Report on the Deliberation Results

September 14, 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	December 22, 2015

Results of Deliberation

In the meeting held on September 9, 2016, the Second Committee on New Drugs concluded that 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 10 years. The drug product and its drug substance are both classified as powerful drugs, and the product is classified as a biological product.

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

August 30, 2016

Pharmaceuticals and Medical Devices Agency

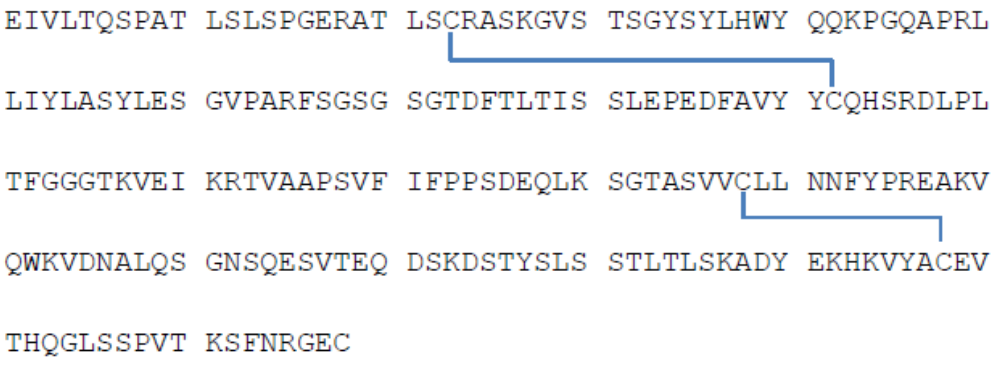
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Keytruda Injection 20 mg, Keytruda Injection 100 mg
Non-proprietary Name	Pembrolizumab (Genetical Recombination)
Applicant	MSD K.K.
Date of Application	December 22, 2015
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 (1) Drug with a new active ingredient
Definition	Pembrolizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human PD-1 monoclonal antibody and framework regions and constant regions derived from human IgG4, whose amino acid residue at position 228 in the H-chain is substituted by Pro. Pembrolizumab is produced in Chinese hamster ovary cells. Pembrolizumab is a glycoprotein (molecular weight: ca. 149,000) composed of 2 H-chains (γ4-chains) consisting of 447 amino acid residues each and 2 L-chains (κ-chains) consisting of 218 amino acid residues each.

Structure

Amino acid sequence:

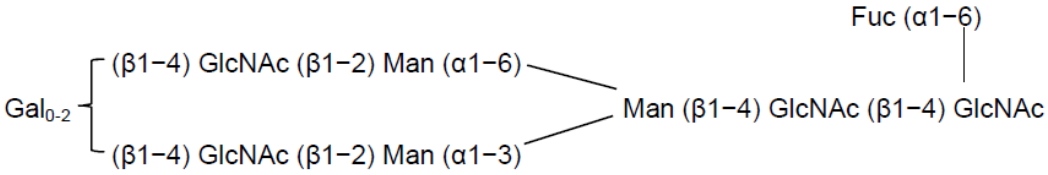
Light chain



Heavy chain

Intramolecular disulfide bonds:	Solid lines
Intermolecular disulfide bonds:	Light chain C218-Heavy chain C134, Heavy chain C226-Heavy chain C226, Heavy chain C229-Heavy chain C229
Partial pyroglutamic acid:	Heavy chain Q1
Glycosylation:	Heavy chain N297
Partial processing:	Heavy chain K447

Presumed main carbohydrate structure



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6504}H_{10004}N_{1716}O_{2036}S_{46}$ (protein segment)
Molecular weight: ca. 149,000

Items Warranting Special Mention

Orphan drug (Drug Designation No. 350 of 2014 [*26 yaku*]; PFSB/ELD Notification No. 0917-6 dated September 17, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)

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 malignant melanoma, 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 disorder (oculomucocutaneous syndrome, erythema multiforme, pemphigoid, etc.); infusion reaction; encephalitis, meningitis; myasthenia gravis; and neurological disorders (Guillain-Barre syndrome, etc.).

Indication

Unresectable malignant melanoma

Dosage and Administration

The usual adult dosage is 2 mg/kg (body weight) 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.

Attachment

Review Report (1)

July 22, 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	December 22, 2015
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	Unresectable or metastatic malignant melanoma
Proposed Dosage and Administration	The usual adult dosage is 2 mg/kg (body weight) of Pembrolizumab (Genetical Recombination) infused intravenously over 30 minutes every 3 weeks.

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List of Abbreviations

ADCC	antibody dependent cell mediated cytotoxicity
[redacted]	[redacted]
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Application	Application for marketing approval
AST	aspartate aminotransferase
$AUC_{ss,6wk}$	area under the concentration-time curve at steady state over a 6-week interval
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CBDCA	carboplatin
CBDCA + PTX + DEX	combination therapy with CBDCA, PTX, and DEX
CDC	complement dependent cytotoxicity
CDDP	cisplatin
CDDP + PEM + DEX	combination therapy with CDDP, PEM, and DEX
CELISA	cellular enzyme-linked immunosorbent assay
CE-SDS	capillary gel electrophoresis with sodium dodecyl sulfate
CEX	cation exchange chromatography
CHO cells	Chinese hamster ovary cells
CI	confidence interval
CQA	critical quality attributes
CRC	colorectal cancer
Dabrafenib	dabrafenib mesilate
DEX	dexamethasone
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DTIC	dacarbazine
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ESMO	European Society for Medical Oncology
FAS	full analysis set
Fc region	fragment, crystallizable
GEM	gemcitabine
GGT	gamma-glutamyltransferase
HIC	hydrophobic-interaction chromatography

HRP	horseradish peroxidase
ICC	investigator-choice chemotherapies
IFN-γ	interferon-γ
Ig	immunoglobulin
ILD	interstitial lung disease
IL-2	interleukin-2
IPI	ipilimumab (genetical recombination)
IRR	infusion related reaction
ITT	intention-to-treat
Japanese clinical practice guideline	Evidence-based clinical practice guideline for malignant skin tumor, 2015 version, edited by the Japanese Dermatological Association and Japanese Skin Cancer Society
K_D	dissociation constant
LC/ESI-QTOF-MS (/MS)	electrospray ionization quadrupole-time-of-flight mass spectrometry
LDH	lactate dehydrogenase
Levothyroxine	levothyroxine sodium
Lys-C	endopeptidase Lys-C
MCB	master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NA	not available
NCCN Guidelines (malignant melanoma)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Malignant Melanoma
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-PDQ	National Cancer Institute Physician Data Query
NE	not estimated
Nivolumab	nivolumab (genetical recombination)
OS	overall survival
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffered saline
PD	pharmacodynamics
PD-L1	programmed cell death-ligand-1
PD-L2	programmed cell death-ligand-2
PD-1	programmed cell death-1
PD-1/CHO cell line	Chinese hamster ovary cell line forcibly expressing PD-1
Pembrolizumab	pembrolizumab (genetical recombination)
PMDA	Pharmaceuticals and Medical Devices Agency
Recombinant PD-1-Fc fusion protein	Recombinant protein in which human PD-1 extracellular domain is fused to Fc fragment of human IgG1
PD-1/PD-1 ligand pathway	Pathway mediated by PD-1 and its ligands (PD-L1 and PD-L2)
PEM	pemetrexed disodium
PEM + DEX	Combination therapy with PEM and DEX
PFS	progression-free survival
PK	pharmacokinetics
PPK	population pharmacokinetics
PS	performance status
PT	preferred term
PTX	paclitaxel
QbD	quality by design
QTcF	QT interval corrected by Fridericia formula
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SEB	*Staphylococcal* Enterotoxin B
SEC	size exclusion chromatography

SJS	Stevens-Johnson syndrome
SMQ	standardised MedDRA queries
SOC	system organ class
Study 001	KEYNOTE-001 study
Study 002	KEYNOTE-002 study
Study 006	KEYNOTE-006 study
Study 011	KEYNOTE-011 study
Study 041	KEYNOTE-041 study
TMZ	temozolomide
Trametinib	trametinib dimethyl sulfoxide
Tregs	regulatory T cells
TT	tetanus toxoid
Vc	central volume of distribution
WCB	working cell bank
5-FU	fluorouracil

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-1 ligands expressed on antigen-presenting cells (CD274 [programmed cell death-ligand-1 (PD-L1)] and CD273 [programmed cell death-ligand-2 (PD-L2)]) 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-1 ligand 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-1 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.

1.2 Development history etc.

Outside Japan:

A phase I study was initiated in patients with advanced solid tumor, malignant melanoma, or non-small cell lung cancer (Study 001) in [redacted]. A phase II study was initiated in patients with unresectable malignant melanoma who had received prior therapy with ipilimumab (IPI) (Study 002) in [redacted]. A phase III study was initiated in patients with unresectable malignant melanoma who had received no prior chemotherapy or only 1 prior chemotherapy regimen without IPI (Study 006) in [redacted].

The application for pembrolizumab was filed in February 2014 in the US and in June 2014 in the EU with the main data from Study 001. Pembrolizumab was approved in September 2014 in the US under accelerated approval and in July 2015 in the EU for the following indications: "KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication is approved under accelerated approval based on tumor response rate and durability of response." in the US; and "KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults." in the EU.

As of May 2016, pembrolizumab has been approved for the treatment of malignant melanoma in 55 countries or regions.

In Japan:
A phase I study was initiated in patients with advanced solid tumor (Study 011) in [redacted]. A phase Ib study was initiated in patients with unresectable malignant melanoma (Study 041) in [redacted].

This application for pembrolizumab was filed with the main data from Studies 002, 006, and 041.

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

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

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Hybridoma cells were prepared by fusing mouse myeloma cells to mouse splenocytes that had been inoculated with a Chinese hamster ovary (CHO) cell line transfected with the human PD-1 gene. Among antibodies produced by these hybridoma cells, anti-PD-1 antibody that inhibited interaction between PD-1 and its ligands was selected. Based on this antibody, humanized antibody constructs containing constant region of IgG4 were generated by complementarity-determining region grafting technology. Then, gene fragments coding heavy and light chains were prepared from the constructs, and were inserted into a plasmid to obtain a gene expression construct of pembrolizumab. The gene expression construct was transfected into a CHO cell line. Among clones obtained from the CHO cell line, the optimal clone for producing pembrolizumab was used to generate master cell bank (MCB) and working cell bank (WCB).

Characterization and purity tests were performed on MCB, WCB, and cells at the limit of *in vitro* cell age, in accordance with ICH Q5A (R1), Q5B, and Q5D guidelines. The results demonstrated genetic stability during the manufacturing period, and neither viral nor non-viral adventitious agents were detected in any of the tests performed.

MCB and WCB are stored in the gas phase of liquid nitrogen. The MCB [redacted], and a new WCB is generated as needed.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of expansion culture; production culture; harvest, [redacted]; [redacted]; [redacted]; [redacted]; [redacted]; virus filtration; [redacted]; [redacted]; and final filtration, testing, and storage. The drug substance is stored at −40°C in a multi-layer plastic bag. The plastic bag consists of an inner layer (a mono-material film made of ethylene vinyl acetate copolymer) contacting the drug solution and an outer layer (a 3-layer film consisting of 2 ethylene vinyl acetate copolymer layers with an ethylene vinyl alcohol layer in between).

Critical steps include [redacted], [redacted], virus inactivation, [redacted], [redacted], virus filtration, [redacted], [redacted], and [redacted].

Process validation was performed for the manufacturing process of the drug substance on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

The manufacturing process of the drug substance uses the CHO cell line, host cells, a biological raw material. MCB generation uses fetal bovine serum from the US, a biological raw material.

The fetal bovine serum in the US used for MCB generation meets the conditions stipulated in "Handling of Drugs etc. Produced from Master Cell Banks or Master Seeds That Do Not Meet the Standards for Biological Ingredients" (Administrative Notice dated March 27, 2009, by the Ministry of Health, Labour and Welfare) and therefore is acceptable for use.

Purity tests have been performed on MCB, WCB, and cells at the limit of *in vitro* cell age. The unprocessed bulk before harvesting on a commercial scale was subjected to sterility testing, mycoplasma testing, and adventitious virus test. Neither viral nor non-viral adventitious agents were detected in any of the tests performed. These tests are in-process control tests on unprocessed bulk.

In the purification process, a viral clearance study was performed using model viruses. The results showed certain levels of virus-clearance capability in the purification process [Table 1].

Table 1. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Mouse minute virus	Reovirus type 3	Pseudorabies virus
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Virus filtration				
Overall virus reduction factor	>22.2	10.0	>13.9	>25.0
[redacted]				

2.1.4 Manufacturing process development

Main changes in the manufacturing process during the development of the drug substance are shown below (each manufacturing process is referred to as Processes I ([redacted]), II ([redacted]), and II ([redacted]) [the proposed manufacturing process]). Japanese and foreign clinical studies mainly used the formulation containing the drug substance manufactured by Process I ([redacted]) or Process II ([redacted]).

- From Process I ([redacted]) to Process II ([redacted]): Changes in [redacted], culture scale, etc.

- From Process II ([redacted]) to Process II ([redacted]): Changes in [redacted] and culture scale.

The comparability assessment of quality attributes showed that the post-change drug substance was comparable to the pre-change drug substance.

Quality by design (QbD) approach was used to develop the manufacturing process [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and properties

The drug substance was characterized mainly by the following parameters [Table 2].

Table 2. Characterization parameters and analytical procedures

Parameters		Analytical procedure
Primary structure	Amino acid sequence	Reduced, alkylated, and Lys-C-digested peptide mapping (LC/ESI-QTOF-MS and LC/ESI-QTOF-MS/MS)
Higher order structure	Secondary structure, higher order structure	Far-ultraviolet circular dichroism spectroscopy, Fourier transform infrared spectroscopy, near-ultraviolet circular dichroism spectroscopy, endogenous tryptophan fluorescence spectrometry
	Disulfide bonds	Non-reduced, alkylated, trypsin-digested peptide mapping (LC/ESI-QTOF-MS and LC/ESI-QTOF-MS/MS)
	Free thiol groups	Ellman analysis
	Particle size	Dynamic light scattering
	Thermostability	Differential scanning calorimetry
Physicochemical properties	Molecular weight	LC/ESI-QTOF-MS
	Absorption coefficient	Ultraviolet-visible spectrophotometry
	Molecular variant	CE-SDS (non-reduced and reduced), SEC multi-angle light scattering, sedimentation velocity analytical ultracentrifugation, HIC, capillary isoelectric focusing, CEX
Carbohydrate structure	N-linked carbohydrate chain	Normal phase ultra-high performance liquid chromatography for 2-aminobenzamide-labeled oligosaccharide
Biological activity	Inhibitory activity against PD-1/PD-L1 binding	Competitive binding ELISA Competitive binding assay using PD-1-expressing cells Inhibitory effect against suppression of T-cell activation
	Binding to PD-1	Surface plasmon resonance
	Binding to human Fcγ receptor	Surface plasmon resonance
	Binding to C1q and neonatal Fc receptor	Surface plasmon resonance

For biological activity, competitive binding enzyme-linked immunosorbent assay (ELISA) has confirmed that pembrolizumab inhibits binding of PD-1 [redacted] recombinant protein to PD-L1 [see Section 3.1.2]. In addition, competitive binding assay using cells has confirmed that pembrolizumab inhibits binding of PD-L1 to PD-1 expressed on [redacted] cell line [see Section 3.1.2].

When pembrolizumab was added to co-culture of [redacted] cells expressing PD-1 and [redacted] cells expressing PD-L1, pembrolizumab inhibited PD-1/PD-L1 binding-induced suppression of T-cell activation, resulting in increased production of interleukin-2 (IL-2).

Surface plasmon resonance analysis showed that the dissociation constant (K_D) of pembrolizumab to PD-1 ranged from [redacted] to [redacted] pmol/L. In addition, the binding of pembrolizumab to human Fcγ receptors (i.e., FcγRI, FcγRIIa, FcγRIIIa, and FcγRIIIb) and C1q was lower than that of the IgG1 control. This suggests that pembrolizumab, an IgG4 antibody, does not have Fc functions causing antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) [see Section 3.1.3].

2.1.5.2 Product-related substances/Product-related impurities

Based on analysis results presented in Section "2.1.5.1 Structure and properties," product-related substances and product-related impurities are controlled by individual peaks detected by each assay.

Product-related substances were defined as substances of an acidic peak and a basic peak before and after the main peak detected by cation exchange chromatography (CEX) as well as those of peaks (e.g., deamidated form, glycated form, [redacted]) after the main peak detected by hydrophobic-interaction chromatography (HIC). In addition, product-related impurities were defined as (a) high molecular weight species (mainly dimers) and low molecular weight species (truncated forms) detected by size exclusion chromatography (SEC), (b) substances of minor peaks detected in capillary gel electrophoresis with sodium dodecyl sulfate (CE-SDS) (non-reducing and reducing conditions) (e.g., truncated forms such as H-chain and L-chain fragments and their various combinations), and (c) substances of peaks detected before the main peak in HIC (mainly [redacted]). Product-related impurities defined by their peak profile are controlled by the specifications for the drug substance and drug product.

2.1.5.3 Process-related impurities

Process-related impurities were defined as host cell deoxyribonucleic acid (DNA), host cell proteins, and [redacted]. All the process-related impurities were confirmed to be adequately removed during the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include the strength, description, identification (biological activity, CEX, peptide mapping), pH, osmotic pressure, purity (CEX, SEC, CE-SDS [non-reducing and reducing conditions], HIC), bacterial endotoxins, bioburden, relative potency (competitive binding ELISA), and assay (ultraviolet spectrophotometry).

2.1.7 Stability of drug substance

Main stability studies for the drug substance are shown in Table 3.

Table 3. Summary of main stability studies for the drug substance

	Manufacturing process	No. of batches	Storage conditions	Period	Storage form
Long-term	Process II ([redacted])	3	−40 ± 5°C	24 months*	Multi-layer plastic bag
	Process II ([redacted])	3	−40 ± 10°C	18 months*	
Accelerated		3	−20 ± 5°C	6 months	
Stress		3	5 ± 3°C	6 months	

* These stability studies are ongoing (continued for [redacted] months).

Long-term and accelerated studies showed no clear changes in quality attributes of the drug substance throughout the study period.

Stress study showed an increased peak area ([redacted]) before the main peak detected by HIC.

Based on the above results, a shelf life of 24 months has been proposed for the drug substance when stored at −40°C in a multi-layer plastic bag.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is supplied in a 0.8 mL vial containing 20 mg pembrolizumab, or in a 4 mL vial containing 100 mg pembrolizumab. The drug product contains excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, and water for injection.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of [redacted]; [redacted]; bioburden reducing filtration and sterile filtration; sterile filling; packaging, labeling, and testing; and storage. Critical steps include [redacted]; [redacted] and sterile filtration; and [redacted]. Process validation was also performed for the manufacturing process of the drug product on a commercial scale.

2.2.3 Manufacturing process development

During the development of the drug product, changes were made to the dosage form (from lyophilized form to liquid form), strength, container and closure system, [redacted], and [redacted]. The comparability assessment of quality attributes showed that the post-change drug product was comparable to the pre-change drug product.

2.2.4 Control of drug product

The proposed specifications for the drug product include the strength, description, identification (biological activity, CEX), pH, purity (CEX, SEC, CE-SDS [non-reducing and reducing conditions], HIC), bacterial endotoxins, sterility, foreign insoluble matters, insoluble particulate matters, extractable volume, potency (competitive binding ELISA), polysorbate 80, and assay (ultraviolet spectrophotometry).

2.2.5 Stability of drug product

Main stability studies for the drug product are shown in Table 4.

Table 4. Summary of main stability studies for the drug product

	Drug product specifications*	No. of batches	Storage conditions	Study period	Storage form
Long-term	20 mg	3	5 ± 3°C	15 months**	Chloro butyl rubber stopper and glass vial
	100 mg	4		24 months**	
Accelerated	20 mg	3	25 ± 5°C, 60 ± 5%RH	6 months	
	100 mg	4			
Stress	20 mg	3	40 ± 2°C, 75 ± 5%RH	3 months	
	100 mg	4			
Photostability	20 mg	1	Overall illumination of ≥1.2 million lux·h, an integrated near ultraviolet energy of ≥200 W·h/m^2		
	100 mg	1			

* The 20-mg formulation contains the drug substance manufactured by Process II ([redacted]), and the 100-mg formulation contains the drug substance manufactured by Process II ([redacted]);
** These stability studies are ongoing.

Long-term studies showed no clear changes in quality attributes of either the 20-mg or 100-mg formulation throughout the study period.

In accelerated studies, both the 20-mg and 100-mg formulations showed (a) changes in [redacted] and (b) a decreasing trend of the main peak area (intact IgG) and increased peak area of the oxidized form in CE-SDS (non-reducing condition).

In stress studies, both the 20-mg and 100-mg formulations showed increasing trends of amounts of high and low molecular weight species and decreased areas of the main peaks (H-chain and L-chain) in CE-SDS (reducing condition), in addition to the changes observed in the accelerated studies. The 100-mg formulation also showed an increased amount of the oxidized form.

Photostability studies showed that the drug product was photolabile.

Based on the above stability data, shelf lives of 15 months (20-mg formulation) and 24 months (100-mg formulation) have been proposed, when the drug product is stored at 2°C to 8°C without freezing in a glass vial with a chloro butyl rubber stopper, protected from light.

2.3 QbD

The QbD approach was applied to develop the drug substance and drug product. The quality control strategy has been established based on the following investigations:

- Identification of critical quality attributes (CQAs): Of the quality attributes of pembrolizumab including product-related substances, product-related impurities, and process-related impurities [see Section 2.1.5], the following CQAs were identified based on the information obtained through the development, general knowledge, etc.

- CQAs for the drug substance: Appearance, clarity, color tone, potency (biological activity), strength (protein concentration), A variant, B variant, oxidized form, osmotic pressure, pH, bacterial endotoxins, bioburden, etc.
- CQAs for [redacted]: Adventitious viruses and microorganisms
- CQAs for the drug product: Appearance, clarity, color tone, potency (biological activity), polysorbate 80, strength (protein concentration), A variant, B variant, oxidized form, extractable volume, osmotic pressure, insoluble particulate matters, pH, sterility, and bacterial endotoxins

- Process characterization: Process parameters were classified according to impact on the quality, and the acceptable control range for each parameter was investigated.

- Development of control method: Based on the process knowledge including the above process characterization, control methods for the quality attributes of pembrolizumab were developed, by combining process parameter control, in-process control, and the specifications [for control of product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is appropriately controlled.

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

3.1 Primary pharmacodynamics

3.1.1 Binding to PD-1 (CTD 4.2.1.1-1, 4.2.1.1-3, and 4.2.1.1-5)

Binding of pembrolizumab to human and cynomolgus monkey PD-1 was investigated by ELISA using recombinant PD-1-Fc fusion protein. The EC_{50} of pembrolizumab (mean ± standard error [SE], n = 3) was 76 ± 6 pmol/L (human) and 93 ± 5 pmol/L (cynomolgus monkey).

Binding of pembrolizumab to human and cynomolgus monkey PD-1 was investigated by cellular enzyme-linked immunosorbent assay (CELISA) using Chinese hamster ovary cell line forcibly expressing PD-1 (PD-1/CHO cell line). The EC_{50} of pembrolizumab (mean ± SE, n = 3) was 618 ± 160 pmol/L (human) and 740 ± 260 pmol/L (cynomolgus monkey).

Binding of pembrolizumab to human and cynomolgus monkey PD-1 was investigated by bio-layer interferometry using recombinant PD-1-Fc fusion protein. The K_D (n = 1) of pembrolizumab to human and cynomolgus monkey PD-1 was 29 and 118 pmol/L, respectively. Binding of pembrolizumab to human PD-1 was investigated by surface plasmon resonance and binding equilibration exclusion assay using recombinant PD-1-Fc fusion protein. The K_D of pembrolizumab to human PD-1 was 26 to 94 pmol/L (surface plasmon resonance) and 0.4 to 1.9 pmol/L (binding equilibration exclusion assay).

Binding of pembrolizumab to PD-1 of various animal origins was investigated by flow cytometry. The results are shown below:

- Pembrolizumab bound to human and cynomolgus monkey PD-1/CHO cell lines, but did not bind to mouse PD-1/CHO cell line.

- Pembrolizumab bound to human and rhesus monkey peripheral blood lymphocytes, but did not bind to dog and rat peripheral blood lymphocytes.

Homology rates of PD-1 extracellular domain amino acid sequence between human and animals were 96% (rhesus monkey), 96% (cynomolgus monkey), 72% (dog), 66% (rat), and 62% (mouse).

3.1.2 Inhibitory effect against binding of PD-1 to PD-L1 or PD-L2 (CTD 4.2.1.1-1)

The inhibitory effect of pembrolizumab against binding of human and cynomolgus monkey PD-1 to PD-L1 or PD-L2 was investigated by competitive inhibition assay using PD-1/CHO cell lines and fluoresceinated recombinant PD-L1 and PD-L2. The IC_{50} of pembrolizumab is shown in Table 5.

Table 5. Inhibitory effect of pembrolizumab against binding of PD-1 to PD-1 ligands

	IC_{50} (pmol/L)	
	PD-L1	PD-L2
Human PD-1	625 ± 130	695 ± 360
Cynomolgus monkey PD-1	721 ± 150	762 ± 200

n = 3, mean ± SE

3.1.3 Effect on immune system (CTD 4.2.1.1-2, 4.2.1.1-4, 4.2.1.1-5, and 4.2.1.1-10)

The effect of pembrolizumab (0.00025-25 μg/mL) on T-cell activation was investigated using peripheral blood samples from healthy adults, patients with cancer (malignant melanoma and prostate cancer), and cynomolgus monkeys. In this assay, IL-2 production in these samples in response to stimulation with *Staphylococcal* Enterotoxin B (SEB) was measured by ELISA as an indicator of T-cell activation. Pembrolizumab (25 μg/mL) increased IL-2 production 3- to 4-fold in samples from healthy adults and patients with cancer and 2- to 3-fold in those from cynomolgus monkeys, compared with IL-2 production in the absence of pembrolizumab.

The effect of pembrolizumab (0.0025-25 μg/mL) on antigen-specific T-cell activation was investigated using human PBMCs taken following re-immunization with tetanus toxoid (TT). In this assay, interferon-γ (IFN-γ) production in the PBMCs in response to stimulation with TT (1 μg/mL) was measured by ELISA as an indicator of antigen-specific T-cell activation. IFN-γ production increased in a pembrolizumab-concentration dependent manner.

The effect of pembrolizumab (25 μg/mL) alone on the immune system activation was investigated using peripheral blood samples from healthy adults. In this assay, IL-2 production was measured by ELISA as an indicator of immune system activation. IL-2 production was observed with pembrolizumab in the

presence of SEB, but was not observed with pembrolizumab alone. The effects of pembrolizumab and anti-CD28 antibody (which is a CD28 agonist [positive control]) on immune system activation were investigated using human PBMCs. In this assay, pembrolizumab and anti-CD28 antibodies were immobilized on a culture plate, and IL-2 production in the PBMCs was measured by ELISA as an indicator of the activation. IL-2 production was observed with anti-CD28 antibody, but was not observed with pembrolizumab. Based on the above results, the applicant explained that pembrolizumab alone was unlikely to cause cytokine release.

Binding of pembrolizumab to human C1q, its corresponding complement component, was investigated by ELISA. EC_{50} of pembrolizumab and controls (i.e., human IgG1 and IgG4 antibodies) are shown in Table 6. The applicant explained that pembrolizumab is unlikely to induce CDC because its EC_{50} was comparable to that of human IgG4 antibody.

Table 6. Binding of pembrolizumab to C1q

	EC_{50} (nmol/L)
Pembrolizumab	12 ± 1
IgG1	0.5 ± 0
IgG4	14, 9

Mean ± standard deviation (SD);
n = 8 for pembrolizumab and IgG1;
n = 2 for IgG4 (individual values shown)

Binding of pembrolizumab to recombinant human CD64 (FcγRI) or CD16a (FcγRIII) protein was investigated by ELISA or surface plasmon resonance. EC_{50} of pembrolizumab and controls (i.e., IgG1 and IgG4 antibodies) are shown in Table 7.

Table 7. Binding of pembrolizumab to CD64 and CD16a

	EC_{50} (pmol/L)	K_D (μmol/L)
	CD64	CD16a
Pembrolizumab	237 ± 57	35 ± 1
IgG1	24 ± 4	4 ± 0
IgG4	345 ± 142	-

Mean ± SD; n = 3 to 10; -, Not measured

3.1.4 Expression of PD-L1 in mouse tumor tissue

B16-F10 mouse malignant melanoma cell line, MC38 mouse colorectal cancer (CRC) cell line, and Renca mouse renal cancer cell line were subcutaneously transplanted into mice, to investigate PD-L1 expression in the tumor tissues by immunohistochemical staining. The PD-L1 expression level was low in the B16-F10 cell line, but moderate to high in MC38 and Renca cell lines.

3.1.5 Inhibitory effect against malignant tumor growth (CTD 4.2.1.1-7, 4.2.1.1-8, and 4.2.1.1-11)

Because pembrolizumab does not bind to mouse PD-1 [see Section 3.1.1], alternative antibodies (i.e., hamster anti-mouse PD-1 antibody [J43]; and murinized rat anti-mouse PD-1 antibody [muDX400]) were used to investigate the inhibitory effect against tumor growth in mice. J43 and muDX400 inhibited binding of mouse PD-1 to mouse PD-L1 and PD-L2 (*J Exp Med.* 2003;198:63-9). K_D for binding to

mouse PD-1 was 643 pmol/L (bio-layer interferometry, n = 1) for J43, and 311 and 637 pmol/L (surface plasmon resonance, n = 2, individual values) for muDX400.

3.1.5.1 Malignant melanoma cell line

The tumor growth inhibitory effect of muDX400 was investigated in mice subcutaneously transplanted with B16-F10 cell line. After the mean tumor volume reached approximately 100 mm^3, the mice began to receive muDX400 (5 or 10 mg/kg) intraperitoneally every 4 days (4 doses in total). Then, the tumor volume was calculated. Mice receiving muDX400 showed no statistically significant inhibition of tumor growth, compared with control mice receiving mouse IgG1 10 mg ($P \geq 0.05$, one-way analysis of variance and Bonferroni's multiple comparison test).

3.1.5.2 Cell lines derived from malignant tumors other than malignant melanoma (CTD 4.2.1.1-6, 4.2.1.1-7, 4.2.1.1-8, 4.2.1.1-9, and 4.2.1.1-11)

The tumor growth inhibitory effect of J43 was investigated in mice subcutaneously transplanted with MC38 cell line (Day 0 = the day of transplantation). On Day 6, when the tumor volume reached 50 to 70 mm^3, the mice began to receive J43 (2 or 10 mg/kg), administered intraperitoneally on Days 6, 10, 13, 16, and 20. Then the tumor volume was calculated. Mice receiving J43 (10 mg/kg) showed statistically significant inhibition of tumor growth, compared with control mice receiving hamster IgG 10 mg/kg ($P \leq 0.05$, one-way analysis of variance and Bonferroni's multiple comparison test).

The tumor growth inhibitory effect of J43 in combination with fluorouracil (5-FU) or gemcitabine (GEM) was investigated in mice subcutaneously transplanted with MC38 cell line. Mice receiving combination therapy showed statistically significant inhibition of tumor growth, compared with control mice receiving hamster IgG 10 mg/kg or mice receiving monotherapy with each drug ($P \leq 0.05$, one-way analysis of variance and Bonferroni's multiple comparison test).

The tumor growth inhibitory effect of muDX400 in combination with the following 4 regimens was investigated in mice subcutaneously transplanted with Renca cell line: (a) carboplatin (CBDCA) + paclitaxel (PTX) + dexamethasone (DEX), (b) pemetrexed disodium (PEM) + DEX, (c) cisplatin (CDDP) + PEM + DEX, and (d) CBDCA + PTX + DEX followed by PEM + DEX. Mice receiving muDX400 in combination with (a), (b), (c), or (d) showed statistically significant inhibition of tumor growth, compared with mice receiving the corresponding regimen without muDX400 ($P \leq 0.05$, one-way analysis of variance).

3.2 Safety pharmacology (CTD 4.2.3.2-1 and 4.2.3.2-2)

Effects of pembrolizumab (6, 40, and 200 mg/kg) on electrocardiogram, body temperature, blood pressure, clinical signs, etc. of cynomolgus monkeys were investigated in 1-month (n = 12/group) and 6-month (n = 10/group) repeated intravenous toxicity studies. No effects of pembrolizumab were observed.

3.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that pembrolizumab may have efficacy against human malignant melanoma.

3.R.1 Mechanism of action and efficacy of pembrolizumab

The applicant's explanation about the mechanism of action and efficacy of pembrolizumab:

Pembrolizumab, a humanized IgG4 monoclonal antibody against human PD-1, binds to the extracellular domain of PD-1 (PD-1 ligand binding site) and blocks the binding of PD-1 to its ligands, PD-L1 and PD-L2 [see Sections 3.1.1 and 3.1.2]. Pembrolizumab thereby enhances the activation of cancer antigen-specific T cells and cytotoxic activation against cancer cells, resulting in decreased tumor growth [see Sections 3.1.3 and 3.1.5].

Mice transplanted with B16-F10 cell line showed no tumor growth inhibition by muDX400, but mice transplanted with MC38 or Renca cell line showed tumor growth inhibition by J43 or muDX400 [see Section 3.1.5]. According to immunohistochemical staining, PD-L1 is moderately or highly expressed in MC38 and Renca cell lines, but poorly expressed in B16-F10 cell line [see Section 3.1.4]. The expression level of PD-L1 in tumors probably affected the tumor growth inhibitory effect of anti-PD-1 antibody.

Pembrolizumab is expected to be effective against human malignant melanoma because of the mechanism of action of pembrolizumab and for the following reasons:(a) PD-L1 expression was observed in patients with malignant melanoma (*Cancer*. 2010;116:1757-66, *Ann Oncol*. 2014;25:2433-42, *Clin Cancer Res.* 2014;20;5064-74); and (b) a report suggested a relationship between PD-L1 expression in malignant melanoma and response to anti-PD-1 antibody therapy (*N Engl J Med.* 2012;366;2443-54).

PMDA's view:

The applicant's explanation that pembrolizumab is expected to be effective against human malignant melanoma is understandable because of the action mechanism of pembrolizumab. However, further work is needed to fully elucidate the relationship between the efficacy of pembrolizumab and expression status of PD-1, PD-L1, PD-L2, and immunoregulatory receptors. Because information about the relationship is important for identifying patients eligible for pembrolizumab therapy in clinical settings, the applicant should continue to investigate this issue and appropriately provide healthcare professionals with new information and findings.

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

The pharmacokinetics (PK) of pembrolizumab in animals was investigated using cynomolgus monkeys.

4.1 Analytical procedures

4.1.1 Pembrolizumab assay

Pembrolizumab in monkey serum was quantified by either of the following methods:

(a) ELISA using immobilized recombinant PD-1-Fc fusion protein and horseradish peroxidase (HRP)-labeled goat anti-human κ chain antibody
(b) Electrochemiluminescence (ECL) assay using immobilized recombinant PD-1-Fc fusion protein and ruthenium-labeled goat anti-human κ chain antibody

4.1.2 Anti-pembrolizumab antibody assay

Anti-pembrolizumab antibody in monkey serum was quantified by either of the following methods:
(a) Bridging ELISA using immobilized pembrolizumab, biotinylated pembrolizumab, and HRP-labeled streptavidin
(b) Bridging ECL assay using biotinylated pembrolizumab and ruthenium-labeled pembrolizumab

Anti-pembrolizumab neutralizing antibody in monkey serum was detected by bridging ECL assay using biotinylated PD-1 and ruthenium-labeled goat anti-human κ chain antibody.

4.2 Absorption

4.2.1 Single dose

Serum concentrations of pembrolizumab were measured in female cynomolgus monkeys following a single intravenous dose of 0.3, 3, or 30 mg/kg of pembrolizumab [Table 8]. Anti-pembrolizumab antibody was detected in all monkeys receiving pembrolizumab 0.3 or 3 mg/kg, and in 2 of 3 monkeys receiving 30 mg/kg.

Table 8. PK parameters of pembrolizumab (female cynomolgus monkeys, single intravenous dose)

Dose (mg/kg)	n	C_{max} (μg/mL)	AUC_{last}* (μg·day/mL)	AUC_{inf} (μg·day/mL)	$t_{1/2}$ (days)	CL (mL/day/kg)	V_{ss} (mL/kg)
0.3	3	15.3 ± 4.3	41.0 ± 2.9	51.1 ± 1.5	3.9 ± 0.7	5.7 ± 0.2	30.9 ± 6.0
3	3	117.7 ± 5.2	700.0 ± 76.5	729.3 ± 79.5	5.9 ± 1.6	4.2 ± 0.4	36.8 ± 4.6
30	3	1265 ± 73	6374 ± 767	8124 ± 416	10.6 ± 0.4	3.7 ± 0.1	54.8 ± 5.7

Mean ± SE; * Because anti-pembrolizumab antibody may have affected serum pembrolizumab concentrations, time points with a value <1 μg/mL were excluded.

4.2.2 Repeated administration

Male and female cynomolgus monkeys were given 6, 40, or 200 mg/kg of pembrolizumab intravenously once weekly for 5 weeks, to measure serum concentrations of pembrolizumab [Table 9]. No clear sex differences in PK parameters of pembrolizumab were observed at any dose. $AUC_{0\text{-}7days}$ of pembrolizumab was higher at Week 5 than at Week 1.

Anti-pembrolizumab antibody was detected in 3 of 6 males and 4 of 6 females in the 6 mg/kg group as well as 1 of 6 males in the 40 mg/kg group. Of monkeys in the 6 mg/kg group positive for anti-pembrolizumab antibody, 1 male and 3 females had neutralizing antibody. C_{max} and $AUC_{0\text{-}7days}$ of pembrolizumab in the 6 mg/kg group at Week 5 were 107 ± 37.5 μg/mL (mean ± SE) and 99.7 μg·day/mL (individual value), respectively, in monkeys positive for anti-pembrolizumab antibody, and 524 ± 95.3 μg/mL and 2350 ± 466 μg·day/mL (mean ± SE), respectively, in monkeys negative for the

antibody. These parameter values tended to be lower in the positive monkeys than in the negative monkeys.

Table 9. PK parameters of pembrolizumab
(male and female cynomolgus monkeys, 5-week repeated intravenous doses)

Dosing period (Week)	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}7days}$ (μg·day/mL)	R[*1]
1	6	Female	7	268 ± 39.1	1.0 ± 0.0	780 ± 36.6[*2]	-
		Male	6	319 ± 34.3	4.8 ± 3.8	1070 ± 87.0	-
	40	Female	6	3080 ± 709	29.0 ± 28.0	7430 ± 1530	-
		Male	6	1930 ± 338	1.3 ± 0.3	7060 ± 1180	-
	200	Female	6	19,300 ± 5100	9.5 ± 7.7	64,500 ± 15,700	-
		Male	6	10,200 ± 747	1.0 ± 0.0	34,900 ± 2150	-
5	6	Female	6	213 ± 58.9	2.2 ± 0.8	1420, 99.7[*3]	1.84, 0.144[*3]
		Male	6	487 ± 140	6.3 ± 3.6	2900, 2720[*3]	2.65, 2.48[*3]
	40	Female	6	6280 ± 1800	13.0 ± 7.9	16,400, 51,200[*3]	2.32, 7.43[*3]
		Male	6	3250 ± 361	30.0 ± 28.0	17,700, 11,100[*3]	1.60, 1.13[*3]
	200	Female	6	133,000 ± 57,600	2.3 ± 0.4	198,000, 224,000[*3]	8.74, 6.33[*3]
		Male	6	39,300 ± 7100	6.3 ± 3.6	149,000, 110,000[*3]	3.86, 3.40[*3]

Mean ± SE; -, Not applicable
*[1] Ratio of $AUC_{0\text{-}7days}$ (Week 5/Week 1)
*[2] n = 6
*[3] n = 2 (individual values)

Male and female cynomolgus monkeys received 6, 40, or 200 mg/kg of pembrolizumab intravenously every 2 weeks for 24 weeks, to measure serum concentrations of pembrolizumab. C_{max} and $AUC_{0\text{-}14days}$ of pembrolizumab at Week 11 were higher than those at Week 1, and C_{max} and $AUC_{0\text{-}14days}$ at Weeks 11 and 21 were similar. Based on the above, the applicant explained that the serum concentration of pembrolizumab reached steady state by Week 11.

Within the dose range investigated (0.3-200 mg/kg) in cynomolgus monkeys, C_{max} and AUC of pembrolizumab increased more than dose-proportionally, suggesting that the PK of pembrolizumab was nonlinear. The applicant's explanation about the nonlinearity:

> The PD-1-mediated elimination pathway is probably involved in the elimination of pembrolizumab. In the monkeys, the pathway was saturated with increase in pembrolizumab doses, resulting in decreased clearance (CL) of pembrolizumab in the high dose groups. This is one of the reasons for the nonlinear PK of pembrolizumab.

4.3 Distribution

The applicant explained that tissue distribution of pembrolizumab was not investigated because this humanized IgG4 antibody is considered to be mainly distributed into circulating blood, for the following reasons:

- In the single-dose study in cynomolgus monkeys, V_{ss} of pembrolizumab [see Section 4.2.1] was similar to plasma volume in monkeys (45 mL/kg) (*Pharm Res.* 1993;10:1093-5), indicating that pembrolizumab is mainly distributed into circulating blood with low tissue distribution.

- In a tissue cross-reactivity studies with normal tissues from cynomolgus monkeys and humans, cross-reactivity of pembrolizumab was mainly observed in the cytoplasm [see Sections 5.6.2 and 5.6.3]. However, because pembrolizumab does not reach the cytoplasm *in vivo*, the drug is unlikely to be distributed into tissues.

The applicant's explanation about placental and fetal transfer of pembrolizumab:
Antibodies in maternal circulating blood in humans are transferred into fetus through neonatal Fc receptors on the chorioallantoic placenta (*J Reprod Immunol.* 1997;37:1-23). This suggests that pembrolizumab, a humanized IgG4 antibody, may be transferred into the fetus through the placenta.

4.4 Metabolism and excretion

The applicant explanation:
Pembrolizumab is an antibody drug product and considered to be eliminated through protein degradation pathway. Therefore metabolism and excretion of pembrolizumab were not investigated based on "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012).

The applicant explained that considering that human IgGs have been reported to be excreted into milk (*Nutrients.* 2011;3:442-74), the possibility of excretion of pembrolizumab into human milk cannot be ruled out.

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the applicant's discussions on absorption, distribution, metabolism, and excretion of pembrolizumab are acceptable.

5. Toxicology and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

No single-dose toxicity study of pembrolizumab has been conducted. Single-dose toxicity was evaluated based on the results following the first dose in 1-month and 6-month repeated intravenous toxicity studies in monkeys [see Sections 5.2.1 and 5.2.2]. No deaths potentially related to pembrolizumab occurred at any dose (6-200 mg/kg of pembrolizumab).

Based on the above result, approximate lethal dose in this study was determined to be >200 mg/kg.

5.2 Repeat-dose toxicity

5.2.1 One-month repeated intravenous toxicity study in monkeys

Cynomolgus monkeys (n = 6/sex/group) received pembrolizumab intravenously at 0 (vehicle control, 10 mmol/L histidine, 7% sucrose, and 0.02% polysorbate 80), 6, 40, or 200 mg/kg once weekly for 1 month (5 doses in total). After the final dose, 4 males and 4 females in each group were subjected to

necropsy, and the remaining 2 males and 2 females in each group were observed for a 4-month recovery period.

Males in the 200 mg/kg group showed increased swelling of the groin (unilateral or bilateral) as a change in clinical signs. They also showed increased spleen weight and enlarged periarterial lymphoid tissue in the spleen after the final dose. However, no histopathological changes were observed in the groin, and changes in the spleen generally fell within the historical data. Thus, these changes were considered to have little toxicological significance.

In monkeys undergoing the recovery period, swelling of the groin disappeared during the recovery period, and no other changes related to pembrolizumab occurred.

Based on the above result, the no observed adverse effect level (NOAEL) in this study was determined to be 200 mg/kg.

5.2.2 Six-month repeated intravenous toxicity study in monkeys

Cynomolgus monkeys (n = 5/sex/group) received pembrolizumab intravenously at 0 (vehicle control, 10 mmol/L histidine, 7% sucrose, and 0.02% polysorbate 80), 6, 40, or 200 mg/kg every 2 weeks for approximately 6 months (12 doses in total). Three days after the final dose, 3 males and 3 females in each group were subjected to necropsy, and the remaining 2 males and 2 females in each group were observed for a 4-month recovery period.

In monkeys subjected to necropsy after the final dose, focal infiltration of monocytes into multiple tissues was observed, but this finding was considered to have little toxicological significance, because it did not involve tissue degeneration or disorder, and it fell within a range of historical data (*J Toxicol Pathol.* 2012;25:63-101, *Toxicol Pathol.* 2010;38:642-57).

In the 40 mg/kg group, 1 of the 2 males undergoing the recovery period showed increased spleen weight, decreased thymus weight, focal infiltration of monocytes into multiple tissues falling beyond the range of historical data, increased lymphoid cells comprising periarterial lymphoid tissue in the spleen, and remarkably decreased lymphoid tissue in the thymic cortex accompanied by increased lymphoid cells in the thymic medulla. These findings may have been related to pembrolizumab, but most probably occurred spontaneously, because they occurred only in 1 monkey in the 40 mg/kg group and in none in the 200 mg/kg group.

Based on the above result, the NOAEL in this study was determined to be 200 mg/kg. The exposure ($AUC_{0\text{-}tau}$) at the 200 mg/kg dose was 67,500 μg·day/mL, which was approximately 85-fold the

estimated exposure[1)] in Japanese patients with solid cancer who received pembrolizumab 2 mg/kg every 3 weeks.

5.3 Genotoxicity

Since pembrolizumab is an antibody drug and thus is highly unlikely to act directly on DNA or other chromosomal components, no genotoxicity study was conducted.

5.4 Carcinogenicity

Since pembrolizumab is intended to be used for treating advanced cancer, no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

Since pembrolizumab is intended to be used for treating advanced cancer and is expected to adversely affect embryo-fetal development due to its pharmacological effect, no study for reproductive and developmental toxicity was conducted.

5.5.1 Effect on fertility

The applicant's explanation about effects of pembrolizumab on male and female fertility:
Pembrolizumab is unlikely to raise major concerns about its effects on male and female fertility, for the following reasons:

(a) In the 1- and 6-month repeated intravenous toxicity studies in cynomolgus monkeys [see Sections 5.2.1 and 5.2.2], of monkeys treated with pembrolizumab, 4 sexually matured males and 11 sexually matured females exhibited no histopathological changes in their reproductive organs.

(b) The following findings on the PD-1/PD-1 ligand pathway.

- PD-1 and its ligands are expressed in the testis, and thus may be involved in the immune mechanism in the blood-testis barrier (e.g., *Cell Mol Immnol.* 2014;11:428-37, *Front Immunol.* 2012;3:Article 152;1-12), but there is no finding that the PD-1/PD-1 ligand pathway plays a major role in maintenance of the blood-testis barrier.
- A report suggested that PD-1 is one of the regulatory factors that induce apoptosis in ovarian germ cells (*Rev Reprod.* 1996;1:162-72), and thus menopause may be delayed due to active ovarian hormone secretion function associated with PD-1 inhibition. There is, however, no finding that inhibition of PD-1/PD-1 ligand pathway affects hormone regulation in the hypothalamo-pituitary-gonadal axis. A survey using a database up to April 30, 2016 in the adverse event report review system in the US MSD (including data from Japanese and foreign clinical studies and foreign post-marketing information) did not provide sufficient data regarding the effect of pembrolizumab on the ovary.

[1)] The estimated exposure ($AUC_{SS,\ 3wks}$) was 795 μg·day/mL in Japanese patients with advanced solid cancer who received pembrolizumab at 2 mg/kg every 3 weeks (Studies 011 and 041).

- PD-1 knockout mice have not been reported to have abnormal reproductive organs or fertility (e.g., *Int Immunol.* 2007;19:813-24, *Science.* 2001;291:319-22).

5.5.2 Effect on embryo-fetal development

The applicant's explanation:

The following findings suggest that pembrolizumab affects embryo-fetal development such as increased incidences of abortion and stillbirth.

- The following findings in mice (*J Exp Med.* 2005;202:231-7), etc. suggest that (a) PD-1 ligands protect the fetus from maternal T cell immunity, and that (b) PD-1/PD-1 ligand pathway is essential for fetomaternal immune tolerance:
  - In pregnant mice resulting from mating between different strains (CBA and C57BL/6 mice), treatment with anti-PD-L1 antibodies resulted in a higher abortion rate (86%) than the spontaneous abortion rate (18%). However, in pregnant mice resulting from mating between male and female CBA mice, treatment with anti-PD-L1 antibody did not affect the outcome of pregnancy.
  - Infiltration and accumulation of T cells were observed at the fetal resorption site in anti-PD-L1 antibody-treated pregnant mice resulting from mating between different strains.
- The following findings in mice suggest that PD-1 plays an important role in protecting fetuses.
  - Mice which had frequently experienced abortions became successfully pregnant following transplantation of regulatory T cells (Tregs) (e.g., *Nature Immunol.* 2004;5:266-71). In addition, the abortion rate increased following administration of anti-PD-1 antibody to pregnant mice (*Am J Reprod Immunol.* 2009;62:283-92).
  - A report suggested that in pregnant mice, PD-1 is involved in fetomaternal immune tolerance by inducing apoptosis in paternal antigen-specific T cells (*J Reprod Immunol.* 2009;80:12-21).
- The following points suggest that exposure of fetuses to pembrolizumab may cause changes in the fetal immune system:
  - Given the placental transfer of IgG4 (*Birth Defects Res B Dev Reprod Toxicol.* 2009;86:328-44), if pregnant women receive pembrolizumab, a humanized IgG4 monoclonal antibody, the pembrolizumab concentration in the fetuses during the third trimester of pregnancy is expected to be similar to that in the maternal circulating blood.
  - Onset of autoimmune disease was reported in PD-1 knockout mice (*Science.* 2001;291:319-22, *Immunity.* 1999;11:141-51, *Proc Natl Acad Sci USA.* 2005;102:11823-8).

5.6 Other toxicity studies

5.6.1 Mouse exploratory immunotoxicity study using anti-mouse PD-1 antibody and hepatitis B vaccine (reference data)

A T-cell dependent antibody production study was conducted to investigate whether pembrolizumab changes immune reactions following vaccination through its mechanism of action.

CD-1 mice (n = 20/sex/group) received subcutaneous muDX400, a mouse anti-PD-1 antibody, as a single dose at 5 mg/kg/day on Day 1, or once weekly for 29 days (5 doses in total). Control mice received phosphate buffered saline (PBS) subcutaneously once weekly for 29 days (5 doses in total). Mice in all the groups received hepatitis B vaccine on Days 2 and 23, and anti-hepatitis B vaccine antibody was measured on Days 10, 18, 27, 32, and 50. The results showed no effect of muDX400 on the anti-hepatitis B virus antibody titer. Mice receiving a single dose or repeated doses of muDX400 showed changes probably related to muDX400: increased absolute splenic lymphocyte count and mildly increased splenic B-cell and T-cell subsets. These changes, however, have been considered to have no toxicological significance, because these increases were mild, and percentages of B-cell and T-cell subsets remained unchanged.

5.6.2 Cross-reactivity study in normal human tissues

The cross reactivity of pembrolizumab was investigated by immunohistochemical technique using frozen sections of normal human tissues, and the following findings were obtained:

- Staining suggestive of binding of pembrolizumab was observed in the cell membrane of mononuclear leukocytes. (PD-1 has been reported to be expressed in the cell membrane of mononuclear leukocytes [*Immunol Lett.* 2002;83:215-20]).

- Staining suggestive of binding of pembrolizumab was observed in the interstitium and in cytoplasm of cells in various tissues.

- No staining was observed in the ovary of cynomolgus monkeys [see Section 5.6.3]. In human tissues, however, staining suggestive of binding of pembrolizumab was observed in the cytoplasm of macrophages in the ovary.

5.6.3 Cross-reactivity study in normal cynomolgus monkey tissues

The cross reactivity of pembrolizumab was investigated by immunohistochemical technique using frozen sections of normal cynomolgus monkey tissues, and the following findings were obtained:

- Staining suggestive of binding of pembrolizumab was observed in the cell membrane of mononuclear leukocytes (PD-1 has been reported to be expressed in the cell membrane of mononuclear leukocytes [*Immunol Lett.* 2002;83:215-20]).

- Staining suggestive of binding of pembrolizumab was observed in the interstitium and in cytoplasm of cells in various tissues.

The applicant explained the staining in the cytoplasm and interstitium observed in the cross-reactivity studies with normal human and cynomolgus monkey tissues [see Sections 5.6.2 and 5.6.3]:

The applicant's explanation:
Staining in the cytoplasm of cells in various tissues and of macrophages in human ovary does not suggest *in vivo* binding of pembrolizumab in the above tissues, etc., because pembrolizumab does not reach the cytoplasm *in vivo*, but reaches there by the immunohistochemical technique (*Toxicol Pathol.* 2010;38:1138-66).

In addition, the 1- and 6-month repeated dose toxicity studies in cynomolgus monkeys [see Section 5.2] did not show pembrolizumab-related histopathological changes in the interstitium. Therefore, staining in the interstitium does not suggest toxicity of pembrolizumab in the interstitium.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that non-clinical toxicity evaluation does not raise concerns regarding clinical use of pembrolizumab.

5.R.1 Use in pregnant women

The proposed package insert (draft) has a precautionary statement that pembrolizumab should not be administered to pregnant or possibly pregnant women in principle. PMDA asked the applicant to explain why this statement is included in the package insert.

The applicant's response:
No studies have been conducted to evaluate the reproductive and developmental toxicity of pembrolizumab, but treatment with pembrolizumab during pregnancy may cause adverse effects such as increased abortion and stillbirth, based on findings about physiological function of the PD-1/PD-1 ligand pathway (e.g., *J Exp Med*. 2005;202:231-7, *Nature Immunol.* 2004;5:266-71, *Am J Reprod Immunol*. 2009;62:283-92). Therefore, pembrolizumab should not be used in pregnant or possibly pregnant women in principle. The applicant included the above precautionary statement for the following reasons: (a) Offspring from PD-1 knockout mice grow normally without any effect on the fertility (e.g., *Int Immunol.* 1998;10:1563-72), indicating that pembrolizumab has a low risk of teratogenicity. (b) The clinical use of pembrolizumab would be acceptable in patients expected to receive therapeutic benefits that outweigh the potential risks associated with the treatment, in light of seriousness of the target disease.

Pembrolizumab has been administered to 4 pregnant women, according to survey using database up to March 15, 2016 in the adverse event report review system in the US MSD (including data from Japanese and foreign clinical studies and foreign post-marketing information). Of the 4 women, 2 chose abortion without aborted fetuses examined, and the remaining 2 women have not provided any data such as outcome of the pregnancy.

PMDA's view:
At present, the teratogenicity risk of pembrolizumab is unknown, for the following reasons:

(a) The teratogenicity risk of pembrolizumab cannot be evaluated based solely on the submitted data on PD-1 knockout mice.

(b) No studies for reproductive and developmental toxicity have been conducted.

(c) There is only limited experience with pembrolizumab in pregnant women, and no data are available on the outcome of pregnant women treated with pembrolizumab.

Because pembrolizumab has a potential risk of embryo-fetal toxicity including abortion and stillbirth, pembrolizumab should be contraindicated in pregnant or possibly pregnant women.

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 Pembrolizumab assay

Pembrolizumab in human serum was quantified by ECL assay using immobilized streptavidin, biotinylated recombinant PD-1-Fc fusion protein, and ruthenium-labeled mouse anti-human IgG4 antibody, and the lower limit of quantitation was 10 ng/mL.

6.1.1.2 Anti-pembrolizumab antibody assay

Anti-pembrolizumab antibody in human serum was detected by ECL assay using immobilized streptavidin, biotinylated pembrolizumab, and ruthenium-labeled pembrolizumab. The concerned analytical method was validated by [redacted][2)] and [redacted].[3)] The detection sensitivity was 4.1 and 4.40 ng/mL, respectively, and the upper limit of pembrolizumab concentration (in a sample) that does not affect anti-pembrolizumab antibody assay was 25 and 124 μg/mL, respectively.

Anti-pembrolizumab neutralizing antibody in human serum was detected by ECL assay using immobilized streptavidin, biotinylated recombinant PD-1-Fc fusion protein, and ruthenium-labeled pembrolizumab. The concerned analytical method was validated by [redacted] and [redacted], with the detection sensitivity of 685 and 97.5 ng/mL, respectively.

6.1.2 Changes in the manufacturing processes of the drug substance and drug product during development phase

The manufacturing processes of the drug substance were modified during the development phase [see Section 2.1.4]. Of studies included in this application, the Japanese phase I study (Study 011), foreign phase I study (Study 001), foreign phase II study (Study 002), and foreign phase III study (Study 006) used the Process I ([redacted]) formulation, and Japanese phase Ib study (Study 041) and foreign phase III study (Study 006) used the Process II ([redacted]) formulation. The Process II ([redacted]) formulation is the proposed formulation.

2) Samples from Study 011 as well as Studies 001, 002, and 006 at the early phase were used in the assay.
3) Samples from Study 041 as well as Studies 001, 002, and 006 at the late phase were used in the assay.

The applicant's explanation:

Changes in manufacturing process of the drug substance did not affect the PK of pembrolizumab for the following reasons.

- Following the process change from Process I ([redacted]) to Process II ([redacted]), the comparability assessment of quality attributes showed that the post-change drug substance was comparable to the pre-change drug substance [see Section 2.1.4].
- Study 011 used Process I ([redacted]) formulation and Study 041 Process II ([redacted]) formulation. A comparison of C_{max} and other parameters following administration of pembrolizumab 2 mg/kg between the 2 studies, suggests no clear differences in PK between the 2 formulations [see Sections 6.2.1.1 and 6.2.1.2].

6.2 Clinical pharmacology

The PK of pembrolizumab in patients with cancer was investigated following administration of pembrolizumab alone.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.5.2.2, Study 011 Part A [ongoing since [redacted] (cutoff date, [redacted])])

An open-label, uncontrolled study was conducted to investigate PK, etc. of pembrolizumab in 10 patients with advanced solid cancer (10 patients included in PK analysis). Subjects received intravenous pembrolizumab 2 or 10 mg/kg as a single dose, followed by a 4-week rest period, and then every 2 weeks (Q2W). Serum concentrations of pembrolizumab were measured [Table 10].

The applicant explained that C_{max} and $AUC_{0\text{-}28day}$ of pembrolizumab increased almost linearly within the dose range investigated.

Ten subjects were tested for anti-pembrolizumab antibody at baseline and after the beginning of pembrolizumab therapy, and none were positive for the antibody.

Table 10. PK parameters of pembrolizumab after the first dose

Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max}* (day)	$AUC_{0\text{-}28day}$ (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_Z (mL/kg)
2	3	47.4 (18.6)	0.22 (0.0021, 0.23)	507 (20.0)	18.4 (56.1)	2.46 (44.7)	65.3 (21.3)
10	7	250 (23.2)	0.0090 (0.00069, 0.23)	2219 (32.4)	18.1 (68.4)	2.93 (56.5)	76.5 (34.4)

Geometric mean (coefficient of variation [CV] %); * Median (range)

6.2.1.2 Japanese phase Ib study (CTD 5.3.5.2.3, Study 041 [ongoing since [redacted] (cutoff date, [redacted])])

An open-label, uncontrolled study was conducted to investigate PK, etc. of pembrolizumab in 42 patients with unresectable (Stage III or IV) malignant melanoma who had received no prior

chemotherapy or only ≤2 prior chemotherapy regimens without IPI (42 patients included in PK analysis). Pembrolizumab 2 mg/kg was intravenously administered every 3 weeks (in 3-week cycles) to investigate serum concentrations of pembrolizumab [Table 11].

C_{max} and $AUC_{0\text{-}21day}$ of pembrolizumab in Cycle 8 were higher than those in Cycle 1. The applicant explained that C_{trough} (geometric mean [coefficient of variation (CV) %]) in Cycles 1 and 8 was 11.3 (19.0) and 24.5 (48.8) μg/mL, respectively, while C_{trough} in Cycles 8 to 13 was almost constant, indicating that the serum concentration reached steady state by Cycle 8.

In total, 42 subjects were tested for anti-pembrolizumab antibody at baseline and after the beginning of pembrolizumab therapy, and none were positive for the antibody.

Table 11. PK parameters of pembrolizumab

Cycle	n	C_{max} (μg/mL)	$AUC_{0\text{-}21day}$ (μg·day/mL)	CL (L/day)
1	42	40.9 (28.1)	393 (18.2)[*1]	-
8	28	61.8 (24.5)	797 (32.4)[*2]	0.158 (38.2)[*2]

Geometric mean (CV%); [*1] n = 41; [*2] n = 25; -, Not calculated

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.5.2.1, Study 001 [ongoing since [redacted] (cutoff date, [redacted])])

An open-label, uncontrolled study was conducted to investigate PK, etc. of pembrolizumab in 17 patients with advanced solid cancer (Parts A and A1), 379 patients with unresectable malignant melanoma (Parts B1 and B3), 173 patients with unresectable malignant melanoma who had received prior IPI therapy (Part B2), and 103 patients with unresectable malignant melanoma who had not received prior IPI therapy (Part D) (669 patients included in PK analysis: 17 in Parts A and A1 and 652 in Parts B1, B2, B3, and D). Subjects in Part A or A1 received intravenous pembrolizumab 1, 3, or 10 mg/kg as a single dose, followed by a 4-week rest period, and then every 2 weeks. Subjects in Part B1, B2, or B3 received intravenous pembrolizumab 2 mg/kg Q3W, 10 mg/kg Q2W, or 10 mg/kg Q3W. Subjects in Part D received intravenous pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W.

PK parameters of pembrolizumab in Parts A and A1 are shown in Table 12. C_{max} and $AUC_{0\text{-}28day}$ of pembrolizumab increased more than dose-proportionally within the dose range investigated. According to the applicant, this result may be attributable to a large dispersion of values due to the limited number of subjects in the 1 and 3 mg/kg groups.

Table 12. PK parameters of pembrolizumab after the first dose

Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max}[*1] (day)	$AUC_{0\text{-}28day}$ (μg·day/mL)	$t_{1/2}$ (day)
1	4	16.4 (22.4)	0.05 (0.02, 0.17)	158 (19.7)[*2]	14.1 (51.2)[*2]
3	3	107 (26.1)	0.17 (0.17, 0.17)	955 (23.3)	21.6 (10.4)
10	10	256 (36.8)	0.17 (0.03, 0.99)	2150 (31.4)[*3]	17.7 (56.3)[*3]

Geometric mean (CV%); *[1] Median (range); *[2] n = 3; *[3] n = 9

Serum concentrations of pembrolizumab in Parts B1, B2, and B3 are shown in Table 13. C_{trough} (geometric mean [CV%]) of pembrolizumab in Cycle 1 in Part D was 10.1 (57) and 62.6 (37) μg/mL in the 2 and 10 mg/kg groups, respectively.

In total, 653 subjects were tested for anti-pembrolizumab antibody at baseline and after the beginning of pembrolizumab therapy in Parts B1, B2, B3, and D. Of the 653 subjects, 1 in the 10 mg/kg Q3W group tested positive for anti-pembrolizumab antibody and neutralizing antibody after the beginning of treatment.

Table 13. Serum concentrations of pembrolizumab (μg/mL) in Part B

Part	Group	Cycle	n	C_{trough}	n	C_{max}
B1	2 mg/kg Q3W	1	11	11.8 (31)	22	39.0 (55)
		12	9	31.4 (45)	-	-
	10 mg/kg Q3W	1	24	47.0 (39)	53	217 (59)
		12	21	150 (35)	-	-
	10 mg/kg Q2W	1	-	-	53	213 (31)
		18	24	253 (30)	-	-
B2	2 mg/kg Q3W	1	80	8.27 (48)	86	46.4 (39)
		12	37	26.2 (51)	-	-
	10 mg/kg Q3W	1	74	50.6 (42)	83	239 (38)
		12	42	155 (49)	-	-
B3	10 mg/kg Q3W	1	113	47.5 (35)	114	220 (24)
		12	43	159 (30)	-	-
	10 mg/kg Q2W	1	-	-	116	228 (21)
		18	36	255 (43)	-	-

Geometric mean (CV%); -, Not calculated

6.2.2.2 Foreign phase II study (CTD 5.3.5.1.1, Study 002 [ongoing since [redacted] (cutoff date, May 12, 2014)])

A partially blinded,[4)] randomized, controlled study was conducted to investigate the efficacy and safety of pembrolizumab in 540 patients with unresectable malignant melanoma who had received prior IPI therapy (435 patients included in PK analysis). Pembrolizumab 2 or 10 mg/kg was intravenously administered every 3 weeks (in 3-week cycles) to investigate serum concentrations of pembrolizumab.

C_{max} of pembrolizumab in Cycle 1 and C_{trough} in Cycles 1 and 7 (geometric mean [CV%] for all values) were 40.4 (54), 7.79 (94), and 27.9 (45) μg/mL, respectively, in the 2 mg/kg group, and 223 (40), 46.1 (54), and 131 (60) μg/mL, respectively, in the 10 mg/kg group.

4) Subject assignment to pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W was blinded.

In total, 441 subjects were tested for anti-pembrolizumab antibody at baseline and after the beginning of pembrolizumab therapy. Of the 441 subjects, 1 in the 2 mg/kg group tested positive for anti-pembrolizumab antibody at baseline. No neutralizing antibody was measured.

6.2.3 Relationship between pembrolizumab exposure and QT/QTc interval changes

In the foreign phase I study (Study 001 Parts A, B1, B2, C, and D), the relationship between QT interval corrected by Fridericia formula (QTcF) and serum concentrations of pembrolizumab was investigated using a linear mixed-effects model. A statistically significant relationship was observed between serum concentrations of pembrolizumab and QTcF, and QTcF was estimated to be prolonged by 0.0116 ms for each increment of 1 μg/mL of serum concentration of pembrolizumab. The applicant, however, explained that the concerned relationship is considered to have no clinical significance. C_{max} [5)] (geometric mean) at steady state was calculated to be 70.2 μg/mL (intravenous pembrolizumab 2 mg/kg Q3W) and 433 μg/mL (intravenous pembrolizumab 10 mg/kg Q2W). The estimated mean changes in QTcF interval (upper limit of 90% confidence interval [CI]) at the steady-state C_{max} was 0.83 (0.93) ms (C_{max} 70.2 μg/mL) and 5.1 (5.7) ms (C_{max} 433 μg/mL).

Based on the above, the applicant explained that the proposed dosage of pembrolizumab (2 mg/kg Q3W) is unlikely to prolong QT/QTc interval.

6.2.4 PPK analysis

Based on PK data of pembrolizumab obtained from foreign clinical studies (Studies 001, 002, and 006) (12,171 time points in 2195 subjects), a population pharmacokinetics (PPK) analysis was performed using a nonlinear mixed-effects model (NONMEM Version 7.1.2). The PK of pembrolizumab was described as a 2-compartment model with first-order elimination.

In this analysis, a model was established by integrating the effect of body weight into CL and central volume of distribution (Vc) as a covariate for PK of pembrolizumab. The following potential covariates for CL and Vc were investigated: Age, ethnicity, sex, estimated glomerular filtration rate (eGFR),[6)] total bilirubin, aspartate aminotransferase (AST), hepatic impairment,[7)] albumin, cancer type, tumor size, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and prior IPI therapy. As a result, the following were identified as significant covariates: albumin, total bilirubin, tumor size, eGFR, sex, cancer type, ECOG PS, and prior IPI therapy for CL; and albumin, sex, and prior IPI therapy for Vc.

The effects of the significant covariates (i.e., albumin, total bilirubin, tumor size, eGFR, sex, cancer type, ECOG PS, and prior IPI therapy) on CL or Vc fell within a range of inter-individual variability of CL (CV, 37.6%) and Vc (CV, 19.1%). The applicant, therefore, explained that the concerned covariates are considered to have little effects on PK of pembrolizumab.

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5) Calculated by a bootstrap method.
6) Calculated according to Modification of Diet in Renal Disease equation.
7) Severity based on the US National Cancer Institute Organ Dysfunction Working Group classification

6.2.5 PK/PD analysis

6.2.5.1 PK/PD analysis based on IL-2

The relationship between C_{trough} of pembrolizumab and the IL-2 stimulation ratio[8)] was investigated using a sigmoid I_{max} model. (The C_{trough} was estimated by PPK analysis of data from Study 001 Parts A and A2. The IL-2 stimulation ratio is an indicator of the inhibition of PD-1/PD-1 ligand pathway.) The steady-state C_{trough} (lower limit of 90% CI, 5.6 μg/mL) following pembrolizumab 1 mg/kg Q3W exceeded the pembrolizumab concentration (5 μg/mL) expected to provide the maximum inhibition of PD-1/PD-1 ligand pathway. In addition, pembrolizumab was estimated to inhibit ≥95% of the PD-1/PD-1 ligand pathway with a probability of ≥64% (1 mg/kg Q3W) and ≥90% (2 mg/kg Q3W).

The applicant's explanation:
The above results suggest that pembrolizumab at ≤1 mg/kg Q3W does not saturate the binding of pembrolizumab to PD-1 and therefore is unlikely to achieve efficacy.

6.2.5.2 Translational PK/PD analysis

Tumor size reduction by pembrolizumab at each dose level was investigated using a translational PK/PD model, based on results from Study 001 and a study using mice subcutaneously transplanted with MC38 cell lines. Pembrolizumab at ≥2 mg/kg Q3W is presumed to achieve complete response[9)] at a higher probability than doses at <2 mg/kg Q3W.

The applicant's explanation:
The above results suggested that the ≥2 mg/kg Q3W regimen is required to provide the maximum tumor size reduction effect.

6.2.5.3 Relationship between pembrolizumab exposure and efficacy or safety

6.2.5.3.1 Relationship between pembrolizumab exposure and efficacy

The relationship between $AUC_{ss,6wk}$ of pembrolizumab and tumor size reduction rate was investigated by linear regression analysis. (The $AUC_{ss,6wk}$ was estimated by PPK analysis based on data from Study 001 Parts B1, B2, B3, and D, Study 002, and Study 006 [see Section 6.2.4].) There was no clear relationship between $AUC_{ss,6wk}$ of pembrolizumab and tumor size reduction rate within the dosage range investigated (2 mg/kg Q2W, 10 mg/kg Q2W, and 10 mg/kg Q3W).

6.2.5.3.2 Relationship between pembrolizumab exposure and safety

The relationship between $AUC_{ss,6wk}$ of pembrolizumab and the incidence of immune-related adverse events was investigated by logistic regression analysis. (The $AUC_{ss,6wk}$ was estimated by PPK analysis based on data from Study 001 Parts B1, B2, B3, and D and Study 002 [see Section 6.2.4].) In addition, the relationship between $AUC_{ss,6wk}$ of pembrolizumab and the incidence of Grade 3 or 4 adverse events

8) The ratio of "SEB + pembrolizumab (25 μg/mL)-stimulated IL-2 concentration" to "SEB-stimulated IL-2 concentration" in *ex vivo* samples.
9) Tumor size reduction by >50%

and serious adverse events was investigated by logistic regression analysis. (The $AUC_{ss,6wk}$ was estimated by PPK analysis based on data from Study 001 Parts B2 and D [see Section 6.2.4].) There was no clear relationship between $AUC_{ss,6wk}$ of pembrolizumab and the incidence of any adverse events within the dose range investigated (2 mg/kg Q2W, 10 mg/kg Q2W, and 10 mg/kg Q3W).

The applicant has proposed the 2 mg/kg Q3W regimen for pembrolizumab based on results from the above PK/PD analyses. The dosage regimens for pembrolizumab in clinical settings are discussed in Section 7.R.5.1, including study data on the efficacy and safety obtained from clinical studies.

6.2.6 Effect of renal or hepatic impairment on PK of pembrolizumab

No clinical studies have been conducted to evaluate PK of pembrolizumab in patients with renal or hepatic impairment. The applicant, however, explained that the dose of pembrolizumab does not have to be adjusted in patients with renal or hepatic impairment, because decreased renal or hepatic function is unlikely to affect PK of pembrolizumab in light of the following points:

- Pembrolizumab is considered to be eliminated through a pathway mediated by binding to the target antigen or a pathway independent of the target antigen, and therefore decreased renal or hepatic function is unlikely to affect exposure to pembrolizumab.
- Pembrolizumab is a high molecular weight compound (molecular weight, approximately 149,000), and it is not renally excreted.
- In the PPK analysis, hepatic impairment was not identified as a significant covariate for PK parameters of pembrolizumab. In addition, although eGFR was identified as a significant covariate for CL of pembrolizumab in the PPK analysis, the effect of eGFR on CL of pembrolizumab is not clinically significant [see Section 6.2.4].

6.R Outline of the review conducted by PMDA

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

The applicant's explanation:

No clear differences were observed in PK of pembrolizumab between Japanese and non-Japanese patients based on the following points:

- Table 14 shows serum concentrations of pembrolizumab in patients with malignant melanoma who received intravenous pembrolizumab at 2 mg/kg Q3W in the Japanese phase Ib study (Study 041), foreign phase I study (Study 001) Parts B and D, and foreign phase II study (Study 002). No clear differences were observed in the serum concentrations between Japanese and non-Japanese patients.
- $AUC_{ss,6wk}$ in Japanese and non-Japanese patients treated with the proposed dosage of pembrolizumab was estimated by PPK analysis[10)]. The estimated $AUC_{ss,6wk}$ (mean ± SD) was similar in Japanese patients (1590 ± 422 μg·day/mL) and non-Japanese patients (1440 ± 575 μg·day/mL).

[10)] The analysis was performed based on PK data of pembrolizumab obtained from foreign clinical studies (Studies 001, 002, and 006) and Japanese clinical studies (Studies 011 and 041) (12,615 time points in 2247 subjects) (NONMEM Version 7.1.2).

Table 14. Serum concentrations of pembrolizumab in Japanese and non-Japanese patients (μg/mL)

	n	C_{max} in Cycle 1	n	C_{trough} in Cycle 1	n	C_{trough} in Cycle 7
Japanese patients	42	41.3 (20.3, 60.5)	41	11.6 (6.04, 14.5)	28	26.5 (10.6, 60.9)
Non-Japanese patients	278	44.5 (12.9, 310)	287	9.35 (0.0470, 68.8)	57	27.6 (5.16, 61.8)

Median (range)

PMDA's view:

The difference in PK between Japanese and non-Japanese patients treated with the proposed dosage of pembrolizumab cannot be strictly evaluated, because the clinical studies have not provided sufficient data to evaluate the difference. In the data submitted, however, PK of pembrolizumab does not tend to clearly differ 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 and D, foreign phase II study (Study 002), foreign phase III study (Study 006), Japanese phase I study (Study 011), and Japanese phase Ib study (Study 041). Some patients were classified as "not assessable" because the pembrolizumab levels in their samples were considered to affect the measurement of anti-pembrolizumab antibody [see Section 6.1.1.2].

Of 1586 patients who provided samples after the first dose of pembrolizumab in the above clinical studies, 439 were classified as "assessable"[11)] and 1147 as "not assessable." Of 439 assessable patients, 4 (1.0%) tested positive for anti-pembrolizumab antibody at baseline, and 2 (0.5%) tested positive for the antibody after the beginning of pembrolizumab therapy. One patient tested positive for neutralizing antibody after the beginning of pembrolizumab therapy. Anti-pembrolizumab antibody was not detected in any of the patients treated with the proposed dosage of pembrolizumab.

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 present in a sample may have affected the results of the anti-pembrolizumab antibody assay used in clinical studies. The applicant, therefore, should continue collecting the 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 foreign phase II study, and a foreign phase III study [Table 15].

11) The total number of subjects who tested positive or negative for anti-pembrolizumab antibody.

Table 15. 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	011	I	Patients with advanced solid cancer	10 (a) 3 (b) 7	(a) Pembrolizumab at 2 mg/kg on Day 1 and at 2 mg/kg Q2W from Day 29 onward (b) Pembrolizumab at 10 mg/kg on Day 1 and at 10 mg/kg Q2W from Day 29 onward	Safety PK
		041	Ib	Patients with unresectable malignant melanoma who had received no prior chemotherapy or only ≤2 prior chemotherapy regimens without IPI	42	Pembrolizumab at 2 mg/kg Q3W	Efficacy Safety
	Foreign	001	I	Parts A, A1, A2: Patients with advanced solid cancer	Part A 10 Part A1 7 Part A2 (a) 4 (b) 3 (c) 6	Part A: Single intravenous dose of pembrolizumab at 1, 3, or 10 mg/kg on Day 1 and then Q2W from Day 29 onward Part A1: Single intravenous dose of pembrolizumab at 10 mg/kg on Day 1 and then Q2W from Day 29 onward Part A2: (a) Pembrolizumab at 0.005 mg/kg on Day 1, at 0.3 mg/kg on Day 8, and at 2 mg/kg Q3W from Day 22 onward (b) Pembrolizumab at 0.02 mg/kg on Day 1, at 0.3 mg/kg on Day 8, and at 2 mg/kg Q3W from Day 22 onward (c) Pembrolizumab at 0.06 mg/kg on Day 1, at 1 mg/kg on Day 8, and at 10 mg/kg Q3W from Day 22 onward	Safety Efficacy PK
				Part B1: Patients with unresectable malignant melanoma	Part B1 (a) 22 (b) 57 (c) 56	Part B1: (a) Pembrolizumab at 2 mg/kg Q3W (b) Pembrolizumab at 10 mg/kg Q2W (c) Pembrolizumab at 10 mg/kg Q3W	
				Part B2: Patients with unresectable malignant melanoma who had received prior IPI therapy	Part B2 (a) 89 (b) 84	Part B2: (a) Pembrolizumab at 2 mg/kg Q3W (b) Pembrolizumab at 10 mg/kg Q3W	
				Part B3: Patients with unresectable malignant melanoma	Part B3 (a) 123 (b) 121	Part B3: (a) Pembrolizumab at 10 mg/kg Q2W (b) Pembrolizumab at 10 mg/kg Q3W	
				Part D: Patients with unresectable malignant melanoma who had not received prior IPI therapy	Part D (a) 51 (b) 52	Part D: (a) Pembrolizumab at 2 mg/kg Q3W (b) Pembrolizumab at 10 mg/kg Q3W	
		002	II	Patients with unresectable malignant melanoma who had received prior IPI therapy	540 (a) 180 (b) 181 (c) 179	(a) Pembrolizumab at 2 mg/kg Q3W (b) Pembrolizumab at 10 mg/kg Q3W (c) ICC	Efficacy Safety
		006	III	Patients with unresectable malignant melanoma who had received no prior chemotherapy or only 1 prior chemotherapy regimen without IPI	834 (a) 277 (b) 279 (c) 278	(a) Pembrolizumab at 10 mg/kg Q3W (b) Pembrolizumab at 10 mg/kg Q2W (c) IPI 3 mg/kg Q3W	Efficacy Safety

* Pembrolizumab was administered intravenously.

The results of 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 Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Japanese phase I study (CTD 5.3.5.2.2, Study 011 Part A [ongoing since [redacted] (cutoff date, [redacted])])

An open-label, uncontrolled study was conducted to investigate the safety and tolerability of pembrolizumab in patients with advanced solid cancer at 2 study sites in Japan.

Subjects received intravenous pembrolizumab 2 or 10 mg/kg as a single dose on Day 1, followed by every 2 weeks from Day 29 onward. Subjects continued treatment until disease progression or the discontinuation criteria were met.

All 10 subjects enrolled were treated with pembrolizumab and included in the safety analysis.

As for safety, no deaths were reported during the pembrolizumab treatment period or within 90 days after the end of treatment.

7.1.1.2 Japanese phase Ib study (CTD 5.3.5.2.3, Study 041 [ongoing since [redacted] (cutoff date, [redacted])])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of pembrolizumab in patients with unresectable malignant melanoma who had received no prior chemotherapy or only ≤2 prior chemotherapy regimens without IPI (target sample size, 35 subjects [up to 7 subjects with mucous malignant melanoma]) at 12 study sites in Japan.

Subjects received intravenous pembrolizumab 2 mg/kg Q3W, and continued the treatment until disease progression or the discontinuation criteria were met.

Of 42 subjects enrolled, 37 were included in the full analysis set (FAS) for efficacy analysis, excluding 5 subjects who had no measurable lesion at baseline. All 42 subjects who received pembrolizumab were included in the safety analysis.

Efficacy results:

The primary endpoint was centrally assessed response rate[12] in patients with skin malignant melanoma. The exploratory endpoint was centrally assessed response rate in patients with mucous malignant melanoma. The results are shown in Table 16.

Table 16. Best overall response and response rate
(RECIST v1.1, central assessment, FAS, cutoff date, [redacted])

Best overall response	n (%)	
	Malignant melanoma N = 29	Mucous malignant melanoma N = 8
Complete response (CR)	2 (6.9)	0
Partial response (PR)	5 (17.2)	2 (25.0)
Stable disease (SD)	7 (24.1)	2 (25.0)
Progressive disease (PD)	14 (48.3)	4 (50.0)
Not evaluable (NE)	1 (3.4)	0
Response (CR + PR) (response rate [95% CI] [%])	7 (24.1 [10.3, 43.5])	2 (25.0 [3.2, 65.1])

Safety results:

Deaths were reported in 7.1% (3 of 42) of subjects during the pembrolizumab treatment period or within 90 days after the end of treatment. Causes of death included acute respiratory failure, unexplained death (death due to fall), and cerebral haemorrhage in 1 subject each, and a causal relationship to pembrolizumab could not be ruled out for unexplained death and cerebral haemorrhage (1 subject each).

7.1.2 Foreign clinical studies

7.1.2.1 Foreign phase I study (CTD 5.3.5.2.1, Study 001 [ongoing since [redacted] (cutoff date, [redacted])])

An open-label, uncontrolled study was conducted at 50 study sites outside Japan, to investigate the safety of pembrolizumab in patients with advanced solid cancer (Parts A, A1, and A2), patients with unresectable malignant melanoma (Parts B1 and B3), patients with unresectable malignant melanoma who had received prior IPI therapy (Part B2), and patients with unresectable malignant melanoma who had not received prior IPI therapy (Part D). The target sample size was 622 subjects: 10 in Part A, 6 in Part A1, 12 in Part A2, 506 in Part B, 88 in Part D.

Subjects received the following treatment:

Parts A and A1

Intravenous pembrolizumab 1, 3, or 10 mg/kg as a single dose on Day 1, followed by every 2 weeks from Day 29 onward.

Part A2

Cohort 1: Intravenous pembrolizumab 0.005 mg/kg on Day 1, 0.3 mg/kg on Day 8, and 2 mg/kg Q3W from Day 22 onward;

[12] The threshold response rate was 10% based on the response rate to DTIC monotherapy in a foreign phase III study in patients with unresectable malignant melanoma (*N Eng J Med.* 2012;367:107-14, etc.).

Cohort 2: Intravenous pembrolizumab 0.02 mg/kg on Day 1, 0.3 mg/kg on Day 8, and 2 mg/kg Q3W from Day 22 onward;

Cohort 3: Intravenous pembrolizumab 0.06 mg/kg on Day 1, 1.0 mg/kg on Day 8, and 10 mg/kg Q3W from Day 22 onward.

Parts B1, B2, and B3

Intravenous pembrolizumab 2 mg/kg Q3W, 10 mg/kg Q2W, or 10 mg/kg Q3W.

Part D

Intravenous pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W.

Treatment was continued until disease progression or the discontinuation criteria were met.

All 685 subjects enrolled were treated with ≥1 dose of pembrolizumab and included in the safety analysis.

During the Cycle 1 (28 days) in the dose escalation parts of this study (Parts A and A1), dose limiting toxicities (DLTs) were evaluated as an indicator of tolerability. All 17 subjects enrolled in Parts A and A1 (4 in the 1 mg/kg Q2W group, 3 in the 3 mg/kg Q2W group, 10 in the 10 mg/kg Q2W group) received pembrolizumab without DLTs.

Safety results:

During the pembrolizumab treatment period or within 90 days after the end of treatment, deaths were reported in 1.5% (10 of 685) of subjects (14.3% [1 of 7] of subjects in the 10 mg/kg Q2W group in Part A1; 7.0% [4 of 57] of subjects in the 10 mg/kg Q2W group and 1.8% [1 of 56] of subjects in the 10 mg/kg Q3W group in Part B1; 1.1% [1 of 89] of subjects in the 2 mg/kg Q3W group in Part B2; and 0.8% [1 of 123] of subjects in the 10 mg/kg Q2W group and 1.7% [2 of 121] of subjects in the 10 mg/kg Q3W group in Part B3). Causes of death included Cryptococcal fungaemia (1 subject) in the 10 mg/kg Q2W group in Part A1; acute myocardial infarction, death, cellulitis, and pulmonary embolism (1 subject each) in the 10 mg/kg Q2W group and pneumonia (1 subject) in the 10 mg/kg Q3W group in Part B1; septic shock (1 subject) in the 2 mg/kg Q3W group in Part B2; and death (1 subject) in the 10 mg/kg Q2W group and death and cardiac arrest (1 subject each) in the 10 mg/kg Q3W group in Part B3. Of these, a causal relationship to pembrolizumab could not be ruled out for cryptococcal fungaemia in the 10 mg/kg Q2W group in Part A1.

7.1.2.2 Foreign phase II study (CTD 5.3.5.1.1, Study 002 [ongoing since [redacted] (cutoff date, [redacted])])

A partially blinded,[13)] randomized, controlled study was conducted to investigate the efficacy and safety of pembrolizumab and investigator-choice chemotherapies (ICC) in patients with unresectable malignant melanoma who had received prior IPI therapy (target sample size, 510 subjects) at 73 study sites outside Japan.

13) Subject assignment to pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W was blinded.

Subjects in the pembrolizumab group received intravenous pembrolizumab 2 or 10 mg/kg Q3W. Subjects in the ICC group received monotherapy with CBDCA, PTX, dacarbazine (DTIC), or temozolomide (TMZ), or combination therapy with CBDCA and PTX chosen by the investigator according to the standard therapy at each study site. Treatment was continued until disease progression or the discontinuation criteria were met. Of subjects assigned to the ICC group, those meeting the criteria for crossover[14)] were allowed to receive pembrolizumab (2 or 10 mg/kg Q3W) at Week 12 or later.

All 540 subjects enrolled and randomized (180 in the 2 mg/kg Q3W group, 181 in the 10 mg/kg Q3W group, 179 in the ICC group) were included in the intention-to-treat (ITT) population for efficacy analysis. Of the ITT population, 528 subjects (178 in the 2 mg/kg Q3W group, 179 in the 10 mg/kg Q3W group, 171 in the ICC group) were included in the safety analysis, excluding 12 subjects (2 in the 2 mg/kg Q3W group, 2 in the 10 mg/kg Q3W group, 8 in the ICC group) who did not receive the study drug.

The primary endpoints[15)] were centrally assessed progression-free survival (PFS) and overall survival (OS), and 2 interim analyses were planned to evaluate efficacy and futility.

The first interim analysis plan:

After 120 subjects have been enrolled, randomized, and observed for ≥3 months, the centrally assessed response rates in the 2 pembrolizumab groups are compared (2 mg/kg Q3W vs. 10 mg/kg Q3W). One pembrolizumab group is discontinued if it has a significantly lower response rate than the other pembrolizumab group (two-sided significance level of 10%).

The second interim analysis plan:

The final analysis of PFS and interim analysis of OS are performed after at least 270 PFS events have occurred (180 PFS events if one pembrolizumab group has been discontinued after the first interim analysis). Pembrolizumab is considered effective if either of the 2 analyses demonstrates the efficacy of pembrolizumab compared with ICC. Pembrolizumab is not considered effective and the study is terminated early for futility, if PFS with pembrolizumab is not significantly prolonged compared with PFS with ICC, and if either of pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W has an OS hazard ratio of >0.82 (vs. ICC).

The final analysis plan:

The final analysis of OS is performed after 370 OS events have occurred.

To adjust the type 1 error probability, the following significance levels were used in the interim analyses and final analysis [Table 17].

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14) Patients were required to meet all of the following criteria (a) to (d):
(a) PS 0 or 1; (b) neither development nor symptoms/signs of new brain metastasis; (c) resolution of chemotherapy-associated adverse events to Grade ≤1; and (d) disease progression confirmed by central imaging assessment

15) The original primary endpoints consisted of response rate, OS, and PFS when the study was designed. Because the response rate was considered highly correlated to PFS, the foreign regulatory authority advised removing either response rate or PFS from the primary endpoints. The protocol was thus revised ([redacted]) to include only PFS and OS in the primary endpoints and reclassify response rate as a secondary endpoint.

Table 17. One-sided significance levels in the analyses

Analysis timepoint	PFS		OS	
	2 mg/kg Q3W vs. ICC	10 mg/kg Q3W vs. ICC	2 mg/kg Q3W vs. ICC	10 mg/kg Q3W vs. ICC
First interim analysis	-	-	0.001%	
Second interim analysis	0.25%	0.25%	0.5% [*1]	
Final analysis	-	-	(1.5%, 1.75%, 2%)[*1, 2]	

[*1] Hochberg procedure. If the first interim analysis results in discontinuation of pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W, the second analysis should be performed with 1/2 of the initially selected significance level;

[*2] Either 1.5% or 2% is selected depending on results for PFS in the second interim analysis.

Efficacy results:

The first interim analysis performed on [redacted] revealed that the response rate in the pembrolizumab 2 mg/kg Q3W group was comparable to that in the 10 mg/kg Q3W group. The data monitoring committee recommended the study be continued without discontinuation of either pembrolizumab regimen.

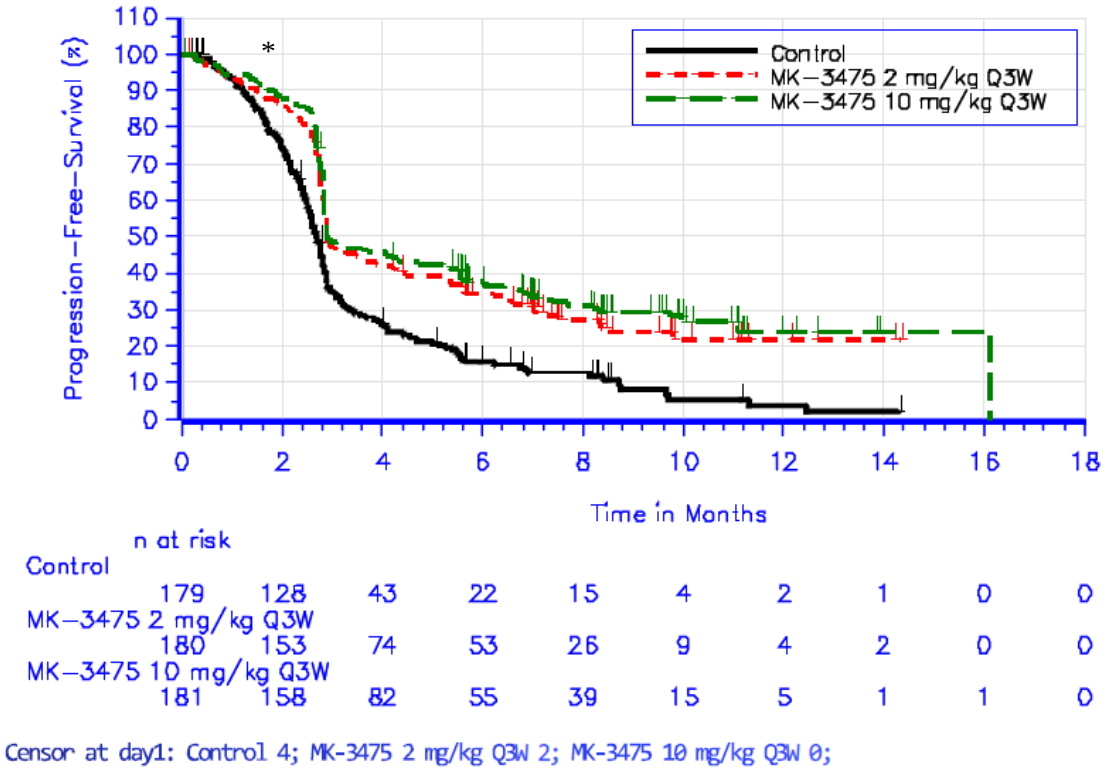
The second interim analysis was performed with a cutoff date of May 12, 2014. Results of the final analysis of centrally assessed PFS are shown in Table 18 and Kaplan-Meier curves in Figure 1. Results of interim analysis of OS are shown in Table 19 and Kaplan-Meier curves in Figure 2. Both pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W were shown to be superior to ICC in PFS. Pembrolizumab was administered to 48.0% (86 of 179) of subjects in the ICC group.

Table 18. Results from final analysis of PFS (central assessment, ITT, cutoff date, May 12, 2014)

	2 mg/kg Q3W	10 mg/kg Q3W	ICC (control)
Number of subjects	180	181	179
Number of events (%)	129 (71.7)	126 (69.6)	155 (86.6)
Median [95% CI] (months)	2.9 [2.8, 3.8]	2.9 [2.8, 4.7]	2.7 [2.5, 2.8]
Hazard ratio [95% CI][*1]	0.57 [0.45, 0.73]	0.50 [0.39, 0.64]	
P value (one-sided)[*2]	<0.0001	<0.0001	

[*1] Cox regression stratified by ECOG PS (0, 1), serum LDH value (normal, high), and BRAF gene (mutant, wild-type).

[*2] Log-rank test stratified by ECOG PS (0, 1), serum LDH value (normal, high), and BRAF gene (mutant, wild-type) at a one-sided significance level of 0.0025.



* Subjects censored on Day 1 (2 subjects in the 2 mg/kg Q3W group, 0 subjects in the 10 mg/kg Q3W group, 4 subjects in the control group)

Figure 1. Kaplan-Meier curves in final analysis of PFS (central assessment, ITT, cutoff date, May 12, 2014)

Table 19. Results from interim analysis of OS (ITT, cutoff date, May 12, 2014)

	2 mg/kg Q3W	10 mg/kg Q3W	ICC (control)
Number of subjects	180	181	179
Number of events (%)	73 (40.6)	69 (38.1)	78 (43.6)
Median [95% CI] (months)	11.4 [10.2, NE]	12.5 [9.7, NE]	11.6 [9.0, 16.3]
Hazard ratio [95% CI][*1]	0.88 [0.64, 1.22]	0.78 [0.56, 1.08]	
P value (one-sided)[*2]	0.2294	0.0664	

[*1] Cox regression stratified by ECOG PS (0, 1), LDH value (normal, high), and BRAF gene (mutant, wild-type).

[*2] Log-rank test stratified by ECOG PS (0, 1), serum LDH value (normal, high), and BRAF gene (mutant, wild-type) at a one-sided significance level of 0.005, Hochberg procedure.

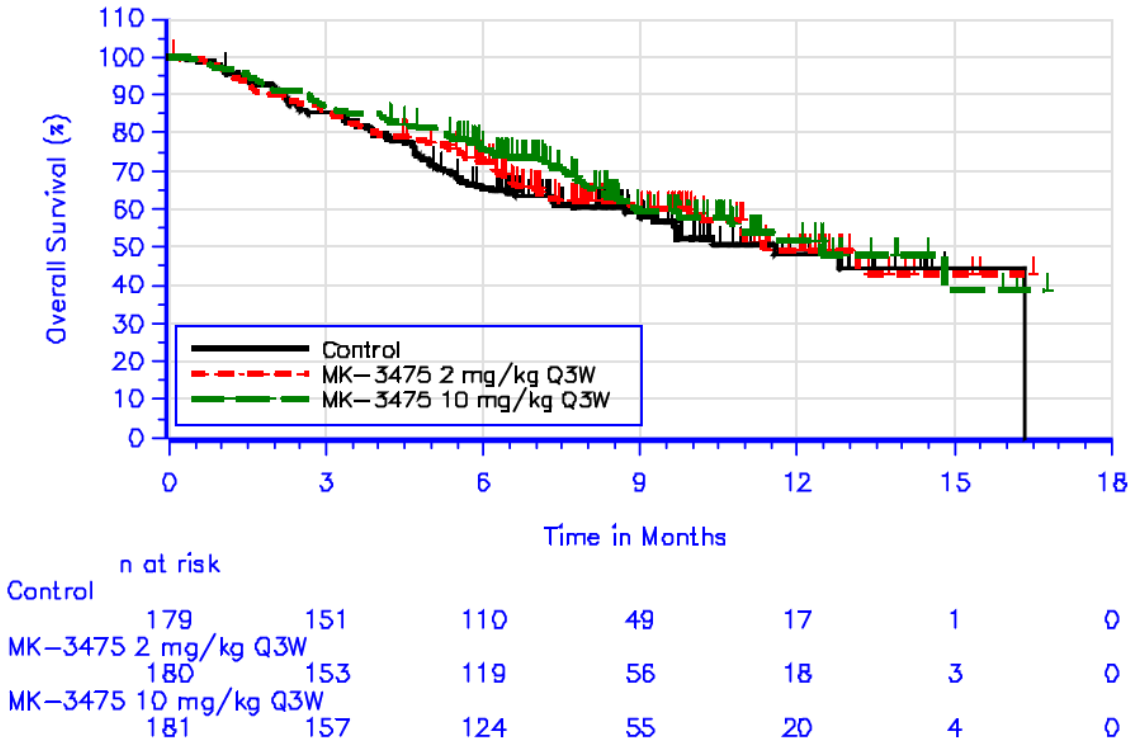


Figure 2. Kaplan-Meier curves in interim analysis of OS (ITT, cutoff date, May 12, 2014)

The final analysis of OS was performed with a cutoff date of [redacted], and the results and Kaplan-Meier curves are shown in Table 20 and Figure 3, respectively. When the final analysis of OS was performed, pembrolizumab had been administered to 54.7% (98 of 179) of subjects in the ICC group.

Table 20. Results from final analysis of OS (ITT, cutoff date, [redacted])

	2 mg/kg Q3W	10 mg/kg Q3W	ICC (control)
Number of subjects	180	181	179
Number of events (%)	123 (68.3)	117 (64.6)	128 (71.5)
Median [95% CI] (months)	13.4 [11.0, 16.4]	14.7 [11.3, 19.5]	11.0 [8.9, 13.8]
Hazard ratio [95% CI]*[1]	0.86 [0.67, 1.10]	0.74 [0.57, 0.96]	
P value (one-sided)*[2]	0.1173	0.0106	

*[1] Cox regression stratified by ECOG PS (0, 1), LDH value (normal, high), and BRAF gene (mutant, wild-type);

*[2] Log-rank test stratified by ECOG PS (0, 1), serum LDH value (normal, high), and BRAF gene (mutant, wild-type) at a one-sided significance level of 0.02, Hochberg procedure.

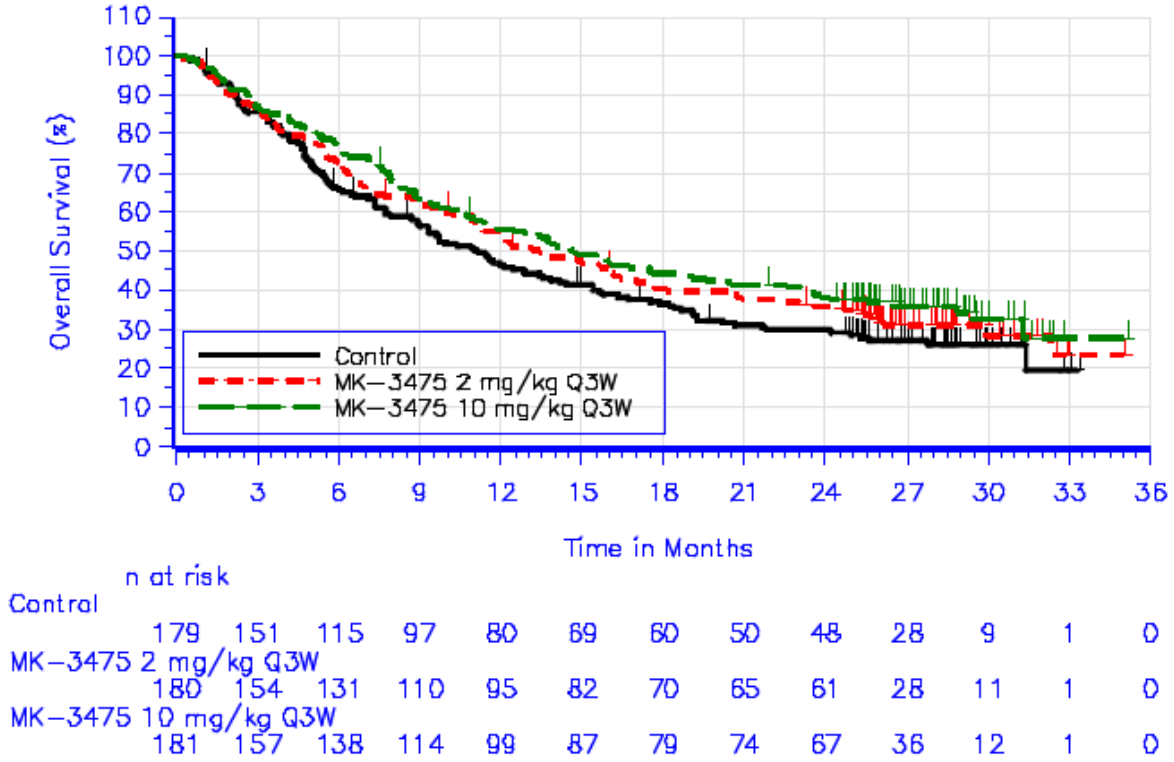


Figure 3. Kaplan-Meier curves in final analysis of OS (ITT, cutoff date, [redacted])

Safety results:

Deaths were reported in 7.3% (13 of 178) of subjects in the 2 mg/kg Q3W group, 4.5% (8 of 179) of subjects in the 10 mg/kg Q3W group, and 6.4% (11 of 171) of subjects in the ICC group during the pembrolizumab treatment period or within 90 days after the end of treatment. Causes of death included death (3 subjects), intestinal obstruction, general physical health deterioration, generalised oedema, hepatic failure, infectious pleural effusion, septic shock, cachexia, mental status changes, haemothorax, and haemorrhagic infarction (1 subject each) in the 2 mg/kg Q3W group; death, general physical health deterioration, and dyspnoea (2 subjects each), and upper gastrointestinal haemorrhage and hepatic failure (1 subject each) in the 10 mg/kg Q3W group; and general physical health deterioration (3 subjects), death (2 subjects), and generalised oedema, atypical pneumonia, pneumonia, subdural haematoma, haemorrhage intracranial, and pulmonary embolism (1 subject each) in the ICC group. Of these, a causal relationship to the study drug could not be ruled out for death (1 subject) in the 2 mg/kg Q3W group.

7.1.2.3 Foreign phase III study (CTD 5.3.5.1.2, Study 006 [ongoing since [redacted] (cutoff date, March 3, 2015)])

An open-label, randomized, controlled study was conducted to investigate the efficacy and safety of pembrolizumab and IPI in patients with unresectable malignant melanoma who had received no prior chemotherapy or only 1 prior chemotherapy regimen without IPI (target sample size, 645 subjects) at 87 study sites outside Japan.

Subjects in the pembrolizumab group received intravenous pembrolizumab 10 mg/kg Q3W or Q2W. Subjects in the IPI group received intravenous IPI 3 mg/kg Q3W up to 4 cycles. These regimens were continued until disease progression or the discontinuation criteria were met.

All 834 subjects enrolled and randomized (277 in the 10 mg/kg Q3W group, 279 in the 10 mg/kg Q2W group, 278 in the IPI group) were included in the ITT population for efficacy analysis. Of the ITT population, 811 subjects (278 in the 10 mg/kg Q2W group, 277 in the 10 mg/kg Q3W group, 256 in the IPI group) were included in the safety analysis, excluding 23 subjects (1 in the 10 mg/kg Q2W group, 22 in the IPI group) who did not receive the study drug.

The primary endpoints were centrally assessed PFS and OS, and 2 interim analyses were planned to evaluate the efficacy and futility.

The first interim analysis plan:

The interim analysis of PFS and the first interim analysis of OS are performed after (a) the occurrence of approximately 260 PFS events and (b) the completion of a ≥6-month observation period in all subjects. Pembrolizumab is considered effective if either of the 2 analyses demonstrates the efficacy of pembrolizumab compared with IPI. Pembrolizumab is not considered effective and the study is terminated early for futility, if PFS with pembrolizumab is not significantly prolonged compared with PFS with IPI, and if pembrolizumab has an OS hazard ratio of >0.9167 (vs. IPI).

The second interim analysis plan:

The final analysis of PFS and the second interim analysis of OS are performed after (a) the occurrence of approximately 67% (290 events) of the number of events required for the final analysis of OS (435 events) and (b) the completion of a ≥9-month observation period in all subjects. Pembrolizumab is considered effective if either of the 2 analyses demonstrates the efficacy of pembrolizumab compared with IPI.

The final analysis plan:

The final analysis of OS is performed after 435 OS events have occurred.

To adjust type 1 error probability, the following significance levels were used in the interim analyses and final analysis [Table 21].

Table 21. One-sided significance levels in the analyses

Analysis timepoint	PFS		OS	
	10 mg/kg Q3W vs. IPI	10 mg/kg Q2W vs. IPI	10 mg/kg Q3W vs. IPI	10 mg/kg Q2W vs. IPI
First interim analysis	0.2%	0.2%	0.002%[*1]	
Second interim analysis	0.05%	0.05%	0.5%[*1]	
Final analysis	-	-	(1.5%, 1.55%, 1.60%, 1.70%, 1.75%, 1.80%, 1.90%, 1.95%, 2%)[*1, 2]	

[*1] Hochberg procedure.

[*2] Either 1.5% or 2% is selected depending on results for PFS in the first and second interim analyses.

Efficacy results:

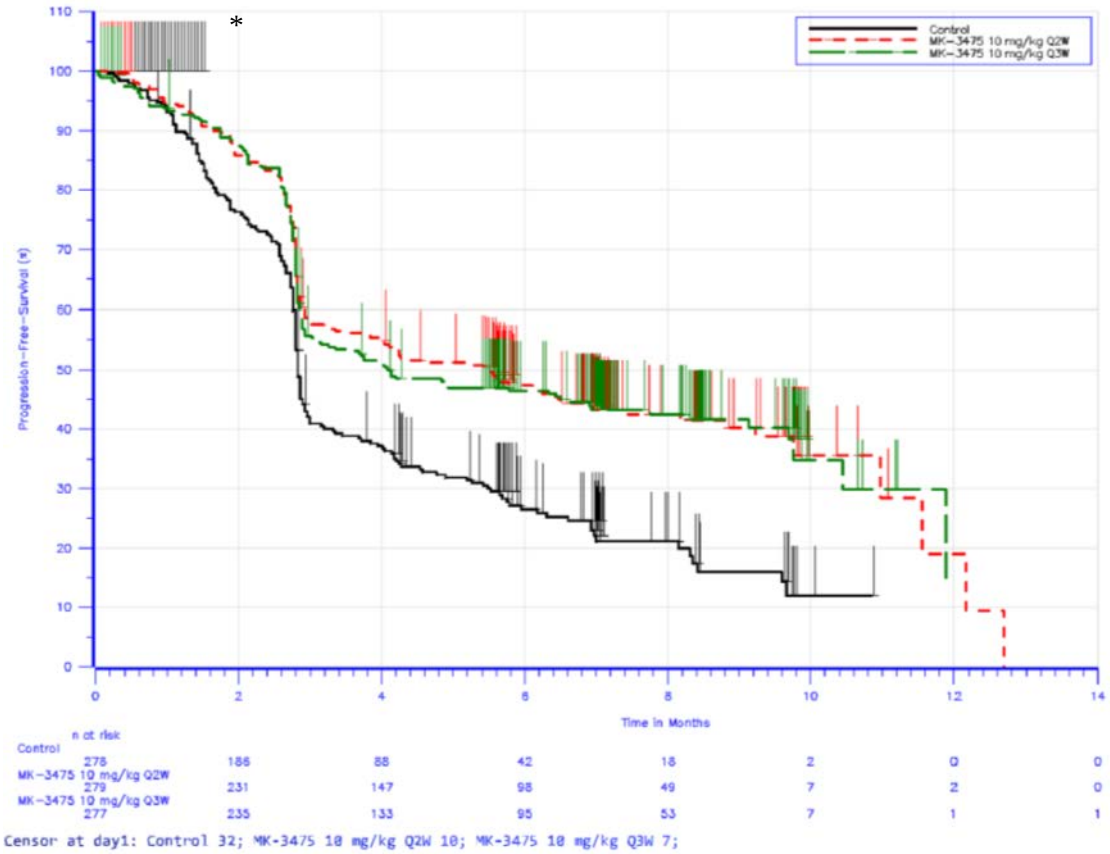
Results of the interim analysis of PFS, one primary endpoint, are shown in Table 22 and Kaplan-Meier curves in Figure 4. Results of the first interim analysis of OS, the other primary endpoint, are shown in Table 23 and Kaplan-Meier curves in Figure 5. Both pembrolizumab 10 mg/kg Q3W and 10 mg/kg Q2W were shown to be superior to IPI in PFS.

Table 22. Results from first interim analysis of PFS
(central assessment, ITT, cutoff date, September 3, 2014)

	10 mg/kg Q3W	10 mg/kg Q2W	IPI (control)
Number of subjects	277	279	278
Number of events (%)	157 (56.7)	157 (56.3)	188 (67.6)
Median [95% CI] (months)	4.1 [2.9, 6.9]	5.5 [3.4, 6.9]	2.8 [2.8, 2.9]
Hazard ratio [95% CI]*1	0.58 [0.47, 0.72]	0.58 [0.46, 0.72]	
P value (one-sided)*2	<0.0001	<0.0001	

*1 Cox regression stratified by the number of prior regimens (0, 1), percentage of PD-L1 positive cells (≥1%, <1%), and ECOG PS (0, 1).

*2 Log-rank test stratified by the number of prior regimens (0, 1), percentage of PD-L1 positive cells (≥1%, <1%), and ECOG PS (0, 1) at a one-sided significance level of 0.002.



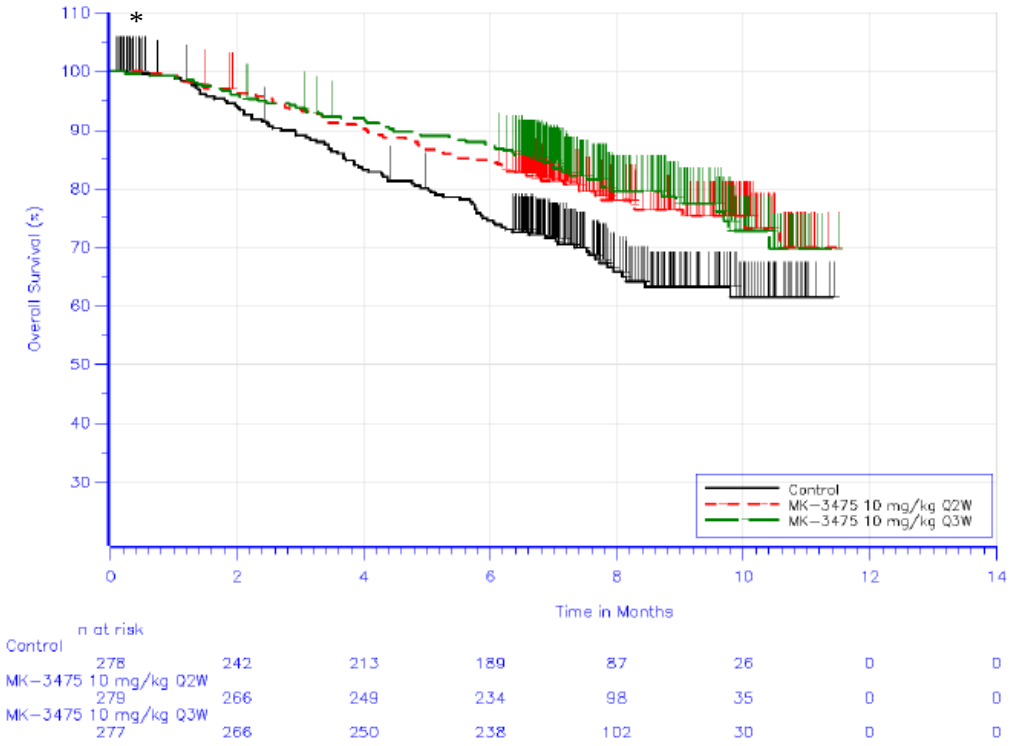
* Subjects censored on Day 1 (32 subjects in the control group, 10 subjects in the 10 mg/kg Q2W group, 7 subjects in the 10 mg/kg Q3W group)

Figure 4. Kaplan-Meier curves in interim analysis of PFS
(central assessment, ITT, cutoff date, September 3, 2014)

Table 23. Results from first interim analysis of OS (ITT, cutoff date, September 3, 2014)

	10 mg/kg Q3W	10 mg/kg Q2W	IPI (control)
Number of subjects	277	279	278
Number of events (%)	56 (20.2)	61 (21.9)	85 (30.6)
Median [95% CI] (months)	NE [NE, NE]	NE [NE, NE]	NE [NE, NE]
Hazard ratio [95% CI]*1	0.56 [0.40, 0.78]	0.60 [0.43, 0.84]	
P value (one-sided)*2	0.0031	0.00132	

*1 Cox regression stratified by the number of prior regimens (0, 1), percentage of PD-L1 positive cells (≥1%, <1%), and ECOG PS (0, 1).
*2 Log-rank test stratified by the number of prior regimens (0, 1), percentage of PD-L1 positive cells (≥1%, <1%), and ECOG PS (0, 1) at a one-sided significance level of 0.00002, Hochberg procedure.



* Subjects censored on Day 1 (0 subjects in the 10 mg/kg Q2W group, 0 subjects in the 10 mg/kg Q3W group, 11 subjects in the control group)

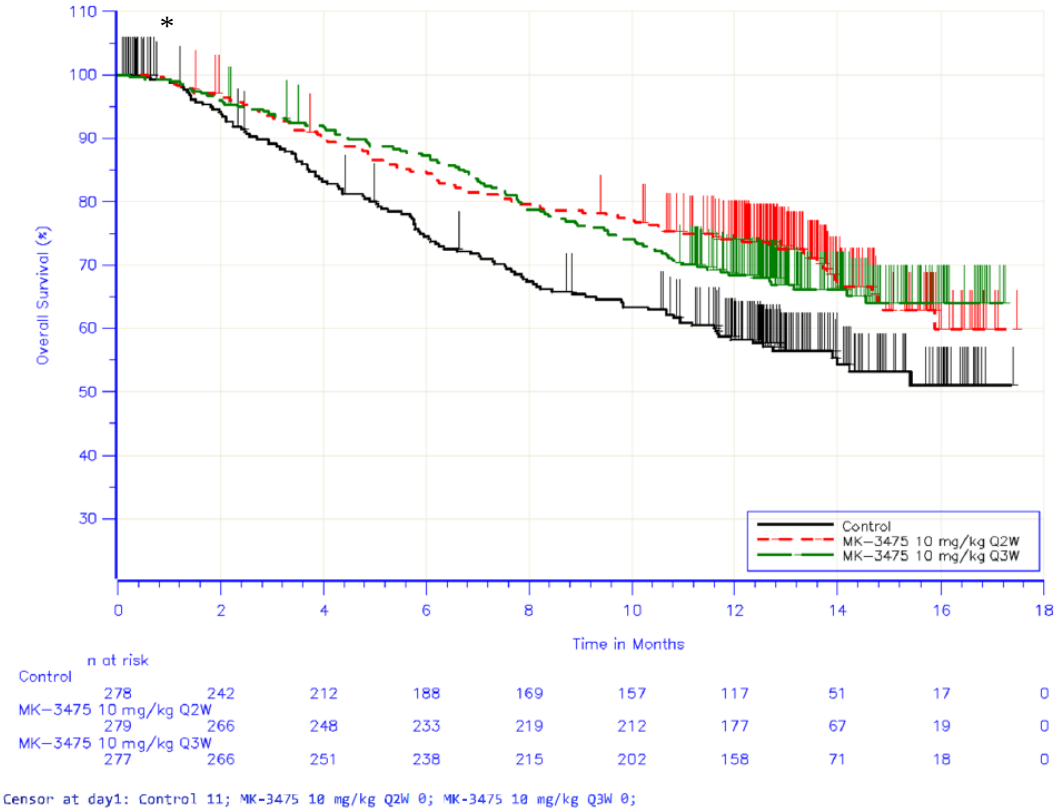
Figure 5. Kaplan-Meier curves in first interim analysis of OS (ITT, cutoff date, September 3, 2014)

Results of the second interim analysis of OS are shown in Table 24 and Kaplan-Meier curves in Figure 6. Both pembrolizumab 10 mg/kg Q3W and 10 mg/kg Q2W were shown to be superior to IPI in OS. As recommended by the data monitoring committee, the efficacy evaluation was terminated early, and the safety evaluation and survival follow-up were continued until the final analysis as initially planned.

Table 24. Results from second interim analysis of OS (ITT, cutoff date, March 3, 2015)

	10 mg/kg Q3W	10 mg/kg Q2W	IPI (control)
Number of subjects	277	279	278
Number of events (%)	92 (33.2)	85 (30.5)	112 (40.3)
Median [95% CI] (months)	NE [NE, NE]	NE [NE, NE]	NE [12.7, NE]
Hazard ratio [95% CI]*1	0.69 [0.52, 0.90]	0.63 [0.47, 0.83]	
P value (one-sided)*2	0.00358	0.00052	

*1 Cox regression stratified by the number of prior regimens (0, 1), percentage of PD-L1 positive cells (≥1%, <1%), and ECOG PS (0, 1);
*2 Log-rank test stratified by the number of prior regimens (0, 1), percentage of PD-L1 positive cells (≥1%, <1%), and ECOG PS (0, 1) at a one-sided significance level of 0.005, Hochberg procedure.



* Subjects censored on Day 1 (0 subjects in the 10 mg/kg Q2W group, 0 subjects in the 10 mg/kg Q3W group, 11 subjects in the control group)

Figure 6. Kaplan-Meier curves in second interim analysis of OS (ITT, cutoff date, March 3, 2015)

Safety results:

Deaths were reported in 1.8% (5 of 277) of subjects in the 10 mg/kg Q3W group, 2.5% (7 of 278) of subjects in the 10 mg/kg Q2W group, and 2.7% (7 of 256) of subjects in the IPI group during the pembrolizumab treatment period or within 90 days after the end of treatment. Causes of death included cardiac failure, cardiac failure congestive, lung infection, soft tissue infection, and completed suicide (1 subject each) in the 10 mg/kg Q3W group; myocardial infarction, death, adenocarcinoma gastric, lymphangiosis carcinomatosa, metastatic malignant melanoma, haemorrhagic stroke, and hypoxia (1 subject each) in the 10 mg/kg Q2W group; and cardio-respiratory arrest, death, endocarditis, pneumonia, tumour lysis syndrome, tumour haemorrhage, and hypoxia (1 subject each) in the IPI group. Of these, a causal relationship to the study drug could not be ruled out for haemorrhagic stroke (1 subject) in the 10 mg/kg Q2W group and death (1 subject) in the IPI 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 from the submitted data: (a) A foreign phase III study (Study 006) to investigate the efficacy and safety of pembrolizumab in patients with unresectable malignant melanoma who had received no prior chemotherapy or only 1 prior chemotherapy regimen without IPI; and (b) a foreign phase II study (Study 002) to investigate the efficacy and safety of pembrolizumab in patients with unresectable malignant melanoma who had

received prior IPI therapy. PMDA decided to evaluate pembrolizumab based mainly on data from these 2 studies.

In addition, PMDA decided to evaluate the efficacy and safety of pembrolizumab in Japanese patients, based mainly on data from Study 041, a Japanese phase Ib study in patients with unresectable malignant melanoma who had received no prior chemotherapy or only ≤2 prior chemotherapy regimens without IPI.

7.R.2 Efficacy

Based on the following review, PMDA has concluded that the efficacy of pembrolizumab in patients with unresectable malignant melanoma was demonstrated.

7.R.2.1 Control treatments

The applicant explained the reasons for using IPI and ICC as control treatments in Study 006 and Study 002, respectively:

The applicant's explanation:

When Study 006 was planned, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Malignant Melanoma (NCCN Guidelines) (ver. 3. 2012), etc. recommended IPI for the patient population eligible for Study 006, because a report (*N Eng J Med.* 2010;363:711-23) showed the efficacy of IPI compared with gp100, an antigen peptide derived from malignant melanoma, in the population. Therefore, IPI was selected as control treatment in Study 006.

When Study 002 was planned, neither NCCN Guidelines (ver. 3. 2012) nor European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (*Ann Oncol*. 2012;23 Suppl 7:vii86-91) recommended any treatment as the established standard therapy for the patient population eligible for Study 002, and therefore such patients were treated with chemotherapy with DTIC, etc. Accordingly, ICC was selected as control treatment in Study 002.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints and efficacy evaluation results

In Studies 006 and 002, centrally assessed PFS was used as a primary endpoint. The applicant explained the rationale for selecting PFS as a primary endpoint:

The applicant's explanation:

In patients with unresectable malignant melanoma, prolonged PFS means a longer period to progressive disease, leading to expectations of improved quality of life of patients, which can be of clinical benefit. It was therefore appropriate to select PFS as a primary endpoint.

Study 006 showed that pembrolizumab 10 mg/kg Q2W and Q3W was superior to IPI in OS [see Section 7.1.2.3].

Study 002:

The interim analysis of centrally assessed PFS, one primary endpoint, revealed the superiority of pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W to ICC. In the final analysis of OS, the other primary endpoint, pembrolizumab was not superior to ICC, but neither of the 2 pembrolizumab regimens tended to be inferior to ICC [see Section 7.1.2.2].

Table 25 shows results of PFS assessed by investigators as a sensitivity analysis.

Table 25. Interim analysis results of investigator-assessed PFS (ITT, cutoff date, May 12, 2014)

	2 mg/kg Q3W	10 mg/kg Q3W	ICC
Number of subjects	180	181	179
Number of events (%)	122 (67.8)	112 (61.9)	157 (87.7)
Median [95% CI] (months)	3.7 [2.9, 5.4]	5.4 [3.8, 6.8]	2.6 [2.4, 2.8]
Hazard ratio [95% CI][*1]	0.49 [0.38, 0.62]	0.41 [0.32, 0.52]	
P value (one-sided)[*2]	<0.0001	<0.0001	

[*1] Cox regression stratified by ECOG PS (0, 1), serum LDH value (normal, high), and BRAF gene (mutant, wild-type).

[*2] Log-rank test stratified by ECOG PS (0, 1), serum LDH value (normal, high), and BRAF gene (mutant, wild-type).

PMDA's view:

It was appropriate to select OS as a primary endpoint in Studies 006 and 002.

Study 006 demonstrated prolonged OS (a primary endpoint) in the pembrolizumab group compared with the IPI group, showing the efficacy of pembrolizumab in the patients in Study 006.

The following findings in Study 002 also demonstrated the efficacy of pembrolizumab in the patients in Study 002, according to: (a) Pembrolizumab was superior to ICC in centrally assessed PFS, a primary endpoint; (b) Pembrolizumab was superior to ICC also in investigators-assessed PFS; (c) In the final analysis of OS, the pembrolizumab groups showed no tendency toward shorter OS compared with the ICC group.

7.R.2.3 Efficacy in Japanese patients

In patients with malignant skin tumor (29 subjects) included in Study 041, centrally assessed response rate [95% CI] (%), the primary endpoint, was 24.1 [10.3, 43.5], and the lower limit of 95% CI exceeded the predetermined threshold (10%) [see Section 7.1.1.2]. The median OS was not reached, and the OS rate at 1 year was 82.7% (OS was a secondary endpoint in Study 041).

PMDA's view:

Based on the above results, PMDA has concluded that pembrolizumab is expected to be effective in Japanese patients with unresectable malignant melanoma.

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 in patients with unresectable malignant melanoma who receive pembrolizumab:

gastrointestinal disorders, skin disorders, neurological disorders, hepatic dysfunction, eye disorders, endocrine dysfunction, renal dysfunction, interstitial lung disease (ILD), infusion related reaction (IRR), pancreatitis, myositis, encephalitis and meningitis, and myasthenia gravis.

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 from Studies 002 and 006:

The safety results of Studies 002 and 006 are summarized in Table 26.

Table 26. Summary of safety (Studies 002 and 006)

	n (%)					
	Study 002			Study 006		
	2 mg/kg Q3W N = 178	10 mg/kg Q3W N = 179	ICC N = 171	10 mg/kg Q3W N = 277	10 mg/kg Q2W N = 278	IPI N = 256
All adverse events	172 (96.6)	178 (99.4)	167 (97.7)	264 (95.3)	275 (98.9)	239 (93.4)
Grade ≥3 adverse events	83 (46.6)	79 (44.1)	88 (51.5)	92 (33.2)	105 (37.8)	94 (36.7)
Adverse events leading to death	13 (7.3)	8 (4.5)	11 (6.4)	5 (1.8)	7 (2.5)	7 (2.7)
Serious adverse events	83 (46.6)	68 (38.0)	59 (34.5)	71 (25.6)	77 (27.7)	81 (31.6)
Adverse events leading to treatment discontinuation	18 (10.1)	26 (14.5)	20 (11.7)	30 (10.8)	20 (7.2)	34 (13.3)
Adverse events leading to dose reduction	NA	NA	26 (15.2)	NA	NA	1 (0.4)
Adverse events leading to treatment interruption	23 (12.9)	26 (14.5)	35 (20.5)	56 (20.2)	61 (21.9)	22 (8.6)

Study 002:

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 ICC group included abdominal pain (13.5% in the 2 mg/kg Q3W group, 13.4% in the 10 mg/kg Q3W group, 8.2% in the ICC group), pyrexia (12.4%, 15.1%, 9.4%), hyponatraemia (10.7%, 6.7%, 4.7%), arthralgia (15.2%, 12.3%, 9.9%), dyspnoea (9.6%, 17.3%, 12.3%), pruritus (25.3%, 30.2%, 7.6%), rash (13.5%, 14.0%, 7.6%), hypothyroidism (6.2%, 8.4%, 0.6%), dry skin (7.3%, 8.4%, 2.9%), and rash maculo-papular (5.1%, 7.3%, 0%). 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 ICC group included hyponatraemia (3.4%, 2.8%, 1.2%) and dehydration (2.8%, 0%, 0.6%). There were no serious adverse events, adverse events leading to treatment discontinuation, or adverse events leading to death with a ≥2% higher incidence in either the pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W group than the ICC group.

Study 006:

Adverse events of any grade with a ≥5% higher incidence in either the pembrolizumab 10 mg/kg Q3W

or 10 mg/kg Q2W group than the IPI group included hypothyroidism (8.3% in the 10 mg/kg Q3W group, 10.1% in the 10 mg/kg Q2W group, 2.0% in the IPI group), dry mouth (6.9%, 9.7%, 0.4%), arthralgia (17.3%, 18.0%, 9.8%), back pain (10.8%, 13.3%, 6.6%), myalgia (6.1%, 11.9%, 4.3%), cough (15.2%, 18.0%, 7.4%), and vitiligo (12.3%, 9.4%, 1.6%). There were no Grade ≥3 adverse events, serious adverse events, adverse events leading to treatment discontinuation, or adverse events leading to death with a ≥2% higher incidence in either the pembrolizumab 10 mg/kg Q3W or 10 mg/kg Q2W group than the IPI group.

The applicant's explanation about the effect of different dosage regimens on the safety:
Study 002:
Adverse events of any grade with a ≥5% higher incidence in the pembrolizumab 2 mg/kg Q3W group than the 10 mg/kg Q3W group included anaemia (17.4% in the 2 mg/kg Q3W group, 11.2% in the 10 mg/kg Q3W group). Grade ≥3 adverse events with a ≥2% higher incidence in the 2 mg/kg Q3W group than the 10 mg/kg Q3W group included anaemia (7.9%, 2.2%), generalised oedema (2.2%, 0%), and dehydration (2.8%, 0%). The serious adverse event with a ≥2% higher incidence in the 2 mg/kg Q3W group was anaemia (3.9%, 0%). There were no adverse events leading to death with a ≥2% higher incidence in the 2 mg/kg Q3W group.

Adverse events of any grade with a ≥5% higher incidence in the pembrolizumab 10 mg/kg Q3W group than the 2 mg/kg Q3W group included fatigue (38.8%, 46.9%), decreased appetite (16.3%, 24.6%), headache (8.4%, 14.0%), dyspnoea (9.6%, 17.3%), vomiting (8.4%, 18.4%), and nasopharyngitis (3.4%, 8.9%). The Grade ≥3 adverse event with a ≥2% higher incidence in the 10 mg/kg Q3W group was dyspnoea (1.1%, 3.9%). The serious adverse event with a ≥2% higher incidence in the 10 mg/kg Q3W group was general physical health deterioration (0.6%, 2.8%). There were no adverse events leading to death with a ≥2% higher incidence in the 10 mg/kg Q3W group.

Study 006:
There were no adverse events of any grade with a ≥5% higher incidence in the pembrolizumab 10 mg/kg Q3W group than the 10 mg/kg Q2W group, or Grade ≥3 adverse events, serious adverse events, or adverse events leading to death with a ≥2% higher incidence in the 10 mg/kg Q3W group.

Adverse events of any grade with a ≥5% higher incidence in the pembrolizumab 10 mg/kg Q2W group than the 10 mg/kg Q3W group included constipation (11.6% in the 10 mg/kg Q3W group, 16.9% in the 10 mg/kg Q2W group), headache (11.2%, 16.2%), and myalgia (6.1%, 11.9%). The Grade ≥3 adverse event with a ≥2% higher incidence in the 10 mg/kg Q2W group was diarrhoea (0.7%, 3.6%). There were no adverse events leading to death with a ≥2% higher incidence in the 10 mg/kg Q2W group.

PMDA's view:
In Studies 002 and 006, the incidence of adverse events was higher in the pembrolizumab group than in the ICC or IPI group, but most of the events were at Grade ≤2. Therefore, pembrolizumab is tolerable

in patients with unresectable malignant melanoma, provided that physicians with sufficient knowledge and experience in cancer chemotherapy take appropriate measures, such as monitoring of relevant adverse events and interruption of pembrolizumab. During treatment with pembrolizumab, however, attention should be paid to events with a higher incidence in the pembrolizumab group than the ICC or IPI group in Studies 002 and 006. Information on these events should be appropriately provided to healthcare professionals through a package insert, etc.

Some adverse events had different incidences between different dosing regimens of pembrolizumab (i.e., 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W), but most of the events were at Grade ≤2 with no clinically relevant differences between the dosing regimens. PMDA has concluded that the safety of pembrolizumab is similar regardless of dosage.

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

The applicant explained differences in safety between Japanese and non-Japanese patients, based on the safety information from patients receiving pembrolizumab 2 mg/kg Q3W in Studies 041 and 002.

The applicant's explanation:

The safety results in the pembrolizumab 2 mg/kg Q3W group in Studies 041 and 002 are summarized in Table 27.

Table 27. Summary of safety (Studies 041 and 002)

	n (%)	
	Study 041 N = 42	Study 002 2 mg/kg Q3W N = 178
Adverse events	41 (97.6)	172 (96.6)
Grade ≥3 adverse events	17 (40.5)	83 (46.6)
Adverse events leading to death	3 (7.1)	13 (7.3)
Serious adverse events	15 (35.7)	83 (46.6)
Adverse events leading to treatment discontinuation	6 (14.3)	18 (10.1)
Adverse events leading to treatment interruption	9 (21.4)	23 (12.9)

The following adverse events of any grade occurred with a ≥10% higher incidence in the pembrolizumab 2 mg/kg Q3W group in Study 041 than in the pembrolizumab 2 mg/kg Q3W group in Study 002: malaise (14.3% in Japanese patients, 3.4% in non-Japanese patients), nasopharyngitis (26.2%, 3.4%), and rash maculo-papular (16.7%, 5.1%) There were no Grade ≥3 adverse events, adverse events leading to death, or adverse events leading to treatment discontinuation, with a ≥5% higher incidence in Study 041 than in Study 002.

PMDA's view:

The safety of pembrolizumab in Japanese and non-Japanese patients cannot be strictly compared because of the limited number of Japanese patients who received pembrolizumab. Some adverse events occurred more frequently in Japanese patients than in non-Japanese patients, but most of the events were at Grade ≤2, and pembrolizumab is intended to be administered by physicians with sufficient knowledge

and experience in cancer chemotherapy. This means that pembrolizumab is expected to be tolerable in Japanese patients as well. Nevertheless, healthcare professionals should be informed, through information materials, about the adverse events that occurred more frequently in Japanese patients than in non-Japanese patients.

Based on safety results of pembrolizumab mainly in Studies 002, 006, and 041, PMDA reviewed (a) adverse events with a higher incidence in the pembrolizumab group than in the control group, and (b) adverse events requiring attention during treatment with drugs with a mechanism of action similar to that of pembrolizumab. The details are presented in the following sections.

Results mainly from Studies 002 and 041 are described below, because the proposed dosage and administration of pembrolizumab is 2 mg/kg Q3W, and there was no clear difference in safety between pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W regimens. Adverse events in Study 006 are described in Section 7.2.5.

7.R.3.3 Gastrointestinal disorders

The applicant's explanation about gastrointestinal disorders in patients treated with pembrolizumab:

The applicant collected data on adverse events of gastrointestinal disorders classified as "Pseudomembranous colitis," "Gastrointestinal nonspecific inflammation," or "Gastrointestinal nonspecific symptoms and therapeutic procedures" under Medical Dictionary for Regulatory Activities (MedDRA) standardised MedDRA queries (SMQ).

Table 28 shows the incidence of gastrointestinal disorders in the pembrolizumab 2 mg/kg Q3W group and ICC group in Study 002 as well as in Study 041.

Table 28. Incidences of gastrointestinal disorders reported by ≥3% of subjects in any group (Studies 002 and 041)

PT (MedDRA ver.18.0)	n (%)					
	Study 002				Study 041 N = 42	
	2 mg/kg Q3W N = 178		ICC N = 171			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal disorders	91 (51.1)	14 (7.9)	109 (63.7)	18 (10.5)	20 (47.6)	2 (4.8)
Constipation	38 (21.3)	1 (0.6)	35 (20.5)	4 (2.3)	9 (21.4)	0
Diarrhoea	37 (20.8)	1 (0.6)	34 (19.9)	4 (2.3)	6 (14.3)	0
Nausea	35 (19.7)	2 (1.1)	71 (41.5)	5 (2.9)	7 (16.7)	1 (2.4)
Abdominal pain	25 (14.0)	4 (2.2)	14 (8.2)	2 (1.2)	2 (4.8)	0
Vomiting	16 (9.0)	4 (2.2)	39 (22.8)	5 (2.9)	4 (9.5)	0
Abdominal distension	8 (4.5)	0	4 (2.3)	0	0	0
Abdominal pain upper	5 (2.8)	0	5 (2.9)	0	3 (7.1)	0
Colitis	2 (1.1)	0	1 (0.6)	1 (0.6)	2 (4.8)	1 (2.4)

Study 002:

No adverse events of gastrointestinal disorders leading to death occurred. Serious gastrointestinal disorders occurred in 6.2% (11 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (vomiting

[3 subjects]; abdominal pain, colitis, and constipation [2 subjects each]; and gastrointestinal pain, nausea, clostridium difficile colitis, and diverticulitis [1 subject each] [including duplicate counting]) and in 4.1% (7 of 171) of subjects in the ICC group (nausea [3 subjects]; and abdominal pain, colitis, constipation, diarrhoea, vomiting, and enterocolitis infectious [1 subject each] [including duplicate counting]). A causal relationship to the study drug could not be ruled out for the colitis in 0.6% (1 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group and events in 1.8% (3 of 171) of subjects in the ICC group (nausea [3 subjects] and vomiting [1 subject] [including duplicate counting]). No gastrointestinal disorders leading to treatment discontinuation occurred in the pembrolizumab 2 mg/kg Q3W group, and such an event (colitis) occurred in 0.6% (1 of 171) of subjects in the ICC group. Gastrointestinal disorders leading to interruption occurred in 1.7% (3 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (colitis [2 subjects] and mucosal inflammation [1 subject]) and in 1.2% (2 of 171) of subjects in the ICC group (abdominal distension, diarrhoea, and gastrointestinal toxicity [including duplicate counting] [1 subject each]).

Study 041:

There were no gastrointestinal disorders leading to death or treatment discontinuation. Serious gastrointestinal disorders occurred in 2.4% (1 of 42) of subjects (abdominal pain, colitis, and diarrhoea [1 subject each] [including duplicate counting]), and a causal relationship to pembrolizumab could not be ruled out for these events. Gastrointestinal disorders leading to treatment interruption occurred in 7.1% (3 of 42) of subjects (colitis [2 subjects]; abdominal pain, diarrhoea, and gastritis [1 subject each] [including duplicate counting]).

The median time (range) to onset of gastrointestinal disorders was 47 days (1-387 days) in the 2 mg/kg Q3W group in Study 002, and 107.5 days (1-322 days) in Study 041.

Table 29 shows the incidences of colitis and diarrhoea in Study 002 (the pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W groups) and Study 041. In clinical studies of pembrolizumab, treatment with corticosteroids was recommended depending on severity of colitis and diarrhoea.

Table 29. Incidences of colitis and diarrhoea (Studies 002 and 041)

PT (MedDRA ver.18.0)	n (%)					
	Study 002				Study 041 N = 42	
	2 mg/kg Q3W N = 178		10 mg/kg Q3W N = 179			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhoea	37 (20.8)	1 (0.6)	33 (18.4)	2 (1.1)	6 (14.3)	0
Colitis	2 (1.1)	0	4 (2.2)	3 (1.7)	2 (4.8)	1 (2.4)

No colitis or diarrhoea leading to death occurred in Study 002 or 041. Serious colitis and diarrhoea occurred in 1.1% (2 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (colitis [2 subjects]) and in 2.2% (4 of 179) of subjects in the 10 mg/kg Q3W group (diarrhoea [3 subjects] and colitis [1 subject]) in Study 002, and in 2.4% (1 of 42) of subjects in Study 041 (colitis and diarrhoea [1 subject each] [including duplicate counting]). Of these, a causal relationship to the study drug could not be ruled out for colitis in 0.6% (1 of 178) of subjects in the 2 mg/kg Q3W group and the diarrhoea in 1.7% (3 of 179) of subjects in the 10 mg/kg Q3W group in Study 002.

The median time (range) to onset of serious colitis and diarrhoea was 140.5 days (42-288 days) in Studies 002 and 041.

PMDA's view:

Because serious gastrointestinal disorders such as colitis and diarrhoea occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of gastrointestinal disorders in patients receiving pembrolizumab. Therefore, information on the occurrence of gastrointestinal disorders in clinical studies should be appropriately provided to healthcare professionals using a package insert, etc. In addition, information on recommended actions to address colitis and diarrhoea should be appropriately provided to healthcare professionals using information materials, etc.

7.R.3.4 Skin disorders

The applicant's explanation about skin disorders in patients treated with pembrolizumab:

The applicant collected data on adverse events of skin disorders coded to "Skin and subcutaneous tissue disorders" (MedDRA system organ class [SOC]).

Table 30 shows the incidences of skin disorders in the pembrolizumab 2 mg/kg Q3W group and ICC group in Study 002 as well as in Study 041.

Table 30. Incidences of skin disorders reported by ≥3% of subjects in any group (Studies 002 and 041)

PT (MedDRA ver.18.0)	n (%)					
	Study 002				Study 041 N = 42	
	2 mg/kg Q3W N = 178		ICC N = 171			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorders	89 (50.0)	4 (2.2)	62 (36.3)	2 (1.2)	28 (66.7)	1 (2.4)
Pruritus	45 (25.3)	0	13 (7.6)	0	10 (23.8)	0
Rash	24 (13.5)	0	13 (7.6)	0	2 (4.8)	0
Dry skin	13 (7.3)	0	5 (2.9)	0	5 (11.9)	0
Vitiligo	11 (6.2)	0	3 (1.8)	0	3 (7.1)	0
Rash maculo-papular	9 (5.1)	1 (0.6)	0	0	7 (16.7)	0
Hyperhidrosis	7 (3.9)	0	3 (1.8)	0	0	0
Alopecia	6 (3.4)	0	35 (20.5)	1 (0.6)	1 (2.4)	0
Erythema	6 (3.4)	1 (0.6)	5 (2.9)	0	0	0
Night sweats	4 (2.2)	0	9 (5.3)	0	0	0
Skin hypopigmentation	4 (2.2)	0	0	0	2 (4.8)	0
Eczema	2 (1.1)	0	0	0	2 (4.8)	0
Miliaria	0	0	0	0	3 (7.1)	0
Eczema asteatotic	0	0	0	0	2 (4.8)	0
Seborrhoeic dermatitis	0	0	0	0	2 (4.8)	0

Study 002:

No skin disorders leading to death occurred. Serious skin disorders occurred in 1.7% (3 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (rash maculo-papular, skin mass, and Stevens-Johnson syndrome [SJS] [1 subject each]), but did not occur in the ICC group. Of these, a causal relationship to the study drug could not be ruled out for the SJS in 0.6% (1 of 178) of subjects in the 2

mg/kg Q3W group. Skin disorders leading to treatment discontinuation occurred in 0.6% (1 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (SJS) and in 0.6% (1 of 171) of subjects in the ICC group (alopecia). Skin disorders leading to treatment interruption occurred in 1.1% (2 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (rash maculo-papular [2 subjects] and palmar-plantar erythrodysaesthesia syndrome [1 subject] [including duplicate counting]) and in 0.6% (1 of 171) of subjects in the ICC group (hyperhidrosis).

Study 041:
No skin disorders leading to death or treatment discontinuation occurred. Serious skin disorders occurred in 2.4% (1 of 42) of subjects (drug eruption), and a causal relationship to pembrolizumab could not be ruled out for this event. Skin disorders leading to treatment interruption occurred in 2.4% (1 of 42) of subjects (drug eruption).

The median time (range) to onset of skin disorders was 53 days (1-365 days) in the pembrolizumab 2 mg/kg Q3W group in Study 002, and 128 days (5-332 days) in Study 041.

Table 31 shows details of patients who experienced SJS, erythema multiforme, pemphigoid, and toxic skin eruption in clinical studies of pembrolizumab.

Table 31. List of patients who experienced SJS, erythema multiforme, pemphigoid, and toxic skin eruption

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 002	76	Male	SJS	3	4	2 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
	60	Male	Erythema multiforme	3	176	10 mg/kg Q3W	None	Interrupted	Yes	Serious	Not resolved
Study 006	71	Male	Pemphigoid	3	8	10 mg/kg Q2W	Corticosteroid	Interrupted	Yes	Non-serious	Not resolved
Study 041	56	Male	Toxic skin eruption	1	13	2 mg/kg Q3W	None	Continued	Yes	Non-serious	Resolved

Outside Japan, pemphigoid occurred in 4 patients in the post-marketing setting, and a causal relationship between the events and pembrolizumab could not be ruled out.

PMDA's view:
Because serious skin disorders such as SJS occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of skin disorders in patients receiving pembrolizumab. Therefore, information on the occurrence of skin disorders in clinical studies, etc. should be appropriately provided to healthcare professionals using a package insert, etc. Information on recommended actions to address serious skin disorders such as SJS, should be appropriately provided to healthcare professionals using information materials, etc.

7.R.3.5 Neurological disorders

The applicant's explanation about neurological disorders in patients treated with pembrolizumab:

The applicant collected data on adverse events of neurological disorders coded to "Nervous system disorders" (MedDRA SOC), except for events coded to "Myasthenic syndrome" or "Encephalitis and meningitis."

Table 32 shows the incidences of neurological disorders in the pembrolizumab 2 mg/kg Q3W group and ICC group in Study 002 as well as in Study 041.

Table 32. Incidences of neurological disorders reported by ≥1% of subjects in any group (Studies 002 and 041)

PT (MedDRA ver.18.0)	n (%)					
	Study 002				Study 041 N = 42	
	2 mg/kg Q3W N = 178		ICC N = 171			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Nervous system disorders	58 (32.6)	10 (5.6)	79 (46.2)	7 (4.1)	5 (11.9)	1 (2.4)
Headache	15 (8.4)	0	22 (12.9)	1 (0.6)	1 (2.4)	0
Dizziness	13 (7.3)	1 (0.6)	15 (8.8)	0	2 (4.8)	0
Paraesthesia	4 (2.2)	1 (0.6)	12 (7.0)	0	0	0
Syncope	4 (2.2)	3 (1.7)	2 (1.2)	2 (1.2)	0	0
Dysgeusia	3 (1.7)	0	11 (6.4)	0	2 (4.8)	0
Hypoaesthesia	3 (1.7)	0	4 (2.3)	0	0	0
Neuropathy peripheral	3 (1.7)	0	18 (10.5)	2 (1.2)	0	0
Presyncope	2 (1.1)	0	0	0	1 (2.4)	0
Peripheral sensory neuropathy	1 (0.6)	0	6 (3.5)	0	0	0
Polyneuropathy	0	0	4 (2.3)	0	0	0
Cerebral haemorrhage	0	0	0	0	1 (2.4)	1 (2.4)
Encephalopathy	0	0	0	0	1 (2.4)	1 (2.4)

Study 002:

No neurological disorders leading to death occurred in the pembrolizumab 2 mg/kg Q3W group, but occurred in 0.6% (1 of 171) of subjects in the ICC group (haemorrhage intracranial). Serious neurological disorders occurred in 6.2% (11 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (syncope and partial seizures [2 subjects each], and cerebrovascular accident, dizziness, encephalopathy, epilepsy, paraesthesia, seizure, and spinal cord compression [1 subject each]), and occurred in 2.9% (5 of 171) of subjects in the ICC group (ataxia, haemorrhage intracranial, myoclonus, syncope, and transient ischaemic attack [1 subject each]), and a causal relationship to the study drug was ruled out for these events. No neurological disorders leading to treatment discontinuation occurred in the pembrolizumab 2 mg/kg Q3W group, but occurred in 2.3% (4 of 171) of subjects in the ICC group (neuropathy peripheral [2 subjects], and haemorrhage intracranial and myoclonus [1 subject each]). Neurological disorders leading to treatment interruption occurred in 0.6% (1 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (neuropathy peripheral) and in 2.9% (5 of 171) of subjects in the ICC group (neuropathy peripheral and polyneuropathy [2 subjects each], and peripheral sensorimotor neuropathy [1 subject]).

Study 041:

Neurological disorders leading to death occurred in 2.4% (1 of 42) of subjects (cerebral haemorrhage). Serious neurological disorders occurred in 2.4% (1 of 42) of subjects (cerebral haemorrhage and encephalopathy [1 subject each] [including duplicate counting]), and a causal relationship to

pembrolizumab could not be ruled out for these events. Neurological disorders leading to treatment discontinuation occurred in 2.4% (1 of 42) of subjects (cerebral haemorrhage and encephalopathy [1 subject each] [including duplicate counting]).

The median time (range) to onset of neurological disorders was 50.5 days (1-303 days) in the pembrolizumab 2 mg/kg Q3W group in Study 002, and 93.5 days (22-253 days) in Study 041.

Table 33 shows details of the patient who experienced Guillain-Barre syndrome in clinical studies of pembrolizumab.

Table 33. List of patients who experienced Guillain-Barre syndrome

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 006	58	Male	Guillain-Barre syndrome	4	28	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved

Outside Japan, Guillain-Barre syndrome was reported in 1 patient in the post-marketing setting, and a causal relationship to pembrolizumab could not be ruled out for this event.

PMDA's view:
Because serious neurological disorders occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of neurological disorders in patients receiving pembrolizumab. Therefore, information on the occurrence of neurological disorders in clinical studies should be appropriately provided to healthcare professionals using a package insert, etc. Guillain-Barre syndrome occurred very rarely in clinical studies of pembrolizumab, and the relationship between pembrolizumab and the event remains unclear at present. However, attention should be paid to Guillain-Barre syndrome in patients receiving pembrolizumab. Thus, information on the occurrence of Guillain-Barre syndrome should be appropriately provided to healthcare professionals through information materials, etc.

7.R.3.6 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction in patients treated with pembrolizumab:
The applicant collected data on adverse events of hepatic dysfunction coded to "Drug related hepatic disorders (severe events only) (broad)" (MedDRA SMQ) or "Liver related investigations, signs and symptoms (broad)" (MedDRA SMQ).

Table 34 shows the incidences of hepatic dysfunction in the pembrolizumab 2 mg/kg Q3W group and the ICC group in Study 002 as well as in Study 041.

Table 34. Incidences of hepatic dysfunction (Studies 002 and 041)

PT (MedDRA ver.18.0)	n (%)					
	Study 002				Study 041 N = 42	
	2 mg/kg Q3W N = 178		ICC N = 171			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction	29 (16.3)	10 (5.6)	24 (14.0)	3 (1.8)	3 (7.1)	0
Blood ALP increased	10 (5.6)	2 (1.1)	3 (1.8)	1 (0.6)	0	0
AST increased	8 (4.5)	1 (0.6)	2 (1.2)	0	3 (7.1)	0
ALT increased	8 (4.5)	0	5 (2.9)	0	2 (4.8)	0
Hypoalbuminaemia	5 (2.8)	2 (1.1)	9 (5.3)	1 (0.6)	0	0
Ascites	4 (2.2)	2 (1.1)	3 (1.8)	1 (0.6)	0	0
Blood bilirubin increased	4 (2.2)	1 (0.6)	4 (2.3)	0	0	0
GGT increased	3 (1.7)	0	3 (1.8)	0	0	0
Autoimmune hepatitis	2 (1.1)	1 (0.6)	0	0	0	0
Hepatic failure	1 (0.6)	1 (0.6)	0	0	0	0
Hyperbilirubinaemia	1 (0.6)	0	1 (0.6)	1 (0.6)	0	0
Hepatic pain	0	0	1 (0.6)	0	0	0
Bilirubin conjugated increased	1 (0.6)	0	0	0	0	0
Hepatitis	0	0	1 (0.6)	0	0	0
Hepatic function abnormal	0	0	0	0	1 (2.4)	0

Hepatic dysfunction leading to death occurred in 0.6% (1 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group in Study 002 (hepatic failure), but did not occur in the ICC group. Serious hepatic dysfunction occurred in 0.6% (1 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (hepatic failure) and in 1.8% (3 of 171) of subjects in the ICC group (ascites, hepatitis, hyperbilirubinaemia, AST increased, and blood bilirubin increased [1 subject each] [including duplicate counting]), but they were unrelated to the study drug. Hepatic dysfunction leading to treatment discontinuation occurred in 0.6% (1 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (hepatic failure) and in 0.6% (1 of 171) of subjects in the ICC group (hyperbilirubinaemia). Hepatic dysfunction leading to treatment interruption occurred in 1.1% (2 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (autoimmune hepatitis and AST increased [1 subject each]), but did not occur in the ICC group.

There were no hepatic dysfunction leading to death, serious hepatic dysfunction, or hepatic dysfunction leading to treatment discontinuation in Study 041. Events leading to treatment interruption occurred in 2.4% (1 of 42) of subjects (alanine aminotransferase [ALT] increased and AST increased [1 subject each] [including duplicate counting]).

The median time (range) to onset of hepatic dysfunction was 43 days (4-253 days) in the pembrolizumab 2 mg/kg Q3W group in Study 002 and 73.5 days (43-278 days) in Study 041.

In addition, there was no hepatic dysfunction corresponding to Hy's law cases (defined based on the Guidance for industry. Drug-Induced Liver Injury: premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009) in clinical studies of pembrolizumab.

Table 35 shows details of patients who experienced autoimmune hepatitis in clinical studies of pembrolizumab.

Table 35. List of patients who experienced autoimmune hepatitis

Study	Age	Sex	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 001	58	Male	4	22	2 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
	82	Male	2	22	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Non-serious	Resolved
	60	Male	3 2	651 658	2 mg/kg Q3W	None	Unknown Interrupted	Yes	Non-serious Non-serious	Resolved
Study 002	64	Male	2	127	2 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Non-serious	Resolved
	53	Female	3	8	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Not resolved
Study 006	66	Male	3	17	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
	42	Female	3	54	10 mg/kg Q2W	Corticosteroid	Interrupted	Yes	Serious	Resolved
	53	Female	3	188	10 mg/kg Q2W	Corticosteroid	Unknown	Yes	Serious	Resolved
	71	Male	3	191	10 mg/kg Q2W	Corticosteroid	Discontinued	Yes	Serious	Resolved

PMDA's view:

In addition to autoimmune hepatitis, hepatic dysfunction leading to treatment discontinuation occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies. Therefore, attention should be paid to development of hepatic dysfunction in patients receiving pembrolizumab. In order to raise awareness among healthcare professionals, the package insert, etc. should include (a) information on the occurrence of hepatic dysfunction in clinical studies and (b) a statement to the effect that hepatic functions should be monitored during treatment with pembrolizumab and appropriate measures such as interruption of pembrolizumab should be taken in case of any abnormalities.

7.R.3.7 Eye disorders

The applicant's explanation about eye disorders in patients treated with pembrolizumab:

The applicant collected data on adverse events of eye disorders coded to "Eye disorders" (MedDRA SOC), except for ones coded to "Myasthenic syndrome."

Table 36 shows the incidences of eye disorders in the pembrolizumab 2 mg/kg Q3W group and ICC group in Study 002 as well as in Study 041.

Table 36. Incidences of eye disorders reported by ≥1% of subjects in any group (Studies 002 and 041)

PT (MedDRA ver.18.0)	n (%)					
	Study 002				Study 041 N = 42	
	2 mg/kg Q3W N = 178		ICC N = 171			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders	24 (13.5)	2 (1.1)	16 (9.4)	0	5 (11.9)	0
Vision blurred	5 (2.8)	0	5 (2.9)	0	1 (2.4)	0
Cataract	3 (1.7)	0	0	0	1 (2.4)	0
Lacrimation increased	3 (1.7)	0	1 (0.6)	0	0	0
Vitreous floaters	3 (1.7)	0	1 (0.6)	0	0	0
Dry eye	2 (1.1)	0	0	0	1 (2.4)	0
Eye pruritus	2 (1.1)	0	0	0	0	0
Visual impairment	1 (0.6)	0	2 (1.2)	0	0	0
Photopsia	0	0	3 (1.8)	0	1 (2.4)	0
Blindness	0	0	2 (1.2)	0	0	0
Diplopia	0	0	0	0	1 (2.4)	0
Keratitis	0	0	0	0	1 (2.4)	0
Uveitis	0	0	0	0	1 (2.4)	0

There were no eye disorders leading to death, eye disorders leading to treatment discontinuation, or eye disorders leading to treatment interruption in the pembrolizumab 2 mg/kg Q3W group or the ICC group in Study 002. Serious eye disorders occurred in 0.6% (1 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (eye movement disorder), but did not occur in the ICC group. A causal relationship to the study drug was ruled out for the eye movement disorder in 0.6% (1 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group.

There were no eye disorders leading to death, serious eye disorders, eye disorders leading to treatment discontinuation, or eye disorders leading to treatment interruption in Study 041.

The median time (range) to onset of eye disorders was 55 days (5-205 days) in the pembrolizumab 2 mg/kg Q3W group in Study 002, and 65 days (1-279 days) in Study 041.

Table 37 shows details of patients who experienced uveitis (including iritis and iridocyclitis) in clinical studies of pembrolizumab.

Table 37. List of patients who experienced uveitis (including iritis and iridocyclitis)

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 001	61	Male	Iritis	1	225	10 mg/kg Q2W	Corticosteroid	Continued	Yes	Non-serious	Not resolved
	60	Male	Uveitis	2	53	10 mg/kg Q3W	Corticosteroid	Continued	Yes	Non-serious	Resolved
	70	Female	Uveitis	2 1	30 42	10 mg/kg Q3W	Corticosteroid Corticosteroid	Interrupted Continued	Yes Yes	Non-serious Non-serious	Resolved Resolved
	47	Female	Iridocyclitis	2	233	10 mg/kg Q3W	Corticosteroid	Continued	Yes	Non-serious	Resolved
	64	Male	Uveitis	2	107	2 mg/kg Q3W	Drugs other than corticosteroids	Continued	Yes	Non-serious	Resolved
	37	Female	Uveitis	2 1	47 62	10 mg/kg Q3W	Corticosteroid Corticosteroid	Continued Continued	Yes Yes	Non-serious Non-serious	Resolved Resolved
Study 002	69	Male	Uveitis	2 1	64 106	10 mg/kg Q3W	Corticosteroid None	Continued Continued	Yes Yes	Non-serious Non-serious	Resolved Resolved
	53	Female	Iritis	3	13	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Serious	Resolved
Study 006	63	Female	Uveitis	2	44	10 mg/kg Q2W	Corticosteroid	Interrupted	Yes	Non-serious	Not resolved
	71	Male	Uveitis	2	63	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Non-serious	Resolved
	65	Male	Iridocyclitis	2	63	10 mg/kg Q3W	Corticosteroid	Continued	Yes	Non-serious	Resolved
	71	Male	Uveitis	2	33	10 mg/kg Q3W	Corticosteroid	Continued	Yes	Non-serious	Resolved
Study 041	43	Female	Uveitis	2	158	2 mg/kg Q3W	Corticosteroid	Continued	Yes	Non-serious	Resolved

PMDA's view:

Uveitis occurred in patients receiving pembrolizumab in Japanese and foreign clinical studies, but most of them were at Grade ≤2 and resolved with treatment such as instillation of corticosteroid preparations. Nevertheless, attention should be paid to development of eye disorders such as uveitis. Information on the occurrence of eye disorders in clinical studies should be appropriately provided to healthcare professionals using a package insert, etc. In addition, information on recommended actions to address uveitis should be appropriately provided to healthcare professionals using information materials, etc.

7.R.3.8 Endocrine dysfunction

The applicant's explanation about endocrine dysfunction in patients treated with pembrolizumab:

The applicant collected data on adverse events of endocrine dysfunction coded to the following MedDRA preferred terms (PTs): "hypothyroidism," "hypothyroidic goitre," "myxoedema," "myxoedema coma," "primary hypothyroidism," "hyperthyroidism," "Basedow's disease," "thyrotoxic crisis," "thyroid disorder," "thyroiditis," "autoimmune thyroiditis," "thyroiditis acute," "hypophysitis," "hypopituitarism," "lymphocytic hypophysitis," "adrenal insufficiency," "adrenocortical insufficiency acute," "secondary adrenocortical insufficiency," "diabetic ketoacidosis," "diabetic ketoacidotic

hyperglycaemic coma," "fulminant type 1 diabetes mellitus," "latent autoimmune diabetes in adults," and "type 1 diabetes mellitus."

(a) Thyroid dysfunction:

Table 38 shows the incidences of thyroid dysfunction in the pembrolizumab 2 mg/kg Q3W group and ICC group in Study 002 as well as in Study 041.

Table 38. Incidences of thyroid dysfunction (Studies 002 and 041)

PT (MedDRA ver.18.0)	n (%)					
	Study 002				Study 041 N = 42	
	2 mg/kg Q3W N = 178		ICC N = 171			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Thyroid dysfunction	18 (10.1)	0	1 (0.6)	0	7 (16.7)	0
Hypothyroidism	11 (6.2)	0	1 (0.6)	0	5 (11.9)	0
Hyperthyroidism	7 (3.9)	0	0	0	2 (4.8)	0

Study 002:

There were no thyroid dysfunction leading to death, serious thyroid function abnormal, or thyroid function abnormal leading to discontinuation or interruption of the study drug.

Study 041:

There were no thyroid dysfunction leading to death, serious thyroid dysfunction, or thyroid dysfunction leading to treatment discontinuation. Thyroid dysfunction leading to treatment interruption occurred in 2.4% (1 of 42) of subjects (hypothyroidism).

Table 39 shows details of patients who experienced autoimmune thyroiditis in clinical studies of pembrolizumab.

Table 39. List of patients who experienced autoimmune thyroiditis

Study	Age	Sex	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 001	71	Female	2	64	10 mg/kg Q3W	None	Continued	Unknown	Non-serious	Resolved
			1	85		Levothyroxine	Continued	No	Non-serious	Not resolved
	87	Male	2	64	10 mg/kg Q3W	None	Continued	Yes	Non-serious	Not resolved
Study 002	62	Female	1	21	10 mg/kg Q3W	Levothyroxine	Continued	Yes	Non-serious	Resolved
	34	Female	2	25	10 mg/kg Q3W	Levothyroxine	Continued	Yes	Non-serious	Resolved

(b) Pituitary dysfunction:

Table 40 shows details of patients who experienced pituitary dysfunction in clinical studies of pembrolizumab.

Table 40. List of patients who experienced pituitary dysfunction

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 001	73	Male	Hypophysitis	4	52	2 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Serious	Resolved
			Hypophysitis	2	58		None	Continued	Yes	Non-serious	Not resolved
	68	Female	Hypophysitis	2	40	2 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
	59	Male	Hypophysitis	2	15	10 mg/kg Q2W	Corticosteroid	Continued	No	Non-serious	Not resolved
	71	Male	Hypopituitarism	1	186	2 mg/kg Q3W	Corticosteroid	Continued	Yes	Non-serious	Not resolved
	63	Female	Hypopituitarism	2	169	2 mg/kg Q3W	Corticosteroid	Continued	No	Non-serious	Not resolved
	38	Female	Hypopituitarism	1	198	10 mg/kg Q2W	Corticosteroid	Continued	Yes	Non-serious	Resolved
Study 002	65	Male	Hypopituitarism	3	28	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Not resolved
	67	Male	Hypophysitis	2	100	10 mg/kg Q3W	None	Unknown	Yes	Non-serious	Not resolved
	76	Male	Hypopituitarism	3	13	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
	69	Female	Hypophysitis	3	1	2 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
Study 006	76	Male	Hypopituitarism	3	131	10 mg/kg Q2W	Corticosteroid	Interrupted	Yes	Serious	Resolved
			Hypopituitarism	2	143		Corticosteroid	Continued	Yes	Non-serious	Not resolved
	74	Male	Hypophysitis	2	148	10 mg/kg Q3W	Corticosteroid	Interrupted	No	Non-serious	Resolved
	63	Male	Hypophysitis	3	219	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Serious	Resolved
Study 041	79	Female	Hypopituitarism	1	27	2 mg/kg Q3W	None	Unknown	No	Non-serious	Not resolved
	43	Female	Hypophysitis	2	220	2 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Not resolved
	56	Male	Hypophysitis	3	242	2 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Serious	Not resolved

(c) Adrenal dysfunction:

Table 41 shows details of patients who experienced adrenal dysfunction in clinical studies of pembrolizumab.

Table 41. List of patients who experienced adrenal dysfunction

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 001	83	Male	Adrenal insufficiency	1	26	10 mg/kg Q3W	None	Unknown	No	Non-serious	Not resolved
	73	Male	Adrenal insufficiency	1	189	10 mg/kg Q3W	None	Unknown	Yes	Non-serious	Resolved
			Adrenal insufficiency	3	194		None	Continued	Yes	Serious	Resolved
			Adrenal insufficiency	2	197		Corticosteroid	Continued	Yes	Non-serious	Not resolved
	87	Male	Adrenal insufficiency	3	360	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Serious	Resolved
			Adrenal insufficiency	2	363		Corticosteroid	Continued	Yes	Non-serious	Not resolved
	68	Female	Adrenal insufficiency	3	44	2 mg/kg Q3W	None	Unknown	No	Non-serious	Resolved
			Adrenal insufficiency	2	49		None	Unknown	No	Non-serious	Not resolved
	52	Female	Adrenal insufficiency	2	58	10 mg/kg Q2W	Corticosteroid	Continued	Yes	Non-serious	Not resolved
	66	Female	Adrenal insufficiency	2	505	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Non-serious	Resolved
Study 002	70	Female	Adrenocortical insufficiency acute	3	132	2 mg/kg Q3W	Corticosteroid	Continued	No	Serious	Resolved
	51	Female	Adrenocortical insufficiency acute	3	108	10 mg/kg Q3W	None	Continued	No	Serious	Not resolved
Study 006	77	Male	Adrenal insufficiency	4	158	10 mg/kg Q2W	Corticosteroid	Discontinued	Yes	Serious	Not resolved
	83	Female	Adrenal insufficiency	3	83	10 mg/kg Q2W	Corticosteroid	Interrupted	Yes	Serious	Not resolved
	53	Female	Adrenal insufficiency	2	128	10 mg/kg Q3W	Corticosteroid	Continued	Yes	Non-serious	Not resolved

(d) Type 1 diabetes mellitus:

Table 42 shows details of patients who experienced type 1 diabetes mellitus or diabetic ketoacidosis in clinical studies of pembrolizumab.

Table 42. List of patients who experienced type 1 diabetes mellitus or diabetic ketoacidosis

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 001	57	Female	Type 1 diabetes mellitus	2	386	10 mg/kg Q3W	Oral antidiabetic	Continued	Yes	Serious	Not resolved
Study 006	64	Female	Type 1 diabetes mellitus	4	106	10 mg/kg Q3W	None	Discontinued	Yes	Serious	Not resolved
	89	Female	Diabetic ketoacidosis	3	37	10 mg/kg Q2W	None	Continued	No	Serious	Resolved

PMDA's view:

Because serious endocrine dysfunction occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of endocrine dysfunction in patients receiving pembrolizumab. In order to raise awareness among healthcare professionals, the package insert, etc. should include (a) information on the occurrence of endocrine disorders in clinical studies

and (b) a statement to the effect that endocrine functions should be monitored during treatment with pembrolizumab and appropriate measures such as interruption of pembrolizumab should be taken in case of any abnormalities. In addition, information on recommended actions to address endocrine dysfunction should be appropriately provided to healthcare professionals using information materials, etc.

7.R.3.9 Renal dysfunction

The applicant's explanation about renal dysfunction in patients treated with pembrolizumab:

The applicant collected data on adverse events of renal dysfunction coded to "Acute renal failure" (MedDRA SMQ), "Glomerulonephritis and nephrotic syndrome" (MedDRA High Level Term [HLT]), or "Nephritis NEC" (MedDRA PT).

Table 43 shows the incidences of renal dysfunction in the pembrolizumab 2 mg/kg Q3W group and ICC group in Study 002 as well as in Study 041.

Table 43. Incidences of renal dysfunction (Studies 002 and 041)

PT (MedDRA ver.18.0)	n (%)					
	Study 002				Study 041 N = 42	
	2 mg/kg Q3W N = 178		ICC N = 171			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal disorders	11 (6.2)	0	10 (5.8)	1 (0.6)	1 (2.4)	0
Blood creatinine increased	6 (3.4)	0	4 (2.3)	0	1 (2.4)	0
Acute kidney injury	2 (1.1)	0	2 (1.2)	1 (0.6)	0	0
Renal failure	1 (0.6)	0	1 (0.6)	0	0	0
Blood urea increased	1 (0.6)	0	2 (1.2)	0	0	0
Urine output decreased	1 (0.6)	0	0	0	0	0
Tubulointerstitial nephritis	1 (0.6)	0	0	0	0	0
Proteinuria	0	0	2 (1.2)	0	0	0
Oliguria	0	0	1 (0.6)	0	0	0

Study 002:

No renal disorders leading to death occurred. Serious renal disorders occurred in 1.1% (2 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (acute kidney injury and tubulointerstitial nephritis [1 subject each]) and 0.6% (1 of 171) of subjects in the ICC group (acute kidney injury). A causal relationship to the study drug could not be ruled out for the tubulointerstitial nephritis in 0.6% (1 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group and the acute kidney injury in 0.6% (1 of 171) of subjects in the ICC group. Renal disorders leading to treatment discontinuation did not occur in the pembrolizumab 2 mg/kg Q3W group, but occurred in 0.6% (1 of 171) of subjects in the ICC group (acute kidney injury). Adverse events leading to treatment interruption occurred in 1.1% (2 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (renal failure and tubulointerstitial nephritis [1 subject each]), but did not occur in the ICC group.

Study 041:

There were no renal disorders leading to death, serious renal disorders, renal disorders leading to treatment discontinuation, or renal disorders leading to treatment interruption.

The median time (range) to onset of renal disorders was 60 days (22-272 days) in the pembrolizumab 2 mg/kg Q3W group in Study 002, and 106 days in Study 041.

One patient died from renal dysfunction in 1 the post-marketing setting outside Japan. A causal relationship to pembrolizumab could not be ruled out for the renal dysfunction. The cause of the death was renal failure.

PMDA's view:
Because serious renal disorders such as tubulointerstitial nephritis occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of renal disorders in patients receiving pembrolizumab. In order to raise awareness among healthcare professionals, the package insert, etc. should include (a) information on the occurrence of renal dysfunction in clinical studies and (b) a statement to the effect that renal functions should be monitored during treatment with pembrolizumab and appropriate measures such as interruption of pembrolizumab should be taken in case of any abnormalities.

7.R.3.10 ILD

The applicant's explanation about ILD in patients treated with pembrolizumab:
The applicant collected data on adverse events of ILD coded to the following MedDRA PTs: "Acute interstitial pneumonitis," "Interstitial lung disease," "Pneumonitis," or "Idiopathic pneumonia syndrome."

Table 44 shows details of pembrolizumab-treated patients who experienced ILD in Studies 002, 006, 011, and 041.

Table 44. List of patients who experienced ILD (Studies 002, 006, 011, and 041)

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 002	58	Male	Pneumonitis	1	170	2 mg/kg Q3W	None	Continued	No	Non-serious	Resolved
	79	Male	Pneumonitis	1	125	2 mg/kg Q3W	None	Continued	No	Non-serious	Resolved
	75	Female	Pneumonitis	1	84	2 mg/kg Q3W	None	Continued	Yes	Non-serious	Not resolved
	54	Male	Pneumonitis	2	93	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
	61	Male	Pneumonitis	3	35	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
	59	Female	Pneumonitis	3	77	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
			Pneumonitis	2	82		Corticosteroid	Discontinued	No	Non-serious	Resolved
	74	Female	Interstitial lung disease	3	85	10 mg/kg Q3W	Antibacterial	Discontinued	Yes	Serious	Not resolved
Study 006	81	Male	Pneumonitis	2	187	10 mg/kg Q3W	Corticosteroid	Unknown	Yes	Serious	Resolved
	59	Male	Pneumonitis	1	247	10 mg/kg Q3W	None	Continued	Yes	Non-serious	Resolved
	79	Male	Pneumonitis	3	29	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Resolved
	67	Female	Pneumonitis	2	169	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Non-serious	Resolved
	89	Female	Pneumonitis	2	209	10 mg/kg Q3W	None	Interrupted	Yes	Non-serious	Not resolved
	87	Male	Pneumonitis	2	40	10 mg/kg Q3W	None	Continued	No	Non-serious	Not resolved
	34	Female	Pneumonitis	2	29	10 mg/kg Q2W	Corticosteroid	Interrupted	Yes	Serious	Resolved
	53	Female	Pneumonitis	3	188	10 mg/kg Q2W	Corticosteroid	Unknown	Yes	Serious	Resolved
Study 011	53	Male	Pneumonitis	1	42	10 mg/kg Q2W	None	Continued	Yes	Non-serious	Not resolved
Study 041	69	Male	Pneumonitis	2	84	2 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Not resolved

No ILD leading to death occurred in pembrolizumab-treated patients in Study 002, 006, 011, or 041.

Three patients died from ILD for which a causal relationship to pembrolizumab could not be ruled out, according to reports from foreign clinical studies, post-marketing spontaneous reports, etc. The cause of the deaths was pneumonitis in all 3 patients.

PMDA's view:

Because serious ILD and ILD leading to death occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of ILD in patients receiving pembrolizumab. In order to raise awareness among healthcare professionals, the package insert, etc. should include (a) information on the occurrence of ILD (including cases resulting in death due to ILD) in clinical studies and (b) the following statements: (1) patients eligible for pembrolizumab therapy should be carefully selected after checking whether they have current or past ILD before the beginning of treatment; (2) attention should be continuously paid to development of ILD during treatment with pembrolizumab, and appropriate measures should be taken in case of symptoms suspected of ILD. Using the package insert, etc., the applicant should inform healthcare professionals about the recommended actions to address ILD (e.g., interruption and discontinuation of pembrolizumab) specified in the study protocols.

7.R.3.11 IRR

The applicant's explanation about IRR in patients receiving pembrolizumab:

The applicant collected data on adverse events of IRR coded to the following MedDRA PTs:

"Hypersensitivity," "Drug hypersensitivity," "Anaphylactic reaction," "Cytokine release syndrome," "Serum sickness," "Serum sickness-like reaction," or "Infusion related reaction."

IRR occurred in 1.1% (2 of 178) of subjects in the pembrolizumab 2 mg/kg Q3W group (hypersensitivity and cytokine release syndrome [1 subject each]) and 2.8% (5 of 179) of subjects in the 10 mg/kg Q3W group (hypersensitivity [2 subjects], and anaphylactic reaction, drug hypersensitivity, and infusion related reaction [1 subject each]) in Study 002; 2.5% (7 of 278) of subjects in the pembrolizumab 10 mg/kg Q2W group (hypersensitivity and infusion related reaction [3 subjects each], and drug hypersensitivity [1 subject]) and 2.9% (8 of 277) of subjects in the 10 mg/kg Q3W group (hypersensitivity and infusion related reaction [4 subjects each]) in Study 006; and 4.8% (2 of 42) of subjects in Study 041 (cytokine release syndrome and infusion related reaction [1 subject each]). Serious IRR occurred in 1.1% (2 of 179) of subjects in the pembrolizumab 10 mg/kg Q3W group (anaphylactic reaction and hypersensitivity [1 subject each]) in Study 002 and in 0.4% (1 of 278) of subjects in the 10 mg/kg Q2W group (drug hypersensitivity) in Study 006. A causal relationship to pembrolizumab could not be ruled out for drug hypersensitivity in 1 subject in the 10 mg/kg Q2W group in Study 006.

No IRR leading to death occurred in clinical studies of pembrolizumab.

The median time (range) to onset of IRR was 162 days (108-216 days) in the pembrolizumab 2 mg/kg Q3W group in Study 002, and 70 days (1-139 days) in Study 041.

PMDA's view:
Because IRR occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of IRR during and after the infusion of pembrolizumab. Using the package insert, etc., the applicant should inform healthcare professionals about the occurrence of IRR in clinical studies and recommended actions to address IRR (e.g., adjustment of infusion rate of pembrolizumab), in order to raise awareness among healthcare professionals.

7.R.3.12 Pancreatitis

The applicant's explanation about pancreatitis in patients treated with pembrolizumab:
The applicant collected data on adverse events of pancreatitis coded to the following MedDRA PTs: "Pancreatitis," "Autoimmune pancreatitis," "Pancreatitis acute," "Pancreatitis haemorrhagic," or "Pancreatitis necrotising."

Table 45 shows details of patients who experienced pancreatitis in clinical studies of pembrolizumab.

Table 45. List of patients who experienced pancreatitis

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 001	68	Male	Pancreatitis	3	76	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Not resolved
Study 002	64	Female	Pancreatitis	2	126	2 mg/kg Q3W	None	Interrupted	Yes	Serious	Resolved
Study 006	68	Male	Pancreatitis	3	183	10 mg/kg Q3W	Laxative	Interrupted	No	Serious	Resolved
	68	Male	Pancreatitis	2	84	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Non-serious	Resolved
	73	Male	Autoimmune pancreatitis	3	116	10 mg/kg Q2W	Corticosteroid	Discontinued	Yes	Serious	Resolved

PMDA's view:

Because serious pancreatitis and autoimmune pancreatitis occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of pancreatitis in patients receiving pembrolizumab. Therefore, cautions about the occurrence of pancreatitis in clinical studies should be appropriately provided to healthcare professionals using a package insert, etc. In addition, information on recommended actions to address pancreatitis should be appropriately provided to healthcare professionals using information materials, etc.

7.R.3.13 Myositis

The applicant's explanation about myositis in patients treated with pembrolizumab:

The applicant collected data on adverse events of myositis coded to the following MedDRA PTs: "Myositis," "Necrotising myositis," "Polymyositis," "Immune-mediated necrotising myopathy," "Rhabdomyolysis," or "Myopathy."

Table 46 shows details of patients who experienced myositis in clinical studies of pembrolizumab.

Table 46. List of patients who experienced myositis

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 001	46	Male	Rhabdomyolysis	3	101	10 mg/kg Q3W	None	Discontinued	Yes	Serious	Resolved
	58	Male	Myopathy	1	258	10 mg/kg Q2W	Nonsteroidal anti-inflammatory	Continued	Yes	Non-serious	Resolved
			Myopathy	2	365		None	Discontinued	Yes	Serious	Resolved
	68	Male	Myositis	1	192	2 mg/kg Q3W	None	Unknown	No	Non-serious	Not resolved
	61	Male	Myositis	2	54	10 mg/kg Q3W	Corticosteroid	Discontinued	Yes	Serious	Not resolved
	49	Male	Myositis	2	459	10 mg/kg Q3W	Nonsteroidal anti-inflammatory	Discontinued	Yes	Non-serious	Not resolved
Study 006	69	Male	Myositis	2	20	10 mg/kg Q3W	Nonsteroidal anti-inflammatory	Interrupted	Yes	Non-serious	Resolved
	80	Male	Myositis	1	85	10 mg/kg Q3W	None	Continued	No	Non-serious	Not resolved

Myositis occurred in 8 patients (myositis [4 patients], myopathy and rhabdomyolysis [2 patients each]) in the post-marketing setting outside Japan, and a causal relationship to pembrolizumab could not be ruled out for these events.

PMDA's view:
Because serious myositis occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of myositis in patients receiving pembrolizumab. Therefore, cautions about the occurrence of myositis in clinical studies should be appropriately provided to healthcare professionals using a package insert, etc. In addition, information on recommended actions to address myositis should be appropriately provided to healthcare professionals using information materials, etc.

7.R.3.14 Encephalitis and meningitis

The applicant's explanation about encephalitis and meningitis in patients treated with pembrolizumab:
The applicant collected data on adverse events of encephalitis and meningitis coded to "Noninfectious encephalitis (narrow)" (MedDRA SMQ) or "Noninfectious meningitis (narrow)" (MedDRA SMQ).

Table 47 shows details of patients who experienced encephalitis or meningitis in clinical studies of pembrolizumab.

Table 47. List of patients who experienced encephalitis or meningitis

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 001	62	Male	Herpes simplex encephalitis	3	145	10 mg/kg Q2W	Acyclovir	Continued	No	Serious	Resolved
			Herpes simplex encephalitis	3	155		Corticosteroid	Continued	No	Serious	Resolved
Study 002	33	Female	Meningitis noninfective	3	177	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Serious	Resolved
Study 006	46	Male	Encephalitis	3	97	10 mg/kg Q2W	Corticosteroid	Discontinued	Yes	Serious	Resolved
	60	Female	Meningitis	3	102	10 mg/kg Q2W	Corticosteroid	Unknown	Yes	Serious	Resolved

Outside Japan, encephalitis and meningitis were reported in 3 patients (pachymeningitis, meningitis aseptic, and encephalitis [1 patient each]) in the post-marketing setting, and a causal relationship to pembrolizumab could not be ruled out for these events.

PMDA's view:
Because encephalitis and meningitis occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of encephalitis and meningitis in patients receiving pembrolizumab. Therefore, cautions about the occurrence of encephalitis and meningitis in clinical studies should be appropriately provided to healthcare professionals using a

package insert, etc. In addition, information on recommended actions to address encephalitis and meningitis should be appropriately provided to healthcare professionals using information materials, etc.

7.R.3.15 Myasthenia gravis

The applicant's explanation about myasthenia gravis in patients treated with pembrolizumab:
The applicant collected data on adverse events of myasthenia gravis coded to the following MedDRA PTs: "Myasthenic syndrome," "Myasthenia gravis," "Myasthenia gravis crisis," or "Ocular myasthenia."

Table 48 shows details of the patient who experienced myasthenia gravis in a clinical study of pembrolizumab.

Table 48. List of patients who experienced myasthenia gravis

Study	Age	Sex	MedDRA PT (MedDRA ver.18.0)	Grade	Time to onset (Day)	Dosage regimen	Treatment	Pembrolizumab therapy	Causality	Seriousness	Outcome
Study 002	69	Female	Myasthenic syndrome	3	74	10 mg/kg Q3W	Corticosteroid	Interrupted	Yes	Serious	Resolved

Outside Japan, myasthenia gravis was reported in 8 patients (myasthenia gravis [5 patients], myasthenic syndrome [2 patients], and myasthenia gravis crisis [1 patient]) in the post-marketing setting, and a causal relationship to pembrolizumab could not be ruled out for myasthenia gravis and myasthenic syndrome (1 patient each).

PMDA's view:
Because myasthenia gravis occurred in subjects receiving pembrolizumab in Japanese and foreign clinical studies, attention should be paid to development of myasthenia gravis in patients receiving pembrolizumab. Therefore, cautions about the occurrence of myasthenia gravis in clinical studies should be appropriately provided to healthcare professionals using a package insert, etc. In addition, information on recommended actions to address myasthenia gravis should be appropriately provided to healthcare professionals using information materials, etc.

7.R.3.16 Myocarditis

The applicant's explanation about myocarditis in patients treated with pembrolizumab:
The applicant collected data on adverse events of myocarditis coded to MedDRA PT "Myocarditis" or "Autoimmune myocarditis."

No myocarditis occurred in clinical studies of pembrolizumab.

Outside Japan, myocarditis was reported in 5 patients (myocarditis [4 patients] and autoimmune myocarditis [1 patient]) in the post-marketing setting, and a causal relationship to pembrolizumab could not be ruled out for myocarditis in 1 patient and autoimmune myocarditis in 1 patient.

PMDA's view:

No myocarditis occurred in patients receiving pembrolizumab in clinical studies, and post-marketing information in foreign counties is limited. At present, therefore, the relationship between myocarditis and pembrolizumab remains unknown. Post-marketing information in Japan should be continuously collected, and new information should be appropriately provided to healthcare professionals if such information becomes available.

7.R.4 Clinical positioning and indication

The proposed indication of pembrolizumab was "unresectable or metastatic malignant melanoma." The Precautions for Indications section in the proposed package insert includes the following statements.

- The efficacy and safety of pembrolizumab as postoperative adjuvant therapy have not been established.

- Eligible patients for pembrolizumab therapy should be selected based on a good understanding of the "Clinical Studies" section and the efficacy and safety of pembrolizumab, after carefully considering other therapeutic options.

PMDA's view:

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 malignant melanoma," and that the following cautionary statement must be included in the Precautions for Indications section:

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

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

Pembrolizumab for the treatment of unresectable malignant melanoma 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), a representative textbook on clinical oncology in Japan.

<u>Clinical guidelines</u>

- NCCN Guidelines (v.2.2016):
  - Pembrolizumab is strongly recommended as the first-line therapy for unresectable malignant melanoma. Pembrolizumab is also recommended as the second-line therapy.

- US National Cancer Institute Physician Data Query (NCI-PDQ) (version dated April 15, 2016):

- Based on results from Study 006, pembrolizumab is recommended for patients with unresectable malignant melanoma who have received no prior chemotherapy.

- ESMO Clinical Practice Guidelines (version 2015):
  - Pembrolizumab is recommended as an option for first-line and second-line therapies for unresectable malignant melanoma.

Textbooks

- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.* 10th edition (PA, USA, Lippincott Williams & Wilkins 2015):
  - In Study 002, pembrolizumab prolonged PFS compared with ICC in patients with unresectable malignant melanoma who had received prior IPI therapy.
  - In Study 006, pembrolizumab prolonged OS compared with IPI in patients with unresectable malignant melanoma who had received no prior chemotherapy or only 1 prior chemotherapy regimen without IPI.

The applicant's explanation about the intended population of pembrolizumab, choice between pembrolizumab and other antineoplastic drugs, and indication:
The results from Studies 006 and 002 suggest that pembrolizumab is potentially positioned as a therapeutic option for patients with unresectable malignant melanoma who have received no prior chemotherapy, who have received only 1 prior chemotherapy regimen without IPI, or who have received prior IPI therapy.

The following passage describes when to use pembrolizumab and when to use the following approved drugs: (a) nivolumab in patients with unresectable malignant melanoma; and (b) dabrafenib, trametinib, and vemurafenib in patients with unresectable malignant melanoma with BRAF gene mutation:

(a) Pembrolizumab versus nivolumab
Because no clinical study has compared the efficacy and safety of nivolumab and pembrolizumab, it remains unclear which drug should be selected over the other. In general, nivolumab is administered over ≥60 minutes every 2 weeks, while pembrolizumab is administered over 30 minutes every 3 weeks. Taking account of its dosing interval, either drug may be selected over the other, depending on the individual patient condition.

(b) Pembrolizumab versus dabrafenib, trametinib, and vemurafenib
In Study 006, PFS (median) [95% CI] in patients with BRAF gene mutation was 3.2 [2.8, 6.5] months in the 10 mg/kg Q3W group, 5.4 [2.9, 8.8] months in the 10 mg/kg Q2W group, and 2.8 [2.8, 3.0] months in the IPI group. Pembrolizumab is expected to be effective even in patients with malignant melanoma with BRAF gene mutation, but no clinical study has compared the efficacy and safety of pembrolizumab, dabrafenib, trametinib, and vemurafenib in the population. It therefore remains unknown which drug should be selected over the others. The NCCN Guidelines (v.2.2016) recommend that dabrafenib, trametinib, and vemurafenib should be selected over

pembrolizumab in patients for whom early response has a clinical significance. For such patients, dabrafenib, trametinib, and vemurafenib should be selected over pembrolizumab.

Pembrolizumab is an antibody drug targeting human PD-1, and the relationship between the efficacy of anti-PD-1 antibody drugs and PD-L1 expression on tumor has been suggested [see Section 3.R.1]. PMDA asked the applicant to explain the efficacy of pembrolizumab in patients with and without expression of PD-L1, a PD-1 ligand.

The applicant's response:
The efficacy of pembrolizumab with and without PD-L1 expression (cutoff value 1%) was analyzed in patients who were confirmed to have, or not to have, PD-L1 expression in Studies 002 and 006. Because the number of patients receiving the same dosage of pembrolizumab was limited, all pembrolizumab-treated patients were pooled into a single group regardless of dosage.

Tables 49 and 50 show results of the efficacy of pembrolizumab in patients with and without PD-L1 expression in Studies 002 and 006. Because this is a subgroup analysis, the results should be interpreted carefully. Nevertheless, pembrolizumab is expected to be effective irrespective of PD-L1 expression, compared with control treatments.

Table 49. Analysis results of centrally assessed PFS in patients with and without PD-L1 expression (Study 002, cutoff date, [redacted])

PD-L1 expression	(i) Pembrolizumab pooled		(ii) ICC (control)		Hazard ratio [95% CI]* (i) vs (ii)
	No. of subjects	Median [95% CI] (months)	No. of subjects	Median [95% CI] (months)	
Yes	196	4.0 [2.9, 5.4]	98	2.8 [2.5, 2.9]	0.50 [0.38, 0.65]
No	94	2.8 [2.8, 2.9]	40	2.6 [2.0, 2.8]	0.57 [0.38, 0.87]

* Cox regression stratified by ECOG PS (0, 1), serum LDH value (normal, high), and BRAF gene (mutant, wild-type)

Table 50. Analysis results of centrally assessed PFS in patients with and without PD-L1 expression (Study 006, cutoff date, September 3, 2014)

PD-L1 expression	(i) Pembrolizumab pooled		(ii) IPI (control)		Hazard ratio [95% CI]* (i) vs (ii)
	No. of subjects	Median [95% CI] (months)	No. of subjects	Median [95% CI] (months)	
Yes	446	6.4 [4.1, 8.8]	225	2.8 [2.8, 3.0]	0.53 [0.43, 0.65]
No	103	2.8 [2.8, 4.0]	47	2.8 [2.6, 3.0]	0.73 [0.47, 1.11]

* Cox regression stratified by the number of prior regimens (0, 1), percentage of PD-L1 positive cells (≥1%, <1%), and ECOG PS (0, 1)

Based on the above, the applicant has proposed the indication of pembrolizumab, "unresectable or metastatic malignant melanoma." The applicant considers that healthcare professionals will properly select eligible patients for pembrolizumab therapy if they are provided with information on patients in Studies 006 and 002. The proposed Precautions for Indications section therefore includes the following cautionary statement, to raise awareness among healthcare professionals:

Eligible patients should be selected based on a good understanding of the "Clinical Studies" section and the efficacy and safety of pembrolizumab, after carefully considering other therapeutic options.

PMDA's view:

Because pembrolizumab is intended to be administered by physicians with sufficient knowledge and experience in cancer chemotherapy, PMDA mostly accepted the above applicant's explanation about the indication of pembrolizumab, etc. The agency has concluded that the indication should be changed from "unresectable or metastatic malignant melanoma" to "unresectable malignant melanoma."

Because pembrolizumab is intended to be administered by physicians with sufficient knowledge and experience in cancer chemotherapy, the Precautions for Indications section need not include the proposed cautionary statement ("Eligible patients should be selected based on a good understanding of the "Clinical Studies" section and the efficacy and safety of pembrolizumab, after carefully considering other therapeutic options.").

7.R.4.2 Efficacy and safety in adjuvant chemotherapy

The applicant's explanation:

Because no clinical study data are available on the efficacy and safety of pembrolizumab in adjuvant chemotherapy, pembrolizumab in adjuvant chemotherapy cannot be recommend. This information should 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 2 mg/kg (body weight) of Pembrolizumab (Genetical Recombination) infused intravenously over 30 minutes every 3 weeks." The following statements and information are included in the Precautions for Dosage and Administration section of the proposed package insert:

- In clinically stable patients with a sign of disease progression, pembrolizumab therapy should be continued until disease progression is confirmed.

- 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 in Sections "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 was acceptable, and that the following statement and information should be included in the Precautions for Dosage and Administration section.

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

- Criteria for interruption and discontinuation of pembrolizumab in case of adverse reactions

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 malignant melanoma:

PK/PD analysis and translational PK/PD analysis based on IL-2, have suggested that pembrolizumab is expected to be effective at doses of ≥2 mg/kg Q3W [see Sections 6.2.5.1 and 6.2.5.2].

Based on results from the above PK/PD analyses, etc., the following dosage regimens of pembrolizumab were selected for patients with unresectable malignant melanoma: 2 mg/kg Q3W, 10 mg/kg Q2W, and 10 mg/kg Q3W. The efficacy and safety of pembrolizumab were not clearly related to pembrolizumab exposure levels within this dosage range [see Section 6.2.5.3].

Tables 51 and 52 show the comparison of efficacy of pembrolizumab between the 3 dosage regimens in patients with unresectable malignant melanoma who had, or had not, received prior IPI therapy. The results showed no clear difference in efficacy and safety between the 3 regimens [see Section 7.R.3.1].

Table 51. Efficacy results from clinical studies in patients with prior IPI therapy

	Study 002		Study 001 Part B2	
	2 mg/kg Q3W N = 180	10 mg/kg Q3W N = 181	2 mg/kg Q3W N = 89	10 mg/kg Q3W N = 84
Response rate [95% CI] (%)	21.1 [15.4, 27.8]	25.4 [19.2, 32.4]	24.7 [16.2, 35.0]	25.0 [16.2, 35.6]
Median PFS [95% CI] (months)	2.9 [2.8, 3.8]	2.9 [2.8, 4.7]	4.9 [2.8, 8.3]	3.2 [2.8, 5.5]
Median OS [95% CI] (months)	11.4 [10.2, NE]	12.5 [9.7, NE]	NE [10.9, NE]	18.3 [11.4, NE]

Cut-off dates: May 12, 2014 in Study 002 and [redacted] in Study 001 Part B2.

Table 52. Efficacy results from clinical studies in patients without prior IPI therapy

	Study 006		Study 001 Part D	
	10 mg/kg Q2W N = 279	10 mg/kg Q3W N = 277	2 mg/kg Q3W N = 51	10 mg/kg Q3W N = 52
Response rate [95% CI] (%)	33.7 [28.2, 39.6]	32.9 [27.4, 38.7]	33.3 [20.8, 47.9]	34.6 [22.0, 49.1]
Median PFS [95% CI] (months)	5.5 [3.4, 6.9]	4.1 [2.9, 6.9]	5.5 [2.8, 14.0]	4.2 [2.8, 9.9]
Median OS [95% CI] (months)	NE [NE, NE]	NE [NE, NE]	NE [14.0, NE]	NE [9.5, NE]

Cut-off dates: September 3, 2014 for the response rate and PFS in Study 006; March 3, 2015 for OS in Study 006; and [redacted] in Study 001 Part D.

The above clinical study data suggest that the efficacy and safety of pembrolizumab do not differ between the 3 regimens (i.e., 2 mg/kg Q3W, 10 mg/kg Q2W, and 10 mg/kg Q3W). The cumulative pembrolizumab dose of the 10 mg/kg Q3W or 10 mg/kg Q2W regimen is higher than that of the 2 mg/kg Q3W regimen. If pembrolizumab 10 mg/kg Q3W or 10 mg/kg Q2W is administered to many patients with unresectable malignant melanoma after the market launch, new adverse events (i.e., those not reported in clinical studies) may occur and raise safety concerns. The proposed dosage and administration of pembrolizumab is therefore 2 mg/kg Q3W.

PMDA's view:

The applicant explained that the efficacy of pembrolizumab is expected at doses of ≥2 mg/kg Q3W, in light of results from PK/PD analysis and translational PK/PD analysis based on IL-2. This explanation lacks sufficient clinical pharmacological evidence because of the unclear relationship between the efficacy of pembrolizumab and the IL-2 stimulation ratio. However, the proposed dosage and administration of pembrolizumab are acceptable based on the results from Studies 002 and 006.

7.R.5.2 Treatment duration of pembrolizumab

The applicant's explanation:

The applicant plans to include the following cautionary statement in the Precautions for Dosage and Administration section:

> In clinically stable patients with a sign of disease progression, pembrolizumab therapy should be continued until disease progression is confirmed.

In clinically stable patients with a sign of disease progression, pembrolizumab is expected to show efficacy if the treatment is continued until disease progression is confirmed, for the following reasons.

- In Studies 041, 002, and 006, patients who showed disease progression on imaging but were clinically stable (e.g., without symptoms of disease progression), were allowed to continue pembrolizumab until disease progression was shown by subsequent imaging.
- In Studies 041, 002, and 006, 50.0% (21 of 42), 27.1% (98 of 361), and 15.8% (88 of 556) of subjects, respectively, underwent imaging after the confirmation of disease progression. Among the subjects, 19.0% (4 of 21), 14.3% (14 of 98), and 19.3% (17 of 88), respectively, of subjects showed a ≥30% tumor size reduction compared with the baseline, in imaging conducted after disease progression was confirmed during study treatment.
- In Studies 041, 002, and 006, there were no adverse events occurring only in clinically stable patients as described above, and thus no additional safety concerns were raised.

PMDA's view:

Whether the treatment can be continued is generally determined based on not only imaging findings but also individual patient conditions in cancer chemotherapy. Therefore there is little need to include the above cautionary statement regarding treatment period of pembrolizumab in the Precautions for Dosage and Administration section. However, the applicant should inform healthcare professionals about the treatment periods used in clinical studies through information materials (e.g., the Clinical Studies section of the package insert), because the clinical usefulness of pembrolizumab was demonstrated with the treatment periods in the clinical studies.

7.R.5.3 Criteria for interruption and discontinuation

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

Studies 002, 006, and 041 used specific criteria for interruption and discontinuation. The studies were conducted in accordance with the criteria and, as a result, demonstrated the tolerability and safety of

pembrolizumab. The Precautions for Dosage and Administration section will include criteria for interruption and discontinuation established based on the criteria used in the studies.

PMDA's view:

PMDA mostly accepts the applicant's explanation, because pembrolizumab is intended to be used by physicians with sufficient knowledge and experience in cancer chemotherapy. In addition to the proposed criteria for interruption and discontinuation of pembrolizumab, the Precautions for Dosage and Administration section should include (a) criteria for resumption of pembrolizumab following resolution of adverse reactions, (b) recommended infusion rate in response to IRR, and (c) the following statement.

- If an adverse reaction associated with pembrolizumab occurs, interrupt or discontinue pembrolizumab in accordance with Table 53.

Table 53. Criteria for interruption and discontinuation

Adverse reaction	Severity	Actions
ILD	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 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 or ALT 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 or ALT increased to ≥5 times the ULN, or total bilirubin increased to ≥3 times the ULN • Patients with liver metastasis: Grade 2 AST or ALT 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.
IRR	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.
Endocrine disorders	• Grade ≥2 hypophysitis • Symptomatic endocrine disorders (except for hypothyroidism) • Grade ≥3 thyroid dysfunction and 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.
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 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.

7.R.5.4 Pembrolizumab in combination with other antineoplastic drugs

The applicant's explanation:

At present, no clinical study data are available for the efficacy and safety of pembrolizumab in combination with other antineoplastic drugs in patients with unresectable malignant melanoma. 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 to investigate the safety of pembrolizumab in clinical settings after the market launch.

Interstitial lung disease (pneumonitis, etc.) was selected as the key survey item of the surveillance, based on (a) the adverse events in Studies 041, 001, 002, and 006 and (b) the death due to ILD in 1 patient with non-small cell lung cancer in Study 001.

The planned sample size is 250 patients based on the incidence of ILD in pooled analysis of Studies 041, 001, 002, and 006.

The observation period was 1 year after the start of treatment with pembrolizumab, because the first episode of most of the adverse events (including ILD, the key survey item) occurred within 1 year after the start of treatment with pembrolizumab in the 2 mg/kg Q3W group in the above pooled analysis.

PMDA's view:
Because the safety information in Japanese patients with malignant melanoma receiving pembrolizumab is extremely limited, the applicant should conduct all-case post-marketing surveillance 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.

In light of adverse events in Japanese and foreign clinical studies, the key survey items should include not only the event selected by the applicant but also the following adverse events, because they require attention in patients receiving pembrolizumab: 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, pancreatitis, severe skin disorders (oculomucocutaneous syndrome, erythema multiforme, pemphigoid, etc.), IRR, encephalitis and meningitis, and myasthenia gravis.

The planned sample size should be reconsidered based on the incidence of the above adverse events (i.e., the additional key survey items) in clinical studies.

The proposed observation period is acceptable for the following reasons: In Studies 041, 001, 002, and 006, (a) most of the adverse events, including ILD and the above additional key survey items, occurred within 1 year after the start of treatment with pembrolizumab; and (b) no adverse events tended to occur more frequently at ≥1 year of the start of pembrolizumab therapy.

7.2 Adverse events, etc. observed in clinical studies

The applicant 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 I study (Study 011)

Adverse events occurred in all 3 subjects receiving 2 mg/kg Q2W and all 7 subjects receiving 10 mg/kg Q2W. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 66.7% (2 of 3) of subjects receiving 2 mg/kg Q2W and 85.7% (6 of 7) receiving 10 mg/kg Q2W. Table 54 shows adverse events reported by ≥2 subjects in any group.

Table 54. Adverse events reported by ≥2 subjects in any group

SOC PT (MedDRA ver.18.0)	n (%)			
	2 mg/kg Q2W N = 3		10 mg/kg Q2W N = 7	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	1 (33.3)	7 (100)	3 (42.9)
Blood and lymphatic system disorders				
Anaemia	0	0	2 (28.6)	0
Gastrointestinal disorders				
Diarrhoea	0	0	2 (28.6)	0
General disorders and administration site conditions				
Fatigue	1 (33.3)	0	3 (42.9)	0
Oedema peripheral	0	0	3 (42.9)	0
Pyrexia	1 (33.3)	0	2 (28.6)	0
Investigations				
ALT increased	0	0	2 (28.6)	1 (14.3)
AST increased	0	0	2 (28.6)	1 (14.3)
Blood thyroid stimulating hormone increased	0	0	2 (28.6)	0
Lymphocyte count decreased	0	0	2 (28.6)	1 (14.3)
Platelet count decreased	0	0	2 (28.6)	1 (14.3)
Weight decreased	0	0	2 (28.6)	0
Metabolism and nutrition disorders				
Decreased appetite	0	0	3 (42.9)	1 (14.3)
Hypercalcaemia	0	0	2 (28.6)	1 (14.3)
Hyperkalaemia	0	0	2 (28.6)	0
Hypermagnesaemia	0	0	2 (28.6)	0
Hypoalbuminaemia	0	0	2 (28.6)	0
Hyponatraemia	0	0	3 (42.9)	3 (42.9)
Hypophosphataemia	0	0	2 (28.6)	1 (14.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Cancer pain	0	0	2 (28.6)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	1 (33.3)	0	2 (28.6)	1 (14.3)
Skin and subcutaneous tissue disorders				
Rash	0	0	2 (28.6)	0
Rash maculo-papular	0	0	2 (28.6)	0

Serious adverse events occurred in 14.3% (1 of 7) of subjects in the 10 mg/kg Q2W group. Serious adverse events included ALT increased, AST increased, and cerebral infarction. A causal relationship to the study drug could not be ruled out for ALT increased and AST increased.

There were no adverse events leading to discontinuation of the study drug.

7.2.2 Japanese phase Ib study (Study 041)

Adverse events occurred in 97.6% (41 of 42) of subjects, and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 81.0% (34 of 42) of subjects. Table 55 shows adverse events with an incidence of ≥10%.

Table 55. Adverse events with an incidence of ≥10%

SOC PT (MedDRA ver.18.0)	n (%) 2 mg/kg Q3W N = 42	
	All Grades	Grade ≥3
All adverse events	41 (97.6)	17 (40.5)
Endocrine disorders		
Hypothyroidism	5 (11.9)	0
Gastrointestinal disorders		
Constipation	9 (21.4)	0
Diarrhoea	6 (14.3)	0
Nausea	7 (16.7)	1 (2.4)
General disorders and administration site conditions		
Malaise	6 (14.3)	0
Pyrexia	5 (11.9)	0
Infections and infestations		
Nasopharyngitis	11 (26.2)	0
Metabolism and nutrition disorders		
Decreased appetite	5 (11.9)	1 (2.4)
Skin and subcutaneous tissue disorders		
Dry skin	5 (11.9)	0
Pruritus	10 (23.8)	0
Rash maculo-papular	7 (16.7)	0

Serious adverse events occurred in 35.7% (15 of 42) of subjects. Serious adverse events included anaemia and hypophysitis in 2 subjects (4.8%) each; and abdominal pain, colitis, diarrhoea, duodenal ulcer haemorrhage, large intestinal obstruction, death, bile duct obstruction, cellulitis, lung infection, vestibular neuronitis, diabetes mellitus, hyperglycaemia, cancer pain, cerebral haemorrhage, encephalopathy, acute respiratory failure, pneumonitis, and drug eruption in 1 subject (2.4%) each. Of these, a causal relationship to the study drug could not be ruled out for hypophysitis in 2 subjects and anaemia, abdominal pain, colitis, diarrhoea, death, bile duct obstruction, lung infection, hyperglycaemia, cerebral haemorrhage, encephalopathy, pneumonitis, and drug eruption (1 subject each).

Adverse events leading to discontinuation of the study drug occurred in 14.3% (6 of 42) of subjects. Adverse events leading to discontinuation of the study drug included hypophysitis, death, hyperglycaemia, marasmus, cerebral haemorrhage, encephalopathy, acute respiratory failure, and pneumonitis in 1 subject (2.4%) each. Of these, a causal relationship to the study drug could not be ruled out for hypophysitis, death, hyperglycaemia, cerebral haemorrhage, encephalopathy, and pneumonitis (1 subject each).

7.2.3 Foreign phase I study (Study 001)

Adverse events occurred in 98.2% (673 of 685) of subjects, and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 82.6% (566 of 685) of subjects. Table 56 shows adverse events with an incidence of ≥10%.

Table 56. Adverse events with an incidence of ≥10%

SOC PT (MedDRA ver.18.0)	n (%) Parts A, A1, A2, B1, B2, B3, and D N = 685	
	All Grades	Grade ≥3
All adverse events	673 (98.2)	282 (41.2)
Blood and lymphatic system disorders		
Anaemia	99 (14.5)	30 (4.4)
Gastrointestinal disorders		
Abdominal pain	82 (12.0)	7 (1.0)
Constipation	131 (19.1)	3 (0.4)
Diarrhoea	202 (29.5)	10 (1.5)
Nausea	215 (31.4)	11 (1.6)
Vomiting	109 (15.9)	10 (1.5)
General disorders and administration site conditions		
Asthenia	87 (12.7)	6 (0.9)
Chills	72 (10.5)	0
Fatigue	330 (48.2)	16 (2.3)
Oedema peripheral	90 (13.1)	3 (0.4)
Pyrexia	98 (14.3)	1 (0.1)
Metabolism and nutrition disorders		
Decreased appetite	144 (21.0)	4 (0.6)
Musculoskeletal and connective tissue disorders		
Arthralgia	167 (24.4)	2 (0.3)
Back pain	92 (13.4)	6 (0.9)
Myalgia	87 (12.7)	2 (0.3)
Pain in extremity	89 (13.0)	3 (0.4)
Nervous system disorders		
Headache	139 (20.3)	6 (0.9)
Respiratory, thoracic and mediastinal disorders		
Cough	180 (26.3)	2 (0.3)
Dyspnoea	132 (19.3)	17 (2.5)
Skin and subcutaneous tissue disorders		
Pruritus	193 (28.2)	3 (0.4)
Rash	161 (23.5)	3 (0.4)
Vitiligo	72 (10.5)	0

Serious adverse events occurred in 34.3% (235 of 685) of subjects. Serious adverse events reported by ≥3 subjects included pneumonia in 20 subjects (2.9%); dyspnoea in 14 subjects (2.0%); cellulitis and pleural effusion in 11 subjects (1.6%) each; anaemia and pyrexia in 10 subjects (1.5%) each; colitis, vomiting, urinary tract infection, dehydration, and squamous cell carcinoma in 9 subjects (1.3%) each; abdominal pain, diarrhoea, nausea, and acute kidney injury in 8 subjects (1.2%) each; hyponatraemia, basal cell carcinoma, spinal cord compression, and renal failure in 7 subjects (1.0%) each; atrial fibrillation, asthenia, pain, sepsis, pneumonitis, and pulmonary embolism in 5 subjects (0.7%) each; cardiac failure congestive, constipation, gastrointestinal haemorrhage, intestinal obstruction, failure to thrive, malignant melanoma, dizziness, seizure, and confusional state in 4 subjects (0.6%) each; and acute myocardial infarction, pericardial effusion, hyperthyroidism, small intestinal obstruction, death,

fatigue, back pain, tumour haemorrhage, tumour pain, and syncope in 3 subjects (0.4%) each. Of these, a causal relationship to the study drug could not be ruled out for colitis (7 subjects); pyrexia (6 subjects); pneumonitis (5 subjects); hyperthyroidism, diarrhoea, nausea, vomiting, asthenia, dehydration, and dyspnoea (3 subjects each); confusional state, acute kidney injury, and renal failure in 2 subjects each; and pericardial effusion, abdominal pain, intestinal obstruction, fatigue, pneumonia, failure to thrive, hyponatraemia, and malignant melanoma (1 subject each).

Adverse events leading to discontinuation of the study drug occurred in 11.4% (78 of 685) of subjects. Adverse events leading to discontinuation of the study drug reported by ≥2 subjects included pneumonitis in 5 subjects (0.7%); colitis, fatigue, pain, spinal cord compression, and dyspnoea in 3 subjects (0.4%) each; and hyperthyroidism, diarrhoea, death, decreased appetite, arthralgia, back pain, cancer pain, and seizure in 2 subjects (0.3%) each. Of these, a causal relationship to the study drug could not be ruled out for pneumonitis (5 subjects); colitis (3 subjects); hyperthyroidism, decreased appetite, and fatigue (2 subjects each, 0.3%); and diarrhoea and arthralgia (1 subject each, 0.1%).

7.2.4 Foreign phase II study (Study 002)

Adverse events occurred in 96.6% (172 of 178) of subjects receiving 2 mg/kg Q3W, 99.4% (178 of 179) of subjects receiving 10 mg/kg Q3W, and 97.7% (167 of 171) of subjects receiving ICC. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 68.0% (121 of 178) of subjects receiving 2 mg/kg Q3W, 74.3% (133 of 179) of subjects receiving 10 mg/kg Q3W, and 80.7% (138 of 171) of subjects receiving ICC. Table 57 shows adverse events with an incidence of ≥10% in any group.

Table 57. Adverse events with an incidence of ≥10% in any group

SOC PT (MedDRA ver.18.0)	n (%)					
	2 mg/kg Q3W N = 178		10 mg/kg Q3W N = 179		ICC N = 171	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	172 (96.6)	83 (46.6)	178 (99.4)	79 (44.1)	167 (97.7)	88 (51.5)
Blood and lymphatic system disorders						
Anaemia	31 (17.4)	14 (7.9)	20 (11.2)	4 (2.2)	45 (26.3)	11 (6.4)
Thrombocytopenia	3 (1.7)	0	1 (0.6)	1 (0.6)	20 (11.7)	7 (4.1)
Gastrointestinal disorders						
Abdominal pain	24 (13.5)	3 (1.7)	24 (13.4)	3 (1.7)	14 (8.2)	2 (1.2)
Constipation	38 (21.3)	1 (0.6)	40 (22.3)	0	35 (20.5)	4 (2.3)
Diarrhoea	37 (20.8)	1 (0.6)	33 (18.4)	2 (1.1)	34 (19.9)	4 (2.3)
Nausea	35 (19.7)	2 (1.1)	43 (24.0)	2 (1.1)	71 (41.5)	5 (2.9)
Vomiting	15 (8.4)	3 (1.7)	33 (18.4)	3 (1.7)	39 (22.8)	5 (2.9)
General disorders and administration site conditions						
Asthenia	16 (9.0)	3 (1.7)	21 (11.7)	4 (2.2)	16 (9.0)	3 (1.8)
Fatigue	69 (38.8)	6 (3.4)	84 (46.9)	4 (2.2)	82 (48.0)	11 (6.4)
Pyrexia	22 (12.4)	1 (0.6)	27 (15.1)	0	16 (9.4)	1 (0.6)
Metabolism and nutrition disorders						
Decreased appetite	29 (16.3)	0	44 (24.6)	3 (1.7)	39 (22.8)	1 (0.6)
Hyponatraemia	19 (10.7)	6 (3.4)	12 (6.7)	5 (2.8)	8 (4.7)	2 (1.2)
Musculoskeletal and connective tissue disorders						
Arthralgia	27 (15.2)	1 (0.6)	22 (12.3)	1 (0.6)	17 (9.9)	2 (1.2)
Back pain	20 (11.2)	0	13 (7.3)	0	17 (9.9)	3 (1.8)
Nervous system disorders						
Headache	15 (8.4)	0	25 (14.0)	0	22 (12.9)	1 (0.6)
Neuropathy peripheral	3 (1.7)	0	3 (1.7)	0	18 (10.5)	2 (1.2)
Respiratory, thoracic and mediastinal disorders						
Cough	31 (17.4)	0	35 (19.6)	0	27 (15.8)	0
Dyspnoea	17 (9.6)	2 (1.1)	31 (17.3)	7 (3.9)	21 (12.3)	5 (2.9)
Skin and subcutaneous tissue disorders						
Alopecia	6 (3.4)	0	2 (1.1)	0	35 (20.5)	1 (0.6)
Pruritus	45 (25.3)	0	54 (30.2)	0	13 (7.6)	0
Rash	24 (13.5)	0	25 (14.0)	0	13 (7.6)	0

Serious adverse events occurred in 46.6% (83 of 178) of subjects in the 2 mg/kg Q3W group, 38.0% (68 of 179) of subjects in the 10 mg/kg Q3W group, and 34.5% (59 of 171) of subjects in the ICC group. Serious adverse events reported by ≥2 subjects in any group included anaemia in 7 subjects (3.9%); vomiting, death, generalised oedema, pyrexia, pneumonia, dehydration, and dyspnoea in 3 subjects (1.7%) each; and abdominal pain, colitis, constipation, chest pain, cholecystitis, bronchitis, skin infection, metastases to central nervous system, tumour pain, partial seizures, syncope, confusional state, mental status changes, and pulmonary embolism in 2 subjects (1.1%) each in the 2 mg/kg Q3W group; general physical health deterioration, and dyspnoea in 5 subjects (2.8%) each; abdominal pain in 4 subjects (2.2%); diarrhoea, pyrexia, hyponatraemia, confusional state, and pneumonitis in 3 subjects (1.7%) each; and hypopituitarism, ileus, death, pneumonia, and arthralgia in 2 subjects (1.1%) each in the 10 mg/kg Q3W group; and anaemia, pneumonia, dyspnoea, and pulmonary embolism in 4 subjects (2.3%) each; febrile neutropenia, nausea, general physical health deterioration, and sepsis in 3 subjects (1.8%) each; and thrombocytopenia, death, pyrexia, erysipelas, infection, platelet count decreased, and dehydration in 2 subjects (1.2%) each in the ICC group. Of these, a causal relationship to the study drug could not be ruled out for generalised oedema (2 subjects); and anaemia, colitis, chest pain, death, and

dyspnoea (1 subject each) in the 2 mg/kg Q3W group; diarrhoea and pneumonitis in 3 subjects each; hypopituitarism and arthralgia (2 subjects each); and abdominal pain, pyrexia, and hyponatraemia (1 subject each) in the 10 mg/kg Q3W group; and anaemia and nausea (3 subjects each); febrile neutropenia, thrombocytopenia, pyrexia, and platelet count decreased (2 subjects each); and pneumonia and dehydration (1 subject each) in the ICC group.

Adverse events leading to discontinuation of the study drug occurred in 10.1% (18 of 178) of subjects in the 2 mg/kg Q3W group, 14.5% (26 of 179) of subjects in the 10 mg/kg Q3W group, and 11.7% (20 of 171) of subjects in the ICC group. Adverse events leading to discontinuation of the study drug included generalised oedema in 3 subjects (1.7%); and anaemia, hypophysitis, asthenia, death, general physical health deterioration, oedema, hepatic failure, infectious pleural effusion, septic shock, cachexia, hypercalcaemia, neck pain, hydronephrosis, pulmonary embolism, and SJS in 1 subject (0.6%) each in the 2 mg/kg Q3W group; asthenia, general physical health deterioration, dyspnoea, and pneumonitis in 3 subjects (1.7%) each; hypopituitarism, colitis, and death in 2 subjects (1.1%) each; and cardiac ventricular disorder, nausea, upper gastrointestinal haemorrhage, vomiting, fatigue, oedema peripheral, autoimmune hepatitis, hepatic failure, gamma-glutamyltransferase (GGT) increased, cell death, hyponatraemia, back pain, interstitial lung disease, and pleural effusion in 1 subject (0.6%) each in the 10 mg/kg Q3W group; and thrombocytopenia in 3 subjects (1.8%); anaemia, general physical health deterioration, and neuropathy peripheral in 2 subjects (1.2%) each; and pancytopenia, atrial fibrillation, colitis, gingival bleeding, asthenia, death, fatigue, hyperbilirubinaemia, anaphylactic reaction, bacterial sepsis, sepsis, soft tissue infection, urosepsis, C-reactive protein increased, lymphocyte count decreased, haemorrhage intracranial, myoclonus, acute kidney injury, dyspnoea, haemoptysis, pulmonary embolism, and alopecia in 1 subject (0.6%) each in the ICC group. Of these, a causal relationship to the study drug could not be ruled out for generalised oedema (2 subjects), and hypophysitis, death, and SJS (1 subject each) in the 2 mg/kg Q3W group; pneumonitis (3 subjects); hypopituitarism and colitis (2 subjects each); and nausea, vomiting, fatigue, autoimmune hepatitis, cell death, hyponatraemia, dyspnoea, and interstitial lung disease (1 subject each) in the 10 mg/kg Q3W group; and thrombocytopenia (3 subjects); anaemia and neuropathy peripheral (2 subjects each), and pancytopenia, asthenia, fatigue, anaphylactic reaction, bacterial sepsis, soft tissue infection, urosepsis, lymphocyte count decreased, acute kidney injury, and alopecia (1 subject each) in the ICC group.

7.2.5 Foreign phase III study (Study 006)

Adverse events occurred in 95.3% (264 of 277) of subjects receiving 10 mg/kg Q3W, 98.9% (275 of 278) of subjects receiving 10 mg/kg Q2W, and 93.4% (239 of 256) of subjects receiving IPI. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 72.9% (202 of 277) of subjects receiving 10 mg/kg Q3W, 79.5% (221 of 278) of subjects receiving 10 mg/kg Q2W, and 73.0% (187 of 256) of subjects receiving IPI. Table 58 shows adverse events with an incidence of ≥10% in any group.

Table 58. Adverse events with an incidence of ≥10% in any group

SOC PT (MedDRA ver.18.0)	n (%)					
	10 mg/kg Q3W N = 277		10 mg/kg Q2W N = 278		IPI N = 256	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	264 (95.3)	92 (33.2)	275 (98.9)	105 (37.8)	239 (93.4)	94 (36.7)
Endocrine disorders						
Hypothyroidism	23 (8.3)	0	28 (10.1)	1 (0.4)	5 (2.0)	0
Gastrointestinal disorders						
Constipation	32 (11.6)	0	47 (16.9)	1 (0.4)	34 (13.3)	1 (0.4)
Diarrhoea	69 (24.9)	3 (1.1)	75 (27.0)	8 (2.9)	76 (29.7)	9 (3.5)
Nausea	60 (21.7)	1 (0.4)	59 (21.2)	3 (1.1)	56 (21.9)	4 (1.6)
Vomiting	21 (7.6)	1 (0.4)	32 (11.5)	2 (0.7)	35 (13.7)	2 (0.8)
General disorders and administration site conditions						
Asthenia	46 (16.6)	1 (0.4)	45 (16.2)	2 (0.7)	32 (12.5)	4 (1.6)
Fatigue	76 (27.4)	2 (0.7)	80 (28.8)	3 (1.1)	71 (27.7)	8 (3.1)
Pyrexia	20 (7.2)	1 (0.4)	33 (11.9)	1 (0.4)	25 (9.8)	1 (0.4)
Metabolism and nutrition disorders						
Decreased appetite	46 (16.6)	1 (0.4)	42 (15.1)	2 (0.7)	37 (14.5)	2 (0.8)
Musculoskeletal and connective tissue disorders						
Arthralgia	48 (17.3)	2 (0.7)	50 (18.0)	0	25 (9.8)	3 (1.2)
Back pain	30 (10.8)	4 (1.4)	37 (13.3)	1 (0.4)	17 (6.6)	2 (0.8)
Myalgia	17 (6.1)	1 (0.4)	33 (11.9)	1 (0.4)	11 (4.3)	2 (0.8)
Nervous system disorders						
Headache	31 (11.2)	0	45 (16.2)	1 (0.4)	35 (13.7)	2 (0.8)
Respiratory, thoracic and mediastinal disorders						
Cough	42 (15.2)	0	50 (18.0)	0	19 (7.4)	1 (0.4)
Dyspnoea	31 (11.2)	4 (1.4)	28 (10.1)	1 (0.4)	19 (7.4)	2 (0.8)
Skin and subcutaneous tissue disorders						
Pruritus	46 (16.6)	1 (0.4)	49 (17.6)	0	70 (27.3)	1 (0.4)
Rash	48 (17.3)	0	52 (18.7)	0	41 (16.0)	2 (0.8)
Vitiligo	34 (12.3)	0	26 (9.4)	0	4 (1.6)	0

Serious adverse events occurred in 25.6% (71 of 277) of subjects in the 10 mg/kg Q3W group, 27.7% (77 of 278) of subjects in the 10 mg/kg Q2W group, and 31.6% (81 of 256) of subjects in the IPI group. Serious adverse events reported by ≥2 subjects in any group included colitis in 6 subjects (2.2%); anaemia and pulmonary embolism in 4 subjects (1.4%) each; and pathological fracture and renal failure in 3 subjects (1.1%) each; thrombocytopenia, cardiac failure, cardiac failure congestive, diarrhoea, gastritis, hepatitis, sepsis, hyponatraemia, metastases to the central nervous system, papillary thyroid cancer, seizure, acute kidney injury, dyspnoea, haemoptysis, and pneumonitis in 2 subjects (0.7%) each in the 10 mg/kg Q3W group; diarrhoea in 10 subjects (3.6%); colitis in 4 subjects (1.4%); autoimmune hepatitis and squamous cell carcinoma in 3 subjects (1.1%) each; and anaemia, adrenal insufficiency, intestinal obstruction, general physical health deterioration, pyrexia, pneumonia, sepsis, hypokalaemia, hyponatraemia, pathological fracture, metastatic malignant melanoma, acute kidney injury, and pneumonitis in 2 subjects (0.7%) each in the 10 mg/kg Q2W group; and colitis in 16 subjects (6.3%); diarrhoea in 10 subjects (3.9%); pyrexia in 4 subjects (1.6%); vomiting, pneumonia, and tumour haemorrhage in 3 subjects (1.2%) each; and hypophysitis, hypopituitarism, abdominal pain, enterocolitis, hepatocellular injury, sepsis, ALT increased, metastases to central nervous system, squamous cell carcinoma, brain oedema, confusional state, renal failure, and pneumonitis in 2 subjects (0.8%) each in the IPI group. Of these, a causal relationship to the study drug could not be ruled out for colitis (5

subjects); hepatitis and pneumonitis (2 subjects each); and thrombocytopenia, diarrhoea, hyponatraemia, and renal failure (1 subject each) in the 10 mg/kg Q3W group; diarrhoea (8 subjects); colitis (4 subjects); autoimmune hepatitis (3 subjects); adrenal insufficiency and pneumonitis (2 subjects each); and anaemia, hypokalaemia, and acute kidney injury (1 subject each) in the 10 mg/kg Q2W group; and colitis (16 subjects); diarrhoea (10 subjects); hypophysitis, hypopituitarism, enterocolitis, hepatocellular injury, ALT increased, and pneumonitis (2 subjects each); and abdominal pain, pyrexia, confusional state, and renal failure (1 subject each) in the IPI group.

Adverse events leading to discontinuation of the study drug occurred in 10.8% (30 of 277) of subjects in the 10 mg/kg Q3W group, 7.2% (20 of 278) of subjects in the 10 mg/kg Q2W group, and 13.3% (34 of 256) of subjects in the IPI group. Adverse events leading to discontinuation of the study drug included colitis in 5 subjects (1.8%); metastases to central nervous system in 2 subjects (0.7%); thrombocytopenia, cardiac failure, cardiac failure congestive, diarrhoea, oesophagitis, salivary gland disorder, autoimmune hepatitis, drug-induced liver injury, hepatitis, anaphylactoid reaction, lung infection, soft tissue infection, lipase increased, type 1 diabetes mellitus, arthralgia, intracranial tumour haemorrhage, cognitive disorder, Guillain-Barre syndrome, haemorrhage intracranial, optic neuritis, polyneuropathy, completed suicide, depression, renal failure, cough, dyspnoea, pneumonitis, pulmonary embolism, and vitiligo in 1 subject (0.4%) each in the 10 mg/kg Q3W group; colitis in 3 subjects (1.1%); and myocardial infarction, adrenal insufficiency, autoimmune pancreatitis, death, general physical health deterioration, autoimmune hepatitis, hepatic function abnormal, drug hypersensitivity, encephalitis, facial bones fracture, gout, hypoalbuminaemia, malnutrition, Sjogren's syndrome, intracranial tumour haemorrhage, lymphangiosis carcinomatosa, metastatic malignant melanoma, epilepsy, partial seizures, and psoriasis in 1 subject (0.4%) each in the 10 mg/kg Q2W group; and colitis in 9 subjects (3.5%); diarrhoea in 5 subjects (2.0%); hepatocellular injury in 2 subjects (0.8%); hypopituitarism, enterocolitis, facial pain, autoimmune hepatitis, bile duct obstruction, cholangitis, liver disorder, hypersensitivity, colonic abscess, ALT increased, AST increased, blood alkaline phosphatase increased, hypercalcaemia, arthralgia, myalgia, rheumatoid arthritis, chronic lymphocytic leukaemia, tumour haemorrhage, dizziness, tubulointerstitial nephritis, hypoxia, rash, and rash maculo-papular in 1 subject (0.4%) each in the IPI group. Of these, a causal relationship to the study drug could not be ruled out for colitis (5 subjects) and thrombocytopenia, oesophagitis, salivary gland disorder, autoimmune hepatitis, drug-induced liver injury, hepatitis, anaphylactoid reaction, lipase increased, type 1 diabetes mellitus, arthralgia, cognitive disorder, Guillain-Barre syndrome, optic neuritis, polyneuropathy, renal failure, cough, pneumonitis, and vitiligo (1 subject each) in the 10 mg/kg Q3W group; colitis (3 subjects), and adrenal insufficiency, autoimmune pancreatitis, autoimmune hepatitis, drug hypersensitivity, encephalitis, Sjogren's syndrome, epilepsy, and psoriasis (1 subject each) in the 10 mg/kg Q2W group; and colitis (9 subjects); diarrhoea (5 subjects); hepatocellular injury (2 subjects); and hypopituitarism, enterocolitis, autoimmune hepatitis, liver disorder, hypersensitivity, colonic abscess, ALT increased, AST increased, arthralgia, myalgia, and rash (1 subject each) in the IPI group.

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 inspection and assessment are ongoing. The results and PMDA's conclusion are reported in the Review Report (2).

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

The inspection is ongoing. The results and PMDA's conclusion are reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that pembrolizumab has efficacy in the treatment of unresectable malignant melanoma, and that pembrolizumab has acceptable safety in view of its benefits. Pembrolizumab, a humanized IgG4 monoclonal antibody against PD-1, binds to the extracellular domain of PD-1 (PD-1 ligand binding site) and blocks the binding of PD-1 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 decreased tumor growth. Pembrolizumab, a drug with a new active ingredient, is clinically meaningful because it offers a new therapeutic option for patients with unresectable malignant melanoma. The safety, 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)

August 29, 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	December 22, 2015

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 advisers 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 the 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 foreign clinical studies demonstrated the efficacy of pembrolizumab (genetical recombination) (hereinafter referred to as "pembrolizumab") in patients with unresectable (stage III/IV) malignant melanoma:

- A foreign phase III study (the KEYNOTE-006 study [Study 006]) was conducted in patients who had received no prior chemotherapy or only 1 prior chemotherapy regimen without ipilimumab (genetical recombination) (IPI). The primary endpoints were overall survival (OS) and progression-free survival (PFS). Patients receiving pembrolizumab (10 mg/kg Q3W or Q2W) showed statistically significantly prolonged OS and PFS, compared with those receiving IPI, the control treatment.

- A foreign phase II study (the KEYNOTE-002 study [Study 002]) was conducted in patients who had received prior IPI therapy. Patients receiving pembrolizumab (10 mg/kg Q3W or 2 mg/kg Q3W) showed statistically significantly prolonged PFS (one of the 2 primary endpoints), compared with those receiving investigator-choice chemotherapy (ICC).

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 unresectable malignant melanoma who receive pembrolizumab: gastrointestinal disorders, skin disorders, neurological disorders, hepatic dysfunction, eye disorders, endocrine dysfunction, 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), pembrolizumab is positioned as a therapeutic option for (a) patients with unresectable malignant melanoma who have received no prior chemotherapy or only 1 prior chemotherapy regimen without IPI and (b) patients with unresectable malignant melanoma who have received prior IPI therapy. The indication for pembrolizumab should therefore be "unresectable malignant melanoma," provided that the following cautionary statement is included in the Precautions for Indications section:

Precautions for Indications

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

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

PMDA instructed the applicant to use the wording "unresectable malignant melanoma" for the indication of pembrolizumab, and to include the above precautionary statement 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), the following cautionary statements should be included in the Precautions for Dosage and Administration section, and the dosage and administration of pembrolizumab should be "The usual adult

dosage is 2 mg/kg (body weight) 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.

- If an adverse reaction associated with pembrolizumab occurs, interrupt or discontinue pembrolizumab in accordance with Table 59.

Table 59. Criteria for interruption or discontinuation*

Adverse reaction	Severity	Actions
ILD	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 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 or ALT 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 or ALT increased to ≥5 times the ULN, or total bilirubin increased to ≥3 times the ULN • Patients with liver metastasis: Grade 2 AST or ALT 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.
IRR	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 within 12 weeks of the last dose of pembrolizumab	Discontinue pembrolizumab.

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; *, Grade is determined in accordance with NCI-CTCAE v4.0.

At the Expert Discussion, the expert advisers made the following comments and supported the PMDA's conclusion presented above:

- In Study 002, compared with the ICC group, the pembrolizumab 2 mg/kg Q3W group showed statistically significantly prolonged PFS, one primary endpoint, but showed no prolongation of OS, the other primary endpoint. From a statistical viewpoint, there is not enough evidence to support "2 mg/kg Q3W" as the dosage and administration of pembrolizumab. From a clinical viewpoint, however, the PMDA's conclusion (that the 2 mg/kg Q3W regimen is acceptable for dosage and administration of pembrolizumab in Japan) is understandable.

Based on the above, PMDA instructed the applicant to use "2 mg/kg Q3W" as the dosage and administration of pembrolizumab, and to include the above precautionary statements in the Precautions for Dosage and Administration sections. The applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to undertake post-marketing surveillance covering all patients receiving pembrolizumab, to investigate the safety of pembrolizumab in clinical settings after the market launch. The planned sample size is 250 patients. The observation period is 1 year. The planned key survey item of the surveillance is ILD.

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 an all-case post-marketing 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 key survey items of the surveillance should include not only ILD, selected by the applicant, but also the following events: 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.), IRR, encephalitis and meningitis, and myasthenia gravis.
- The planned sample size should be reconsidered based on the incidence of the above adverse events (i.e., the above additional key survey items) in clinical studies.
- The proposed observation period is acceptable.

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

- In light of the mechanism of action of pembrolizumab, attention should be paid to development of neurological disorders such as Guillain-Barre syndrome. Information on neurological disorders should be collected in the post-marketing surveillance.

Taking account of the above discussion, PMDA instructed the applicant to reconsider the surveillance plan.

The applicant's response:

- The key survey items of the surveillance will include not only ILD but also 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.), IRR, encephalitis and meningitis, myasthenia gravis, and neurological disorders (Guillain-Barre syndrome, etc.).
- The planned sample size is 250 based on the incidence of adverse events selected as the key survey items, in Studies 002 and 006, and the Japanese phase Ib study (the KEYNOTE-041 study [Study 041]).

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for pembrolizumab should include the safety and efficacy specifications presented in Table 60, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 61.

Table 60. 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 • Severe skin disorders (oculomucocutaneous syndrome, erythema multiforme, pemphigoid, etc.) • IRR • Encephalitis and meningitis • Myasthenia gravis • Neurological disorders (Guillain-Barre syndrome, etc.)	• Myocarditis	• None
Efficacy specification		
• Efficacy in routine clinical use		

Table 61. 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 • Use-results survey (all-case surveillance) • Post-marketing clinical study (extension study of Study 041)	• Provision of data from early post-marketing phase vigilance • Preparation and distribution of information materials for healthcare professionals • Preparation and provision of information materials for patients

Table 62. 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 patients treated with pembrolizumab
Observation period	1 year after the start of pembrolizumab therapy
Planned sample size	250 patients
Main survey items	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, severe skin disorders (oculomucocutaneous syndrome, erythema multiforme, pemphigoid, etc.), IRR, encephalitis and meningitis, myasthenia gravis, and neurological disorders (Guillain-Barre syndrome, etc.) Other main survey items: patient characteristics (disease stage, prior treatment, etc.), use status of pembrolizumab, concomitant drugs, adverse events, etc.

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

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

The new drug application data were subjected to s document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 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. As a result, PMDA concluded that the clinical studies as a whole was conducted in compliance with GCP, and that there were no obstacles to conducting its regulatory review based on the application documents submitted. PMDA identified the following problem to be solved in a study site, although it had no significant impact on the review of the overall clinical studies. PMDA notified the head of the site of the problem.

Problem to be solved

A study site

- Some subjects were included in a clinical study and received the study drug, despite a failure to meet the inclusion criteria (lactate dehydrogenase less than ULN of the study site).

3. 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 medical institutions that can provide adequate emergency medical care. Since the product is designated as an orphan drug, the re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs and the product is classified as a biological product.

Indication

Unresectable malignant melanoma

Dosage and Administration

The usual adult dosage is 2 mg/kg (body weight) 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

(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

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

(2) Pregnant or possibly pregnant women

Precautions for Indications

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

Precautions for Dosage and Administration

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

(2) If an adverse 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 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 ≥5 times the ULN, or total bilirubin increased to ≥3 times the ULN • Patients with liver metastasis: Grade 2 AST (GOT) or ALT (GPT) at baseline with a ≥50% increase from baseline persisting for ≥1 week	Discontinue pembrolizumab.
Renal 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 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.