Report on the Deliberation Results

December 2, 2016

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	October 6, 2016

Results of Deliberation

In the meeting held on November 24, 2016, 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 is 5 years and 10 months.

Conditions of Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

November 15, 2016
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	October 6, 2016
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 a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The following events should be further studied through post-marketing surveillance: interstitial lung disease, colitis and severe diarrhoea, hepatic dysfunction, renal dysfunction (tubulointerstitial nephritis, etc.), endocrine disorders (pituitary dysfunction, thyroid dysfunction, adrenal dysfunction), type 1 diabetes mellitus, uveitis, myositis and rhabdomyolysis, pancreatitis, severe skin disorders (oculomucocutaneous syndrome, erythema multiforme, pemphigoid, etc.), infusion reaction, encephalitis and meningitis, myasthenia gravis, and neurological disorders (Guillain-Barre syndrome, etc.).

Indications

1. Unresectable malignant melanoma

2. Unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer

(Underline denotes additions.)

Dosage and Administration

1. 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.

2. Unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer

The usual adult dosage is 200 mg of Pembrolizumab (Genetical Recombination) infused intravenously over 30 minutes every 3 weeks.

(Underline denotes additions.)

Conditions of Approval

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

Attachment

Review Report (1)

October 14, 2016

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.

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	October 6, 2016
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 Indication(s)	1. Unresectable malignant melanoma <u>2. Unresectable, advanced or recurrent non-small cell lung cancer</u> (Underline denotes additions.)

Proposed Dosage and Administration

<u>1. Unresectable malignant melanoma</u>

The usual adult dosage is 2 mg/kg body weight of Pembrolizumab (Genetical Recombination) infused intravenously over 30 minutes every 3 weeks.

<u>2. Unresectable, advanced or recurrent non-small cell lung cancer</u>

<u>The usual adult dosage is 200 mg of Pembrolizumab (Genetical Recombination) infused intravenously over 30 minutes every 3 weeks.</u>

(Underline denotes additions.)

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List of Abbreviations

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
BQL	below the quantification limit
CBDCA	carboplatin
CBDCA + GEM	combination therapy with CBDCA and GEM
CBDCA + PEM	combination therapy with CBDCA and PEM
CBDCA + PTX	combination therapy with CBDCA and PTX
CDDP	cisplatin
CDDP + GEM	combination therapy with CDDP and GEM
CDDP + PEM	combination therapy with CDDP and PEM
CI	confidence interval
DOC	docetaxel hydrate
eDMC	external Data Monitoring Committee
EGFR	epidermal growth factor receptor
GEM	gemcitabine
GGT	gamma-glutamyltransferase
IHC	immunohistochemistry
ILD	interstitial lung disease
IL-2	interleukin-2
IRR	infusion related reaction
ITT	intention-to-treat
Japanese clinical practice guideline	Clinical practice guideline for lung cancer according to evidence-based medicine (EBM) [in Japanese] 2015 version edited by the Japan Lung Cancer Society
MedDRA	Medical Dictionary for Regulatory Activities
NCCN guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NCI-PDQ	National Cancer Institute Physician Data Query
NA	not available
NE	not estimated
NSCLC	non-small cell lung cancer
OS	overall survival
Partial change application	Partial change approval application
PD-L	programmed cell death-ligand
PD-1	programmed cell death-1
PD-L1 negative (TPS <1%)	<1% of tumor cells express PD-L1 (tumor proportion score <1%)
PD-L1 positive (TPS ≥50%)	≥50% of tumor cells express PD-L1 (tumor proportion score ≥50%)
PD-L1 positive (TPS ≥1%)	≥1% of tumor cells express PD-L1 (tumor proportion score ≥1%)
PEM	pemetrexed sodium hydrate
PFS	progression free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PS	performance status
PT	preferred term
PTX	paclitaxel
Q	inter-compartmental clearance

Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
SOC	standard of care
Study 001	KEYNOTE-001 study
Study 002	KEYNOTE-002 study
Study 006	KEYNOTE-006 study
Study 010	KEYNOTE-010 study
Study 011	KEYNOTE-011 study
Study 024	KEYNOTE-024 study
Study 025	KEYNOTE-025 study
Study 041	KEYNOTE-041 study
Vc	central volume of distribution
Vp	peripheral volume of distribution

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

1.1 Overview of the product submitted for approval

CD279 (programmed cell death-1 [PD-1]) is a receptor belonging to the CD28 superfamily (a group of molecules that provide co-stimulatory signals involved in the control of T-cell activation) and is expressed on activated lymphocytes (including T cells, B cells, 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 IgG4 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.

1.2 Development history etc.

Outside Japan:

As a part of clinical development of pembrolizumab for the treatment of non-small cell lung cancer (NSCLC), a phase I study (Study 001) was initiated in patients with advanced solid tumor, malignant melanoma or NSCLC in April 2011. A global phase II/III study (Study 010) was initiated in patients with advanced or recurrent PD-L1 positive (Tumor Proportion Score [TPS] ≥1%) NSCLC who had received prior platinum-based chemotherapy in August 2013. A global phase III study (Study 024) was initiated in patients with advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC who had not received prior chemotherapy in September 2014.

In the US, the application for pembrolizumab for the treatment of patients with advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC who have received prior chemotherapy, was submitted based on data mainly from Study 001 in April 2015. In October 2015, pembrolizumab was approved under accelerated approval for the following indication: "KEYTRUDA is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval

for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials."

In the EU, the application for pembrolizumab for the treatment of patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who have received prior chemotherapy, was submitted based on data mainly from Study 010 in January 2016. In July 2016, pembrolizumab was approved for the following indication: "KEYTRUDA is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumors express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these mutations prior to receiving KEYTRUDA."

In addition, the application for pembrolizumab for the treatment of the patients with advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC who have not received prior chemotherapy, was submitted based on data mainly from Study 024 in the US in June 2016 and in EU in August 2016. Currently, the above applications are under review.

As of August 2016, pembrolizumab has been approved for the treatment of NSCLC in 48 countries or regions.

In Japan:
The applicant initiated a phase Ib study in patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who had received prior chemotherapy (Study 025) in March 2014. The enrollment of patients in Studies 010 and 024 was initiated in November 2013 and October 2014, respectively.

The applicant submitted the present partial change application for an additional indication of NSCLC based on data mainly from Studies 010, 024, and 025.

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 had been evaluated during the review process for 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 had been evaluated during the review process for 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

6.1.1.1 Assays for PD-L1 expression

Tumor PD-L1 expression levels were measured by (a) "PD-L1 IHC 22C3 pharmDx 'Dako'" (Dako Japan Co., Ltd.) in Study 024, and by (b) immunohistochemistry (IHC) using a prototype kit of "PD-L1 IHC 22C3 pharmDx 'Dako'" in Study 010. In March 25, 2016, Dako Japan Co., Ltd., submitted application for the approval of "PD-L1 IHC 22C3 pharmDx 'Dako'" as an *in vitro* diagnostic intended to support assessment of patient eligibility for pembrolizumab therapy.

6.2 Clinical pharmacology

The pharmacokinetics (PK) of pembrolizumab monotherapy was investigated in patients with cancer.

6.2.1 Global phase II/III study (CTD 5.3.5.1.1, Study 010 [ongoing since August 2013 (cutoff date, September 30, 2015)])

An open-label, randomized, controlled study was conducted to investigate the efficacy and safety of pembrolizumab in 1034 patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who had received prior platinum-based chemotherapy[1)] (660 patients included in PK analysis). Subjects were treated with intravenous pembrolizumab 2 or 10 mg/kg Q3W (in 3-week cycles) to investigate serum concentrations of pembrolizumab.

C_{max} and C_{min} of pembrolizumab were as follows (geometric mean [coefficient of variation (CV), %]):
C_{max} in Cycle 1: 45.5 (27.6) μg/mL in the 2 mg/kg group; 235 (34.9) μg/mL in the 10 mg/kg group.
C_{max} in Cycle 6: 66.7 (37.5) μg/mL in the 2 mg/kg group; 338 (25.6) μg/mL in the 10 mg/kg group.
C_{min} in Cycle 8: 24.0 (51.1) μg/mL in the 2 mg/kg group; 116 (47.6) μg/mL in the 10 mg/kg group.

In total, 704 patients were tested for anti-pembrolizumab antibody at baseline and after start of treatment. Among them, 4 patients in the 2 mg/kg group and 1 patient in the 10 mg/kg group tested positive for the antibody at baseline, and 5 patients in the 2 mg/kg group tested positive for the antibody after start of treatment.

1) Enrolled patients with *EGFR* mutation had received prior treatment with an EGFR inhibitor as well as platinum-based chemotherapy. Enrolled patients with *ALK* fusion genes had received prior treatment with an ALK inhibitor as well as platinum-based chemotherapy.

6.2.2 Global phase III study (CTD 5.3.5.1.2, Study 024 [ongoing since September 2014 (cutoff date, May 9, 2016)])

An open-label, randomized, controlled study was conducted to investigate the efficacy and safety of pembrolizumab in 305 chemotherapy-naïve patients with advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC without *EGFR* mutation or *ALK* fusion genes (152 patients included in PK analysis). Subjects were treated with intravenous pembrolizumab 200 mg/body Q3W (in 3-week cycles) to investigate serum concentrations of pembrolizumab.

C_{max} and C_{min} of pembrolizumab were as follows (geometric mean [CV%]):
C_{max} in Cycle 1: 67.5 (23) μg/mL.
C_{min} in Cycle 2: 11.1 (54) μg/mL.
C_{min} in Cycle 4: 22.5 (52) μg/mL.
C_{min} in Cycle 8: 30.6 (50) μg/mL.

In total, 161 patients were tested for anti-pembrolizumab antibody at baseline and after start of treatment. Among them, 5 patients tested positive for the antibody after the start of treatment, and 1 patient tested positive for the antibody both at baseline and after the start of treatment.

6.2.3 Foreign phase I study (CTD 5.3.5.2.1.2, Study 001 Parts C and F [ongoing since [redacted] (cutoff date, [redacted])])

An open-label, uncontrolled study was conducted to investigate the PK of pembrolizumab in 560 patients with advanced or recurrent NSCLC who had received prior chemotherapy (550 patients included in PK analysis).[2)] Subjects were treated with intravenous pembrolizumab 2 or 10 mg/kg Q3W (in 3-week cycles) or 10 mg/kg Q2W (in 2-week cycles) to investigate serum concentrations of pembrolizumab (Table 1).

In total, 559 patients were tested for anti-pembrolizumab antibody at baseline and after start of treatment. Among them, 1 patient in the 2 mg/kg Q3W group tested positive for the antibody at baseline, and 3 patients in the 2 mg/kg Q3W group, 5 patients in the 10 mg/kg Q3W group, and 3 patients in the 10 mg/kg Q2W group tested positive for the antibody after the start of treatment.

2) In Parts F1 and F2, subjects were randomized to one of several doses of pembrolizumab.

Table 1. Serum concentrations of pembrolizumab by dosage (μg/mL)

Dosage	Cycle	n	C_{min}	n	C_{max}
2 mg/kg Q3W	1	53	BQL	53	42.4 (31.6)
	2	43	8.09 (39.0)	-	-
	6	28	18.6 (41.0)	27	58.9 (42.0)
	8	21	18.9 (54.6)	-	-
10 mg/kg Q3W	1	283	BQL	278	229 (26.8)
	2	253	43.8 (40.5)	30	260 (32.9)
	6	125	101 (52.3)	117	328 (29.9)
	8	105	118 (51.9)	-	-
	12	67	126 (44.3)	-	-
10 mg/kg Q2W	1	202	BQL	198	227 (25.1)
	2	187	54.6 (32.8)	-	-
	18	28	218 (37.4)	-	-

Geometric mean (CV%);
-, Not calculated;
below the quantification limit (BQL), <10 ng/mL (see "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016")

6.2.4 PPK analysis

Based on the PK data of pembrolizumab obtained from Japanese clinical studies (Studies 011, 025, and 041), foreign clinical studies (Studies 001, 002, and 006), and global clinical study (Study 010) (17,341 time points in 2946 subjects), a population pharmacokinetics (PPK) analysis was performed using the non-linear mixed-effects model (NONMEM Version 7.3.0). The PK of pembrolizumab was described as the 2-compartment model with first-order elimination.

Ethnicity was not identified as a significant covariate for clearance (CL) or Vc.

Based on the PK data of pembrolizumab obtained from foreign clinical studies (Studies 001, 002, and 006) (12,233 time points in 2188 subjects), PPK analysis was performed using the non-linear mixed-effects model (NONMEM Version 7.1.2). Since body weight had been identified as a covariate for the PK of pembrolizumab (see "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016"), the applicant investigated the relationship between body weight (range, 35.7-210 kg) and (a) CL and Q or (b) Vc and Vp. As a result, the estimated allometric exponents[3)] for both relationships were approximately 0.5: 0.595 [95% confidence interval (CI), 0.506, 0.686] for CL and Q; and 0.489 [95% CI, 0.431, 0.545] for Vc and Vp. According to the applicant, these results suggest that weight-based dosing and fixed dosing result in similar inter-individual variability in the PK parameter of pembrolizumab.

Based on the PK data of pembrolizumab obtained from foreign clinical studies (Studies 001, 002, and 006) and global clinical studies (Studies 010 and 024) (16,800 time points in 2993 subjects), PPK analysis was performed using the non-linear mixed-effects model (NONMEM Version 7.2.0). The median $AUC_{ss,6wk}$ [90% CI] of pembrolizumab in patients receiving 200 mg/body Q3W, 2 mg/kg Q3W, and 10 mg/kg Q3W was estimated to be 1751 [955, 3136], 1316 [732, 2354], and 6600 [3678, 11,711] μg·day/mL, respectively.

3) If the allometric exponent is zero (0), body weight is considered to have no effect on PK parameters; and if it is 1, PK parameters are considered to increase in proportion to body weight (*J Clin Pharmacol*.2009;49:1012-24).

6.2.5 Relationship between exposure and efficacy or safety

6.2.5.1 Relationship between exposure and efficacy

The relationship between tumor size reduction rate and $AUC_{ss,6wk}$ of pembrolizumab (which was estimated by PPK analysis[4)] based on data from Study 001 Parts C and F and Study 010) was investigated by a linear regression analysis. Within the dosage range investigated (2 mg/kg Q3W, 10 mg/kg Q2W, and 10 mg/kg Q3W), no clear relationship was found between tumor size reduction rate and $AUC_{ss,6wk}$ of pembrolizumab.

The relationship between tumor size reduction rate and $AUC_{ss,6wk}$ of pembrolizumab (which was estimated by PPK analysis[5)] based on data from Study 001 Parts C and F, Study 010, and Study 024) was investigated. Within the dosage range investigated (200 mg/body Q3W, 2 mg/kg Q3W, 10 mg/kg Q2W, and 10 mg/kg Q3W), no clear relationship was found between tumor size reduction rate and $AUC_{ss,6wk}$ of pembrolizumab.

6.2.5.2 Relationship between exposure and safety

The relationship between incidence of autoimmune-related adverse events and $AUC_{ss,6wk}$ of pembrolizumab (which was estimated by PPK analysis[4)] based on data from Study 001 Parts B, C, D, and F, Study 002, Study 006, and Study 010) was investigated by logistic regression analysis. Within the dosage range investigated (2 mg/kg Q3W, 10 mg/kg Q2W, and 10 mg/kg Q3W), no clear relationship was found between the incidence of autoimmune-related adverse events and $AUC_{ss,6wk}$ of pembrolizumab.

The relationship between incidence of autoimmune-related adverse events and $AUC_{ss,6wk}$ of pembrolizumab (which was estimated by PPK analysis[5)] based on data from Study 001 Parts B, C, D, and F, Study 002, Study 006, Study 010, and Study 024) was investigated by logistic regression analysis. Within the dosage range investigated (200 mg/body Q3W, 2 mg/kg Q3W, 10 mg/kg Q2W, and 10 mg/kg Q3W), no clear relationship was found between the incidence of autoimmune-related adverse events and $AUC_{ss,6wk}$ of pembrolizumab.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK of pembrolizumab between Japanese and non-Japanese patients with NSCLC

The applicant's explanation:

The following findings suggest that there are no clear differences in PK of pembrolizumab between Japanese and non-Japanese patients with NSCLC:

- Table 2 shows serum concentrations of pembrolizumab in patients receiving intravenous pembrolizumab 2 mg/kg Q3W or 200 mg/body Q3W in the foreign phase I study (Study 001) Parts

[4)] The analysis was performed based on PK data of pembrolizumab obtained from foreign clinical studies (Studies 001, 002, and 006) and global clinical study (Study 010) (16,673 time points in 2856 subjects) (NONMEM Version 7.2.0).

[5)] The analysis was performed based on PK data of pembrolizumab obtained from foreign clinical studies (Studies 001, 002, and 006) and global clinical studies (Studies 010 and 024) [see Section 6.2.4].

C and F, global phase II/III study (Study 010), and global phase III study (Study 024). No clear differences were observed in the serum concentrations between Japanese and non-Japanese patients.

- In the PPK analysis, ethnicity was not identified as a significant covariate for PK parameters of pembrolizumab [see Section 6.2.4].

Table 2. Serum concentrations of pembrolizumab in Japanese and non-Japanese patients by dosage (μg/mL)

Dosage		n	Japanese patients	n	Non-Japanese patients
2 mg/kg	C_{max} in Cycle 1	28	47.7 (24.2, 68.4)	337	45.6 (13.9, 99.1)
	C_{min} in Cycle 2	26	10.7 (1.05, 16.6)	307	9.30 (1.32, 22.0)
	C_{min} in Cycle 6	17	22.5 (9.96, 41.9)	163	22.1 (2.75, 49.9)
	C_{min} in Cycle 8	8	36.0 (21.0, 81.3)	116	23.5 (0.689, 59.9)
200 mg/body	C_{max} in Cycle 1	20	74.8 (54.6, 107)	127	65.8 (36.6, 132)
	C_{min} in Cycle 2	20	14.0 (6.00, 28.5)	112	12.1 (0.535, 23.9)
	C_{min} in Cycle 8	16	40.1 (20.1, 64.1)	66	31.6 (5.26, 58.5)

Median (range)

PMDA's view:

The difference in PK of pembrolizumab between Japanese and non-Japanese patients with NSCLC cannot be strictly evaluated because study data available are limited. Nevertheless, the data submitted suggest no clear different trends in PK of pembrolizumab between Japanese and non-Japanese patients.

6.R.2 Effect of anti-pembrolizumab antibody on PK of pembrolizumab

Development of anti-pembrolizumab antibody was investigated in the foreign phase I study (Study 001) Parts B, C, D, and F, foreign phase II study (Study 002), foreign phase III study (Study 006), global phase II/III study (Study 010), global phase III study (Study 024), Japanese phase I study (Study 011), and Japanese phase Ib study (Studies 025 and 041). Some patients were classified as "not assessable" because the pembrolizumab levels in their samples[6] were considered to affect the measurement of anti-pembrolizumab antibody (see "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016")

Of 2862 patients who provided samples after the first dose of pembrolizumab in the above clinical studies, 1300 were classified as "assessable"[7] and 1562 as "not assessable." Of 1300 assessable patients, 10 (0.8%) tested positive for anti-pembrolizumab antibody at baseline, and 27 (2.1%)[8] tested positive for the antibody after the start of treatment. Of these patients, 4 were tested for neutralizing antibody and, as a result, 1 was found to be positive for the antibody.

[6] [redacted] assayed samples from Study 011 and samples obtained during the early stage of Studies 001, 002, and 006. [redacted] assayed samples from Studies 010, 025, 041 and samples obtained during the late stage of Studies 001, 002, and 006.

[7] The total number of subjects who tested positive or negative for anti-pembrolizumab antibody.

[8] Including 1 subject who tested positive for anti-pembrolizumab antibody both at baseline and after the start of pembrolizumab therapy.

Detection timing of anti-pembrolizumab antibody varied from patient to patient. There was no clear differences in status of anti-pembrolizumab antibody between all the patients tested for the antibody and patients with NSCLC.

PMDA's view:
It is difficult to evaluate the effect of anti-pembrolizumab antibody on PK of pembrolizumab for the following reasons: (1) The number of patients with anti-pembrolizumab antibody is limited; and (2) pembrolizumab simultaneously present in a sample may have affected the results of the anti-pembrolizumab antibody assay performed in clinical studies. The applicant, therefore, should continue to collect relevant information and provide information appropriately to healthcare professionals when new findings become available.

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

The applicant submitted efficacy and safety evaluation data. The data include the results from 5 studies: 2 Japanese phase I studies, a foreign phase I study, a global phase II/III study, and a global phase III study (Table 3). The results from a Japanese phase I study (Study 011) and a foreign phase I study (Study 001) Parts B and D are not discussed in this section, because these data were submitted in the initial application for Keytruda and already evaluated (see "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016").

Table 3. List of clinical studies for efficacy and safety

Data category	Region	Study	Phase	Study population	No. of patients enrolled	Outline of dosage regimen*	Main endpoints
Evaluation data	Japan	025	Ib	Patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who have received prior platinum-based chemotherapy	38	Pembrolizumab 10 mg/kg Q3W	Safety PK
	Global	010	II/III	Patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who have received prior platinum-based chemotherapy	1034 [1] 345 [2] 346 [3] 343	[1] Pembrolizumab 2 mg/kg Q3W [2] Pembrolizumab 10 mg/kg Q3W [3] DOC 75 mg/m^2 Q3W	Efficacy Safety
		024	III	Patients with advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC who have not received prior chemotherapy	305 [1] 154 [2] 151	[1] Pembrolizumab 200 mg/body Q3W [2] SOC	Efficacy Safety
	Foreign	001	I	Part C: Patients with advanced or recurrent NSCLC who have received prior chemotherapy Part F1: Patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who have not received prior chemotherapy Part F2: Patients with prior platinum-based chemotherapy who have advanced or recurrent NSCLC that is: [1] positive for PD-L1 (TPS ≥1%); [2] negative for PD-L1 (TPS <1%); or [3] positive for PD-L1 (TPS ≥1%). Part F3: Patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who have received prior platinum-based chemotherapy	Part C 41 Part F1 103 [1] 6 [2] 50 [3] 47 Part F2 361 [1] 33 [2] 43 [3] 285 Part F3 55	Part C: Pembrolizumab 10 mg/kg Q3W Part F1: [1] Pembrolizumab 2 mg/kg Q3W [2] Pembrolizumab 10 mg/kg Q3W [3] Pembrolizumab 10 mg/kg Q2W Part F2: [1] Pembrolizumab 10 mg/kg Q3W [2] Pembrolizumab 10 mg/kg Q2W [3] Pembrolizumab 10 mg/kg Q2W or Q3W Part F3: Pembrolizumab 2 mg/kg Q3W	Safety Efficacy PK

* Pembrolizumab was intravenously administered.

Individual clinical studies are summarized below.

The main adverse events other than deaths reported in individual clinical studies are presented in Section "7.2 Adverse events, etc. observed in clinical studies," and PK study data are presented in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase Ib study (CTD 5.3.5.2.3, Study 025 [ongoing since [redacted] (cutoff date, July 9, 2015)])

An open-label, uncontrolled study was conducted to investigate the safety and PK of pembrolizumab in patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who had received prior platinum-based chemotherapy[1)] (target sample size, 24 subjects) at 13 study sites in Japan.

Subjects received intravenous pembrolizumab 10 mg/kg Q3W. Treatment was continued until disease progression or a status meeting the discontinuation criteria.

All 38 subjects enrolled and treated with pembrolizumab were included in the safety analysis.

Safety results:

Death occurred in 2.6% (1 of 38) of subjects during the pembrolizumab treatment period or within 90 days after the end of treatment. The death was caused by interstitial lung disease (ILD), and a causal relationship to pembrolizumab could not be ruled out for the death.

7.1.2 Foreign clinical study

7.1.2.1 Foreign phase I study (CTD 5.3.5.2.1.2, Study 001 Parts C and F [ongoing since [redacted] (cutoff date, [redacted])])

An open-label, uncontrolled study[2)] was conducted at 47 study sites in foreign countries, to investigate the safety of pembrolizumab in patients with advanced or recurrent NSCLC who had received prior chemotherapy (Part C); chemotherapy-naïve patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC without *EGFR* mutation or *ALK* fusion genes (Part F1); patients with advanced or recurrent NSCLC who had received prior platinum-based chemotherapy[1)] (Part F2); and patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who had received prior platinum-based chemotherapy[1)] (Part F3) (target sample size, 559 subjects [35 in Part C, 132 in Part F1, 352 in Part F2, 40 in Part F3]).

Subjects received intravenous pembrolizumab 10 mg/kg Q3W in Part C; 2 mg/kg Q3W, or 10 mg/kg Q2W or Q3W in Part F1; 10 mg/kg Q2W or Q3W in Part F2; and 2 mg/kg Q3W in Part F3. Treatment was continued until disease progression or a status meeting the discontinuation criteria.

Of 560 subjects enrolled, 550 were treated with pembrolizumab and included in the safety analysis.

Safety results:

Deaths occurred in 3.5% (19 of 550) of subjects (2.2% [1 of 46] of subjects in the 10 mg/kg Q2W group and 2.0% [1 of 49] of subjects in the 10 mg/kg Q3W group in Part F1; 3.8% [6 of 156] of subjects in the 10 mg/kg Q2W group and 4.5% [9 of 200] of subjects in the 10 mg/kg Q3W group in Part F2; 3.6% [2 of 55] of subjects in the 2 mg/kg Q3W group in Part F3) during the pembrolizumab treatment period or within 90 days after the end of treatment. Causes of death were as follows:

Part F1: Death (1 subject) in the 10 mg/kg Q2W group;
Septic shock (1 subject) in the 10 mg/kg Q3W group;

Part F2: Gastrointestinal perforation, death, sepsis, diffuse alveolar damage, respiratory failure, and embolism (1 subject each) in the 10 mg/kg Q2W group;
Respiratory failure (3 subjects) and intestinal perforation, acute respiratory failure, ILD, pneumothorax, pulmonary embolism, and embolism (1 subject each) in the 10 mg/kg Q3W group;

Part F3: Cardio-respiratory arrest and pneumonia (1 subject each) in the 2 mg/kg Q3W group.

With regard to these events, a causal relationship to pembrolizumab could not be ruled out for ILD and respiratory failure (1 subject each) in the 10 mg/kg Q3W group in Part F2 and cardio-respiratory arrest (1 subject) in the 2 mg/kg Q3W group in Part F3.

7.1.3. Global clinical studies

7.1.3.1 Global phase II/III study (CTD5.3.5.1.1, Study 010 [ongoing since August 2013 (cutoff date, September 30, 2015)])

An open-label, randomized, controlled study[9] was conducted to investigate the efficacy and safety of pembrolizumab and docetaxel hydrate (DOC) in patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who had received prior platinum-based chemotherapy[1] (target sample size, 920 subjects) at 198 study sites in 24 countries including Japan.

Subjects in the pembrolizumab group received intravenous pembrolizumab 2 or 10 mg/kg Q3W, and subjects in the DOC group received intravenous DOC 75 mg/m^2 Q3W. Treatment was continued until disease progression or a status meeting the discontinuation criteria.

Of 1034 subjects enrolled and randomized (345 in the 2 mg/kg Q3W group, 346 in the 10 mg/kg Q3W group, 343 in the DOC group), 1033 (344 in the 2 mg/kg Q3W group, 346 in the 10 mg/kg Q3W group, 343 in the DOC group) were included in the intention-to-treat (ITT) population and also in the efficacy analysis; the remaining 1 subject in the pembrolizumab 2 mg/kg Q3W group was excluded because disease progression after the prior chemotherapy was not confirmed by imaging. Of subjects in the ITT population, 991 subjects (339 in the 2 mg/kg Q3W group, 343 in the 10 mg/kg Q3W group, 309 in the DOC group) were included in the safety analysis; the remaining 42 subjects were excluded because they did not receive the study drug.

At the start of this study, the primary endpoints were overall survival (OS) and centrally assessed progression free survival (PFS) in PD-L1 positive patients (TPS ≥1%), and 2 interim analyses were planned to evaluate the efficacy and futility of treatment. Subsequently, evaluation of OS and centrally assessed PFS in PD-L1 positive patients (TPS ≥50%) was added to the analysis plan based on findings from Study 001 (the revised study protocol, version 8 dated [redacted]). Furthermore, reports showed the efficacy of nivolumab (genetical recombination) compared with DOC in patients with advanced or recurrent NSCLC who had received prior platinum-based chemotherapy, irrespective of PD-L1 expression status (*N Engl J Med.* 2015;373:123-35, etc.). In response to the reports, the plans of second interim and final analyses were modified to change the time of analysis and other matters (the revised study protocol, version 10 dated July 6, 2015).

The first interim analysis plan:
The centrally assessed response rates are evaluated after 120 PD-L1 positive patients (TPS ≥50%) have been enrolled, randomized, and observed for ≥3 months.

[9] The original protocol (used at the start of this study) specified 2 stratification factors: region (East Asia, other regions) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0, 1). The protocol was subsequently revised to include PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%) as a new stratification factor (the protocol version 8 [redacted]), based on findings from Study 001. Patients enrolled on [redacted] or later were therefore randomized according to 3 stratification factors. Patients randomized before the date were treated as having unknown PD-L1 expression status.

- Pembrolizumab is not considered effective and the study is terminated early for futility, if neither pembrolizumab 2 mg/kg Q3W nor 10 mg/kg Q3W was significantly superior to DOC in centrally assessed response rate in PD-L1 positive patients (TPS ≥50%) (two-sided significance level of 20%).

- One pembrolizumab group (2 mg/kg Q3W or 10 mg/kg Q3W) is discontinued if it has a significantly lower response rate (i.e., centrally assessed response rate in PD-L1 positive patients [TPS ≥50%]) than the other pembrolizumab group (two-sided significance level of 2.5%).

The second interim analysis plan:
The analysis of PFS and OS is performed after at least 175 PFS events (approximately 125 PFS events if one pembrolizumab group has been discontinued after the first interim analysis) have occurred in PD-L1 positive patients (TPS ≥50%).

The final analysis plan:
The analysis of PFS and OS is performed after at least 200 OS events (approximately 140 OS events if one pembrolizumab group has been discontinued after the first interim analysis) have occurred in PD-L1 positive patients (TPS ≥50%).

According to the study protocol, pembrolizumab is considered effective if the second interim analysis or final analysis demonstrates the efficacy of pembrolizumab in OS or PFS compared with DOC in PD-L1 positive patients (TPS ≥50%) or PD-L1 positive (TPS ≥1%).

Figure 1 shows the plan of the second interim and final analyses. Hochberg step-up procedure was used to adjust type 1 error probability for multiple comparisons of 2 pembrolizumab doses. A gate-keeping procedure was used at each analysis in PD-L1 strongly positive patients (TPS ≥50%) and PD-L1 positive patients (TPS ≥1%), except for the final analysis of OS. If both pembrolizumab doses show a statistically significant difference from the DOC group in PD-L1 strongly positive patients (TPS ≥50%), the significance level used in the analysis in PD-L1 strongly positive patients (TPS ≥50%) was reallocated to the analysis in overall PD-L1 positive patients. A Bonferroni correction was used at the final analysis of OS in PD-L1 strongly positive patients (TPS ≥50%) and in PD-L1 positive patients (TPS ≥1%); the one-sided significance level to be used at each final analysis of OS was 0.825%, 0.875%, 0.95%, or 1%, depending on results from the second interim and final analyses of PFS. In addition, if the first interim analysis results in discontinuation of either pembrolizumab dose, the subsequent analyses were to be performed at half the initially designed significance levels.

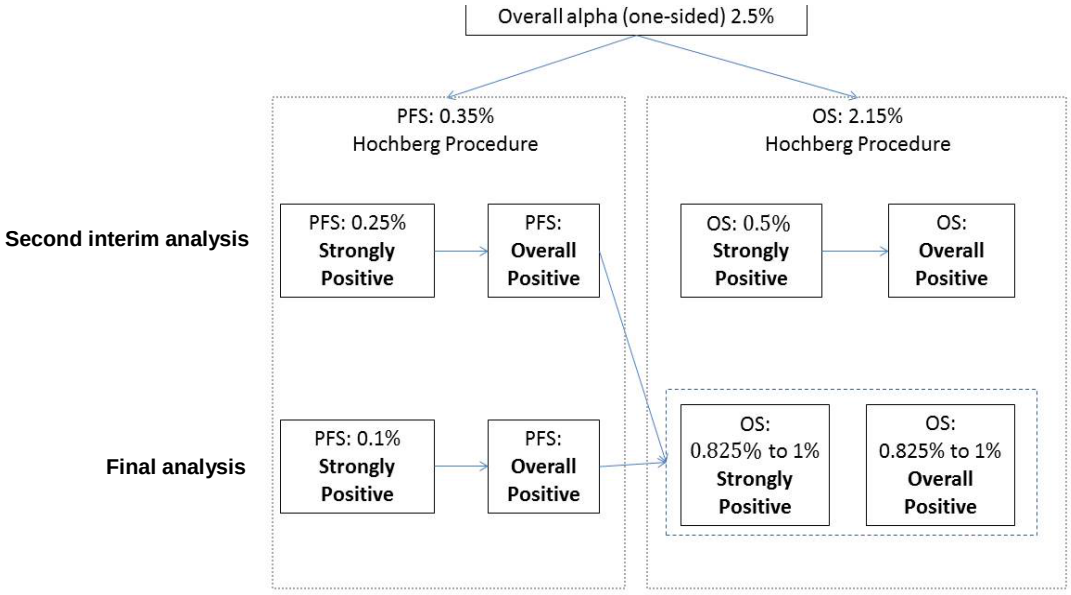

Figure 1. Analysis plan for the second interim and final analyses

Efficacy results:

The first interim analysis of efficacy (cutoff date, [redacted]) revealed that the response rates [95% CI] (%) in the pembrolizumab 2 mg/kg Q3W group, 10 mg/kg Q3W group, and DOC group were 11.4 [3.2, 26.7], 23.3 [11.8, 38.6], and 9.8 [2.7, 23.1], respectively. The external Data Monitoring Committee (eDMC), therefore, recommended the study be continued without discontinuation of either pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W regimen.

The second interim analysis (cutoff date, [redacted]) revealed that the result from comparison between the 10 mg/kg Q3W group and DOC group met the predetermined significance level. The eDMC, therefore, suggested that the study could be terminated early for efficacy, but the applicant decided to continue the study until the final analysis in accordance with the predetermined protocol.

The final analysis was performed (cutoff date, September 30, 2015). Tables 4 and 5 and Figure 2 show the final analysis results of OS and centrally assessed PFS and their Kaplan-Meier curves in PD-L1 positive patients (TPS ≥50%). In PD-L1 positive patients (TPS ≥50%), pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W were shown to be superior to DOC in OS and centrally assessed PFS.

Table 4. Results from final analysis of OS
(PD-L1 positive patients [TPS ≥50%], cutoff date, September 30, 2015)

	2 mg/kg Q3W	10 mg/kg Q3W	DOC
Number of subjects	139	151	152
Number of events (%)	58 (41.7)	60 (39.7)	86 (56.6)
Median [95% CI] (months)	14.9 [10.4, NE]	17.3 [11.8, NE]	8.2 [6.4, 10.7]
Hazard ratio [95% CI][*1]	0.54 [0.38, 0.77]	0.50 [0.36, 0.70]	
P value (one-sided)[*2]	0.00024	0.00002	

*1 Cox regression stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG performance status (PS) (0, 1), and region (East Asia, other regions)
*2 Log-rank test stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions) at a one-sided significance level of 0.00825

Table 5. Results from final analysis of PFS
(central assessment, PD-L1 positive patients [TPS ≥50%], cutoff date, September 30, 2015)

	2 mg/kg Q3W	10 mg/kg Q3W	DOC
Number of subjects	139	151	152
Number of events (%)	89 (64.0)	97 (64.2)	118 (77.6)
Median [95% CI] (months)	5.2 [4.0, 6.5]	5.2 [4.1, 8.1]	4.1 [3.6, 4.3]
Hazard ratio [95% CI]*1	0.58 [0.43, 0.77]	0.59 [0.45, 0.78]	
P value (one-sided)*2	0.00009	0.00007	

*1 Cox regression stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions)
*2 Log-rank test stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions) at a one-sided significance level of 0.001

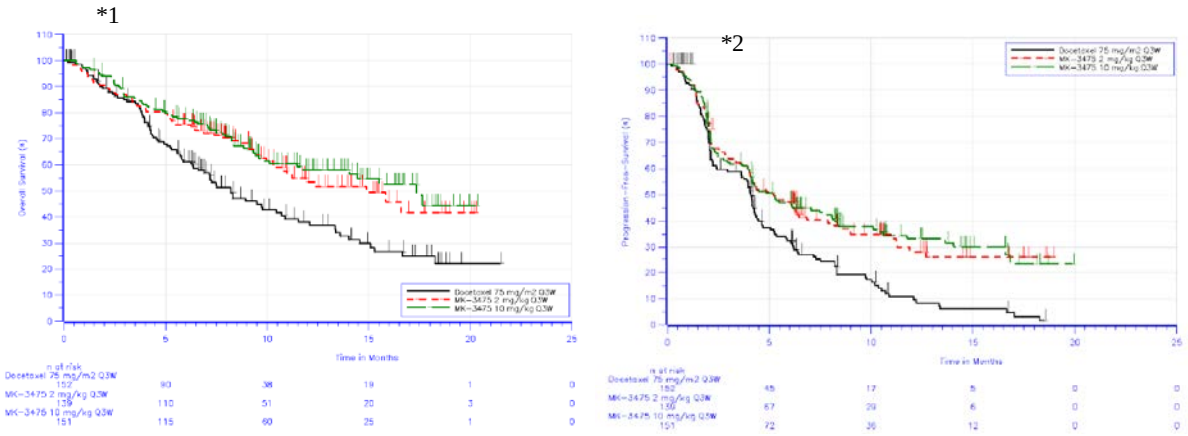

Figure 2. Kaplan-Meier curves of OS and centrally assessed PFS in the final analysis
(PD-L1 positive patients [TPS ≥50%]; cutoff date, September 30, 2015; left for OS and right for PFS)
*1 Patients censored on Day 1 (0 subjects in the 2 mg/kg Q3W group, 0 subjects in the 10 mg/kg Q3W group, 6 subjects in the DOC group);
*2 Patients censored on Day 1 (2 subjects in the 2 mg/kg Q3W group, 0 subjects in the 10 mg/kg Q3W group, 15 subjects in the DOC group)

Tables 6 and 7 and Figure 3 show the final analysis results of OS and centrally assessed PFS and their Kaplan-Meier curves in PD-L1 positive patients (TPS ≥1%). In PD-L1 positive patients (TPS ≥1%), pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W were shown to be superior to DOC in OS.

Table 6. Results from final analysis of OS
(PD-L1 positive patients [TPS ≥1%], cutoff date, September 30, 2015)

	2 mg/kg Q3W	10 mg/kg Q3W	DOC
Number of subjects	344	346	343
Number of events (%)	172 (50.0)	156 (45.1)	193 (56.3)
Median [95% CI] (months)	10.4 [9.4, 11.9]	12.7 [10.0, 17.3]	8.5 [7.5, 9.8]
Hazard ratio [95% CI]*1	0.71 [0.58, 0.88]	0.61 [0.49, 0.75]	
P value (one-sided)*2	0.00076	<0.00001	

*1 Cox regression stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions)
*2 Log-rank test stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions) at a one-sided significance level of 0.00825

Table 7. Results from final analysis of PFS
(central assessment, PD-L1 positive patients [TPS ≥1%), cutoff date, September 30, 2015)

	2 mg/kg Q3W	10 mg/kg Q3W	DOC
Number of subjects	344	346	343
Number of events (%)	266 (77.3)	255 (73.7)	257 (74.9)
Median [95% CI] (months)	3.9 [3.1, 4.1]	4.0 [2.6, 4.3]	4.0 [3.1, 4.2]
Hazard ratio [95% CI][*1]	0.88 [0.73, 1.04]	0.79 [0.66, 0.94]	
P value (one-sided)[*2]	0.06758[*3]	0.00462[*4]	

*[1] Cox regression stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions)
*[2] Log-rank test stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions)
*[3] A one-sided significance level of 0.001
*[4] A one-sided significance level of 0.0005

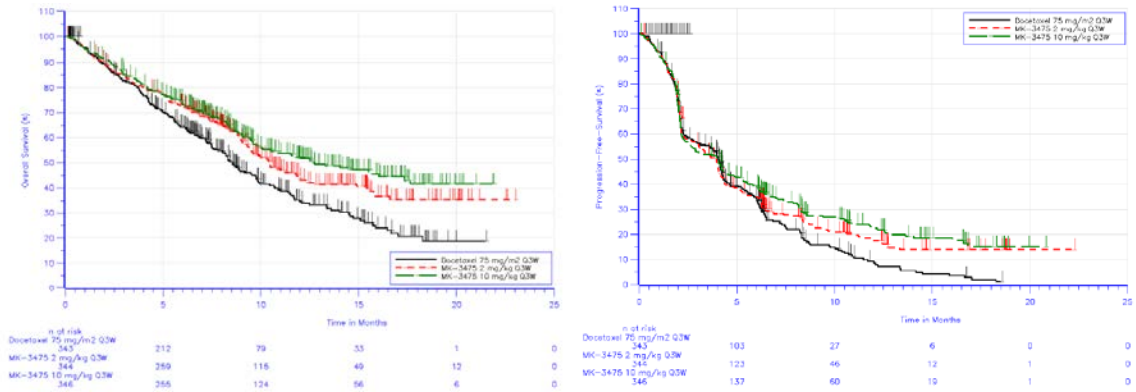

Figure 3. Kaplan-Meier curves of OS and centrally assessed PFS in the final analysis
(PD-L1 positive patients [TPS ≥1%], cutoff date, September 30, 2015, left for OS and right for PFS)
*1 Patients censored on Day 1 (1 patient in the 2 mg/kg Q3W group, 0 patients in the 10 mg/kg Q3W group, 9 patients in the DOC group)
*2 Patients censored on Day 1 (3 patients in the 2 mg/kg Q3W group, 4 patients in the 10 mg/kg Q3W group, 31 patients in the DOC group)

Safety results:

Deaths occurred in 5.0% (17 of 339) of subjects in the 2 mg/kg Q3W group, 7.6% (26 of 343) of subjects in the 10 mg/kg Q3W group, and 4.9% (15 of 309) of subjects in the DOC group during the treatment period or within 90 days after the end of treatment. Causes of death included death (3 subjects), pneumonia and pneumonitis (2 subjects each), and multi-organ failure, acute renal failure, brain oedema, respiratory failure, pneumocystis jirovecii pneumonia, pneumonia aspiration, lung neoplasm malignant, haemoptysis, acute coronary syndrome, and cardiac failure (1 subject each) in the 2 mg/kg Q3W group; pneumonia (5 subjects), death (3 subjects), and pneumonitis, pneumonia aspiration, aspiration bronchial, respiratory distress, pulmonary embolism, pulmonary oedema, respiratory failure, pulmonary haemorrhage, cerebrovascular accident, cardiopulmonary failure, cardiac arrest, cardiac tamponade, myocardial infarction, spinal cord compression, anaemia, hepatic failure, embolism, and completed suicide (1 subject each) in the 10 mg/kg Q3W group; and respiratory failure and pneumonia (2 subjects each), and cardiac failure acute, cardio-respiratory arrest, ILD, pulmonary embolism, death, dehydration, contusion, brain oedema, cerebrovascular accident, respiratory tract infection, and febrile neutropenia (1 subject each) in the DOC group. Of these, a causal relationship to the study drug could not be ruled out for pneumonitis (2 subjects) and pneumonia (1 subject) in the 2 mg/kg Q3W group, myocardial infarction, pneumonia, and pneumonitis (1 subject each) in the 10 mg/kg Q3W group, and cardiac failure acute, ILD, dehydration, respiratory tract infection, and febrile neutropenia (1 subject each) in the DOC group.

7.1.3.2 Global phase III study (CTD 5.3.5.1.2, Study 024 [ongoing since September 2014 (cutoff date, May 9, 2016)])

An open-label, randomized, controlled study was conducted to investigate the efficacy and safety of pembrolizumab versus standard of care (SOC) in chemotherapy-naïve patients with advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC without *EGFR* mutation or *ALK* fusion genes (target sample size, 300 subjects) at 149 study sites in 16 countries including Japan.

Subjects in the pembrolizumab group received intravenous pembrolizumab 200 mg/body Q3W. Subjects in the SOC group received investigator-choice SOC chemotherapy performed at individual study sites (i.e., either of carboplatin [CBDCA] + gemcitabine [GEM]; CBDCA + pemetrexed sodium hydrate [PEM]; CBDCA + paclitaxel [PTX]; cisplatin [CDDP] + PEM; or CDDP + GEM). Treatment was continued until disease progression or a status meeting the discontinuation criteria. Subjects in the SOC group who met the criteria for crossover[10)] were allowed to receive pembrolizumab ≥30 days after the final dose of antineoplastic drugs.

All 305 subjects enrolled and randomized (154 in the pembrolizumab group, 151 in the SOC group) were included in the ITT population for efficacy analysis. Of the 305 subjects (ITT population), 304 (154 in the pembrolizumab group, 150 in the SOC group) were included in the safety analysis, excluding 1 subject in the SOC group who did not receive the study drug.

The primary endpoint was centrally assessed PFS. The original protocol did not include interim analysis for efficacy evaluation before the final analysis of PFS (the final analysis means interim analysis in this study). However, the applicant subsequently planned to submit a marketing application for pembrolizumab based on results of centrally assessed response rate (which had been the secondary endpoint), and therefore changed the protocol to include the interim analysis (the revised study protocol, version 3 dated January 28, 2016).

The first interim analysis plan:
An analysis of the response rate is performed after 191 patients have been enrolled, randomized, and observed for ≥6 months.

The second interim analysis plan:
The final analysis of PFS and interim analysis of OS are performed after approximately 175 PFS events have been reported. In addition, the interim analysis of OS is performed if pembrolizumab significantly prolongs PFS compared with SOC, and if at least 110 OS events are reported. If the number of OS events is far below 110 at the time of final analysis of PFS, the interim analysis of OS is performed with a nominal significance level of 0.01%. If the number of OS events reaches ≥110 at the time of final analysis of PFS, the interim analysis is performed as well.

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10) Patients were required to meet all of the criteria (a) to (g):
(a) Resolution of chemotherapy-associated adverse events to Grade ≤1; (b) major organ functions maintained; (c) no symptoms of brain metastasis; (d) PS 0 or 1; (e) disease progression confirmed by central image assessment; (f) no experience with antineoplastic drugs, other than those defined as SOC, during the study period; and (g) no radiation therapy planned within 7 days after the first dose of pembrolizumab.

The final analysis plan:

The final analysis of OS is performed after approximately 170 OS events are reported. The following significance levels were used in the interim and final analyses, to adjust type 1 error probability (Table 8).

Table 8. One-sided significance level in each analysis

Analysis	Response rate	PFS	OS[*1]
First interim analysis	0.5%	-	-
Second interim analysis	-	(2.0%, 2.5%)[*2]	0.01%[*3] or (2.0%, 2.5%)[*2, *4]
Third interim analysis[*3]	-	-	(2.0%, 2.5%)[*2, *4]
Final analysis	-	-	(2.0%, 2.5%)[*2, *4]

[*1] Perform OS test only if PFS test is significant.
[*2] Either 2.0% or 2.5% is selected depending on results from the first interim analysis.
[*3] This analysis is performed if the number of OS events is far below 110 at the time of the final analysis of PFS.
[*4] Hwang-Shih-DeCani spending function α (γ value, −0.4)

Efficacy results:

The first interim analysis (cutoff date, January 8, 2016) revealed that the response rates [95% CI] (%) in the pembrolizumab group and the SOC group were 41.7 [31.7, 52.2] and 27.4 [18.7, 37.5], respectively. The eDMC, therefore, recommended the study be continued.

The second interim analysis was performed (cutoff date, May 9, 2016). Table 9 and Figure 4 show results from the final analysis of centrally assessed PFS and Kaplan-Meier curves, respectively. Pembrolizumab was shown to be superior to SOC in PFS. In the SOC group, 43.7% (66 of 151) of subjects received pembrolizumab.

Table 9. Results from final analysis of PFS (central assessment, ITT, cutoff date, May 9, 2016)

	Pembrolizumab	SOC
Number of subjects	154	151
Number of events (%)	73 (47.4)	116 (76.8)
Median [95% CI] (months)	10.3 [6.7, NE]	6.0 [4.2, 6.2]
Hazard ratio [95% CI][*1]	0.50 [0.37, 0.68]	
P value (one-sided)[*2]	<0.001	

[*1] Cox regression stratified by tissue type (squamous cell carcinoma, non-squamous cell carcinoma), ECOG PS (0, 1), and region (East Asia, other regions)
[*2] Log-rank test stratified by tissue type (squamous cell carcinoma, non-squamous cell carcinoma), ECOG PS (0, 1), and region (East Asia, other regions) at a one-sided significance level of 0.02

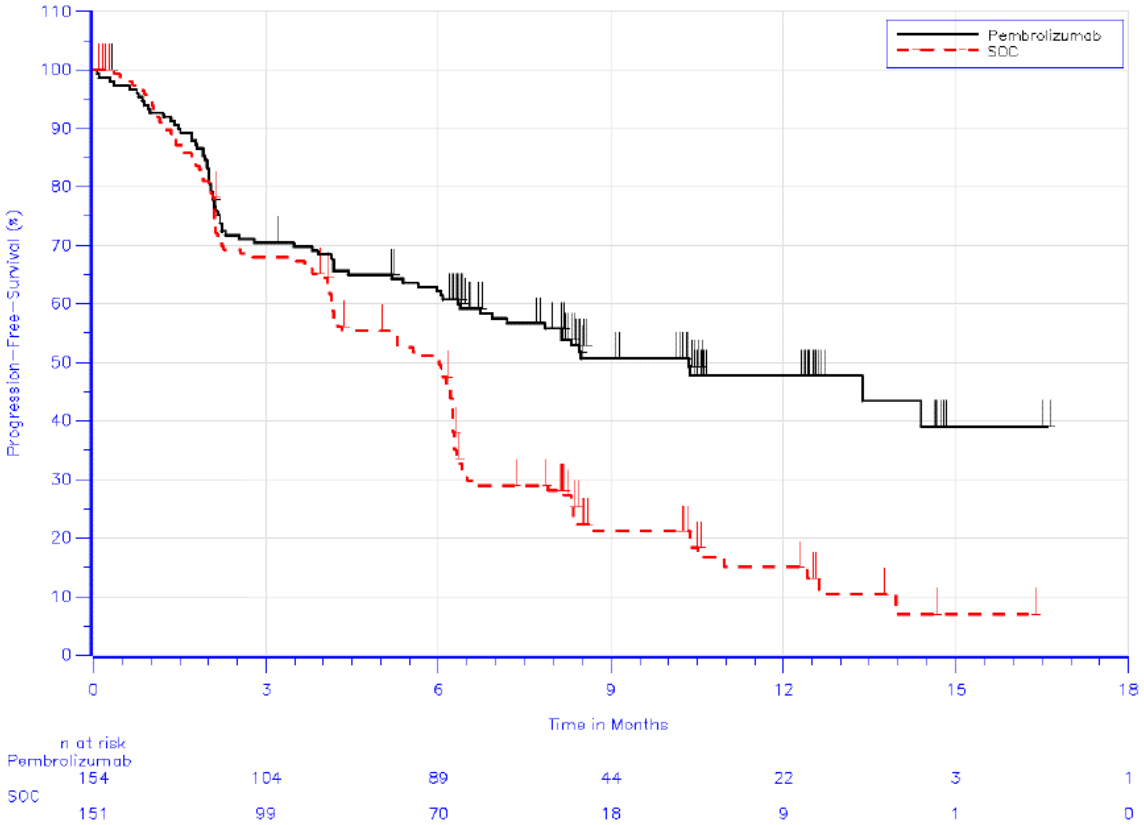

Figure 4. Kaplan-Meier curves of PFS in the final analysis (central assessment, ITT, cutoff date, May 9, 2016)

Table 10 and Figure 5 show results of OS, a secondary endpoint, and Kaplan-Meier curves, respectively. Pembrolizumab was shown to be superior to SOC in OS, and the eDMC proposed early study termination for efficacy.

Table 10. Results from interim analysis of OS (ITT, cutoff date, May 9, 2016)

	Pembrolizumab	SOC
Number of subjects	154	151
Number of events (%)	44 (28.6)	64 (42.4)
Median [95% CI] (months)	NE [NE, NE]	NE [9.4, NE]
Hazard ratio [95% CI][*1]	0.60 [0.41, 0.89]	
P value (one-sided)[*2]	0.005	

*[1] Cox regression stratified by tissue type (squamous cell carcinoma, non-squamous cell carcinoma), ECOG PS (0, 1), and region (East Asia, other regions)
*[2] Log-rank test stratified by tissue type (squamous cell carcinoma, non-squamous cell carcinoma), ECOG PS (0, 1), and region (East Asia, other regions) at a one-sided significance level of 0.0118.

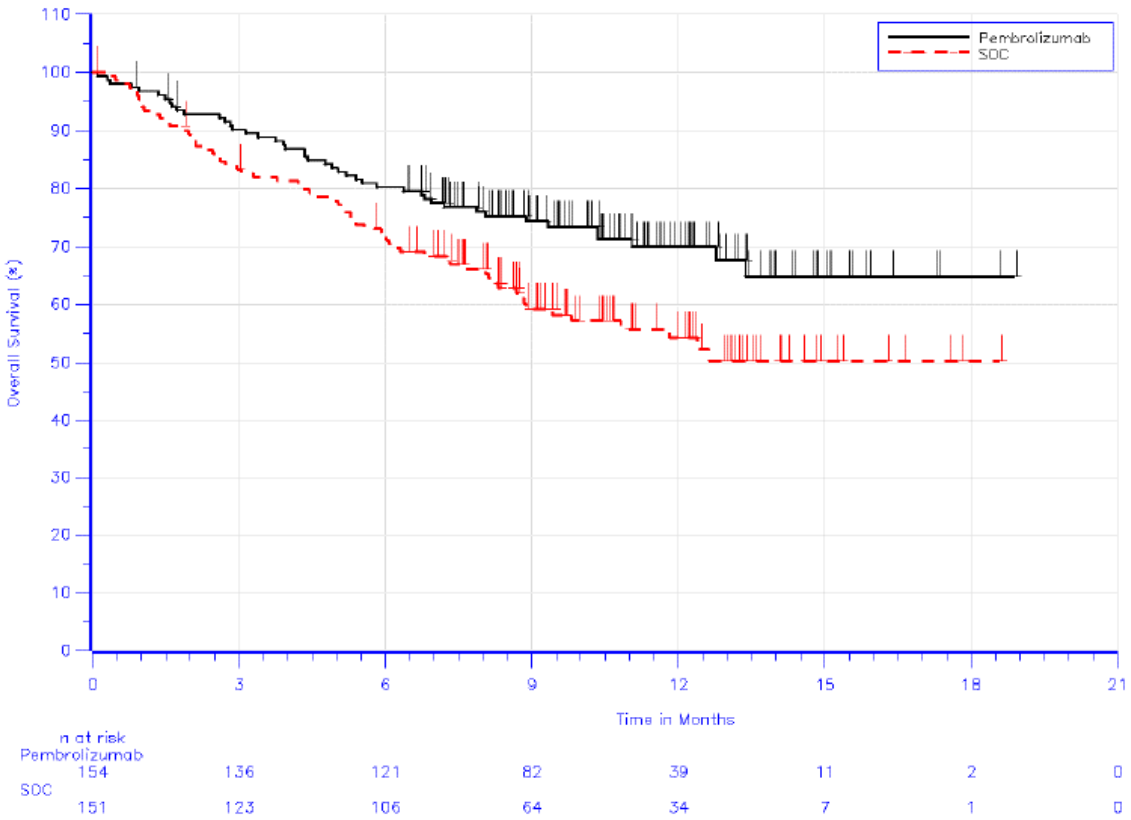

Figure 5. Kaplan-Meier curves of OS in interim analysis (ITT, cutoff date, May 9, 2016)

Safety results:

Deaths occurred in 5.8% (9 of 154) of subjects in the pembrolizumab group and in 4.7% (7 of 150) of subjects in the SOC group during the treatment period or within 90 days after the end of treatment. Causes of death included pneumonia, cardiac arrest, acute respiratory failure, pneumonia streptococcal/multiple organ dysfunction syndrome, general physical health deterioration, respiratory failure, haemorrhagic stroke, neutropenic sepsis, and sudden death (1 subject each) in the pembrolizumab group; and pulmonary sepsis, pulmonary embolism, cardiac failure, death, cardiac arrest, pulmonary alveolar haemorrhage, and cardio-respiratory arrest (1 subject each) in the SOC group. Of these, a causal relationship to the study drug could not be ruled out for sudden death (1 subject) in the pembrolizumab group and pulmonary sepsis, death, and pulmonary alveolar haemorrhage (1 subject each) in the SOC group.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA identified the following clinical studies as pivotal studies in evaluating the efficacy and safety of pembrolizumab from the submitted data: (a) A global phase III study (Study 024) to investigate the efficacy and safety of pembrolizumab in patients with advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC who have not received prior chemotherapy; and (b) a global phase II/III study (Study 010) to investigate the efficacy and safety of pembrolizumab in patients with advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who have received prior platinum-based chemotherapy. PMDA thus decided to evaluate these studies mainly.

7.R.2 Efficacy

Based on the following review, PMDA has concluded that pembrolizumab was shown to have efficacy in patients with advanced or recurrent PD-L1 positive NSCLC.

7.R.2.1 Control treatments

The applicant's rationale for the control treatments used in Studies 024 and 010:

When Study 024 was planned, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer (NCCN guideline) (v.2. 2013), etc. recommended regimens including CDDP + GEM for the patient population eligible for Study 024, because a report (*J Clin Oncol.* 2000;18:122-30, etc.) and other data had demonstrated the superior efficacy of CDDP + GEM over CDDP alone in the population. SOC was therefore selected as control treatment.

When Study 010 was planned, the NCCN guideline (v.2. 2012), etc. recommended DOC for the patient population eligible for Study 010, because a report (*J Clin Oncol.* 2000;18:2095-103, etc.) and other data had demonstrated the superior efficacy of DOC over the best supportive care in the population. DOC was therefore selected as control treatment.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints and evaluation results

Study 024 showed the superiority of pembrolizumab to SOC, according to the final analysis of centrally assessed PFS (the primary endpoint) and the interim analysis of OS (one of the secondary endpoints) [see Section 7.1.3.2].

Study 010 demonstrated the superiority of pembrolizumab (2 mg/kg Q3W and 10 mg/kg Q3W) to DOC in OS [see Section 7.1.3.1].

The applicant's rationale for using centrally assessed PFS as the primary endpoint in Study 024:

In patients with advanced or recurrent NSCLC that is considered incurable, prolonged PFS is clinically meaningful, because it means longer time to progressive disease, potentially delaying the worsening of clinical symptoms associated with disease progression. The applicant therefore considered PFS was appropriate as the primary endpoint.

PMDA's view:

The primary endpoint in Study 024 should have been OS, because treatment for the patient population of Study 024 is usually intended to prolong survival. However, PMDA has concluded that the efficacy of pembrolizumab has been demonstrated in the patient population of Study 024, because pembrolizumab was shown to be superior to SOC in the interim analysis of OS (a secondary endpoint) as well as in the final analysis of centrally assessed PFS (the primary endpoint) [see Section 7.1.3.2].

The selection of OS as one of the primary endpoints in Study 010 was appropriate. PMDA has concluded that the efficacy of pembrolizumab has been demonstrated in the patient population of Study 010, because pembrolizumab (2 mg/kg Q3W and 10 mg/kg Q3W) prolonged OS compared with DOC [see Section 7.1.3.1].

7.R.2.3 Efficacy in Japanese patients

Table 11 and Figure 6 show the results of centrally assessed PFS and Kaplan-Meier curves, respectively, in the Japanese subgroup in Study 024.

Table 11. Results from final analysis of PFS in Japanese patients (central assessment, ITT, cutoff date, May 9, 2016)

	Pembrolizumab	SOC
Number of subjects	21	19
Number of events (%)	6 (28.6)	15 (78.9)
Median [95% CI] (months)	NE [4.2, NE]	4.1 [2.8, 8.3]
Hazard ratio [95% CI][*1]	0.35 [0.14, 0.91]	
P value (one-sided)[*2]	0.013	

[*1] Cox regression stratified by tissue type (squamous cell carcinoma, non-squamous cell carcinoma), ECOG PS (0, 1), and region (East Asia, other regions)
[*2] Log-rank test stratified by tissue type (squamous cell carcinoma, non-squamous cell carcinoma), ECOG PS (0, 1), and region (East Asia, other regions)

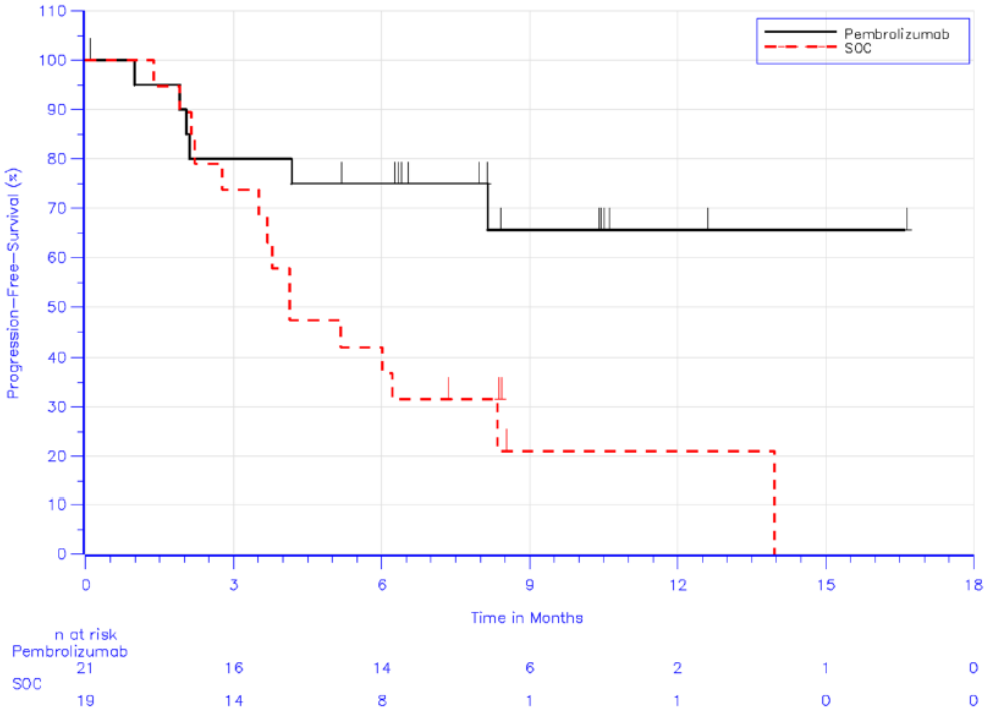

Figure 6. Kaplan-Meier curves of PFS in Japanese patients in the final analysis (central assessment, ITT, cutoff date, May 9, 2016)

The results of OS final analysis in the Japanese subgroup in Study 010 could not be easily interpreted, because the number of OS events at the time of the final analysis (September 30, 2015) was limited to 12 of 28 subjects (42.9%) in the pembrolizumab 2 mg/kg Q3W group, 11 of 34 subjects (32.4%) in the 10 mg/kg Q3W group, and 11 of 29 subjects (37.9%) in the DOC group. An additional OS analysis in the Japanese subgroup was therefore performed (cutoff date, [redacted]). Table 12 and Figure 7 show the results from the additional analysis of OS and Kaplan-Meier curves, respectively.

Table 12. Results from additional analysis of OS in Japanese patients (PD-L1 positive patients [TPS ≥1%], cutoff date, [redacted])

	2 mg/kg Q3W	10 mg/kg Q3W	DOC
Number of subjects	28	34	29
Number of events (%)	14 (50.0)	15 (44.1)	19 (65.5)
Median [95% CI] (months)	13.3 [9.6, NE]	19.0 [8.5, NE]	11.9 [7.5, 19.1]
Hazard ratio [95% CI]*1	0.76 [0.36, 1.61]	0.74 [0.36, 1.52]	
P value (one-sided)*2	0.23387	0.19878	

*1 Cox regression stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions)
*2 Log-rank test stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions)

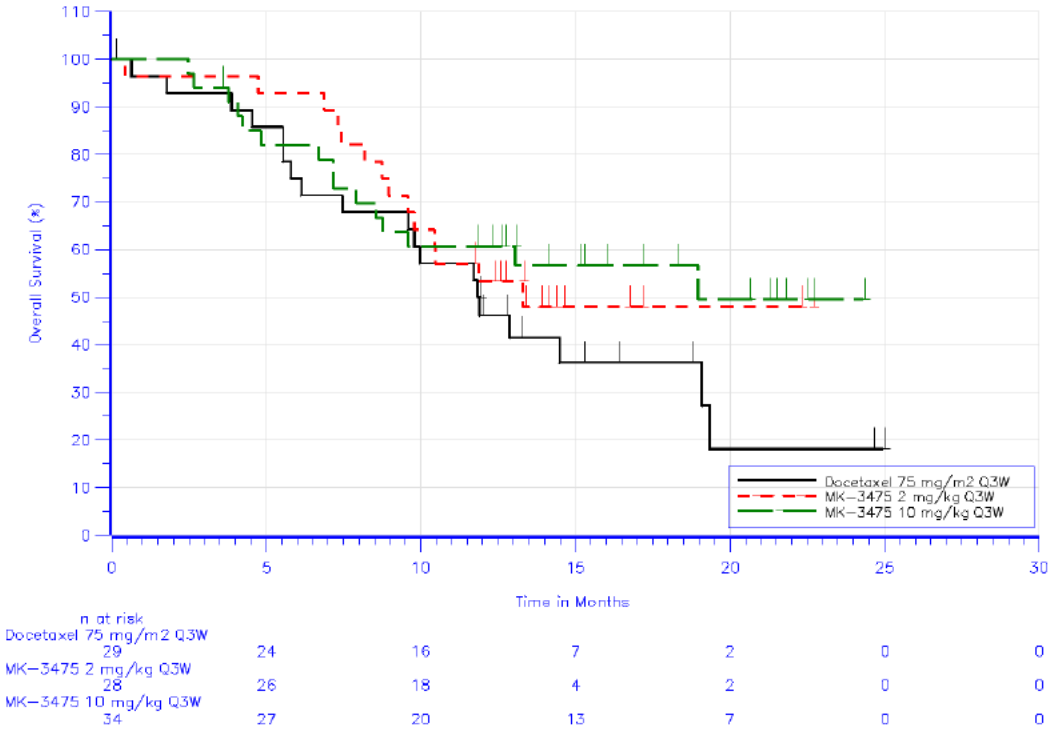

Figure 7. Kaplan-Meier curves of OS in Japanese patients in additional analysis (PD-L1 positive patients [TPS ≥1%], cutoff date, [redacted])

PMDA's view:

As the numbers of Japanese patients and their events in Studies 024 and 010 are limited, the efficacy of pembrolizumab in Japanese patients cannot be fully evaluated based on results from these studies. Nevertheless, the efficacy of pembrolizumab can be expected in Japanese patients with advanced or recurrent PD-L1 positive NSCLC, according to the results described above.

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

Based on the following review, PMDA has concluded that attention should be paid to the following adverse events when administering pembrolizumab to patients with unresectable advanced or recurrent PD-L1 positive NSCLC (these events were identified as requiring attention at the regulatory reviews for the previously approved indication of unresectable malignant melanoma): gastrointestinal disorders, skin disorders, neurological disorders, hepatic dysfunction, eye disorders, endocrine disorders, renal dysfunction, ILD, infusion related reaction (IRR), pancreatitis, myositis, encephalitis and meningitis,

and myasthenia gravis (see “Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016”).

PMDA, however, has concluded that pembrolizumab is tolerable, provided that physicians with sufficient knowledge and experience in cancer chemotherapy take appropriate measures such as monitoring of adverse events, differential diagnosis and patient management in anticipation of adverse reactions due to excessive immune response, and interruption of pembrolizumab.

7.R.3.1 Safety profile of pembrolizumab

The applicant’s explanation about the safety profile of pembrolizumab based on the safety information of pembrolizumab obtained from Studies 024 and 010:

The safety results of Studies 024 and 010 are summarized in Table 13.

Table 13. Summary of safety (Studies 024 and 010)

	n (%)				
	Study 024		Study 010		
	Pembrolizumab N = 154	SOC N = 150	Pembrolizumab 2 mg/kg Q3W N = 339	Pembrolizumab 10 mg/kg Q3W N = 343	DOC N = 309
All adverse events	148 (96.1)	145 (96.7)	331 (97.6)	330 (96.2)	297 (96.1)
Grade ≥3 adverse events	82 (53.2)	109 (72.7)	158 (46.6)	156 (45.5)	173 (56.0)
Adverse events leading to death	9 (5.8)	7 (4.7)	17 (5.0)	26 (7.6)	15 (4.9)
Serious adverse events	68 (44.2)	66 (44.0)	115 (33.9)	131 (38.2)	107 (34.6)
Adverse events leading to treatment discontinuation	14 (9.1)	21 (14.0)	28 (8.3)	26 (7.6)	42 (13.6)
Adverse events leading to dose reduction	NA	28 (18.7)	NA	NA	49 (15.9)
Adverse events leading to treatment interruption	53 (34.4)	51 (34.0)	73 (21.5)	83 (24.2)	73 (23.6)

Study 024:

Adverse events of any grade with a ≥5% higher incidence in the pembrolizumab group than the SOC group included dyspnoea (22.1% [34 subjects] in the pembrolizumab group, 16.0% [24 subjects] in the SOC group), arthralgia (15.6% [24 subjects], 10.0% [15 subjects]), pyrexia (15.6% [24 subjects], 9.3% [14 subjects]), pruritus (14.9% [23 subjects], 3.3% [5 subjects]), rash (14.3% [22 subjects], 4.0% [6 subjects]), nasopharyngitis (10.4% [16 subjects], 1.3% [2 subjects]), hypothyroidism (9.1% [14 subjects], 1.3% [2 subjects]), dry skin (8.4% [13 subjects], 0.7% [1 subject]), and hyperthyroidism (7.8% [12 subjects], 1.3% [2 subjects]). Grade ≥3 adverse events with a ≥2% higher incidence in the pembrolizumab group than the SOC group included chronic obstructive pulmonary disease (3.9% [6 subjects], 0.7% [1 subject]). Serious adverse events with a ≥2% higher incidence in the pembrolizumab group than the SOC group included pneumonitis (4.5% [7 subjects], 0.7% [1 subject]) and hyponatraemia (2.6% [4 subjects], 0 subjects). Adverse events leading to treatment discontinuation with a ≥2% higher incidence in the pembrolizumab group than the SOC group included pneumonitis (3.9% [6 subjects], 0 subjects). There were no adverse events leading to deaths with a ≥2% higher incidence in the pembrolizumab group than the SOC group.

Study 010:

Adverse events of any grade with a ≥5% higher incidence in either the pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W group than the DOC group included decreased appetite (28.3% [96 subjects] in the 2 mg/kg Q3W group, 21.0% [72 subjects] in the 10 mg/kg Q3W group, 23.3% [72 subjects] in the DOC group), cough (21.2% [72 subjects], 16.9% [58 subjects], 13.6% [42 subjects]), pruritus (9.4% [32 subjects], 12.0% [41 subjects], 3.2% [10 subjects]), musculoskeletal pain (10.0% [34 subjects], 9.0% [31 subjects], 3.2% [10 subjects]), rash (12.1% [41 subjects], 15.5% [53 subjects], 7.1% [22 subjects]), weight decreased (8.0% [27 subjects], 9.0% [31 subjects], 2.9% [9 subjects]), hypothyroidism (8.3% [28 subjects], 8.2% [28 subjects], 0.3% [1 subject]), and alanine aminotransferase (ALT) increased (7.1% [24 subjects], 4.7% [16 subjects], 1.3% [4 subjects]). Grade ≥3 adverse events with a ≥2% higher incidence in either the pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W group than the DOC group included hyponatraemia (1.8% [6 subjects], 2.0% [7 subjects], 0 subjects). Serious adverse events with a ≥2% higher incidence in either the pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W group than the DOC group included pneumonitis (2.4% [8 subjects], 2.6% [9 subjects], 0.6% [2 subjects]). There were neither adverse events leading to treatment discontinuation nor to death with a ≥2% higher incidence in either the pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W group than the DOC group.

The applicant explained differences in safety profile between pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W regimens based on data from Study 010.

The applicant's explanation:
The adverse event of any grade with a ≥5% higher incidence in the pembrolizumab 2 mg/kg Q3W group than the 10 mg/kg Q3W group was decreased appetite (28.3% [96 subjects] in the 2 mg/kg Q3W group, 21.0% [72 subjects] in the 10 mg/kg Q3W group). There were no Grade ≥3 adverse events, serious adverse events, or adverse events leading to treatment discontinuation with a ≥2% higher incidence in the pembrolizumab 2 mg/kg Q3W group than the 10 mg/kg Q3W group.

There were no adverse events of any grade with a ≥5% higher incidence in the 10 mg/kg Q3W group than the 2 mg/kg Q3W group. The Grade ≥3 adverse event with a ≥2% higher incidence in the 10 mg/kg Q3W group than the 2 mg/kg Q3W group was pneumonia (4.1% [14 subjects] in the 2 mg/kg Q3W group, 6.4% [22 subjects] in the 10 mg/kg Q3W group). There were neither serious adverse events nor adverse events leading to treatment discontinuation with a ≥2% higher incidence in the 10 mg/kg Q3W group than the 2 mg/kg Q3W group.

Based on the above, the applicant considers that there is no clear difference in safety profile of pembrolizumab between 2 mg/kg Q3W and 10 mg/kg Q3W regimens.

The applicant also explained differences in safety profile of pembrolizumab between patients with NSCLC and patients with malignant melanoma, the approved indication.

The applicant's explanation:

Table 14 shows a comparison of incidences of adverse events between (a) the pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W groups in Study 010, (b) the pembrolizumab 2 mg/kg Q3W group in Study 002 (a foreign phase II study in patients with unresectable malignant melanoma), and (c) a pooled analysis of the pembrolizumab 10 mg/kg Q3W groups from Study 002 and Study 006 (a foreign phase III study in patients with unresectable malignant melanoma).

Table 14. Summary of safety in patients with NSCLC and patients with malignant melanoma

	n (%)			
	Patients with NSCLC		Patients with malignant melanoma	
	Study 010 2 mg/kg Q3W N = 339	Study 010 10 mg/kg Q3W N = 343	Study 002 2 mg/kg Q3W N = 178	Pooled data from Studies 002 and 006 10 mg/kg Q3W N = 456
All adverse events	331 (97.6)	330 (96.2)	172 (96.6)	444 (97.4)
Grade ≥3 adverse events	158 (46.6)	156 (45.5)	98 (55.1)	206 (45.2)
Adverse events leading to death	17 (5.0)	26 (7.6)	14 (7.9)	16 (3.5)
Serious adverse events	115 (33.9)	131 (38.2)	94 (52.8)	162 (35.5)
Adverse events leading to treatment discontinuation	28 (8.3)	26 (7.6)	29 (16.3)	64 (14.0)
Adverse events leading to treatment interruption	73 (21.5)	83 (24.2)	26 (14.6)	109 (23.9)

Pembrolizumab 2 mg/kg Q3W (Study 010 versus Study 002):

The adverse event of any grade with a ≥10% higher incidence in Study 010 than in Study 002 was dyspnoea (24.8% [84 subjects] in Study 010, 11.8% [21 subjects] in Study 002). The Grade ≥3 adverse event with a ≥3% higher incidence in Study 010 than in Study 002 was pneumonia (4.1% [14 subjects], 1.1% [2 subjects]). The serious adverse event with a ≥2% higher incidence in Study 010 than in Study 002 was pneumonia (4.4% [15 subjects], 1.7% [3 subjects]). There were no adverse events leading to treatment discontinuation with a ≥2% higher incidence in Study 010 than in Study 002.

Pembrolizumab 10 mg/kg Q3W (Study 010 versus pooled data from Studies 002 and 006):

There were no adverse events of any grade with a ≥10% higher incidence in Study 010 than the pooled data from Studies 002 and 006. The Grade ≥3 adverse event with a ≥3% higher incidence in Study 010 than the pooled data from Studies 002 and 006 was pneumonia (6.4% [22 subjects] in Study 010, 0.2% [1 subject] in the pooled data from Studies 002 and 006). The serious adverse event with a ≥2% higher incidence in Study 010 than the pooled data from Studies 002 and 006 was pneumonia (6.1% [21 subjects], 0.9% [4 subjects]). There were no adverse events leading to treatment discontinuation with a ≥2% higher incidence in Study 010 than the pooled data from Studies 002 and 006.

PMDA's view:

PMDA has accepted the applicant's explanation that there is no clear difference in safety profile of pembrolizumab between 2 mg/kg Q3W and 10 mg/kg Q3W regimens.

Some adverse events had a higher incidence in patients with NSCLC than in patients with malignant melanoma, the approved indication, but all of them were known adverse events of pembrolizumab. Therefore pembrolizumab is tolerable by patients with NSCLC, provided that physicians with sufficient knowledge and experience in cancer chemotherapy take appropriate measures such as monitoring of

adverse events, differential diagnosis and patient management in anticipation of adverse reactions due to excessive immune response, and interruption of pembrolizumab. Nevertheless, when administering pembrolizumab to a patient, special attention should be paid to the adverse events that occurred more frequently in the pembrolizumab groups than the control groups in clinical studies. PMDA thus considers that information on the incidence of these events in clinical studies should be appropriately provided to healthcare professionals through materials, etc.

7.R.3.2 Difference in safety between Japanese and non-Japanese patients

The applicant's explanation about differences in safety between Japanese and non-Japanese patients based on safety information obtained from pembrolizumab-treated patients in Studies 024 and 010:

Table 15 summarizes safety results in Japanese and non-Japanese patients treated with pembrolizumab in Study 024.

Table 15. Summary of safety (Study 024)

	n (%)	
	Japanese patients N = 21	Non-Japanese patients N = 133
All adverse events	21 (100)	127 (95.5)
Grade ≥3 adverse events	10 (47.6)	72 (54.1)
Adverse events leading to death	0	9 (6.8)
Serious adverse events	7 (33.3)	61 (45.9)
Adverse events leading to treatment discontinuation	2 (9.5)	12 (9.0)
Adverse events leading to treatment interruption	6 (28.6)	47 (35.3)

Study 024:

Adverse events of any grade with a ≥10% higher incidence in Japanese patients than non-Japanese patients treated with pembrolizumab included pyrexia (33.3% [7 Japanese patients], 12.8% [17 non-Japanese patients]), stomatitis (19.0% [4 patients], 2.3% [3 patients]), rash maculo-papular (14.3% [3 patients], 2.3% [3 patients]), malaise (14.3% [3 patients], 0.8% [1 patient]), infusion related reaction (14.3% [3 patients], 0 patients), and urticaria (14.3% [3 patients], 0 patients). The Grade ≥3 adverse event with a ≥5% higher incidence in Japanese patients than non-Japanese patients treated with pembrolizumab was hypoalbuminaemia (9.5% [2 patients], 0 patients). There were neither serious adverse events nor adverse events leading to treatment discontinuation with a ≥5% higher incidence in Japanese patients than non-Japanese patients.

Table 16 summarizes safety results in Japanese patients and non-Japanese patients in the pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W groups in Study 010.

Table 16. Summary of safety (Study 010)

	n (%)			
	Japanese patients		Non-Japanese patients	
	2 mg/kg Q3W N = 28	10 mg/kg Q3W N = 34	2 mg/kg Q3W N = 311	10 mg/kg Q3W N = 309
All adverse events	28 (100)	34 (100)	303 (97.4)	296 (95.8)
Grade ≥3 adverse events	12 (42.9)	16 (47.1)	146 (46.9)	140 (45.3)
Adverse events leading to death	0	2 (5.9)	17 (5.5)	24 (7.8)
Serious adverse events	7 (25.0)	15 (44.1)	108 (34.7)	116 (37.5)
Adverse events leading to treatment discontinuation	1 (3.6)	3 (8.8)	27 (8.7)	23 (7.4)
Adverse events leading to treatment interruption	6 (21.4)	10 (29.4)	67 (21.5)	73 (23.6)

The pembrolizumab 2 mg/kg Q3W group in Study 010:

Adverse events of any grade with a ≥10% higher incidence in Japanese patients than non-Japanese patients included stomatitis (21.4% [6 Japanese patients]), 4.2% [13 non-Japanese patients]), malaise (21.4% [6 patients], 1.0% [3 patients]), and rash (25.0% [7 patients], 10.9% [34 patients]). The Grade ≥3 adverse event with a ≥5% higher incidence in Japanese patients than non-Japanese patients was decreased appetite (7.1% [2 patients], 1.3% [4 patients]). There were neither serious adverse events nor adverse events leading to treatment discontinuation with a ≥5% higher incidence in Japanese patients than non-Japanese patients.

The pembrolizumab 10 mg/kg Q3W group in Study 010:

Adverse events of any grade with a ≥10% higher incidence in Japanese patients than non-Japanese patients included diarrhoea (23.5% [8 Japanese patients], 11.0% [34 non-Japanese patients]), malaise (29.4% [10 patients], 1.6% [5 patients]), rash (26.5% [9 patients], 14.2% [44 patients]), and dysgeusia (11.8% [4 patients], 1.0% [3 patients]). The Grade ≥3 adverse event with a ≥5% higher incidence in Japanese patients than non-Japanese patients was lymphocyte count decreased (5.9% [2 patients], 0 patients). There were neither serious adverse events nor adverse events leading to treatment discontinuation with a ≥5% higher incidence in Japanese patients than non-Japanese patients.

PMDA's view:

Although experience with pembrolizumab in Japanese patients with NSCLC is limited, most of the events with a higher incidence in Japanese patients than non-Japanese patients were of Grade ≤2, and pembrolizumab is intended to be used by physicians with sufficient knowledge and experience in cancer chemotherapy. Therefore, pembrolizumab is tolerable also in Japanese patients with NSCLC. However, information on the adverse events with a higher incidence in Japanese patients than non-Japanese patients in clinical studies should be appropriately provided to healthcare professionals using materials, etc.

7.R.4 Clinical positioning and indication

The proposed indication of pembrolizumab is "unresectable, advanced or recurrent non-small cell lung cancer." The Precautions for Indications section of the proposed package insert includes the following statements:

- The efficacy and safety of pembrolizumab have not been established in patients with *EGFR* mutation or *ALK* fusion genes who have not received prior molecular targeted therapy.

- Pembrolizumab should be administered only to patients testing positive for PD-L1 as determined by a highly experienced pathologist or laboratory facility staff. PD-L1 testing should be performed using the approved *in vitro* diagnostics.

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

Based on the findings in Sections "7.R.2 Efficacy" and "7.R.3 Safety" as well as results from the following review, PMDA has concluded that the indication for pembrolizumab should be "unresectable, advanced or recurrent PD-L1-positive non-small cell lung cancer," and that the following precautionary statements must be included in the Precautions for Indications and Clinical Studies sections of the package insert.

Precautions for Indications

- Eligible 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.

- Pembrolizumab should be administered only to patients testing positive for PD-L1 as determined by a highly experienced pathologist or laboratory facility staff who fully understand the "Clinical Studies" section in terms of the percentage of PD-L1-expressing tumor cells. PD-L1 testing should be performed using the approved *in vitro* diagnostics.

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

Clinical Studies

- Study 024 did not include patients with NSCLC with EGFR mutation or ALK fusion genes.

- Study 24 showed the clinical usefulness of pembrolizumab in patients with PD-L1 positive (TPS ≥50%) NSCLC. Study 010 showed the clinical usefulness of pembrolizumab in patients with PD-L1 positive (TPS ≥1%) NSCLC. (TPS is defined as the percentage of tumor cells expressing PD-L1.)

7.R.4.1 Clinical positioning of pembrolizumab and intended population

Pembrolizumab for the treatment of unresectable advanced or recurrent NSCLC is mentioned in foreign clinical practice guidelines and representative textbooks for clinical oncology (see below). At present, pembrolizumab is not mentioned in the Japanese clinical guidelines or *Shin Rinsho Shuyo Gaku* [New Clinical Oncology], fourth edition (Nankodo, 2015).

<u>Clinical practice guideline</u>

- NCCN guideline (v.4. 2016):
  Pembrolizumab is strongly recommended as the second-line therapy for unresectable advanced or recurrent PD-L1 positive NSCLC.

- US National Cancer Institute Physician Data Query (NCI PDQ) (version dated July 7, 2016):
  In Study 001, pembrolizumab resulted in high response rates in patients with unresectable advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC who had received prior chemotherapy.

Textbooks

- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 10th edition (PA, USA, Lippincott Williams & Wilkins 2015):
  Study 010 significantly prolonged OS in the pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W groups in comparison with the DOC group.

The applicant's explanation about the intended population and indication of pembrolizumab:
The results from Studies 024 and 010 suggest that pembrolizumab is positioned as one of the therapeutic options for (a) chemotherapy-naïve patients with unresectable advanced or recurrent PD-L1 positive (TPS ≥50%) NSCLC without *EGFR* mutation or *ALK* fusion genes; and for (b) patients with unresectable advanced or recurrent PD-L1 positive (TPS ≥1%) NSCLC who had received prior platinum-based chemotherapy. There are no clinical study data on the efficacy and safety of pembrolizumab in patients with *EGFR* mutation-positive NSCLC who have not received prior treatment with EGFR inhibitors or patients with *ALK* fusion gene-positive NSCLC who have not received prior treatment with ALK inhibitors, because these populations were excluded from Studies 024 and 010. This means that pembrolizumab is not recommended for these populations.

Based on the above rationale, the applicant proposed the following indication of pembrolizumab and precautionary statements:

Indication: Unresectable, advanced or recurrent non-small cell lung cancer

Precautionary statements (in the Precautions for Indications section of the package insert):

- The efficacy and safety of pembrolizumab have not been established in patients with EGFR mutation or ALK fusion genes who have not received respective molecular targeted drugs.
- Pembrolizumab should be administered only to patients testing positive for PD-L1 as determined by a highly experienced pathologist or laboratory facility staff. PD-L1 testing should be performed using the approved *in vitro* diagnostics.

The applicant's explanation about PD-L1 testing:
Study 024 included patients testing positive for PD-L1 (TPS ≥50%) by "PD-L1 IHC 22C3 pharmDx 'Dako'" distributed by Dako Japan Co., Ltd. Study 010 included patients testing positive for PD-L1 (TPS ≥1%) by a prototype kit of "PD-L1 IHC 22C3 pharmDx 'Dako'" [see Section 6.1.1.1].

The equivalence between the prototype kit and "PD-L1 IHC 22C3 pharmDx 'Dako'" was investigated using samples from the patients enrolled in Study 010. The results showed that 80.0% (557 of 696) of patients testing positive by the prototype kit, also tested positive by "PD-L1 IHC 22C3 pharmDx 'Dako,'" (positive agreement rate, 80.0%), and that 94.5% (294 of 311) of patients testing negative by the prototype kit, also tested negative by "PD-L1 IHC 22C3 pharmDx 'Dako'" (negative agreement rate, 94.5%). Although the positive agreement rate is low, the efficacy of pembrolizumab compared with DOC is suggested by OS analysis in patients in Study 010 who tested positive for PD-L1 (TPS ≥1%) by "PD-L1 IHC 22C3 pharmDx 'Dako'" (Table 17). This means that patients eligible for pembrolizumab therapy should be selected based on PD-L1 testing using "PD-L1 IHC 22C3 pharmDx 'Dako'" even after marketing of pembrolizumab; this information will be included in the Precautions for Indications section of the package insert.

Table 17. OS analysis in patients testing positive for PD-L1 (TPS ≥1%) by "PD-L1 IHC 22C3 pharmDx 'Dako'" (Study 010, cutoff date, September 30, 2015)

	2 mg/kg Q3W	10 mg/kg Q3W	DOC
Number of subjects	140	142	131
Number of events (%)	59 (42.1)	59 (41.5)	67 (51.1)
Median [95% CI] (months)	11.8 [9.6, NE]	12.0 [8.7, NE]	7.5 [6.3, 9.9]
Hazard ratio [95% CI]*	0.54 [0.37, 0.78]	0.57 [0.39, 0.82]	-

* Cox regression stratified by PD-L1 expression status (TPS ≥50%, TPS ≥1% and <50%), ECOG PS (0, 1), and region (East Asia, other regions)

PMDA's view:

Treatment strategy for patients with NSCLC has been established according to the presence or absence of *EGFR* mutation or *ALK* fusion genes (Japanese clinical practice guideline). EGFR inhibitors are primarily indicated for patients with *EGFR* mutation-positive NSCLC, and ALK inhibitors for patients with *ALK* fusion gene-positive NSCLC. In view of the fact that pembrolizumab is intended to be used by physicians with sufficient knowledge and experience in cancer chemotherapy, the "Clinical Studies" section of the package insert should state that these patient populations were not enrolled in Study 024, to raise awareness of healthcare professionals. Further, the precautionary statement (a) should be included in the Precautions for Indications section (see below).

Because both Studies 024 and 010 enrolled PD-L1 positive patients, the Indication section should clearly state that pembrolizumab is indicated for "PD-L1 positive patients." The indication for pembrolizumab should be "unresectable, advanced or recurrent PD-L1-positive non-small cell lung cancer" identified by the companion diagnostics "PD-L1 IHC 22C3 pharmDx 'Dako.'" Further, the clinical usefulness of pembrolizumab for NSCLC was demonstrated in PD-L1 positive patients with TPS ≥50% in Study 024, and in PD-L1 positive patients with TPS ≥1% in Study 010. This information should be included in the Clinical Studies section of the package insert, and the following precautionary statement (b) should be included in the Precautions for Indications section, to raise awareness of healthcare professionals.

Precautions for Indications

(a) Eligible 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.

(b) Pembrolizumab should be administered only to patients testing positive for PD-L1 as determined by a highly experienced pathologist or laboratory facility staff who fully understand the "Clinical Studies" section in terms of the percentage of PD-L1-expressing tumor cells. PD-L1 testing should be performed using the approved *in vitro* diagnostics.

7.R.4.2 Efficacy and safety in adjuvant chemotherapy

The applicant's explanation:

Because no clinical study data are available on the efficacy or safety of pembrolizumab in adjuvant chemotherapy, pembrolizumab in adjuvant chemotherapy cannot be recommend. This information will be included in the Precautions for Indications section, to raise awareness among healthcare professionals.

PMDA accepted the applicant's explanation.

7.R.5 Dosage and administration

The proposed dosage and administration for pembrolizumab is "The usual adult dosage is 200 mg of Pembrolizumab (Genetical Recombination) infused intravenously over 30 minutes every 3 weeks." In addition, the following statements and information are included in the Precautions for Dosage and Administration section of the proposed package insert:

- 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

Based on the findings described in"7.R.2 Efficacy" and "7.R.3 Safety" as well as results from the following review, PMDA has concluded that the proposed dosage and administration and the proposed precautions for dosage administration are acceptable.

7.R.5.1 Dosage and administration of pembrolizumab

The applicant's rationale for the proposed dosage and administration of pembrolizumab in patients with unresectable advanced or recurrent NSCLC:

PK/PD analysis and translational PK/PD analysis based on interleukin-2 (IL-2), suggested that pembrolizumab was expected to be effective at doses of ≥2 mg/kg Q3W (see "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016").

Based on results from the above PK/PD analyses, etc., Study 010 was conducted in patients with advanced or recurrent NSCLC who had received prior chemotherapy. In this study, both pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W showed statistically significant prolongation of OS compared with DOC [see Section 7.1.3.1], and there was no clear difference in safety of pembrolizumab between the 2 regimens [see Section 7.R.3.1]. Based on the above results, the applicant considered that the dose increase from 2 mg/kg Q3W to 10 mg/kg Q3W would not improve the efficacy of pembrolizumab.

The subsequent Study 024 was conducted in patients with advanced or recurrent NSCLC who had not received prior chemotherapy. In the study, pembrolizumab was administered at a fixed dose of 200 mg/body, which was estimated to achieve comparable exposure to 2 mg/kg, a weight-based dose, for the reasons listed below. As a result, pembrolizumab 200 mg/body Q3W showed statistically significant prolongation of PFS and OS compared with SOC [see Section 7.1.3.2], with tolerable safety [see Section 7.R.3.1].

- PPK analysis suggested that weight-based dosing and fixed dosing result in similar inter-individual variability in the PK parameter of pembrolizumab [see Section 6.2.4].
- Using the PPK model constructed based on PK data of pembrolizumab obtained from foreign clinical studies (Studies 001, 002, and 006) (see "Review Report of Keytruda Injection 20 mg, Keytruda Injection 100 mg dated August 30, 2016"), pembrolizumab exposures with weight-based dosing and fixed dosing were simulated (supposed body weight range, 33.2-231 kg). As a result, $AUC_{ss,6wk}$ (range) of pembrolizumab 200 mg/body Q3W, 2 mg/kg Q3W, and 10 mg/kg Q3W was estimated to be 444.8 to 7892.4, 355.6 to 6118.0, and 1778 to 30,590 μg·day/mL, respectively. The 200 mg/body Q3W dose was estimated to achieve similar pembrolizumab exposure to the 2 mg/kg Q3W dose, but lower pembrolizumab exposure than the 10 mg/kg Q3W dose.
- In clinical practice, the fixed dosing has advantages over weight-based dosing, because it reduces the risk of human error incidents during drug preparation, and because it does not cause unused drug to be disposed of.

There are no clinical study data on the efficacy and safety of pembrolizumab 200 mg/body Q3W in patients with advanced or recurrent NSCLC who have received prior chemotherapy. Nevertheless, based on the above discussion and for the reasons listed below, the dosage and administration of pembrolizumab should be the fixed dose of 200 mg/body Q3W for patients with advanced or recurrent NSCLC irrespective of prior chemotherapy:

- The distribution of pembrolizumab exposures at 200 mg/body Q3W and 2 mg/kg Q3W was similar. (The 2 mg/kg Q3W dose was demonstrated to be clinically useful in Study 010 [see Section 6.2.4].)
- If the dose of pembrolizumab in patients with NSCLC varies depending on prior chemotherapy, confusion may occur in clinical practice.

PMDA accepted the applicant's explanation.

7.R.5.2 Criteria for interruption and discontinuation

The applicant's explanation about criteria for interruption and discontinuation of pembrolizumab:

The criteria for adjustment of infusion rate and dose (criteria for treatment interruption, discontinuation, and resumption) used in Studies 010 and 024 were similar to those used in Studies 002, 006, and 041 (i.e., studies in patients with malignant melanoma, the approved indication). Studies 010 and 024, conducted in accordance with the criteria, demonstrated the efficacy and safety of pembrolizumab. Thus, the Precautions for Dosage and Administration section of the package insert will include the same dose adjustment criteria for NSCLC and malignant melanoma, the approved indication of pembrolizumab.

PMDA accepted the applicant's explanation.

7.R.5.3 Pembrolizumab in combination with other antineoplastic drugs

At present, no clinical study data are available for the efficacy and safety of pembrolizumab in combination with other antineoplastic drugs in patients with NSCLC. This information will be included in the Precautions for Dosage and Administration section of the package insert, in order to raise awareness among and healthcare professionals.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan:

The applicant plans to undertake post-marketing surveillance covering all patients receiving pembrolizumab for the treatment of NSCLC, to investigate the safety of pembrolizumab in clinical settings after the market launch.

The safety profile of pembrolizumab observed in Studies 010 and 024 were comparable to that observed in clinical studies in patients with unresectable malignant melanoma, the approved indication. Accordingly, this surveillance uses the same key survey items as in the post-marketing surveillance in patients with unresectable malignant melanoma.

Key survey items:

ILD, colitis and severe diarrhoea, hepatic dysfunction, renal dysfunction (tubulointerstitial nephritis, etc.), endocrine disorders (pituitary dysfunction, thyroid dysfunction, 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, and IRR.

The planned sample size is 1000 patients based on the incidences of ILD, colitis/severe diarrhoea, thyroid dysfunction, etc. in Studies 010 and 024. (These events are key survey items of the surveillance.)

The planned observation period is 1 year after the start of pembrolizumab therapy, for the following reasons: In Studies 010 and 024, most of the adverse events defined as key survey items, occurred within 1 year after the start of pembrolizumab therapy, and no adverse events tended to occur more frequently at ≥1 year after the start of pembrolizumab therapy.

PMDA's view:

The safety information in Japanese patients with NSCLC receiving pembrolizumab is limited, and at present no results are available from the post-marketing surveillance in patients with unresectable malignant melanoma. The applicant should therefore conduct all-case post-marketing surveillance in patients with NSCLC for a certain period after the market launch to collect the safety information promptly without bias, and should immediately provide the obtained safety information to healthcare professionals.

PMDA considers that the key survey items, target sample size, and observation period of this surveillance proposed by the applicant, are acceptable.

7.2 Adverse events, etc. observed in clinical studies

Among the submitted clinical study data for safety evaluation, data on deaths are presented in Section "7.1 Evaluation data." Other main adverse events are shown below.

7.2.1 Japanese phase Ib study (Study 025)

Adverse events occurred in all 38 subjects. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 86.8% (33 of 38) of subjects. Table 18 shows adverse events with an incidence of ≥10%.

Table 18. Adverse events with an incidence of ≥10%

SOC PT (MedDRA ver.18.0)	n (%) 10 mg/kg Q3W N = 38	
	All Grades	Grade ≥3
All adverse events	38 (100)	19 (50.0)
Gastrointestinal disorders		
Diarrhoea	8 (21.1)	1 (2.6)
Nausea	5 (13.2)	0
General disorders and administration site conditions		
Fatigue	5 (13.2)	0
Malaise	9 (23.7)	0
Pyrexia	10 (26.3)	0
Investigations		
ALT increased	6 (15.8)	2 (5.3)
AST increased	8 (21.1)	3 (7.9)
Blood ALP increased	6 (15.8)	0
GGT increased	4 (10.5)	2 (5.3)
Lymphocyte count decreased	5 (13.2)	3 (7.9)
Weight decreased	5 (13.2)	0
Metabolism and nutrition disorders		
Decreased appetite	8 (21.1)	1 (2.6)
Hypoalbuminaemia	4 (10.5)	1 (2.6)
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (10.5)	0
Back pain	4 (10.5)	0
Nervous system disorders		
Headache	5 (13.2)	0
Respiratory, thoracic and mediastinal disorders		
Cough	4 (10.5)	0
Dyspnoea	4 (10.5)	0
Skin and subcutaneous tissue disorders		
Pruritus	5 (13.2)	0
Rash	6 (15.8)	0
Rash maculo-papular	5 (13.2)	0

Serious adverse events occurred in 28.9% (11 of 38) of subjects. Observed serious adverse events included ILD in 2 subjects (5.3%), and inguinal hernia, diverticulitis, decreased appetite, oesophageal carcinoma, cerebrovascular accident, optic neuritis, organising pneumonia, pneumonia aspiration, pulmonary embolism, and pelvic venous thrombosis in 1 subject (2.6%) each. Of these, a causal relationship to the study drug could not be ruled out for ILD (2 subjects), and diverticulitis, decreased appetite, oesophageal carcinoma, cerebrovascular accident, optic neuritis, organising pneumonia, and pneumonia aspiration (1 subject each).

Adverse events leading to discontinuation of the study drug occurred in 7.9% (3 of 38) of subjects. Observed adverse events leading to discontinuation of the study drug included ILD in 2 subjects (5.3%) and optic neuritis in 1 subject (2.6%). A causal relationship to the study drug could not be ruled out for all events.

7.2.2 Global phase II/III study (Study 010)

Adverse events occurred in 97.6% (331 of 339) of subjects in the 2 mg/kg Q3W group, 96.2% (330 of 343) of subjects in the 10 mg/kg Q3W group, and 96.1% (297 of 309) of subjects in the DOC group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 63.4% (215 of 339) of subjects in the 2 mg/kg Q3W group, 65.9% (226 of 343) of subjects in the 10

mg/kg Q3W group, and 81.2% (251 of 309) of subjects in the DOC group. Table 19 shows adverse events with an incidence of ≥10% in any group.

Table 19. Adverse events with an incidence of ≥10% in any group

SOC PT (MedDRA ver.18.0)	n (%)					
	2 mg/kg Q3W N = 339		10 mg/kg Q3W N = 343		DOC N = 309	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	331 (97.6)	158 (46.6)	330 (96.2)	156 (45.5)	297 (96.1)	173 (56.0)
Blood and lymphatic system disorders						
Anaemia	35 (10.3)	10 (2.9)	31 (9.0)	6 (1.7)	60 (19.4)	7 (2.3)
Neutropenia	1 (0.3)	0	2 (0.6)	0	50 (16.2)	42 (13.6)
Gastrointestinal disorders						
Stomatitis	19 (5.6)	0	11 (3.2)	1 (0.3)	46 (14.9)	3 (1.0)
Constipation	55 (16.2)	2 (0.6)	50 (14.6)	2 (0.6)	38 (12.3)	2 (0.6)
Diarrhoea	53 (15.6)	3 (0.9)	42 (12.2)	0	80 (25.9)	8 (2.6)
Nausea	74 (21.8)	6 (1.8)	65 (19.0)	3 (0.9)	57 (18.4)	2 (0.6)
Vomiting	45 (13.3)	3 (0.9)	43 (12.5)	3 (0.9)	32 (10.4)	2 (0.6)
General disorders and administration site conditions						
Asthenia	38 (11.2)	4 (1.2)	38 (11.1)	5 (1.5)	47 (15.2)	8 (2.6)
Fatigue	91 (26.8)	12 (3.5)	80 (23.3)	9 (2.6)	99 (32.0)	17 (5.5)
Oedema peripheral	30 (8.8)	1 (0.3)	23 (6.7)	0	33 (10.7)	0
Pyrexia	41 (12.1)	3 (0.9)	36 (10.5)	2 (0.6)	44 (14.2)	3 (1.0)
Metabolism and nutrition disorders						
Decreased appetite	96 (28.3)	6 (1.8)	72 (21.0)	4 (1.2)	72 (23.3)	8 (2.6)
Musculoskeletal and connective tissue disorders						
Arthralgia	40 (11.8)	3 (0.9)	35 (10.2)	4 (1.2)	28 (9.1)	1 (0.3)
Back pain	36 (10.6)	3 (0.9)	37 (10.8)	7 (2.0)	24 (7.8)	1 (0.3)
Musculoskeletal pain	34 (10.0)	5 (1.5)	31 (9.0)	1 (0.3)	10 (3.2)	0
Myalgia	20 (5.9)	1 (0.3)	15 (4.4)	0	34 (11.0)	0
Nervous system disorders						
Headache	36 (10.6)	2 (0.6)	28 (8.2)	1 (0.3)	19 (6.1)	1 (0.3)
Neuropathy peripheral	6 (1.8)	0	8 (2.3)	0	36 (11.7)	1 (0.3)
Respiratory, thoracic and mediastinal disorders						
Cough	72 (21.2)	3 (0.9)	58 (16.9)	1 (0.3)	42 (13.6)	0
Dyspnoea	84 (24.8)	13 (3.8)	72 (21.0)	12 (3.5)	62 (20.1)	8 (2.6)
Skin and subcutaneous tissue disorders						
Alopecia	5 (1.5)	0	4 (1.2)	0	105 (34.0)	2 (0.6)
Pruritus	32 (9.4)	0	41 (12.0)	0	10 (3.2)	1 (0.3)
Rash	41 (12.1)	1 (0.3)	53 (15.5)	1 (0.3)	22 (7.1)	0

Serious adverse events occurred in 33.9% (115 of 339) of subjects in the 2 mg/kg Q3W group, 38.2% (131 of 343) of subjects in the 10 mg/kg Q3W group, and 34.6% (107 of 309) of subjects in the DOC group.

Serious adverse events reported by ≥2 subjects in the 2 mg/kg Q3W group:

Pneumonia in 15 subjects (4.4%); pneumonitis and pulmonary embolism in 8 subjects (2.4%) each; chronic obstructive pulmonary disease and dyspnoea in 6 subjects (1.8%) each; pericardial effusion and pleural effusion in 4 subjects (1.2%) each; colitis, death, general physical health deterioration, respiratory tract infection, confusional state, and haemoptysis in 3 subjects (0.9%) each; and anaemia, atrial fibrillation, faecaloma, nausea, pancreatitis, chest pain, pain, pyrexia, lung infection, upper limb fracture, back pain, musculoskeletal pain, acute renal failure, respiratory failure, and superior vena cava syndrome in 2 subjects (0.6%) each.

Serious adverse events reported by ≥2 subjects in the 10 mg/kg Q3W group:

Pneumonia in 21 subjects (6.1%); pneumonitis in 9 subjects (2.6%); pulmonary embolism in 7 subjects (2.0%); hypercalcaemia in 5 subjects (1.5%); anaemia and pleural effusion in 4 subjects (1.2%) each; dysphagia, death, pyrexia, and respiratory tract infection in 3 subjects (0.9%) each; and pericardial effusion, hyperthyroidism, dehydration, hyponatraemia, back pain, ischaemic stroke, spinal cord compression, syncope, acute renal failure, dyspnoea, pneumonia aspiration, pulmonary haemorrhage, and pulmonary oedema in 2 subjects (0.6%) each.

Serious adverse events reported by ≥2 subjects in the DOC group:

Pneumonia in 16 subjects (5.2%); febrile neutropenia in 11 subjects (3.6%); dyspnoea in 6 subjects (1.9%); neutropenia and pulmonary embolism in 5 subjects (1.6%) each; pyrexia and dehydration in 4 subjects (1.3%) each; bronchitis, lung infection, respiratory tract infection, upper respiratory tract infection, decreased appetite, pleural effusion, and pneumothorax in 3 subjects (1.0%) each; and atrial fibrillation, constipation, diarrhoea, oesophageal stenosis, lower respiratory tract infection, septic shock, metastases to central nervous system, pneumonitis, pulmonary haemorrhage, respiratory failure, deep vein thrombosis, and hypotension in 2 subjects (0.6%) each.

Among these adverse events, a causal relationship to the study drug could not be ruled out for the following:

The 2 mg/kg Q3W group: pneumonitis (7 subjects); colitis and pneumonia (3 subjects each); pleural effusion (2 subjects); and pancreatitis, confusional state, chronic obstructive pulmonary disease, dyspnoea, and pulmonary embolism (1 subject each).

The 10 mg/kg Q3W group: pneumonitis (8 subjects); pneumonia (3 subjects); hyperthyroidism and hyponatraemia (2 subjects each); and anaemia, pericardial effusion, pyrexia, and dyspnoea (1 subject each).

The DOC group: febrile neutropenia (10 subjects); neutropenia and pneumonia (4 subjects each); upper respiratory tract infection, dehydration, and dyspnoea (3 subjects each); diarrhoea, pleural effusion, and pneumonitis (2 subjects each); and atrial fibrillation, pyrexia, lung infection, respiratory tract infection, septic shock, decreased appetite, and hypotension (1 subject each).

Adverse events leading to discontinuation of the study drug occurred in 8.3% (28 of 339) of subjects in the 2 mg/kg Q3W group, 7.6% (26 of 343) of subjects in the 10 mg/kg Q3W group, and 13.6% (42 of 309) of subjects in the DOC group.

Adverse events leading to discontinuation of the study drug in the 2 mg/kg Q3W group:

Pneumonitis in 6 subjects (1.8%); and acute coronary syndrome, acute myocardial infarction, atrial fibrillation, fatigue, multi-organ failure, pneumonia, radiation pneumonitis, aspartate aminotransferase (AST) increased, arthritis, muscle necrosis, gastric cancer, lung neoplasm malignant, ataxia, cerebrovascular accident, ischaemic stroke, toxic leukoencephalopathy, tubulointerstitial

nephritis, dyspnoea, pleural effusion, pneumonia aspiration, respiratory failure, and femoral artery occlusion in 1 subject (0.3%).

Adverse events leading to discontinuation of the study drug in the 10 mg/kg Q3W group:

Pneumonitis in 6 subjects (1.7%); and atrioventricular block complete, hypothyroidism, gastritis, death, general physical health deterioration, pneumonia, pneumonitis chemical, hyponatraemia, arthralgia, malignant neoplasm progression, myelitis transverse, spinal cord compression, disorientation, bronchostenosis, dyspnoea, hypoxia, pulmonary haemorrhage, respiratory distress, lichen planus, embolism, and peripheral ischaemia in 1 subject (0.3%).

Adverse events leading to discontinuation of the study drug in the DOC group:

Asthenia and pneumonitis in 3 subjects (1.0%) each; polyneuropathy and ILD in 2 subjects (0.6%) each; and thrombocytopenia, arteriosclerosis coronary artery, ventricular fibrillation, lacrimation increased, abdominal pain, colitis ischaemic, gastrointestinal inflammation, stomatitis, adverse drug reaction, fatigue, oedema, herpes zoster, lung infection, pneumonia, respiratory tract infection, septic shock, toxicity to various agents, musculoskeletal chest pain, myalgia, neck pain, metastases to central nervous system, cerebrovascular accident, cognitive disorder, neuropathy peripheral, peripheral sensory neuropathy, pleural effusion, pulmonary embolism, respiratory failure, alopecia, onycholysis, rash, deep vein thrombosis, and superior vena cava syndrome in 1 subject (0.3%) each.

Among these adverse events, a causal relationship to the study drug could not be ruled out for the following:

The 2 mg/kg Q3W group: pneumonitis (6 subjects); and fatigue, pneumonia, AST increased, arthritis, muscle necrosis, ataxia, cerebrovascular accident, toxic leukoencephalopathy, and tubulointerstitial nephritis (1 subject each).

The 10 mg/kg Q3W group: pneumonitis (6 subjects); and atrioventricular block complete, hypothyroidism, gastritis, pneumonitis chemical, hyponatraemia, malignant neoplasm progression, myelitis transverse, disorientation, dyspnoea, hypoxia, lichen planus, and peripheral ischaemia (1 subject each).

The DOC group: asthenia and pneumonitis (3 subjects each); polyneuropathy and ILD (2 subjects each); and thrombocytopenia, arteriosclerosis coronary artery, lacrimation increased, colitis ischaemic, gastrointestinal inflammation, stomatitis, adverse drug reaction, fatigue, oedema, herpes zoster, pneumonia, respiratory tract infection, septic shock, toxicity to various agents, myalgia, cognitive disorder, neuropathy peripheral, peripheral sensory neuropathy, pleural effusion, alopecia, onycholysis, and rash (1 subject each).

7.2.3 Global phase III study (Study 024)

Adverse events occurred in 96.1% (148 of 154) of subjects in the pembrolizumab group and 96.7% (145 of 150) of subjects in the SOC group. Adverse events for which a causal relationship to the study drug

could not be ruled out occurred in 73.4% (113 of 154) of subjects in the pembrolizumab group and 90.0% (135 of 150) of subjects in the SOC group. Table 20 shows adverse events with an incidence of ≥10% in any group.

Table 20. Adverse events with an incidence of ≥10% in any group

SOC PT (MedDRA ver.19.0)	n (%)			
	Pembrolizumab N = 154		SOC N = 150	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	148 (96.1)	82 (53.2)	145 (96.7)	109 (72.7)
Blood and lymphatic system disorders				
Anaemia	20 (13.0)	7 (4.5)	79 (52.7)	35 (23.3)
Neutropenia	2 (1.3)	0	36 (24.0)	21 (14.0)
Thrombocytopenia	2 (1.3)	0	20 (13.3)	9 (6.0)
Gastrointestinal disorders				
Constipation	32 (20.8)	1 (0.6)	34 (22.7)	1 (0.7)
Diarrhoea	32 (20.8)	6 (3.9)	33 (22.0)	3 (2.0)
Nausea	30 (19.5)	0	70 (46.7)	4 (2.7)
Stomatitis	7 (4.5)	0	18 (12.0)	2 (1.3)
Vomiting	12 (7.8)	1 (0.6)	36 (24.0)	3 (2.0)
General disorders and administration site conditions				
Asthenia	10 (6.5)	1 (0.6)	16 (10.7)	4 (2.7)
Fatigue	32 (20.8)	2 (1.3)	53 (35.3)	7 (4.7)
Oedema peripheral	16 (10.4)	1 (0.6)	15 (10.0)	0
Pyrexia	24 (15.6)	0	14 (9.3)	0
Infections and infestations				
Nasopharyngitis	16 (10.4)	0	2 (1.3)	0
Investigations				
ALT increased	17 (11.0)	2 (1.3)	11 (7.3)	0
Blood creatinine increased	10 (6.5)	0	20 (13.3)	1 (0.7)
Neutrophil count decreased	1 (0.6)	0	20 (13.3)	6 (4.0)
Platelet count decreased	1 (0.6)	0	19 (12.7)	9 (6.0)
White blood cell count decreased	1 (0.6)	0	16 (10.7)	3 (2.0)
Metabolism and nutrition disorders				
Decreased appetite	31 (20.1)	2 (1.3)	49 (32.7)	5 (3.3)
Musculoskeletal and connective tissue disorders				
Arthralgia	24 (15.6)	0	15 (10.0)	1 (0.7)
Back pain	20 (13.0)	2 (1.3)	21 (14.0)	5 (3.3)
Nervous system disorders				
Dizziness	16 (10.4)	1 (0.6)	12 (8.0)	0
Dysgeusia	3 (1.9)	0	18 (12.0)	0
Respiratory, thoracic and mediastinal disorders				
Cough	26 (16.9)	0	21 (14.0)	0
Dyspnoea	34 (22.1)	3 (1.9)	24 (16.0)	4 (2.7)
Skin and subcutaneous tissue disorders				
Pruritus	23 (14.9)	0	5 (3.3)	0
Rash	22 (14.3)	2 (1.3)	6 (4.0)	0

Serious adverse events occurred in 44.2% (68 of 154) of subjects in the pembrolizumab group and in 44.0% (66 of 150) of subjects in the SOC group.

Serious adverse events in the pembrolizumab group:

Pneumonitis in 7 subjects (4.5%); pleural effusion in 5 subjects (3.2%); hyponatraemia and chronic obstructive pulmonary disease in 4 subjects (2.6%) each; diarrhoea, pneumonia, and hyperglycaemia in 3 subjects (1.9%) each; anaemia, colitis, pyrexia, lower respiratory tract infection, lung infection, ALT increased, diabetes mellitus, haemoptysis, and pulmonary embolism in 2 subjects (1.3%) each; and cardiac arrest, cardiac failure, pericardial effusion, pericarditis, supraventricular tachycardia,

hyperthyroidism, hypophysitis, abdominal pain, enterocolitis, gastric ulcer, gastritis erosive, pancreatitis, vomiting, face oedema, fatigue, general physical health deterioration, multiple organ dysfunction syndrome, oedema peripheral, sudden death, acute hepatic failure, anaphylactic shock, hypersensitivity, appendicitis, bronchitis, cellulitis, device related infection, gastroenteritis viral, infectious pleural effusion, neutropenic sepsis, oral candidiasis, pneumonia streptococcal, splenic abscess, urinary tract infection, urosepsis, infusion related reaction, AST increased, bilirubin conjugated increased, hepatic enzyme increased, transaminases increased, decreased appetite, dehydration, diabetic ketoacidosis, hypovolaemia, back pain, musculoskeletal pain, osteolysis, spinal pain, gastrointestinal carcinoma, infected neoplasm, metastases to meninges, cerebrovascular accident, haemorrhagic stroke, ischaemic stroke, tubulointerstitial nephritis, ovarian haemorrhage, acute respiratory failure, atelectasis, organising pneumonia, painful respiration, pneumothorax, respiratory failure, lichenoid keratosis, and rash in 1 subject (0.6%) each.

Serious adverse events in the SOC group:

Pneumonia in 9 subjects (6.0%); anaemia in 5 subjects (3.3%); febrile neutropenia, pancytopenia, thrombocytopenia, hypercalcaemia, back pain, acute kidney injury, and pleural effusion in 3 subjects (2.0%) each; atrial fibrillation, cardiac failure, nausea, lower respiratory tract infection, lung infection, pulmonary sepsis, respiratory tract infection, urinary tract infection, epistaxis, pulmonary embolism, and pulmonary oedema in 2 subjects (1.3%) each; and leukocytosis, angina pectoris, bradycardia, cardiac arrest, cardio-respiratory arrest, coronary artery disease, ischaemic cardiomyopathy, pericardial effusion, right ventricular failure, supraventricular tachycardia, constipation, diarrhoea, faecaloma, small intestinal obstruction, stomatitis, chest pain, death, gait disturbance, pyrexia, cellulitis, Clostridium difficile colitis, infective exacerbation of chronic obstructive airways disease, neutropenic sepsis, peritonsillar abscess, sepsis, septic shock, skin infection, pulmonary radiation injury, radiation oesophagitis, rib fracture, toxicity to various agents, platelet count decreased, hypocalcaemia, arthralgia, muscle haemorrhage, musculoskeletal pain, bladder neoplasm, cancer pain, malignant neoplasm progression, cerebral infarction, cerebrovascular accident, ischaemic stroke, transient ischaemic attack, device dislocation, insomnia, restlessness, hypertensive nephropathy, bronchial obstruction, chronic obstructive pulmonary disease, pneumonitis, pneumothorax, pulmonary alveolar haemorrhage, peripheral embolism, and vasospasm in 1 subject (0.7%) each.

Among these adverse events, a causal relationship to the study drug could not be ruled out for the following:

<u>The pembrolizumab group:</u> pneumonitis (7 subjects [4.5%]); diarrhoea (3 subjects [1.9%]); colitis, lower respiratory tract infection, ALT increased, and diabetes mellitus (2 subjects [1.3%] each); and anaemia, pericarditis, hyperthyroidism, hypophysitis, enterocolitis, gastric ulcer, pancreatitis, vomiting, face oedema, fatigue, oedema peripheral, sudden death, acute hepatic failure, infusion related reaction, AST increased, bilirubin conjugated increased, hepatic enzyme increased, transaminases increased, diabetic ketoacidosis, hypovolaemia, musculoskeletal pain, cerebrovascular accident, tubulointerstitial nephritis, organising pneumonia, pulmonary embolism, lichenoid keratosis, and rash (1 subject each).

The SOC group: anaemia (4 subjects [2.7%]); febrile neutropenia, pancytopenia, thrombocytopenia, and pneumonia (3 subjects [2.0%] each); lung infection, acute kidney injury, and epistaxis (2 subjects [1.3%] each); and leukocytosis, diarrhoea, nausea, stomatitis, death, gait disturbance, pyrexia, cellulitis, neutropenic sepsis, pulmonary sepsis, respiratory tract infection, skin infection, urinary tract infection, platelet count decreased, malignant neoplasm progression, pneumonitis, pulmonary alveolar haemorrhage, and vasospasm (1 subject [0.7%] each).

Adverse events leading to discontinuation of the study drug occurred in 9.1% (14 of 154) of subjects in the pembrolizumab group and in 14.0% (21 of 150) of subjects in the SOC group.

Adverse events leading to discontinuation of the study drug in the pembrolizumab group:

Pneumonitis in 6 subjects (3.9%); and cardiac arrest, vomiting, fatigue, sudden death, pneumonia, ALT increased, transaminases increased, and haemorrhagic stroke in 1 subject (0.6%) each.

Adverse events leading to discontinuation of the study drug in the SOC group:

Fatigue in 3 subjects (2.0%); blood creatinine increased in 2 subjects (1.3%); and febrile neutropenia, leukocytosis, coronary artery disease, hypoacusis, nausea, vomiting, enanthema, gait disturbance, pneumonia, pulmonary sepsis, respiratory tract infection, blood creatinine increased, C-reactive protein increased, creatinine renal clearance decreased, platelet count decreased, decreased appetite, cerebral infarction, lethargy, peripheral sensory neuropathy, acute kidney injury, hypoxia, pulmonary alveolar haemorrhage, and pulmonary embolism in 1 subject (0.7%) each.

Among these adverse events, a causal relationship to the study drug could not be ruled out for the following:

The pembrolizumab group: pneumonitis (6 subjects [3.9%]); and vomiting, fatigue, sudden death, ALT increased, and transaminases increased (1 subject [0.6%] each).

The SOC group: fatigue and blood creatinine increased (2 subjects [1.3%] each); and febrile neutropenia, leukocytosis, hypoacusis, nausea, vomiting, enanthema, gait disturbance, pulmonary sepsis, respiratory tract infection, blood creatinine increased, creatinine renal clearance decreased, platelet count decreased, decreased appetite, lethargy, peripheral sensory neuropathy, acute kidney injury, hypoxia, and pulmonary alveolar haemorrhage (1 subject [0.7%] each).

7.2.4 Foreign phase I study (Study 001)

Adverse events occurred in 96.5% (531 of 550) of subjects. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 69.1% (380 of 550) of subjects. Table 21 shows adverse events with an incidence of ≥10%.

Table 21. Adverse events with an incidence of ≥10%

SOC PT (MedDRA ver.18.0)	n (%) Part C, F1, F2, and F3 N = 550	
	All Grades	Grade ≥3
All adverse events	531 (96.5)	254 (46.2)
Blood and lymphatic system disorders		
Anaemia	69 (12.5)	11 (2.0)
Gastrointestinal disorders		
Constipation	88 (16.0)	2 (0.4)
Diarrhoea	94 (17.1)	4 (0.7)
Nausea	108 (19.6)	5 (0.9)
Vomiting	69 (12.5)	3 (0.5)
General disorders and administration site conditions		
Asthenia	56 (10.2)	7 (1.3)
Fatigue	203 (36.9)	16 (2.9)
Oedema peripheral	61 (11.1)	0
Pyrexia	68 (12.4)	3 (0.5)
Metabolism and nutrition disorders		
Decreased appetite	142 (25.8)	5 (0.9)
Musculoskeletal and connective tissue disorders		
Arthralgia	92 (16.7)	4 (0.7)
Back pain	60 (10.9)	10 (1.8)
Nervous system disorders		
Headache	58 (10.5)	0
Respiratory, thoracic and mediastinal disorders		
Cough	126 (22.9)	0
Dyspnoea	130 (23.6)	23 (4.2)
Skin and subcutaneous tissue disorders		
Pruritus	75 (13.6)	0
Rash	68 (12.4)	2 (0.4)

Serious adverse events occurred in 41.5% (228 of 550) of subjects.

Serious adverse events reported by ≥2 subjects:

Pleural effusion in 26 subjects (4.7%); pneumonia in 20 subjects (3.6%); dyspnoea in 15 subjects (2.7%); pneumonitis in 14 subjects (2.5%); pulmonary embolism in 13 subjects (2.4%); pyrexia in 11 subjects (2.0%); respiratory failure in 9 subjects (1.6%); nausea and pneumothorax in 7 subjects (1.3%) each; chronic obstructive pulmonary disease and hypoxia in 6 subjects (1.1%) each; cardiac tamponade, pericardial effusion, fatigue, lower respiratory tract infection, dehydration, acute respiratory failure, and embolism in 5 subjects (0.9%) each; colitis, pain, lung infection, hypercalcaemia, arthralgia, and tumour pain in 4 subjects (0.7%) each; acute myocardial infarction, cardiac failure congestive, abdominal pain, vomiting, asthenia, chest pain, bronchitis, sepsis, hyponatraemia, back pain, malignant pleural effusion, cerebrovascular accident, syncope, acute renal failure, haemoptysis, and deep vein thrombosis in 3 subjects (0.5%) each; and atrial fibrillation, atrial flutter, cardio-respiratory arrest, supraventricular tachycardia, adrenal insufficiency, hypothyroidism, ascites, gastrointestinal haemorrhage, chills, death, general physical health deterioration, oedema, cholecystitis, herpes zoster, respiratory tract infection, blood bilirubin increased, decreased appetite, bone pain, muscular weakness, musculoskeletal chest pain, musculoskeletal pain, basal cell carcinoma, pericardial effusion malignant, headache, seizure, dysuria, renal failure, pulmonary oedema, rash, and hypotension in 2 subjects (0.4%) each.

Among these adverse events, a causal relationship to the study drug could not be ruled out for the following:

Pneumonitis (14 subjects); colitis and nausea (3 subjects each); adrenal insufficiency, hypothyroidism, vomiting, pyrexia, hyponatraemia, and rash (2 subjects each); and acute myocardial infarction, cardiac tamponade, cardio-respiratory arrest, pericardial effusion, chills, blood bilirubin increased, acute renal failure, dysuria, hypoxia, pleural effusion, pneumothorax, and respiratory failure (1 subject each).

Adverse events leading to discontinuation of the study drug occurred in 15.5% (85 of 550) of subjects:

Pneumonitis in 11 subjects (2.0%); respiratory failure in 6 subjects (1.1%); pleural effusion in 5 subjects (0.9%); fatigue, pain, pneumonia, and dyspnoea in 4 subjects (0.7%) each; colitis, death, general physical health deterioration, bronchitis, hypercalcaemia, acute respiratory failure, pneumothorax, and embolism in 2 subjects (0.4%) each; and autoimmune haemolytic anaemia, neutropenia, cardio-respiratory arrest, abdominal pain upper, gastrointestinal perforation, impaired gastric emptying, intestinal perforation, generalised oedema, malaise, oedema, hepatic failure, serum sickness, herpes zoster, pulmonary sepsis, respiratory tract infection, sepsis, septic shock, thrombophlebitis septic, blood bilirubin increased, weight decreased, failure to thrive, arthralgia, back pain, bone pain, joint stiffness, neck pain, squamous cell carcinoma, tumour pain, embolic stroke, neuralgia, acute renal failure, chronic obstructive pulmonary disease, diffuse alveolar damage, haemoptysis, ILD, pulmonary embolism, hyperkeratosis, and rash in 1 subject (0.2%) each.

Among these adverse events, a causal relationship to the study drug could not be ruled out for the following:

Pneumonitis (11 subjects); colitis (2 subjects); and autoimmune haemolytic anaemia, neutropenia, cardio-respiratory arrest, impaired gastric emptying, generalised oedema, serum sickness, weight decreased, joint stiffness, neuralgia, acute renal failure, ILD, respiratory failure, hyperkeratosis, and rash (1 subject each).

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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.

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

The new drug application data (CTD 5.3.5.1.1, 5.3.5.1.2, 5.3.5.2.3) 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, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that pembrolizumab has efficacy in the treatment of unresectable, advanced or recurrent PD-L1 positive NSCLC, and that pembrolizumab has acceptable safety in view of its benefits. Pembrolizumab is clinically meaningful because it offers a new therapeutic option for patients with unresectable advanced or recurrent PD-L1 positive NSCLC. However, the indication, dosage and administration, and post-marketing investigation of pembrolizumab should be further discussed.

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

Review Report (2)

November 14, 2016

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	October 6, 2016

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

1.1 Efficacy

PMDA's conclusion:

Based on the results of the review in Section "7.R.2 Efficacy" in the Review Report (1), PMDA has concluded that the following 2 global clinical studies demonstrated the efficacy of pembrolizumab (genetical recombination) (hereinafter referred to as "pembrolizumab") in patients with advanced or recurrent programmed cell death-ligand-1 (PD-L1) positive non-small cell lung cancer (NSCLC):

- A global phase III study (KEYNOTE-024 study [Study 024]) was conducted in chemotherapy-naïve patients with advanced or recurrent PD-L1 positive NSCLC (tumor proportion score [TPS] ≥50%) without epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) fusion genes. In comparison with control treatment (the standard of care [SOC]), pembrolizumab 200 mg/body every 3 weeks (Q3W) showed a statistically significant prolongation of centrally assessed progression-free survival (PFS), the primary endpoint, and of overall survival (OS), a secondary endpoint.

- A global phase II/III study (KEYNOTE-010 study [Study 010]) was conducted in patients with advanced or recurrent PD-L1 positive NSCLC (TPS ≥1%) who had received prior platinum-based chemotherapy. In comparison with control treatment (docetaxel hydrate), pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W showed a statistically significant prolongation of OS, one of the primary endpoints.

This conclusion was supported by the expert advisers at the Expert Discussion.

1.2 Safety

PMDA's conclusion:

Based on the results of the review in Section "7.R.3 Safety" in the Review Report (1), PMDA has concluded that special attention should be paid to the following adverse events in patients with advanced or recurrent PD-L1 positive NSCLC who receive pembrolizumab: gastrointestinal disorders, skin disorders, neurological disorders, hepatic dysfunction, eye disorders, endocrine disorders, renal dysfunction, interstitial lung disease (ILD), infusion-related reaction (IRR), pancreatitis, myositis, encephalitis and meningitis, and myasthenia gravis.

Although attention should be paid to the above adverse events, pembrolizumab is tolerable provided that physicians with sufficient knowledge and experience in cancer chemotherapy take appropriate measures, such as monitoring of adverse events, differential diagnosis and patient management in anticipation of adverse reactions due to excessive immune response, and interruption of pembrolizumab.

This conclusion was supported by the expert advisers at the Expert Discussion.

1.3 Clinical positioning and indication

PMDA's conclusion:

Based on the results of the review in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), PMDA has concluded that the indication for pembrolizumab should be "unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer." The Clinical Studies section of the package insert should include the following information: (a) Patients with NSCLC with EGFR mutation or ALK fusion genes were excluded from Study 024; and (b) Patients showing the clinical usefulness of pembrolizumab in Studies 024 and 010 had different TPS: ≥50% in Study 024 and ≥1% in Study 010. Further, the following precautionary statements should be included in the Precautions for Indications section of the package insert.

Precautions for Indications

- Eligible 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.

- Pembrolizumab should be administered only to patients testing positive for PD-L1 as determined by a highly experienced pathologist or laboratory facility staff who fully understand the "Clinical Studies" section in terms of the percentage of PD-L1-expressing tumor cells (tumor proportion score [TPS]). PD-L1 testing should be performed using the approved *in vitro* diagnostics.

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

The following comments were raised from the expert advisers at the Expert Discussion, but the above conclusion was supported by the expert advisers.

- The information (a) and (b) included in the "Clinical Studies" section is important to ensure proper use of pembrolizumab in patients with advanced or recurrent NSCLC. This information should therefore be thoroughly disseminated so that physicians will not have the wrong understanding.

PMDA's view:
Pembrolizumab is not recommended for patients with EGFR mutation or ALK fusion genes who have not received prior chemotherapy. This information should be appropriately provided to healthcare professionals through materials, etc., in addition to the precautionary statements in the Precautions for Indications section:

In conclusion, PMDA instructed the applicant to thoroughly disseminate the information (a) and (b) to healthcare professionals using materials, etc., to use the wording "unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer" for the indication of pembrolizumab, and to include the above precautionary statements in the Precautions for Indications section. The applicant agreed.

1.4 Dosage and administration

PMDA's conclusion:
Based on the results of the review in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA has concluded that the following precautionary statements should be included in the Precautions for Dosage and Administration section, and that the dosage and administration of pembrolizumab, irrespective of prior chemotherapy, should be the following: "The usual adult dosage is 200 mg of Pembrolizumab (Genetical Recombination) infused intravenously over 30 minutes every 3 weeks."

Precautions for Dosage and Administration

- 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

This conclusion was supported by the expert advisers at the Expert Discussion.

Based on the above, PMDA instructed the applicant to use the above wording for the Dosage and Administration and Precautions for Dosage and Administration sections. The applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance covering all patients receiving pembrolizumab for the treatment of NSCLC, to investigate the safety of pembrolizumab in clinical settings after the market launch. The planned sample size is 1000 patients. The planned observation period is 1 year.

PMDA's conclusion:
Based on the results of the review in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA has concluded that the applicant should conduct all-case surveillance for a certain period after the market launch to collect safety information promptly without bias, and should immediately provide the obtained safety information to healthcare professionals. The proposed key survey items, planned sample size, and planned observation period are acceptable.

This conclusion was supported by the expert advisers at the Expert Discussion. The following comment was raised from the expert advisers.

- The safety profile of pembrolizumab in patients with NSCLC may differ according to presence or absence of prior chemotherapy. The surveillance plan should be designed to evaluate the difference.

Based on the above discussion, PMDA instructed the applicant to reconsider the surveillance plan.

The applicant's response:
The target sample size will be changed to include 500 patients with prior chemotherapy and 500 patients without prior chemotherapy, to avoid bias due to uneven distribution of patients with and without prior chemotherapy.

PMDA accepted the applicant's response.

In view of the above discussions, PMDA has concluded that the risk management plan (draft) should include the safety and efficacy specifications presented in Table 22, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 23.

Table 22. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Colitis and severe diarrhoea • Hepatic dysfunction • Renal dysfunction (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 • IRR	• Myocarditis	• None
Efficacy specification		
• Efficacy in routine clinical use		

Table 23. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (unresectable malignant melanoma) • Early post-marketing phase vigilance (unresectable advanced or recurrent PD-L1 positive NSCLC) • 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) • Post-marketing clinical study (extension study of Japanese phase Ib study KEYNOTE-041) • Post-marketing clinical study (extension study of Study 010) • Post-marketing clinical study (extension study of Study 024) • Post-marketing clinical study (extension study of Japanese phase Ib study KEYNOTE-025)	• Provision of data from early post-marketing phase vigilance (unresectable malignant melanoma) • Provision of data from early post-marketing phase vigilance (unresectable, advanced or recurrent PD-L1 positive NSCLC) • Preparation and distribution of information materials for healthcare professionals • Preparation and provision of information materials for patients

Underlines indicate activities related to the proposed new indication to be approved.

Table 24. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety of pembrolizumab in routine clinical use after the market launch
Survey method	All-case surveillance by central registration system
Population	All pembrolizumab-treated patients with unresectable, advanced or recurrent PD-L1 positive NSCLC
Observation period	1 year after the start of pembrolizumab therapy
Planned sample size	1000 patients (500 patients with PD-L1 positive [TPS ≥50%] NSCLC who have not received prior chemotherapy; 500 patients with PD-L1 positive [TPS ≥1%] NSCLC who have received prior chemotherapy).
Main survey item(s)	Key survey items: ILD, colitis and severe diarrhoea, hepatic dysfunction, renal dysfunction (tubulointerstitial nephritis, etc.), endocrine disorders (pituitary dysfunction, thyroid dysfunction, 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, and IRR Other main survey items: Patient characteristics (age, sex, date of diagnosis, information about onset, disease type classification, staging, prior treatment, etc.), use status of pembrolizumab, concomitant drugs, concomitant therapies, adverse events, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the following indication and dosage and administration (modified from the proposed wording), with the conditions of approval shown below. Necessary precautionary statements must be included in the package insert, and information on the proper use of the product must be properly disseminated after the market launch. The product must be used properly under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at a medical institution that can provide adequate emergency medical care. Although the product was previously approved as an orphan drug with a new active ingredient approved, the present application is intended to add an indication outside of the scope of orphan drug designation. Therefore, the re-examination period for the new indication should be 5 years and 10 months.

Indications (Underline denotes additions.)

1. Unresectable malignant melanoma
2. Unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer

Dosage and Administration (Underline denotes additions.)

1. 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.

2. Unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer

The usual adult dosage is 200 mg of Pembrolizumab (Genetical Recombination) infused intravenously over 30 minutes every 3 weeks.

Conditions of Approval

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

Warnings (no change)

(1) Pembrolizumab should be administered only to patients eligible for 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)

(1) Patients with a history of hypersensitivity to any ingredient of the product

(2) Pregnant or possibly pregnant women

Precautions for Indications (Underline denotes additions.)

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

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

(2) Pembrolizumab should be administered only to patients testing positive for PD-L1 as determined by a highly experienced pathologist or laboratory facility staff who fully understand the "Clinical Studies" section in terms of the percentage of PD-L1-expressing tumor cells (tumor proportion score [TPS]). PD-L1 testing should be performed using the approved *in vitro* diagnostics.

(3) Eligible 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.

Precautions for Dosage and Administration (Underline denotes additions and strike-through denotes deletions.)

(1) The efficacy and safety of pembrolizumab in combination with other antineoplastic drugs have not been established.

(2) 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 ~~4~~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 dysfunction	AST (GOT) or ALT (GPT) increased to 3 to 5 times the upper limit of normal (ULN), or total bilirubin increased to 1.5 to 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 ~~≥~~more than 5 times the ULN, or total bilirubin increased to ~~≥~~more than 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 dysfunction	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 ≤10 mg/day prednisolone equivalent within 12 weeks of start of treatment. • Adverse reactions that have not resolved to Grade ≤1 after >12 weeks of interruption ~~within 12 weeks of the last dose of pembrolizumab~~.	Discontinue pembrolizumab.

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