly, for the treatment of MSI-High solid tumors (except colorectal cancer), it should be clearly stated in the "Indications" section that pembrolizumab is indicated for patients who are not candidates for standard treatments. In addition, precautionary statements to the effect that the efficacy and safety of pembrolizumab as a first-line therapy have not been established, and that standard treatments, if available, should be chosen before pembrolizumab for the second-line therapy should be included in the "Precautions for Indications" section, since no confirmatory clinical data are available.

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[20] A global, open-label, randomized, phase III study in patients with unresectable, advanced, or recurrent gastric or esophagogastric junction cancer that has progressed after a first-line chemotherapy containing a fluoropyrimidine or a platinum-based chemotherapy, to evaluate the efficacy of safety of pembrolizumab versus PTX

The efficacy of pembrolizumab was evaluated primarily based on the results for the response rate, with no survival benefit data available, and the use of alternative treatments should be considered carefully. Therefore, a precautionary statement to the effect that the appropriateness of pembrolizumab therapy should be carefully determined after sufficiently considering the possible use of alternative treatments should be included in the "Precautions for Indications" section.

Based on the above, PMDA has concluded that the appropriate indication of pembrolizumab should be "advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)" and that the characteristics (e.g., cancer type) and response to treatment (e.g., best overall response) of the patients enrolled in Study 158 should be detailed in the "Clinical Studies" section of the package insert. In addition, the precautionary statements below should be included in the "Precautions for Indications" section:

- Pembrolizumab should be administered to patients who have been demonstrated to have an advanced MSI-High solid tumor by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic.
- In the treatment of colorectal cancer, the efficacy and safety of pembrolizumab have not been established in patients with no prior therapy with a fluoropyrimidine + L-OHP + CTP-11.
- In the treatment of solid tumors (except colorectal cancer), the efficacy and safety of pembrolizumab as a first-line therapy have not been established. In the second-line therapy for these solid tumors, standard treatments, if available, should be chosen before pembrolizumab.
- The efficacy and safety of pembrolizumab in adjuvant therapy have not been established.
- Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand particularly for the characteristics (e.g., cancer type) of the patients enrolled in the clinical studies as well as a careful consideration of the choice of alternative therapies.

7.3.R.2.3 Efficacy and safety of pembrolizumab by PD-L1 expression status (combined positive score [CPS]), and the intended population

Pembrolizumab is an antibody against human PD-1. PMDA therefore asked the applicant to explain the efficacy and safety of pembrolizumab according to the expression status (CPS) of PD-L1, a ligand of PD-1, and to identify the intended population of pembrolizumab.

The applicant's explanation about the efficacy and safety of pembrolizumab according to the PD-L1expression status (CPS):

MSI-High and PD-L1 are predictors of response to pembrolizumab with different characteristics (*Cancer Discov* 2015;5:43-51).

In Study 158, PD-L1 expression status in tumor tissue samples were measured using "PD-L1 IHC 22C3 pharmDx assay 'Dako' (Dako Japan Co., Ltd.)" to evaluate the (a) efficacy and (b) safety of pembrolizumab, by CPS.

(a) Efficacy:
The efficacy of pembrolizumab was assessed by CPS (cutoff value, 1), in patients with evaluable CPS data in Study 158. Table 36 shows the response rates by CPS (cutoff value, 1).

As responders were present in both PD-L1-positive (CPS ≥1) and -negative (CPS <1) populations, the efficacy of pembrolizumab can be expected, regardless of PD-L1 expression status.

Table 36. Efficacy by CPS (Study 158)

PD-L1 expression	Responders/N	Response rate [95% CI*] (%)
CPS <1	6/19	31.6 [12.6, 56.6]
CPS ≥1	11/22	50.0 [28.2, 71.8]

*, Exact test

(b) Safety:
The incidences of adverse events in patients with CPS <1 were 94.7% (any grade), 52.6% (Grade ≥3), and 47.4% (serious adverse events), while the incidences of adverse events in patients with CPS ≥1 were 95.5% (any grade), 45.5% (Grade ≥3), and 36.4% (serious adverse events).

The safety of pembrolizumab did not clearly differ between PD-L1 positive (CPS ≥1) and PD-L1 negative (CPS <1) patients, indicating that pembrolizumab is tolerable, regardless of PD-L1 expression status.

The investigations in (a) and (b), above suggest that response to pembrolizumab is independent of PD-L1 expression status in patients with MSI-High solid tumors.

Based on the above, pembrolizumab therapy can be recommended, regardless of PD-L1 expression status, for the treatment of chemotherapy-treated patients with advanced or recurrent MSI-High solid tumors who have no other standard treatment options.

PMDA's view:
PMDA accepted the applicant's explanation in general. However, the applicant should continue to collect information on possible predictors of response to pembrolizumab in addition to PD-L1 expression, and appropriately provide any new findings to healthcare professionals.

7.3.R.3 Dosage and administration

In the present partial change application, the proposed dosage regimen for the treatment of MSI-High solid tumors was "The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks" (unchanged from the previous approvals). In addition, the

following precautionary statements were included in the proposed “Precautions for Dosage and Administration” section:

- The efficacy and safety of pembrolizumab in combination with other antineoplastic drugs have not been established.
- Criteria for interruption and discontinuation of pembrolizumab in case of adverse reactions (unchanged from the previous approval)

As a result of its review described in Sections “7.3.R.1 Safety,” “7.3.R.2 Clinical positioning, efficacy and indication,” and the section below, PMDA concluded that the appropriate dosage regimen for the treatment of MSI-High solid tumors is “The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks,” and that the proposed precautionary statements should be included in the “Precautions for Dosage and Administration” section.

7.3.R.3.1 Dosage and administration of pembrolizumab

The applicant's rationale for the dosage regimen of pembrolizumab selected for the treatment of MSI-High solid tumors:

In Studies 164 and 158, a fixed dose of 200 mg every 3 weeks, rather than a body weight-based dose, was selected based on data including the results of a PK/PD analysis (see “Review Report for Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016” and “Review Report for Keytruda Injection 20 mg, Keytruda Injection 100 mg dated November 15, 2016”). As a result, Studies 164 and 158 demonstrated the clinically significant efficacy [see Section 7.3.R.2] and acceptable tolerability [see Section 7.3.R.1] of pembrolizumab. Both the proposed dosage and administration and the precautionary statements in the proposed “Precautions for Dosage and Administration” section are based on the dosage regimen used in Studies 164 and 158.

PMDA accepted the applicant's explanation.

7.3.R.4 Post-marketing investigations

The applicant's explanation on the post-marketing surveillance plans for (a) malignant melanoma, (b) NSCLC, and (c) MSI-High solid tumors:

(a) The initiation of a post-marketing surveillance covering patients treated with pembrolizumab for malignant melanoma immediately after the approval is not necessary, in view of the following facts.
    - A certain amount of data have been collected as to the safety of pembrolizumab in patients with malignant melanoma through the ongoing post-marketing surveillance, in patients treated with pembrolizumab for the previously approved indication of “unresectable malignant melanoma.”
    - The safety profile of pembrolizumab observed in Study 054 did not clearly differ from that in patients treated for the approved indications [see Section 7.1.R.2.1].
    - No particular safety concerns in Japanese patients have been raised in Study 054 [see Section 7.1.R.2.1].
    - In view of the results of a PPK analysis and an investigation based on the data from Studies 001, 002, and 006 [see Sections 6.2.1 and 7.1.R.4.1], the change in the dosage regimens of pembrolizumab for

the treatment of malignant melanoma from a body weight-based dose to a fixed dose is unlikely to raise any particular safety concerns.

(b) The initiation of a post-marketing surveillance covering patients treated with pembrolizumab for NSCLC immediately after the approval is not necessary, in view of the following facts.
- The post-marketing surveillance covering patients treated with pembrolizumab for the approved indication of "unresectable, advanced or recurrent PD-L1 positive NSCLC" is ongoing, and a certain amount of data have been collected from Japanese patients treated with pembrolizumab for NSCLC.
- No new adverse events requiring attention were identified from the results of Studies 189, 407, or 042 [see Section 7.2.R.2.1].
- No particular safety concerns in Japanese patients have been raised in Studies 189, 407, or 042 [see Section 7.2.R.2.1].

(c) In Studies 164 and 158, the duration of response did not reach the median, and currently available long-term efficacy data are limited. Furthermore, clinical experience in Japanese patients is also limited. In view of these facts, the applicant plans to conduct post-marketing surveillance covering patients with MSI-High solid tumors treated with pembrolizumab, with the target sample size and observation period specified below. The purpose of the surveillance is to evaluate the long-term efficacy of pembrolizumab in clinical practice.
- Based on available data including the results of Studies 164 and 158, an expected response rate of 35% with a null hypothesis of 5% was assumed in patients treated with pembrolizumab in clinical practice. To reject the null hypothesis at a level of significance of 0.025 (one-sided), 20 patients are needed. Considering dropouts, the target sample size is 30 patients.
- The average time to response (median) in Studies 164 and 158 was 4 months. In addition, considering the follow-up periods in Studies 164 and 158 (12 months), the observation period required to evaluate the duration of response as an endpoint of the long-term efficacy of pembrolizumab (the objective of the surveillance) is 16 months.

On the other hand, it is not necessary to initiate the post-marketing surveillance to evaluate the safety of pembrolizumab in patients treated with pembrolizumab for MSI-High solid tumors in a clinical setting immediately after the approval, in view of the following facts.
- The safety profile of pembrolizumab did not clearly differ between patients enrolled in Study 164 and patients treated for the approved indications [see Section 7.3.R.1].
- Post-marketing surveillance in patients treated for the approved indications is ongoing, and a certain amount of data have been collected from Japanese patients treated with pembrolizumab.

For (a) malignant melanoma, (b) NSCLC, and MSI-High colorectal cancer among (c) MSI-High solid tumors, PMDA's view on the plan for colorectal cancer is as follows:

As a result of its review described in Sections "7.1.R.2 Safety," "7.1.R.4 Dosage and administration," and a certain amount of safety information collected from Japanese patients in addition to its review described in Section "7.2.R.2 Safety," PMDA concluded that there is little need to conduct a new post-marketing

surveillance to collect safety information immediately after the approval, and safety information may be collected through routine pharmacovigilance activities.

PMDA's view on the post-marketing surveillance plan for (c) MSI-High solid tumors (except colorectal cancer) is as follows:

- Since the cancer types investigated in Study 158 were limited, post-marketing surveillance should be conducted to evaluate the efficacy of pembrolizumab administered to Japanese patients with MSI-High solid tumors (except colorectal cancer) in clinical practice.
- In clinical practice, pembrolizumab is also expected to be administered to patients with solid tumor types other than those investigated in Study 158. Therefore, as much safety information as possible should be collected, including adverse reactions that are listed as the important identified risks included under the RMP, through a post-marketing surveillance in Japanese patients with MSI-High solid tumors (except colorectal cancer).
- The proposed target sample size and observation period in the post-marketing surveillance in Japanese patients who are treated with pembrolizumab for MSI-High solid tumors (except colorectal cancer) in clinical practice should be reconsidered to ensure the appropriate evaluation of the efficacy of pembrolizumab in patients with MSI-High solid tumors (except colorectal cancer).

Studies 164 and 158 are still ongoing. Efficacy information should be collected continuously from these studies, and the obtained information should be promptly provided to healthcare professionals.

7.4 Adverse events reported in clinical studies

Among the clinical study data submitted for safety evaluation, data on death are presented in the sections on "Evaluation data" [Sections 7.1.1, 7.2.1, and 7.3.1]. Other major adverse events are presented below.

7.4.1 Adverse events reported in a clinical study in patients with malignant melanoma

7.4.1.1 Global phase III study (Study 054)

Adverse events were reported in 475 of 509 patients (93.3%) in the pembrolizumab group and 453 of 502 patients (90.2%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 396 of 509 patients (77.8%) in the pembrolizumab group and 332 of 502 patients (66.1%) in the placebo group. Table 37 shows the adverse events reported with a ≥15% incidence in either treatment group.

Table 37. Adverse events with a ≥15% incidence

SOC PT (MedDRA ver. 20.1)	n (%)			
	Pembrolizumab N = 509		Placebo N = 502	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	475 (93.3)	158 (31.0)	453 (90.2)	96 (19.1)
Gastrointestinal disorders				
Diarrhoea	141 (27.7)	6 (1.2)	130 (25.9)	6 (1.2)
Nausea	88 (17.3)	1 (0.2)		
General disorders and administration site conditions				
Fatigue	168 (33.0)	4 (0.8)	168 (33.5)	3 (0.6)
Investigations				
Weight increased	63 (12.4)	0	82 (16.3)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	79 (15.5)	6 (1.2)	72 (14.3)	0
Nervous system disorders				
Headache	95 (18.7)	0	93 (18.5)	1 (0.2)
Skin and subcutaneous tissue disorders				
Pruritus	99 (19.4)	0	58 (11.6)	0
Vascular disorders				
Hypertension	74 (14.5)	28 (5.5)	77 (15.3)	18 (3.6)

Serious adverse events were reported in 128 of 509 patients (25.1%) in the pembrolizumab group and 82 of 502 patients (16.3%) in the placebo group. Serious adverse events reported in ≥5 patients in the pembrolizumab group were basal cell carcinoma in 17 patients (3.3%), colitis in 8 patients (1.6%), pneumonitis in 7 patients (1.4%), squamous cell carcinoma in 6 patients (1.2%), and diarrhoea in 5 patients (1.0%). Serious adverse events reported in ≥5 patients in the placebo group were basal cell carcinoma in 25 patients (5.0%), cellulitis in 7 patients (1.4%), and malignant melanoma in situ in 6 patients (1.2%). A causal relationship to the study drug could not be ruled out for the colitis in 8 patients, pneumonitis in 7 patients, and diarrhoea in 4 patients in the pembrolizumab group, and cellulitis in 1 patient in the placebo group.

Adverse events led to drug discontinuation in 70 of 509 patients (13.8%) in the pembrolizumab group and 18 of 502 patients (3.6%) in the placebo group. Adverse events that led to drug discontinuation in ≥5 patients in either treatment group were pneumonitis in 7 patients (1.4%), colitis in 6 patients (1.2%), and diarrhoea in 5 patients (1.0%) in the pembrolizumab group. A causal relationship to the study drug could not be ruled out for all of these events.

7.4.2 Adverse events reported in clinical studies in patients with NSCLC

7.4.2.1 Japanese phase I study (Study 011)

7.4.2.1.1 Part B

Adverse events were reported in 6 of 6 patients (100%) in Cohort 1 and 6 of 6 patients (100%) in Cohort 2. Adverse events for which a causal relationship to the study drug could not be ruled out were 6 of 6 patients (100%) in Cohort 1 and 6 of 6 patients (100%) in Cohort 2. Adverse events reported with a ≥60% incidence in either cohort were nausea and decreased appetite in 6 patients (100%) each, neutropenia in 5 patients (83.3%), anaemia, leukopenia, constipation, malaise, and hiccups in 4 patients (66.7%) each in Cohort 1; and nausea in 5 patients (83.3%), and anaemia and leukopenia in 4 patients (66.7%) each in Cohort 2.

Serious adverse events were reported in 2 of 6 patients (33.3%) in Cohort 1 and 4 of 6 patients (66.7%) in Cohort 2. The serious adverse event reported in ≥2 patients in either cohort was pulmonary embolism in 2 patients (33.3%) in Cohort 2. A causal relationship to the study drug could not be ruled out for the pulmonary embolism in 1 patient.

Adverse events led to drug discontinuation in 1 of 6 patients (16.7%) in Cohort 1, and 4 of 6 patients (66.7%) in Cohort 2. The adverse event that led to drug discontinuation in ≥2 patients in either cohort was pulmonary embolism in 2 patients (33.3%) in Cohort 2. A causal relationship to the study drug could not be ruled out for the pulmonary embolism in 1 patient.

7.4.2.1.2 Part C

Adverse events were reported in 8 of 8 patients (100%) in Cohort 1 and 6 of 6 patients (100%) in Cohort 2. Adverse events for which a causal relationship to the study drug could not be ruled out were 8 of 8 patients (100%) in Cohort 1 and 6 of 6 patients (100%) in Cohort 2. Adverse events reported with a ≥60% incidence in either cohort were neutropenia, peripheral sensory neuropathy, and alopecia in 5 patients (62.5%) each in Cohort 1, anaemia, leukopenia, neutropenia, and decreased appetite in 6 patients (100%) each, nausea and alopecia in 5 patients (83.3%) each, and thrombocytopenia, diarrhoea, and peripheral sensory neuropathy in 4 patients (66.7%) each in Cohort 2.

Serious adverse events were reported in 3 of 8 patients (37.5%) in Cohort 1, and 3 of 6 patients (50.0%) in Cohort 2. The serious adverse event reported in ≥2 patients in either cohort was lung infection in 2 patients (33.3%) in Cohort 2. A causal relationship to the study drug could not be ruled out for the lung infection in 1 patient.

Adverse events led to drug discontinuation in 3 of 8 patients (37.5%) in Cohort 1 and 3 of 6 patients (50.0%) in Cohort 2. The adverse event that led to drug discontinuation in ≥2 patients in either cohort was lung infection in 2 patients (33.3%) in Cohort 2. A causal relationship to the study drug could not be ruled out for the lung infection in 1 patient.

7.4.2.2 Global phase III study (Study 189)

Adverse events were reported in 404 of 405 patients (99.8%) in the pembrolizumab group and 200 of 202 patients (99.0%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 372 of 405 patients (91.9%) in the pembrolizumab group and 183 of 202 patients (90.6%) in the placebo group. Table 38 shows adverse events reported with a ≥20% incidence in either treatment group.

Table 38. Adverse events with a ≥20% incidence

SOC PT (MedDRA ver. 20.1)	n (%)			
	Pembrolizumab N = 405		Placebo N = 202	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	404 (99.8)	272 (67.2)	200 (99.0)	133 (65.8)
Blood and lymphatic system disorders				
Anaemia	187 (46.2)	66 (16.3)	94 (46.5)	31 (15.3)
Neutropenia	110 (27.2)	64 (15.8)	49 (24.3)	24 (11.9)
Gastrointestinal disorders				
Constipation	141 (34.8)	4 (1.0)	64 (31.7)	1 (0.5)
Diarrhoea	125 (30.9)	21 (5.2)	43 (21.3)	6 (3.0)
Nausea	225 (55.6)	14 (3.5)	105 (52.0)	7 (3.5)
Vomiting	98 (24.2)	15 (3.7)	47 (23.3)	6 (3.0)
General disorders and administration site conditions				
Asthenia	83 (20.5)	25 (6.2)	49 (24.3)	7 (3.5)
Fatigue	165 (40.7)	23 (5.7)	77 (38.1)	5 (2.5)
Metabolism and nutrition disorders				
Decreased appetite	114 (28.1)	6 (1.5)	61 (30.2)	1 (0.5)
Respiratory, thoracic, and mediastinal disorders				
Cough	87 (21.5)	0	57 (28.2)	0
Dyspnoea	86 (21.2)	15 (3.7)	52 (25.7)	11 (5.4)
Skin and subcutaneous tissue disorders				
Rash	82 (20.2)	7 (1.7)	23 (11.4)	3 (1.5)

Serious adverse events were reported in 202 of 405 patients (49.9%) in the pembrolizumab group and 95 of 202 patients (47.0%) in the placebo group. Serious adverse events reported in ≥10 patients in the pembrolizumab group were febrile neutropenia and pneumonia in 23 patients (5.7%) each, diarrhoea in 15 patients (3.7%), thrombocytopenia in 13 patients (3.2%), anaemia and pneumonitis in 12 patients (3.0%) each, and neutropenia in 10 patients (2.5%). Serious adverse events reported in ≥10 patients in the placebo group were pneumonia in 17 patients (8.4%) and anaemia in 10 patients (5.0%). A causal relationship to the study drug could not be ruled out for the febrile neutropenia in 21 patients, thrombocytopenia in 13 patients, diarrhoea in 12 patient, pneumonitis in 11 patients, anaemia in 9 patients, neutropenia in 7 patient, and pneumonia in 4 patients in the pembrolizumab group, and anaemia in 10 patients and pneumonia in 1 patient in the placebo group.

Adverse events led to drug discontinuation in 112 of 405 patients (27.7%) in the pembrolizumab group and 30 of 202 patients (14.9%) in the placebo group. Adverse events that led to drug discontinuation in ≥10 patients in either treatment group were acute kidney injury and pneumonitis in 12 patients (3.0%) in the pembrolizumab group. A causal relationship to the study drug could not be ruled out for the pneumonitis in 11 patients and acute kidney injury in 10 patients.

7.4.2.3 Global phase III study (Study 407)

Adverse events were reported in 273 of 278 patients (98.2%) in the pembrolizumab group and 274 of 280 patients (97.9%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were in 265 of 278 patients (95.3%) in the pembrolizumab group and 249 of 280 patients

(88.9%) in the placebo group. Table 39 shows adverse events reported with a ≥20% incidence in either treatment group.

Table 39. Adverse events with a ≥20% incidence

SOC PT (MedDRA ver. 20.1)	n (%)			
	Pembrolizumab N = 278		Placebo N = 280	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	273 (98.2)	194 (69.8)	274 (97.9)	191 (68.2)
Blood and lymphatic system disorders				
Anaemia	148 (53.2)	43 (15.5)	145 (51.8)	57 (20.4)
Neutropenia	105 (37.8)	63 (22.7)	92 (32.9)	69 (24.6)
Thrombocytopenia	85 (30.6)	19 (6.8)	65 (23.2)	18 (6.4)
Gastrointestinal disorders				
Constipation	64 (23.0)	2 (0.7)	61 (21.8)	3 (1.1)
Diarrhoea	83 (29.9)	11 (4.0)	65 (23.2)	6 (2.1)
Nausea	99 (35.6)	3 (1.1)	90 (32.1)	4 (1.4)
General disorders and administration site conditions				
Asthenia	60 (21.6)	6 (2.2)	59 (21.1)	10 (3.6)
Fatigue	63 (22.7)	9 (3.2)	72 (25.7)	11 (3.9)
Metabolism and nutrition disorders				
Decreased appetite	68 (24.5)	6 (2.2)	82 (29.3)	5 (1.8)
Musculoskeletal and connective tissue disorders				
Arthralgia	57 (20.5)	4 (1.4)	40 (14.3)	2 (0.7)
Nervous system disorders				
Peripheral neuropathy	57 (20.5)	3 (1.1)	45 (16.1)	2 (0.7)
Skin and subcutaneous tissue disorders				
Alopecia	128 (46.0)	1 (0.4)	102 (36.4)	3 (1.1)

Serious adverse events were reported in 113 of 278 patients (40.6%) in the pembrolizumab group and 107 of 280 patients (38.2%) in the placebo group. Serious adverse events reported in ≥10 patients in the pembrolizumab group were pneumonia in 16 patients (5.8%) and febrile neutropenia in 15 patients (5.4%). Serious adverse events reported in ≥10 patients in the placebo group were pneumonia in 17 patients (6.1%) and febrile neutropenia in 10 patients (3.6%). A causal relationship to the study drug could not be ruled out for the febrile neutropenia in 14 patients and pneumonia in 7 patients in the pembrolizumab group, and febrile neutropenia in 9 patients and pneumonia in 3 patients in the placebo group.

Adverse events led to drug discontinuation in 65 of 278 patients (23.4%) in the pembrolizumab group and 33 of 280 patients (11.8%) in the placebo group. Adverse events that led to drug discontinuation in ≥5 patients in either treatment group were autoimmune hepatitis, neutropenia, and pneumonitis in 5 patients (1.8%) each in the pembrolizumab group. A causal relationship to the study drug could not be ruled out for the autoimmune hepatitis and neutropenia in 5 patients each, and pneumonitis in 4 patients.

7.4.2.4 Global phase III study (Study 042)

Adverse events were reported in 610 of 636 patients (95.9%) in the pembrolizumab group and 606 of 615 patients (98.5%) in the chemotherapy group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 399 of 636 patients (62.7%) in the pembrolizumab group and 553 of

615 patients (89.9%) in the chemotherapy group. Table 40 shows the adverse events reported with a ≥15% incidence in either treatment group.

Table 40. Adverse events with a ≥15% incidence

SOC PT (MedDRA ver. 20.1)	n (%)			
	Pembrolizumab N = 636		Chemotherapy N = 615	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	610 (95.9)	318 (50.0)	606 (98.5)	351 (57.1)
Blood and lymphatic system disorders				
Anaemia	99 (15.6)	17 (2.7)	259 (42.1)	92 (15.0)
Gastrointestinal disorders				
Constipation	77 (12.1)	0	130 (21.1)	1 (0.2)
Nausea	74 (11.6)	3 (0.5)	196 (31.9)	7 (1.1)
Vomiting	51 (8.0)	3 (0.5)	107 (17.4)	3 (0.5)
General disorders and administration site conditions				
Fatigue	101 (15.9)	12 (1.9)	126 (20.5)	9 (1.5)
Metabolism and nutrition disorders				
Decreased appetite	110 (17.3)	11 (1.7)	131 (21.3)	9 (1.5)
Respiratory, thoracic, and mediastinal disorders				
Cough	99 (15.6)	1 (0.2)	65 (10.6)	2 (0.3)
Dyspnoea	105 (16.5)	13 (2.0)	70 (11.4)	5 (0.8)
Skin and subcutaneous tissue disorders				
Alopecia	3 (0.5)	0	138 (22.4)	7 (1.1)

Serious adverse events were reported in 259 of 636 patients (40.7%) in the pembrolizumab group and 187 of 615 patients (30.4%) in the chemotherapy group. Serious adverse events reported in ≥10 patients in the pembrolizumab group were pneumonia in 47 patients (7.4%), pneumonitis in 25 patients (3.9%), pulmonary embolism in 15 patients (2.4%), pleural effusion in 14 patients (2.2%), and death in 10 patients (1.6%). Serious adverse events reported in ≥10 patients in the chemotherapy group were pneumonia in 32 patients (5.2%), anaemia in 17 patients (2.8%), febrile neutropenia in 15 patients (2.4%), and pulmonary embolism in 11 patients (1.8%). A causal relationship to the study drug could not be ruled out for the pneumonitis in 25 patients, pleural effusion in 6 patients, pulmonary embolism in 2 patients, and pneumonia and death in 1 patient each in the pembrolizumab group, and anaemia in 15 patients, pneumonia and febrile neutropenia in 13 patients each, and pulmonary embolism in 4 patients in the chemotherapy group.

Adverse events led to drug discontinuation in 122 of 636 patients (19.2%) in the pembrolizumab group and 89 of 615 patients (14.5%) in the chemotherapy group. Adverse events that led to drug discontinuation in ≥10 patients in either treatment group were pneumonitis in 19 patients (3.0%) and death in 10 patients (1.6%) in the pembrolizumab group. A causal relationship to the study drug could not be ruled out for the pneumonitis in 19 patients and death in 1 patient.

7.4.2.5 Foreign phase I/II study (Study 021)

7.4.2.5.1 Cohort A

Adverse events were reported in 13 of 13 patients (100%) in the 2 mg/kg group and 12 of 12 patients (100%) in the 10 mg/kg group. Adverse events for which a causal relationship to the study drug could not be ruled out

were reported in 13 of 13 patients (100%) in the 2 mg/kg group and 12 of 12 patients (100%) in the 10 mg/kg group. Adverse events reported with a ≥50% incidence in the 2 mg/kg group were constipation and fatigue in 8 patients (61.5%) each, nausea, decreased appetite, cough, and alopecia in 7 patients (53.8%) each. Adverse events reported with a ≥50% incidence in the 10 mg/kg group were fatigue in 8 patients (66.7%), constipation and alopecia in 7 patients (58.3%) each.

Serious adverse events were reported in 7 of 13 patients (53.8%) in the 2 mg/kg group and 5 of 12 patients (41.7%) in the 10 mg/kg group. Serious adverse events reported in ≥2 patients in the 2 mg/kg group were pneumonia in 3 patients (23.1%) and febrile neutropenia in 2 patients (15.4%). Serious adverse event reported in ≥2 patients in the 10 mg/kg group was pneumonia in 2 patients (16.7%). A causal relationship to the study drug could not be ruled out for the febrile neutropenia in 2 patients in the 2 mg/kg group.

Adverse events led to drug discontinuation in 2 of 13 patients (15.4%) in the 2 mg/kg group and 1 of 12 patients (8.3%) in the 10 mg/kg group. No adverse events led to drug discontinuation in ≥2 patients in either treatment group.

7.4.2.5.2 Cohort C

Adverse events were reported in 12 of 12 patients (100%) in the 2 mg/kg group and 12 of 12 patients (100%) in the 10 mg/kg group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 12 of 12 patients (100%) in the 2 mg/kg group and 12 of 12 patients (100%) in the 10 mg/kg group. Adverse events reported with a ≥50% incidence in the 2 mg/kg group were constipation in 8 patients (66.7%), nausea in 7 patients (58.3%), and fatigue in 6 patients (50.0%). Adverse events reported with a ≥50% incidence in the 10 mg/kg group were fatigue in 11 patients (91.7%), constipation in 7 patients (58.3%), and anaemia in 6 patients (50.0%).

Serious adverse events were reported in 6 of 12 patients (50.0%) in the 2 mg/kg group and 7 of 12 patients (58.3%) in the 10 mg/kg group. The serious adverse event reported in ≥2 patients in the 2 mg/kg group was anaemia in 2 patients (16.7%). Serious adverse events reported in ≥2 patients in the 10 mg/kg group were chronic obstructive pulmonary disease and death in 2 patients (16.7%) each. A causal relationship to the study drug could not be ruled out for the anaemia in 1 patient in the 2 mg/kg group.

Adverse events led to drug discontinuation in 4 of 12 patients (33.3%) in the 2 mg/kg group and 3 of 12 patients (25.0%) in the 10 mg/kg group. The adverse event that led to drug discontinuation in ≥2 patients in either treatment group was rash in 2 patients (16.7%) in the 10 mg/kg group. A causal relationship to the study drug could not be ruled out for both of these events.

7.4.2.5.3 Cohort G

Adverse events were reported in 59 of 59 patients (100%) in the pembrolizumab + CBDCA + PEM group and 61 of 62 patients (98.4%) in the CBDCA + PEM group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 55 of 59 patients (93.2%) in the pembrolizumab + CBDCA

+ PEM group and 57 of 62 patients (91.9%) in the CBDCA + PEM group. Adverse events reported with a ≥50% incidence in the pembrolizumab + CBDCA + PEM group were nausea in 44 patients (74.6%), fatigue in 43 patients (72.9%), and constipation in 32 patients (54.2%). Adverse events reported with a ≥50% incidence in the CBDCA + PEM group were anaemia and nausea in 36 patients (58.1%) each, and fatigue in 34 patients (54.8%).

Serious adverse events were reported in 29 of 59 patients (49.2%) in the pembrolizumab + CBDCA + PEM group and 20 of 62 patients (32.3%) in the CBDCA + PEM group. Serious adverse event reported in ≥3 patients in either treatment group were acute kidney injury in 6 patients (10.2%), cellulitis in 4 patients (6.8%), and pleural effusion in 3 patients (5.1%) in the pembrolizumab + CBDCA + PEM group. A causal relationship to the study drug could not be ruled out for the acute kidney injury in 3 patients and cellulitis in 1 patient.

Adverse events led to drug discontinuation in 10 of 59 patients (16.9%) in the pembrolizumab + CBDCA + PEM group and 9 of 62 patients (14.5%) in the CBDCA + PEM group. Adverse events that led to drug discontinuation in ≥2 patients in either treatment group were acute kidney injury in 3 patients (5.1%) in the pembrolizumab + CBDCA + PEM group, and fatigue and stomatitis in 2 patients (3.2%) each in the CBDCA + PEM group. A causal relationship to the study drug could not be ruled out for all the events.

7.4.3 Adverse events reported in clinical studies in patients with MSI-High solid tumors

7.4.3.1 Global phase II study (Study 164)

Adverse events were reported in 60 of 61 patients (98.4%), and adverse events for which a causal relationship to the study drug could not be ruled out were reported in 35 of 61 patients (57.4%). Table 41 shows adverse events reported with a ≥15% incidence.

Table 41. Adverse events with a ≥15% incidence

SOC PT (MedDRA ver. 19.1)	n (%) N = 61	
	All grades	Grade ≥3
All adverse events	60 (98.4)	36 (59.0)
Blood and lymphatic system disorders		
Anaemia	11 (18.0)	4 (6.6)
Gastrointestinal disorders		
Abdominal pain	19 (31.1)	4 (6.6)
Constipation	12 (19.7)	0
Diarrhoea	21 (34.4)	0
Nausea	20 (32.8)	0
Vomiting	16 (26.2)	0
General disorders and administration site conditions		
Asthenia	14 (23.0)	2 (3.3)
Fatigue	18 (29.5)	2 (3.3)
Pyrexia	15 (24.6)	1 (1.6)
Metabolism and nutrition disorders		
Decreased appetite	12 (19.7)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	11 (18.0)	0
Respiratory, thoracic, and mediastinal disorders		
Cough	12 (19.7)	0

Serious adverse events were reported in 29 of 61 patients (47.5%). Serious adverse events reported in ≥2 patients were ileus in 4 patients (6.6%), and abdominal pain, pulmonary embolism, pyrexia, small intestinal obstruction, and urinary tract infection in 2 patients (3.3%) each. A causal relationship to the study drug was denied for all the events.

Adverse events led to drug discontinuation in 4 of 61 patients (6.6%). Adverse events that led to drug discontinuation were autoimmune arthritis, pneumonitis, decreased appetite, and aspiration in 1 patient (1.6%) each. A causal relationship to the study drug could not be ruled out for the pneumonitis in 1 patient.

7.4.3.2 Global phase II study (Study 158)

Adverse events were reported in 91 of 94 patients (96.8%), and adverse events for which a causal relationship to the study drug could not be ruled out were reported in 58 of 94 patients (61.7%). Table 42 shows adverse events reported with a ≥15% incidence.

Table 42. Adverse events with a ≥15% incidence

SOC PT (MedDRA ver. 20.0)	n (%) N = 94	
	All grades	Grade ≥3
All adverse events	91 (96.8)	41 (43.6)
Gastrointestinal disorders		
Constipation	16 (17.0)	1 (1.1)
Diarrhoea	27 (28.7)	2 (2.1)
Nausea	24 (25.5)	0
Vomiting	15 (16.0)	0
General disorders and administration site conditions		
Asthenia	17 (18.1)	1 (1.1)
Fatigue	26 (27.7)	2 (2.1)
Pyrexia	15 (16.0)	0

Serious adverse events were reported in 32 of 94 patients (34.0%). The serious adverse events reported in ≥2 patients were sepsis in 3 patients (3.2%), and death, pneumonia, and pneumonitis in 2 patients (2.1%) each. A causal relationship to the study drug could not be ruled out for the pneumonitis in 2 patients.

Adverse events led to drug discontinuation in 13 of 94 patients (13.8%). The adverse events that led to drug discontinuation in ≥2 patients were blood ALP increased and death in 2 patients (2.1%) each. A causal relationship to the study drug could not be ruled out for the blood ALP increased in 2 patients.

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 inspections and assessment are currently ongoing. The results of the inspections and assessment, and PMDA's conclusion are reported in the Review Report (2).

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

The inspections and assessment are currently ongoing. The results of the inspections and assessment, and PMDA's conclusion are reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that pembrolizumab has efficacy for the indications described below, and that pembrolizumab has acceptable safety in view of its benefits, and therefore that pembrolizumab therapy is clinically significant as a therapeutic option for each of these indications. PMDA has also concluded that the dosage regimen of pembrolizumab for the treatment of unresectable malignant melanoma can be changed from the body weight-based dose to a fixed dose.

- Pembrolizumab monotherapy for the adjuvant treatment of malignant melanoma
- Pembrolizumab in combination with platinum-based chemotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC

- Pembrolizumab monotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC
- Pembrolizumab monotherapy for the treatment of chemotherapy-treated patients with advanced or recurrent MSI-High solid tumors, who have no other standard treatment options

For the treatment of MSI-High solid tumors, PMDA considers that the indication and post-marketing investigation items, including the conditions for approval, should be further discussed.

PMDA has concluded that pembrolizumab may be approved if pembrolizumab is considered to have no particular problems based on comments from the Expert Discussion.

Review Report (2)

November 16, 2018

Product Submitted for Approval

Brand Name	Keytruda Injection 20 mg Keytruda Injection 100 mg
Non-proprietary Name	Pembrolizumab (genetical recombination)
Applicant	MSD K.K.
Date of Application	March 30, 2018, May 10, 2018, August 9, 2018[21)]

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 Safety

PMDA's conclusion:

As a result of its review described in Sections "7.1.R.2 Safety," "7.2.R.2 Safety," and "7.3.R.1 Safety" of the Review Report (1), PMDA concluded that the adverse events that require special attention after the administration of pembrolizumab are those identified as requiring attention at the regulatory reviews for the approved indications[22)] and should also be closely monitored when pembrolizumab is administered for the following indications.

(a) Pembrolizumab monotherapy for patients with resected malignant melanoma at high risk for recurrence[23)]

(b) Pembrolizumab in combination with platinum-based chemotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent non-small cell lung cancer (NSCLC)

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21) Partial change applications for (a) a new indication for the treatment of MSI-High solid tumors and a modified dosage and administration for the treatment of unresectable malignant melanoma, (b) a new indication, and a dosage and administration for the adjuvant treatment of malignant melanoma, and (c) a modified indication for the treatment of NSCLC were filed on (a) March 30, 2018, (b) May 10, 2018, and (c) August 9, 2018, respectively.

22) Gastrointestinal disorders, skin disorders, neurological disorders, hepatic function disorder, cholangitis sclerosing, eye disorders, endocrine disorders, renal impairment, interstitial lung disease (ILD), infusion-related reaction (IRR), pancreatitis, myositis, rhabdomyolysis, encephalitis and meningitis, myasthenia gravis, myocarditis, immune thrombocytopenic purpura, haemolytic anaemia, and pure red-cell aplasia (see "Review Report for Keytruda Injection 20 mg, Keytruda Injection 100 mg dated November 15, 2016").

23) Patients with (a) stage IIIA (>1 mm lymph node metastasis), (b) stage IIIB, or (c) stage IIIC melanoma were defined as being at high risk for recurrence.

(c) Pembrolizumab monotherapy for the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC
(d) Pembrolizumab monotherapy for chemotherapy-treated patients with advanced or recurrent microsatellite instability-high (MSI-High) solid tumors

Attention should be paid to the occurrence of the above-described adverse events; however, pembrolizumab is also tolerable when administered for the above indications (a) to (d), as long as the patients are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis and patient management in anticipation of adverse reactions due to an excessive immune response, drug interruption, or other appropriate actions.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

1.2 Efficacy, clinical positioning, and indications

PMDA's conclusion:

As a result of its review described in Sections "7.1.R.1 Efficacy," "7.2.R.1 Efficacy," and "7.3.R.2 Clinical positioning, efficacy, and indication" of the Review Report (1), PMDA concluded the efficacy of pembrolizumab in the treatment of (a) malignant melanoma, (b) NSCLC, and (c) MSI-High solid tumors as follows:

(a) A global phase III study in patients with resected malignant melanoma at high risk for recurrence (Study 054) demonstrated the superiority of pembrolizumab to placebo in investigator-assessed RFS[24)] (the primary endpoint); therefore, the efficacy of pembrolizumab has been demonstrated in the target patient population of the study.
(b) Based on data, including the results of the following 3 global phase III studies (Studies 189, 407, and 042), the efficacy of pembrolizumab has been demonstrated in the target patient populations of these studies.
    - In a global phase III study in chemotherapy-naïve patients with unresectable, advanced or recurrent non-squamous (NSQ)-NSCLC (Study 189) and a global phase III study in chemotherapy-naïve patients with unresectable, advanced or recurrent squamous (SQ)-NSCLC (Study 407), pembrolizumab was superior to placebo in OS (one of the primary endpoints).
    - In a global phase III study in chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC (Study 042), pembrolizumab was superior to chemotherapy in OS (the primary endpoint).
(c) In a global phase II study in chemotherapy-treated patients with radically unresectable, advanced or recurrent dMMR or MSI-High (PCR) colorectal cancer (Study 164) and a global phase II study in chemotherapy-treated patients with radically unresectable, advanced or recurrent solid tumors (Study 158) (Group K[25)]), the centrally assessed response rates (the primary endpoints) were 27.9 [95% CI, 17.1-40.8] and 34.9 [95% CI, 24.8-46.2], respectively. Based on the study results, and taking into account the

24) RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first.
25) Patients with MSI-High solid tumors (except colorectal cancer) were enrolled.

molecular pathogenesis of MSI-High solid tumors [see Section 7.3.R.2.1], a certain level of efficacy of pembrolizumab has been demonstrated in the target study populations of the studies.

As a result of its review described in Sections "7.1.R.3 Clinical positioning and indication," "7.2.R.3 Clinical positioning and indication," and "7.3.R.2 Clinical positioning, efficacy, and indication" of the Review Report (1), PMDA concluded that the statements for (a) malignant melanoma, (b) NSCLC, and (c) MSI-High solid tumors presented in the table below should be included in the "Indications" and "Precautions for Indications" sections of the package insert.

	Indications	Precautions for Indications
(a)	Malignant melanoma*1	• Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section.
(b)	Unresectable, advanced or recurrent NSCLC*2	• The efficacy and safety of pembrolizumab in adjuvant therapy have not been established. • When used as a monotherapy, pembrolizumab should be administered to patients whose tumors have been demonstrated to express PD-L1. The "Clinical Studies" section should be carefully read to understand the percentage of PD-L1-expressing tumor cells (TPS). PD-L1 testing should be performed by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic. • Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand the status of *EGFR* mutation or *ALK* fusion genes in patients enrolled in the clinical studies.
(c)	Advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)	• Pembrolizumab should be administered to patients who have been demonstrated to have an advanced MSI-High solid tumor by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic. • In the treatment of colorectal cancer, the efficacy and safety of pembrolizumab have not been established in patients with no prior therapy with a fluoropyrimidine + L-OHP + CTP-11. • In the treatment of solid tumors (except colorectal cancer), the efficacy and safety of pembrolizumab as a first-line therapy have not been established. In the second-line therapy for these solid tumors, standard treatments, if available, should be chosen before pembrolizumab. • The efficacy and safety of pembrolizumab in adjuvant therapy have not been established. • Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand the characteristics (e.g., cancer type) of the patients enrolled in the clinical studies as well as carefully considering the choice of alternative therapies.

*1, Changed from the approved indication of "unresectable malignant melanoma"
*2, Changed from the approved indication of "unresectable, advanced or recurrent PD-L1 positive NSCLC"

Discussion at the Expert Discussion:
Some expert advisors supported the above conclusions of the PMDA, while others made the following comment:

- One suggestion is that a more detailed precautionary statement should be included in the "Precautions for Indications" section when selecting patients for adjuvant treatment with pembrolizumab for malignant melanoma.

PMDA's view:
Based on the comment of expert advisors, PMDA has concluded that the following precautionary statement for the adjuvant treatment of malignant melanoma should be included in the "Precautions for Indications" section.

- Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand particularly for the disease stages of patients enrolled in the clinical studies.

In view of the above, PMDA instructed the applicant to include the above statement in the "Indications" and "Precautions for Indications" sections of the package insert. The applicant agreed.

1.3 Dosage and administration

As a result of its review described in Sections "7.1.R.4 Dosage and administration," "7.2.R.4 Dosage and administration," and "7.3.R.3 Dosage and administration" of the Review Report (1), PMDA concluded that the following statements should be included in the "Dosage and administration" and "Precautions for Dosage and Administration" sections of the package insert.

[Dosage and Administration]

- Malignant melanoma
  - The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks. For the adjuvant treatment of malignant melanoma, the maximum duration of treatment is 12 months.
- Unresectable, advanced or recurrent non-small cell lung cancer, or advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)
  - The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks.

[Precautions for Dosage and Administration]

- Malignant melanoma
  - The efficacy and safety of pembrolizumab in combination with other antineoplastic drugs have not been established.
  - Criteria for interruption and discontinuation of pembrolizumab in case of adverse reactions (unchanged from the previous approval)
- Unresectable, advanced or recurrent NSCLC
  - When pembrolizumab is used with other antineoplastic drugs, the "Clinical Studies" section should be understood sufficiently before selecting concomitant antineoplastic drugs.
  - Criteria for interruption and discontinuation of pembrolizumab in case of adverse reactions (unchanged from the previous approval)
- Advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)
  - The efficacy and safety of pembrolizumab in combination with other antineoplastic drugs have not been established.
  - Criteria for the interruption and discontinuation of pembrolizumab in case of adverse reactions (unchanged from the previous approval)

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

PMDA instructed the applicant to include the above statements in the “Dosage and Administration” and “Precautions for Dosage and Administration” sections of the package insert. The applicant agreed.

1.4 Risk management plan (draft)

The applicant's explanation on the post-marketing surveillance plans for (a) malignant melanoma, (b) NSCLC, and (c) MSI-High solid tumors:

For (a) and (b), there is little need to conduct post-marketing surveillance in association with the present partial change application, immediately after the approval [see Section 7.3.R.4].

For (c), the applicant plans to conduct post-marketing surveillance covering patients treated with pembrolizumab for MSI-High solid tumors, to evaluate the long-term efficacy of pembrolizumab in clinical practice. The proposed target sample size is 30 patients, and the proposed observation period is 16 months. On the other hand, it is not necessary to conduct post-marketing surveillance to evaluate the safety of pembrolizumab in clinical practice, immediately after the approval [see Section 7.3.R.4].

As a result of its review described in Section “7.3.R.4 Post-marketing investigations” of the Review Report (1), PMDA reached the following conclusions:

For (a) malignant melanoma, (b) NSCLC, and MSI-High colorectal cancer among (c) MSI-High solid tumors, there is little need to conduct post-marketing surveillance in association with the present partial change applications, immediately after the approval, and safety information may be collected through routine pharmacovigilance activities.

For (c) MSI-High solid tumors (except colorectal cancer)

- Since only limited cancer types have been investigated, post-marketing surveillance should be conducted to evaluate the efficacy of pembrolizumab administered to Japanese patients with MSI-High solid tumors (except colorectal cancer) in clinical practice.The proposed target sample size and observation period should be reconsidered to ensure the appropriate evaluation of the efficacy of pembrolizumab in Japanese patients with MSI-High solid tumors (except colorectal cancer).
- As much safety information as possible should be collected from patients treated with pembrolizumab for MSI-High solid tumors (except colorectal cancer), including the adverse reactions listed as important identified risks under the risk management plan.

Studies 164 and 158 are still ongoing. Efficacy information should be collected continuously from these studies, and the obtained information should be communicated promptly to healthcare professionals.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

Based on the above review, PMDA instructed the applicant to reconsider the plan of the post-marketing surveillance in patients treated with pembrolizumab for MSI-High solid tumors (except colorectal cancer).

The applicant's response:

- Based on the response rate of 37.2% (35 of 94 patients) observed in the pembrolizumab group of Study 158 and other relevant data, the number of patients required to achieve a statistical power of 95% is calculated to be 20, when an expected response rate of 37.2% with a threshold response rate of 5% are assumed, and a level of significance of 0.025 (one-sided) is used. Considering dropouts, the target sample size is therefore 30 patients. Since the currently available data as to clinical experience with pembrolizumab for MSI-High solid tumors (except colorectal cancer) are limited to several cancer types, ≥30 patients with MSI-High solid tumors (except colorectal cancer) will be enrolled, and data will be collected from all possible patients who are treated with pembrolizumab for MSI-High solid tumors (except colorectal cancer) during the enrollment period. A total of 94 patients with MSI-High solid tumors are aimed to be treated with pembrolizumab during the enrollment period.
- In Study 158, the maximum duration of pembrolizumab therapy to a response was 10.2 months. Based on this, and considering the time needed to confirm best overall response, the observation period will be 12 months.
- The adverse reactions specified as important identified risks under the risk management plan (excluding "Use in patients with a history of organ transplantation [including hematopoietic stem cell transplantation]") will be selected as the safety specifications for the surveillance, and information regarding these adverse reactions will be collected.

PMDA accepted the applicant's response.

In view of the above discussions, PMDA has concluded that the risk management plan (draft) for pembrolizumab should include the safety and efficacy specifications presented in Table 43, and that the applicant should conduct additional pharmacovigilance activities, efficacy investigations or studies, and the risk minimization activities presented in Tables 44 and 45.

Table 43. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• ILD • Colitis and severe diarrhoea • Hepatic function disorder and cholangitis sclerosing • Renal impairment (tubulointerstitial nephritis, etc.) • Endocrine disorders (pituitary dysfunction, thyroid dysfunction, and adrenal dysfunction) • Type 1 diabetes mellitus • Uveitis • Myositis and rhabdomyolysis • Pancreatitis • Neurological disorders (Guillain-Barre syndrome, etc.) • Severe skin disorders (oculomucocutaneous syndrome, erythema multiforme, pemphigoid, etc.) • Encephalitis and meningitis • Myasthenia gravis • Myocarditis • Immune thrombocytopenic purpura • Haemolytic anaemia • Pure red-cell aplasia • Infusion related reaction (IRR) • Use in patients with a history of organ transplantation (including hematopoietic stem cell transplantation)	• Increased risk of severe comorbidities associated with allogenic hematopoietic stem cell transplantation after pembrolizumab therapy (hematological malignancies) • Embryonic/fetal toxicities	None
Efficacy specification		
• Efficacy in patients with unresectable malignant melanoma in clinical practice • Efficacy in patients with unresectable, advanced or recurrent PD-L1 positive NSCLC in clinical practice • Efficacy in patients with relapsed or refractory cHL in clinical practice • Efficacy in patients with advanced or recurrent MSI-High solid tumors (except colorectal cancer) that have progressed after cancer chemotherapy in clinical practice		

Underline denotes specifications to be added after the present partial change approval.

Table 44. Summary of additional pharmacovigilance activities, efficacy investigations or studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy investigations/studies	Additional risk minimization activities
• Use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Use-results survey in patients with unresectable, advanced or recurrent PD-L1 positive NSCLC (all-case surveillance) • Use-results survey in patients with relapsed or refractory cHL (all-case surveillance) • Use-results survey in patients with radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy (all-case surveillance) • Use-results survey in patients with advanced or recurrent MSI-High solid tumors (except colorectal cancer) that have progressed after cancer chemotherapy • Post-marketing clinical studies (extension studies of Studies 041, 025, 010, 024, 087, 204, 045, 189, 407, and 042)	• Use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Use-results survey in patients with unresectable, advanced or recurrent PD-L1 positive NSCLC (all-case surveillance) • Use-results survey in patients with relapsed or refractory cHL (all-case surveillance) • Use-results survey in patients with radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy (all-case surveillance) • Use-results survey in patients with advanced or recurrent MSI-High solid tumors (except colorectal cancer) that have progressed after cancer chemotherapy • Post-marketing clinical studies (extension studies of Studies 041, 025, 010, 024, 087, 204, and 045)	• Organize and disseminate information for healthcare professionals • Organize and disseminate information for patients

Underlines denote activities to be performed after the new indications are added.

Table 45. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate the efficacy of pembrolizumab in patients with advanced or recurrent MSI-High solid tumors (except colorectal cancer) that have progressed after cancer chemotherapy, and to collect safety information from those patients in clinical practice after the market launch
Survey method	Central registration system
Population	Patients with advanced or recurrent MSI-High solid tumors (except colorectal cancer) that have progressed after cancer chemotherapy
Observation period	12 months
Planned sample size	≥30 patients (Data will be collected from all possible patients who are treated with pembrolizumab for MSI-High solid tumors [except colorectal cancer] during the enrollment period [A total of 94 patients with MSI-High solid tumors are expected to be treated with pembrolizumab during the enrollment period]).)
Main survey items	Efficacy survey item: Efficacy of pembrolizumab in patients with advanced or recurrent MSI-High solid tumors (except colorectal cancer) that have progressed after cancer chemotherapy in clinical practice Safety survey items: ILD, colitis and severe diarrhoea, hepatic function disorder and cholangitis sclerosing, renal impairment (tubulointerstitial nephritis, etc.), endocrine disorders (pituitary dysfunction, thyroid dysfunction, and adrenal dysfunction), type 1 diabetes mellitus, uveitis, myositis and rhabdomyolysis, pancreatitis, neurological disorders (Guillain-Barre syndrome, etc.), severe skin disorders (oculomucocutaneous syndrome, erythema multiforme, pemphigoid, etc.), encephalitis and meningitis, myasthenia gravis, myocarditis, immune thrombocytopenic purpura, haemolytic anaemia, pure red-cell aplasia, and IRR Other main survey items: patient characteristics (e.g., age, sex, prior treatments, cancer type, disease stage classification), exposure to pembrolizumab, concomitant drugs and treatments, etc.

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

2.1 PMDA's conclusion on 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

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

The new drug application data (CTD 5.3.5.1.1 [malignant melanoma], CTD 5.3.5.1.1, CTD 5.3.5.1.5, CTD 5.3.5.1.6, and CTD 5.3.5.2.1 [NSCLC], and CTD 5.3.5.2.1 and CTD 5.3.5.2.2 [MSI-High solid tumors]) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications and the proposed dosage regimen as shown below, with the following condition of approval, provided that the necessary precautionary statements are included in the package insert and information on the proper use of the product is properly disseminated after the market launch, and provided that the product is used under the supervision of physicians with sufficient knowledge and experience in cancer

chemotherapy at medical institutions capable of emergency response. The re-examination periods for the present partial change applications are as follows:

- Malignant melanoma (The re-examination period is the reminder of the ongoing re-examination period [until September 27, 2026].)
- Unresectable, advanced or recurrent non-small cell lung cancer (The re-examination period is the reminder of the ongoing re-examination period [until October 18, 2022].)
- Advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments) (The re-examination period is 4 years.)

Indications (Underline denotes additions. Strikethrough denotes deletions.)
~~Unresectable~~ Malignant melanoma
Unresectable, advanced or recurrent ~~PD-L1 positive~~ non-small cell lung cancer
Relapsed or refractory classical Hodgkin lymphoma
Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy
Advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)

Dosage and administration (Underlines denote additions. Strikethrough denotes deletions.)
[~~Unresectable~~ Malignant melanoma]
The usual adult dosage is 200 mg ~~2 mg/kg body weight~~ of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks. For the adjuvant treatment of malignant melanoma, the maximum duration of treatment is 12 months.

[Unresectable, advanced or recurrent ~~PD-L1 positive~~ non-small cell lung cancer, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, or advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)]
The usual adult dosage is 200 mg of pembrolizumab (genetical recombination) infused intravenously over 30 minutes every 3 weeks.

Conditions of Approval
[Malignant melanoma, unresectable, advanced or recurrent non-small cell lung cancer]
The applicant is required to develop and appropriately implement a risk management plan.

[Advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)]
1. The applicant is required to develop and appropriately implement a risk management plan.

2. The applicant is required to provide healthcare professionals with the results of 2 ongoing phase II studies, in patients with advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy, promptly after the studies are completed.
3. Since only limited data are available as to the efficacy of the product in the treatment of MSI-High solid tumors (except colorectal cancer), the applicant is required to conduct a use-results survey after the market launch to collect information on the characteristics of patients treated with the product, to promptly collect data on the efficacy and safety of the product, and to take necessary actions for the proper use of the product.

Warning (no change)

(1) Pembrolizumab should be administered only to patients considered appropriate to receive pembrolizumab therapy by a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution that can provide adequate emergency medical care. Inform the patient or their family members of the effectiveness and risks of pembrolizumab and obtain their consent before the start of treatment.

(2) There have been reports of patients who died after experiencing interstitial lung disease. Patients should be closely monitored for initial symptoms (shortness of breath, dyspnoea, cough, etc.) and examined by chest X-rays. If any abnormalities are observed, discontinue pembrolizumab and take appropriate measures such as treatment with corticosteroids.

Contraindications (no change)

Patients with a history of hypersensitivity to any ingredient of the product

Precautions for Indications (Underlines denote additions. Strikethrough denotes deletions.)

[~~Unresectable~~ Malignant melanoma]

~~The efficacy and safety of pembrolizumab in adjuvant chemotherapy have not been established.~~

Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand particularly for the characteristics (e.g., disease stage) of patients enrolled in the clinical studies.

[Unresectable, advanced or recurrent ~~PD-L1 positive~~ non-small cell lung cancer]

(1) The efficacy and safety of pembrolizumab in adjuvant ~~chemo~~therapy have not been established.

(2) When used as monotherapy, pembrolizumab should be administered to patients whose tumors have been demonstrated to express PD-L1. The "Clinical Studies" section should be carefully read to understand the percentage of PD-L1-expressing tumor cells (TPS). ~~Pembrolizumab should be administered to patients whose tumors have been demonstrated to express PD-L1.~~ PD-L1 testing should be performed by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic.

(3) Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand the status of *EGFR* mutation or *ALK* fusion genes in patients enrolled in the clinical studies.

[Relapsed or refractory cHL]
Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand particularly for the characteristics (e.g., prior treatments) of patients enrolled in the clinical studies.

[Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy]
(1) The efficacy and safety of pembrolizumab as the first-line therapy have not been established.
(2) Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand particularly for the characteristics (e.g., prior treatments) of patients enrolled in the clinical studies.
(3) The efficacy and safety of pembrolizumab in adjuvant ~~chemo~~therapy have not been established.

[Advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)]
(1) Pembrolizumab should be administered to patients who have been demonstrated to have an advanced or recurrent MSI-High solid tumor by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic.
(2) In the treatment of colorectal cancer, the efficacy and safety of pembrolizumab have not been established in patients with no prior therapy with a fluoropyrimidine + oxaliplatin + irinotecan hydrochloride hydrate.
(3) In the treatment of solid tumors (except colorectal cancer), the efficacy and safety of pembrolizumab as the first-line therapy have not been established. In the second-line therapy for these solid tumors, standard treatments, if available, should be chosen before pembrolizumab.
(4) The efficacy and safety of pembrolizumab in adjuvant therapy have not been established.
(5) Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the Clinical Studies" section to understand particularly for the characteristics (e.g., cancer type) of patients enrolled in the clinical studies as well as carefully considering the choice of alternative therapies.

Precautions for Indications (Underlines denote additions.)
[Unresectable, advanced or recurrent non-small cell lung cancer]
When pembrolizumab is used with other antineoplastic drugs, the "Clinical Studies" section should be understood sufficiently before selecting concomitant antineoplastic drugs.

[Malignant melanoma, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, or advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)]
The efficacy and safety of pembrolizumab in combination with other antineoplastic drugs have not been established.

[All the indications]
If an adverse drug reaction associated with pembrolizumab occurs, interrupt or discontinue pembrolizumab in accordance with the table below.

Adverse reaction	Severity	Actions
Interstitial lung disease	Grade 2	Interrupt pembrolizumab until the reaction resolves to Grade ≤1. If the reaction has resolved to Grade ≤1 over a >4-week period, resume pembrolizumab every 3 weeks. Discontinue pembrolizumab if the reaction has not resolved to Grade ≤1 after >12 weeks of interruption.
	Grade ≥3 or relapsed Grade 2	Discontinue pembrolizumab.
Colitis or diarrhoea	Grade 2 or 3	Interrupt pembrolizumab until the reaction resolves to Grade ≤1. Discontinue pembrolizumab if the reaction has not resolved to Grade ≤1 after >12 weeks of interruption.
	Grade 4	Discontinue pembrolizumab.
Hepatic function disorder	AST (GOT) or ALT (GPT) increased to 3-5 times the upper limit of normal (ULN), or total bilirubin increased to 1.5-3 times the ULN	Interrupt pembrolizumab until the value decreases to below the criteria on the left. Discontinue pembrolizumab if the value has not decreased to below the criteria on the left after >12 weeks of interruption.
	• AST (GOT) or ALT (GPT) increased to >5 times the ULN, or total bilirubin increased to >3 times the ULN • Patients with liver metastasis: Grade 2 AST (GOT) or ALT (GPT) at baseline with a ≥50% increase from baseline persisting for ≥1 week	Discontinue pembrolizumab.
Renal impairment	Grade 2	Interrupt pembrolizumab until the reaction resolves to Grade ≤1. Discontinue pembrolizumab if the reaction has not resolved to Grade ≤1 after >12 weeks of interruption.
	Grade ≥3	Discontinue pembrolizumab.
Endocrine disorders	• Grade ≥2 hypophysitis • Symptomatic endocrine disorders (except for hypothyroidism) • Grade ≥3 thyroid dysfunction • Grade ≥3 hyperglycaemia • Type 1 diabetes mellitus	Interrupt pembrolizumab until the reaction resolves to Grade ≤1. Consider discontinuing pembrolizumab if the reaction has not resolved to Grade ≤1 after >12 weeks of interruption.
Infusion reaction	Grade 2	Stop infusion immediately. If the reaction has resolved within 1 hour, resume pembrolizumab by reducing the infusion rate by 50%.
	Grade ≥3 or relapsed Grade 2	Stop infusion immediately, and do not resume pembrolizumab.
Other adverse reactions	• Grade 4 adverse reactions • If the dose of corticosteroid to treat an adverse reaction cannot be reduced to the dose equivalent to ≤10 mg/day prednisolone within 12 weeks of start of treatment: • Adverse reactions that have not resolved to Grade ≤1 after >12 weeks of interruption	Discontinue pembrolizumab. If Grade 4 hematotoxicity occurs in a patient with relapsed or refractory cHL, interrupt pembrolizumab until the reaction resolves to Grade ≤1.

Grade is determined in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0.

Appendix

List of Abbreviations

a platinum	CBDCA or CDDP
a platinum + PEM	a combination of a platinum-based chemotherapy and PEM
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{ss,6wk}$	area under the concentration-time curve at steady state over a 6-week interval
AUC5	area under the concentration-time curve over a 5-week interval
AUC6	area under the concentration-time curve over a 6-week interval
bevacizumab	bevacizumab (genetical recombination)
CBDCA	carboplatin
CBDCA/nab-PTX	a combination of CBDCA nab-PTX
CBDCA/PEM	a combination of CBDCA and PEM
CBDCA/PTX	a combination of CBDCA and PTX
CDDP	cisplatin
CDDP/PEM	a combination of CDDP and PEM
cetuximab	cetuximab (genetical recombination)
cHL	classical Hodgkin lymphoma
CI	confidence interval
CPS	combined positive score
CPT-11	irinotecan hydrochloride hydrate
CR	complete response
dabrafenib	dabrafenib mesilate
dabrafenib + trametinib	a combination of dabrafenib and trametinib
DLT	dose limiting toxicity
DMFS	distant metastasis-free survival
DOC	docetaxel hydrate
dMMR	deficient mismatch repair
EGFR	epidermal growth factor receptor
FOLFIRI	a combination of 5-FU, calcium folinate (or levofolinate), and CPT-11
FOLFOX	a combination of 5-FU, calcium folinate (or levofolinate), and L-OHP
FOLFOXIRI	a combination of 5-FU, calcium folinate (or levofolinate), L-OHP, and CPT-11
GGT	gamma-glutamyltransferase
IHC	immunohistochemistry
ILD	interstitial lung disease
ipilimumab	ipilimumab (genetical recombination)
IRR	infusion related reaction
ITT	intention-to-treat
Japanese clinical practice guidelines (large intestine cancer)	Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for the Treatment of Colorectal Cancer
Japanese clinical practice guidelines (malignant melanoma)	Scientific Evidence-based Cutaneous Malignant Tumor Treatment Guidelines, Version 2. edited by the Japanese Skin Cancer Society
Japanese clinical practice guidelines (NSCLC)	Guidelines for Diagnosis and Treatment of the Lung Cancer 2017, edited by the Japan Lung Cancer Society
KRAS	Kirsten rat sarcoma viral oncogene homolog

L-OHP	oxaliplatin
MedDRA	MedicalDictionary for Regulatory Activities
MEL score ≤1	melanoma score ≤1
MEL score ≥2	melanoma score ≥2
MLH1	mutL homolog 1
MSH2	mutS homolog 2
MSH6	mutS homolog 6
MSI	microsatellite instability
MSI-High	microsatellite instability-high
nab-PTX	nanoparticle albumin-bound paclitaxel
NCCN guidelines (Bone Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Bone Cancer
NCCN guidelines (Cervical Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Cervical Cancer
NCCN guidelines (Colon Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Colon Cancer
NCCN guidelines (Esophageal and Esophagogastric Junction Cancers)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Esophageal and Esophagogastric Junction Cancers
NCCN guidelines (Gastric Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Gastric Cancer
NCCN guidelines (Hepatobiliary Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Hepatobiliary Cancer
NCCN guidelines (Melanoma)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Melanoma
NCCN guidelines (Non-Small Cell Lung Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NCCN guidelines (Ovarian Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Ovarian Cancer
NCCN guidelines (Pancreatic Adenocarcinoma)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Pancreatic Adenocarcinoma
NCCN guidelines (Prostate Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Prostate Cancer
NCCN guidelines (Rectal Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Rectal Cancer
NCCN guidelines (Uterine Neoplasms)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Uterine Neoplasms
NCI-PDQ	National Cancer Institute Physician Data Query
NE	not evaluable
nivolumab	nivolumab (genetical recombination)
NSCLC	non-small cell lung cancer
NSQ	non-squamous
NSQ-NSCLC	non-squamous non-small cell lung cancer
OS	overall survival
panitumumab	panitumumab (genetical recombination)
partial change application	application of partial change approval
PCR	polymerase chain reaction
PD	progressive disease
PD-L	programmed cell death-ligand
PD-1	programmed cell death-1
PEM	pemetrexed sodium hydrate
pembrolizumab	pembrolizumab (genetical recombination)

pembrolizumab + CBDCA + nab-PTX	a combination of pembrolizumab, CBDCA, and nab-PTX
pembrolizumab + CBDCA + PEM	a combination of pembrolizumab, CBDCA, and PEM
pembrolizumab + CBDCA + PTX	a combination of pembrolizumab, CBDCA and PTX
pembrolizumab + PEM	a combination of pembrolizumab and PEM
pembrolizumab + a platinum + PEM	a combination of pembrolizumab, a platinum, and PEM
PFS	progression free survival
PK	pharmacokinetics
PK/PD	pharmacokinetics/pharmacodynamics
placebo + PEM	a combination of placebo and PEM
PMDA	Pharmaceuticals and Medical Devices Agency
PMS2	postmeiotic segregation increased 2
PPK	population pharmacokinetics
PR	partial response
PT	preferred term
PTX	paclitaxel
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
regorafenib	regorafenib hydrate
RFS	Recurrence free survival
RMP	risk management plan
RNA	ribonucleic acid
SD	stable disease
SQ	squamous
SQ-NSCLC	squamous non-small cell lung cancer
Study 001	Study KEYNOTE-001
Study 002	Study KEYNOTE-002
Study 006	Study KEYNOTE-006
Study 010	Study KEYNOTE-010
Study 011	Study KEYNOTE-011
Study 012	Study KEYNOTE-012
Study 021	Study KEYNOTE-021
Study 024	Study KEYNOTE-024
Study 025	Study KEYNOTE-025
Study 028	Study KEYNOTE-028
Study 037	Study KEYNOTE-037
Study 041	Study KEYNOTE-041
Study 042	Study KEYNOTE-042
Study 045	Study KEYNOTE-045
Study 052	Study KEYNOTE-052
Study 054	Study KEYNOTE-054
Study 055	Study KEYNOTE-055
Study 059	Study KEYNOTE-059
Study 064	Study KEYNOTE-064
Study 087	Study KEYNOTE-087
Study 158	Study KEYNOTE-158
Study 164	Study KEYNOTE-164
Study 177	Study KEYNOTE-177
Study 189	Study KEYNOTE-189
Study 204	Study KEYNOTE-204
Study 407	Study KEYNOTE-407
TPS	tumor proportion score

trametinib	trametinib dimethyl ulfoxide
5-FU	5-fluorouracil