Review Report

July 7, 2020
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 100 mg
Non-proprietary Name	Pembrolizumab (Genetical Recombination) (JAN*)
Applicant	MSD K.K.
Date of Application	November 8, 2019
Dosage Form/Strength	Injection: Each 4 mL vial contains 100 mg of Pembrolizumab (Genetical Recombination).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy, 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 indications and dosage and administration shown below, with the following conditions.

Indications

Malignant melanoma

Unresectable, advanced or recurrent non-small cell lung cancer

Relapsed or refractory classical Hodgkin lymphoma

Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy

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

Radically unresectable or metastatic renal cell carcinoma

Recurrent or metastatic head and neck cancer

Radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy

(Underline denotes additions. Double-underline denotes additions made as of December 20, 2019 after the present application.)

Dosage and Administration

[Malignant melanoma]

The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months.

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

The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes.

[Radically unresectable or metastatic renal cell carcinoma]

In combination with axitinib, the usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes.

(Underline denotes additions. Double-underline denotes additions made as of December 20, 2019 after the present application.)

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

June 4, 2020

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

Product Submitted for Approval	
Brand Name	Keytruda Injection 100 mg
Non-proprietary Name	Pembrolizumab (Genetical Recombination)
Applicant	MSD K.K.
Date of Application	November 8, 2019
Dosage Form/Strength	Injection: Each 4 mL vial contains 100 mg of Pembrolizumab (Genetical Recombination).
Proposed Indications	Malignant melanoma Unresectable, advanced or recurrent non-small cell lung cancer Relapsed or refractory classical Hodgkin lymphoma Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy Advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments) <u>Unresectable, advanced or recurrent esophageal cancer</u> (Underline denotes additions.)
Proposed Dosage and Administration	[Malignant melanoma] The usual adult dosage is 200 mg every 3 weeks <u>or 400 mg every 6 weeks</u> of pembrolizumab (genetical recombination) infused intravenously over 30 minutes. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. [Unresectable, advanced or recurrent non-small cell lung cancer, relapsed or refractory classical Hodgkin lymphoma, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or

intolerant to standard treatments), or unresectable, advanced or recurrent esophageal cancer]

The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes.

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

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

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

In Japan, pembrolizumab was approved for the indications of (a) "unresectable malignant melanoma" in September 2016, (b)"unresectable, advanced or recurrent PD-L1 positive non-small cell lung cancer (NSCLC)" in December 2016, (c) "relapsed or refractory classical Hodgkin lymphoma (cHL)" in November 2017, (d)"radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy" in December 2017, and (e) "advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)" in December 2018. After the present partial change application was filed, pembrolizumab was also approved for the indications of "radically unresectable or metastatic renal cell carcinoma (RCC)" and "recurrent or metastatic head and neck cancer" in December 2019. The above indications (a) and (b) were changed to "malignant melanoma" and "unresectable, advanced or recurrent NSCLC," respectively, in December 2018.

1.2 Development history etc.

The applicant has conducted 2 clinical studies in chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer, as a global phase II study (Study 180) and a global phase III study (Study 181) since December 2015. In Japan, patient enrollment in these 2 studies started in [redacted] 20[redacted]. With the results from Study 181 serving as pivotal data, the applicant has filed a partial change approval application for pembrolizumab to add an indication and a dosage regimen for esophageal cancer.

The present application also proposed an update of the dosage and administration to add a regimen of 400 mg every 6 weeks to the approved dosage regimen of 200 mg every 3 weeks, for all of the approved indications, including esophageal cancer, based on the results of the population pharmacokinetics (PPK) analyses, etc.

As of April 2020, the approval status of pembrolizumab outside Japan is as follows:

(a) Esophageal cancer

In the US and the EU, partial change applications were filed in January 2019 and February 2019, respectively, based on the pivotal data from Study 181. In the US, pembrolizumab was approved in July 2019 for the following indication: "KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (combined positive score [CPS] ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy." In the EU, the application was withdrawn in December 2019, after the European Medicines Agency (EMA) commented that the results from Study 181 were insufficient to conclude the clinical usefulness of pembrolizumab in the treatment of esophageal cancer. Currently, pembrolizumab is approved for the treatment of esophageal cancer in 10 countries or regions.

(b) The 400 mg every 6 weeks regimen

In the US and the EU, partial change applications to add a regimen of 400 mg every 6 weeks were filed in April 2019 and September 2018, respectively, based primarily on the results of PPK analyses, and pembrolizumab was approved for the new dosage regimen in April 2020 and March 2019, respectively. Currently, the 400 mg every 6 weeks regimen is approved in 43 countries or regions.

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

Because the present application is intended for a new indication and a new dosage regimen, no additional quality data have been submitted.

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

Although the present application is intended for a new indication and a new dosage regimen, no new data on non-clinical pharmacology have been submitted. The non-clinical pharmacology of pembrolizumab was evaluated during the review for the initial approval.

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

Although the present application is intended for a new indication and a new dosage regimen, no new data on non-clinical pharmacokinetics have been submitted. The non-clinical pharmacokinetics of pembrolizumab was evaluated during the review for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication and a new dosage regimen, no additional toxicity data have been submitted.

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

Although the present application is intended for a new indication and a new dosage regimen, no new data on biopharmaceutic studies or associated analytical methods have been submitted. The biopharmaceutic studies and associated analytical methods for pembrolizumab were evaluated during the reviews for the initial and subsequent approvals.

6.1 Clinical pharmacology

The applicant has submitted the results of PPK analyses and an assessment of the relationship between exposure and efficacy and safety based on the data from the clinical studies presented in Table 1 as clinical pharmacology data for the present application.

Table 1. Clinical studies used in PPK analyses, and assessment of the relationship between exposure and efficacy and safety

Geographical location	Study identifier	Phase	Study population	Summary of dosage regimen
Global	Study 010	II/III	Patients with NSCLC	Pembrolizumab 2 or 10 mg/kg every 3 weeks
	Study 012	Ib	Cohorts B and B2: Patients with head and neck squamous cell carcinoma, etc.	Pembrolizumab 10 mg/kg every 2 weeks or 200 mg every 3 weeks
	Study 024	III	Patients with NSCLC	Pembrolizumab 200 mg every 3 weeks
	Study 045	III	Patients with urothelial carcinoma	Pembrolizumab 200 mg every 3 weeks
	Study 048	III	Patients with head and neck squamous cell carcinoma	Pembrolizumab 200 mg every 3 weeks as a monotherapy or in combination with a platinum + 5-fluorouracil (5-FU)[*1]
	Study 087	II	Patients with cHL	Pembrolizumab 200 mg every 3 weeks
	Study 158	II	Patients with MSI-High solid tumors (except colorectal cancer)	Pembrolizumab 200 mg every 3 weeks
	Study 164	II	Patients with MSI-High colorectal cancer, etc.	Pembrolizumab 200 mg every 3 weeks
	Study 181	III	Patients with esophageal cancer	Pembrolizumab 200 mg every 3 weeks
	Study 189	III	Patients with non-squamous (NSQ)-NSCLC	Pembrolizumab 200 mg every 3 weeks in combination with a platinum + PEM[*2]
	Study 426	III	Patients with RCC	Pembrolizumab 200 mg every 3 weeks in combination with axitinib 5 mg twice daily
Foreign	Study 001	I	Patients with malignant melanoma, etc.	Pembrolizumab 2 or 10 mg/kg every 3 weeks, etc.
	Study 002	II	Patients with malignant melanoma	Pembrolizumab 2 or 10 mg/kg every 3 weeks
	Study 006	III	Patients with malignant melanoma	Pembrolizumab 10 mg/kg every 2 or 3 weeks
	Study 012	Ib	Cohort C: Patients with urothelial carcinoma	Pembrolizumab 10 mg/kg every 2 weeks
	Study 013	Ib	Patients with hematological malignancies	Pembrolizumab 10 mg/kg every 2 weeks
	Study 040	III	Patients with head and neck squamous cell carcinoma	Pembrolizumab 200 mg every 3 weeks
	Study 052	II	Patients with urothelial carcinoma	Pembrolizumab 200 mg every 3 weeks
	Study 055	II	Patients with head and neck squamous cell carcinoma	Pembrolizumab 200 mg every 3 weeks

*1 A platinum (cisplatin [CDDP] 100 mg/m^2 or carboplatin [CBDCA] AUC 5 mg·min/mL) was intravenously administered on Day 1, with 5-FU 1000 mg/m^2/day on Days 1 to 4 of each 3-week cycle.

*2 A platinum (CDDP 75 mg/m^2 or CBDCA AUC 5 mg·min/mL) and pemetrexed sodium hydrate (PEM) 500 mg/m^2 were intravenously administered on Day 1 of each 3-week cycle.

6.1.1 PPK analyses

6.1.1.1 Assessment of exposure to pembrolizumab administered at a dose of 400 mg every 6 weeks

A PPK analysis was conducted using a nonlinear mixed effects model based on the pharmacokinetic data from patients treated with pembrolizumab for malignant melanoma (Studies 001, 002, and 006) and NSCLC (Studies

001, 010, and 024) (2,993 patients, 16,800 sampling points) (Software: NONMEM, Version 7.2.0). The pharmacokinetics of pembrolizumab were well described by a 2-compartment model in which first-order time-dependent elimination from the central compartment was assumed. Table 2 shows the estimated pharmacokinetic parameters of pembrolizumab. The estimated exposure to pembrolizumab in the overall population was characterized as follows:

- The $C_{avg,ss}$ value following administration of pembrolizumab 400 mg every 6 weeks was comparable to that of pembrolizumab 200 mg every 3 weeks.
- The $C_{min,ss}$ value following administration of pembrolizumab 400 mg every 6 weeks was lower than that of pembrolizumab 2 mg/kg or 200 mg every 3 weeks.
- The $C_{max,ss}$ value following administration of pembrolizumab 400 mg every 6 weeks was higher than that of pembrolizumab 200 mg every 3 weeks, but lower than that of pembrolizumab 10 mg/kg every 2 weeks, a dosage regimen that has been demonstrated to be tolerable in both Japanese and non-Japanese patients (see "Review Report for Keytruda Injection 20 mg, Keytruda Injection 100 mg, dated August 30, 2016").

Table 2. Estimated pharmacokinetic parameters of pembrolizumab

	Dosage regimen	C_{max} (μg/mL)	C_{avg} (μg/mL)	C_{min} (μg/mL)	$C_{max,ss}$ (μg/mL)	$C_{avg,ss}$ (μg/mL)	$C_{min,ss}$ (μg/mL)
Overall population (n = 2,993)	2 mg/kg every 3 weeks	44.1 (43.7, 44.5)	20.8 (20.7, 21.0)	13.5 (13.3, 13.6)	69.2 (68.4, 70.2)	37.6 (37.1, 38.0)	23.1 (22.7, 23.4)
	200 mg every 3 weeks	59.1 (58.5, 59.7)	27.9 (27.7, 28.1)	18.1 (17.8, 18.3)	92.8 (91.7, 94.1)	50.4 (49.8, 51.0)	30.9 (30.5, 31.4)
	400 mg every 6 weeks	123 (122, 124)	32.4 (32.0, 32.7)	10.6 (10.4, 10.8)	148 (146, 149)	50.7 (50.1, 51.3)	20.3 (19.8, 20.9)
	10 mg/kg every 2 weeks	220 (218, 223)	144 (143, 145)	119 (117, 121)	428 (424, 433)	279 (276, 282)	197 (193, 200)
Japanese subpopulation (n = 83)	2 mg/kg every 3 weeks	39.3 (37.1, 41.8)	18.1 (17.3, 18.9)	11.5 (10.4, 12.4)	60.7 (56.0, 65.1)	32.6 (29.7, 34.6)	19.7 (17.7, 22.0)
	200 mg every 3 weeks	69.3 (65.4, 73.9)	32.0 (30.5, 33.4)	20.3 (18.4, 21.9)	107 (98.9, 115)	57.5 (52.5, 61.1)	34.7 (31.3, 38.8)
	400 mg every 6 weeks	145 (134, 154)	37.2 (35.1, 38.8)	11.7 (10.4, 13.1)	173 (159, 183)	57.2 (52.6, 61.1)	22.1 (19.3, 25.5)
	10 mg/kg every 2 weeks	197 (184, 211)	125 (119, 130)	102 (93, 110)	372 (345, 393)	239 (221, 258)	167 (151, 185)

Each figure represents a median of the geometric mean values of 100 simulations (2.5 percentile, 97.5 percentile).

After the present partial change application, the applicant submitted pharmacokinetic data from a foreign phase I study that investigated pembrolizumab administered at a dose of 400 mg every 6 weeks in patients with malignant melanoma (Study 555). In the study, the observed C_{max} and C_{min} values were 136.0 (135.6, 136.4) and 14.9 (14.4, 15.4) μg/mL, respectively, which were comparable to the estimated C_{max} and C_{min} values at a dose of 400 mg every 6 weeks.

6.1.1.2 Differences in the pharmacokinetics of pembrolizumab across cancer types

The serum pembrolizumab concentrations observed in patients receiving pembrolizumab 200 mg every 3 weeks for cHL (Study 087), urothelial carcinoma (Study 045), MSI-High solid tumors (Studies 158 and 164), RCC (Study 426), head and neck squamous cell carcinoma (Studies 040, 048, and 055), or esophageal cancer (Study 181) were compared with the serum pembrolizumab concentrations estimated via simulations using the above PPK model. The comparison showed that the observed serum pembrolizumab concentrations were roughly consistent with the 90% prediction interval of the simulation-estimated concentrations. The applicant

has explained that the pharmacokinetics of pembrolizumab does not differ clearly across the cancer types based on the results.

6.1.2 Relationship between exposure and efficacy and safety

6.1.2.1 Relationship between exposure and efficacy

The relationship between exposure to pembrolizumab and its efficacy was investigated as follows:

- The relationship between exposure to pembrolizumab (AUC_{wk6} and C_{min}) and the percent change from baseline in tumor size was assessed based on: the data from patients who received pembrolizumab 2 or 10 mg/kg every 3 weeks for malignant melanoma (Studies 001 and 002) or NSCLC (Study 010); the data from patients receiving pembrolizumab 200 mg every 3 weeks or 10 mg/kg every 2 weeks for cHL (Studies 013 and 087), urothelial carcinoma (Studies 012, 045, and 052), or head and neck squamous cell carcinoma (Studies 012 and 055); and the data from patients receiving pembrolizumab 200 mg every 3 weeks for MSI-High solid tumors (Studies 158 and 164) or esophageal cancer (Study 181). The assessment showed a flat exposure-response relationship within the range of dosage regimens across all of the cancer types (Figure 1).

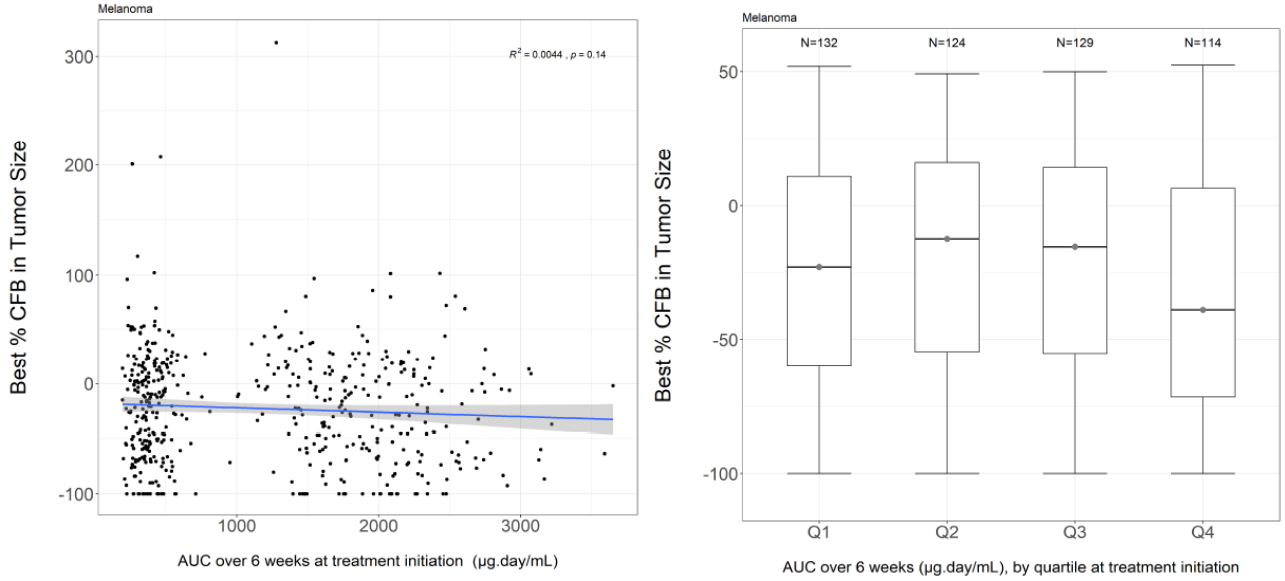

Figure 1. Exposure-response relationship between AUC_{wk6} and the percent change from baseline in tumor size (malignant melanoma)

CFB, change from baseline, is a change from baseline in tumor size.

- The overall survival (OS) following administration of pembrolizumab 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 400 mg every 6 weeks was assessed based on the data from patients with malignant melanoma (Study 002) or NSCLC (Study 010) who received pembrolizumab 2 or 10 mg/kg every 3 weeks. The assessment predicted no clear differences in OS among the dosage regimens (Figure 2).[1)]

1) Similar Kaplan-Meier curves were obtained for the OS predicted using simulation-estimated C_{min} values.

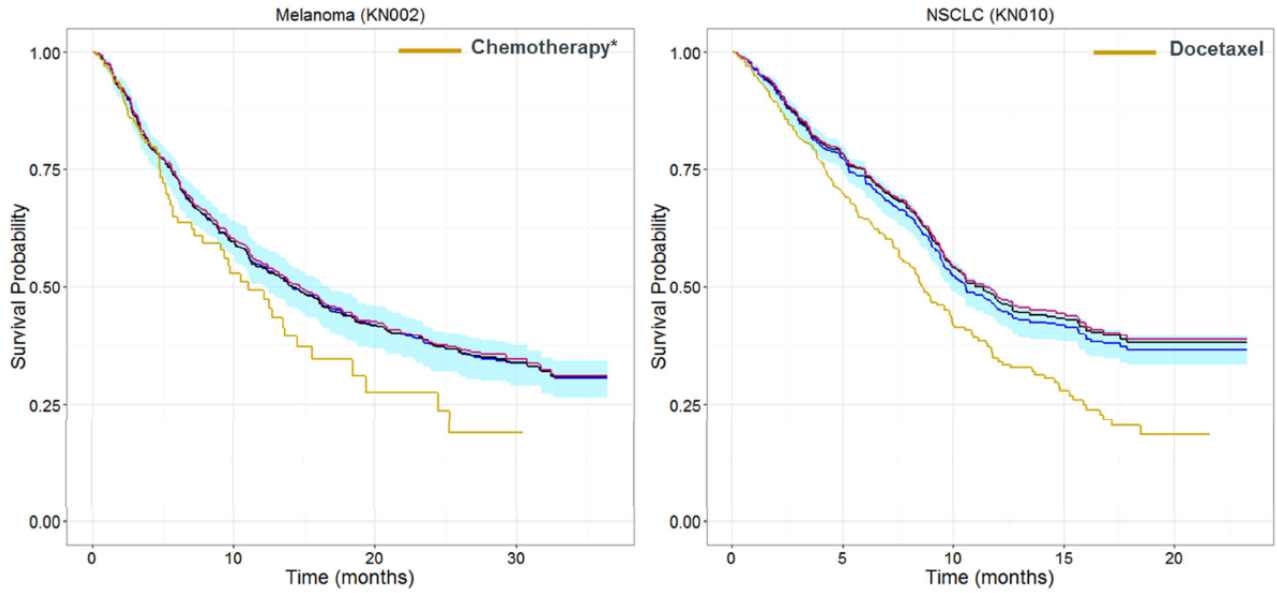

Figure 2. Kaplan-Meier curves of the OS predicted using simulation-estimated C_{avg} values by dosage regimen (malignant melanoma or NSCLC)

- The relationship between exposure to pembrolizumab (C_{min})[2)] and the percent change from baseline in tumor size was assessed based on the data from patients who received pembrolizumab 200 mg every 3 weeks in combination with other antineoplastic drugs (e.g., platinum agents) for NSCLC (Study 189), head and neck squamous cell carcinoma (Study 048), or RCC (Study 426). The assessment showed a flat exposure-response relationship for all of the dosage regimens across all of the cancer types (Figure 3).

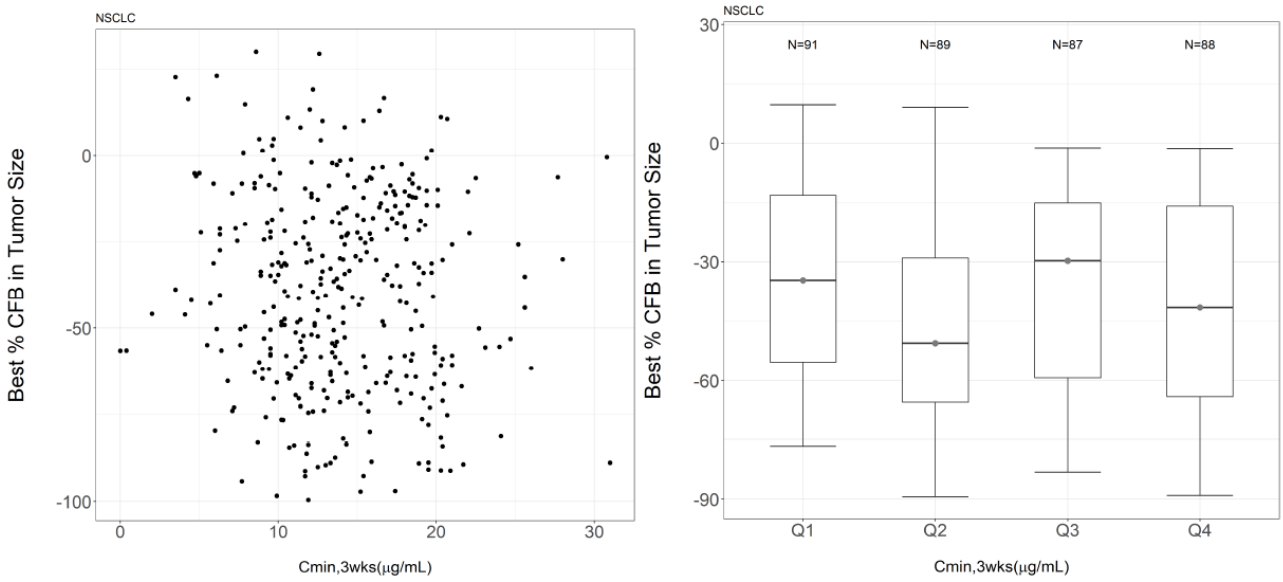

Figure 3. Exposure-response relationship between C_{min} and the percent change from baseline in tumor size (NSCLC)

CFB, change from baseline, is a change from baseline in tumor size.

2) In patients with RCC, the minimum serum pembrolizumab concentrations in Cycle 2 were used as C_{min} values.

6.1.2.2 Relationship between exposure and safety

The relationship between exposure to pembrolizumab and its safety was investigated as follows:

- The relationships between exposure to pembrolizumab (AUC_{wk6} and $AUC_{wk6,ss}$) and the incidences of adverse events (adverse events of special interest [AEOSI] and Grade ≥3 adverse events[3)]) were assessed based on the data from patients who received pembrolizumab 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks or every 3 weeks for malignant melanoma (Studies 001, 002, and 006) or NSCLC (Studies 001 and 010). The assessment showed a flat exposure-response relationship within the range of the dosage regimens (Figures 4 and 5).

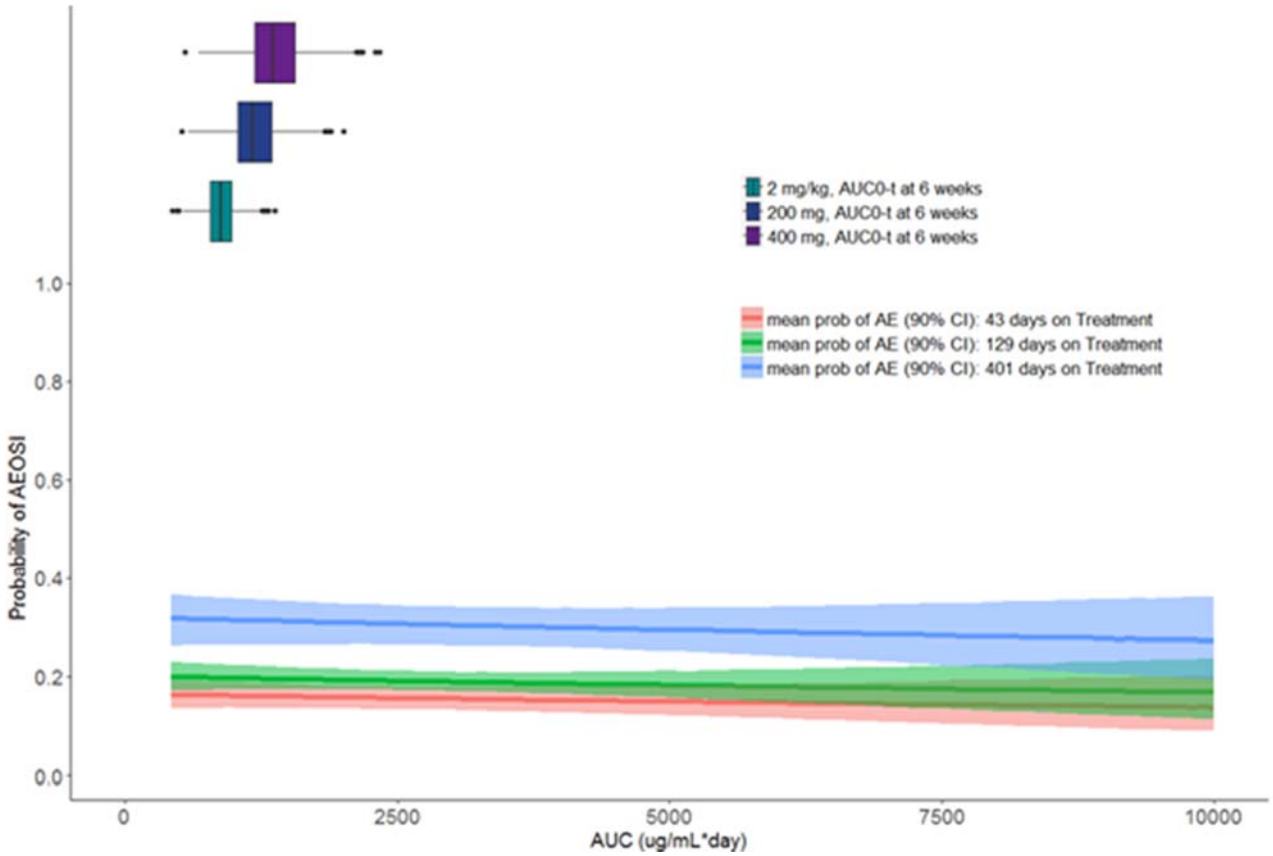

Figure 4. Exposure-response relationship between AUC_{wk6} and the incidence of AEOSI by treatment duration (malignant melanoma [Studies 001 and 002] or NSCLC [Studies 001 and 010])

The treatment duration is divided into 3 periods, with medians for the first, second, and third tertile of 43, 129, and 401 days, respectively.

The box-and-whisker plots represent the distribution of AUC_{wk6} by pembrolizumab administered at doses of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, and 400 mg every 6 weeks.

3) Data from patients with malignant melanoma who received pembrolizumab 2 mg/kg every 3 weeks, or 10 mg/kg every 2 weeks or every 3 weeks were used.

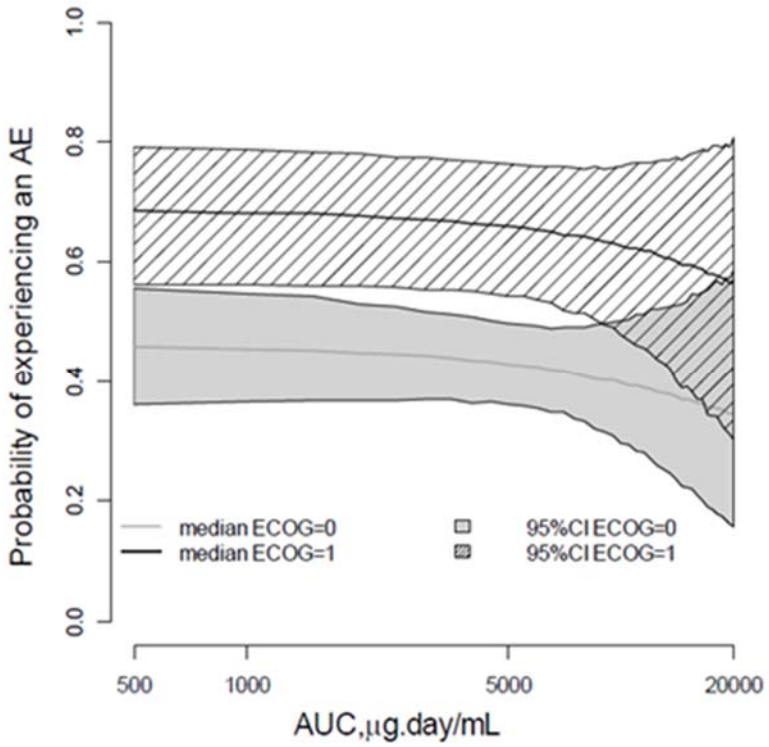

Figure 5. Exposure-response relationship between $AUC_{wk6,ss}$ and the incidence of Grade ≥3 adverse events by ECOG PS (malignant melanoma [Study 001])

- The relationships between exposure to pembrolizumab (C_{max} or C_{min}[4)]) and the incidences of adverse events (AEOSI and Grade ≥3 adverse events) were assessed based on the data from patients who received pembrolizumab 200 mg every 3 weeks in combination with other antineoplastic drugs (e.g., platinum agents) for NSCLC (Study 189), head and neck squamous cell carcinoma (Study 048), or RCC (Study 426). The assessment showed no clear relationship between exposure to pembrolizumab and the incidence of adverse events for all of the dosage regimens across all of the cancer types.

The applicant has explained that the efficacy and safety of pembrolizumab do not clearly differ between the 200 mg every 3 weeks regimen and the 400 mg every 6 weeks regimen in patients with the approved cancer types or esophageal cancer, in view of the available data, including the results of the PPK analyses, exposure-efficacy or exposure-safety analyses described above, and no clear differences noted in the safety profile of pembrolizumab between patients with the approved cancer types and patients with esophageal cancer (see "Review Report for Keytruda Injection 20 mg, Keytruda Injection 100 mg, dated November 19, 2018," etc.) [see Section 7.R.2].

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA concluded that the applicant's explanation about the clinical pharmacology of pembrolizumab was acceptable.

4) In patients with RCC, the minimum pembrolizumab concentrations in Cycle 2 were used as C_{min} values.

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

The applicant submitted efficacy and safety evaluation data, in the form of result data from a global phase II study and a global phase III study (Table 3). The applicant also submitted the results of a global phase Ib clinical study as reference data (Table 3).

Table 3. Clinical studies on the efficacy and safety of pembrolizumab

Data	Geographical location	Study identifier	Phase	Study population	Number of subjects treated	Dosage regimen	Main endpoints
Evaluation	Global	Study 180	II	Chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer	121	Pembrolizumab 200 mg intravenously every 3 weeks	Efficacy Safety
		Study 181	III	Chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer	Global cohort*1 628 (a) 314 (b) 314 Chinese cohort*2 123 (a) 62 (b) 61	(a) Pembrolizumab 200 mg intravenously every 3 weeks (b) Investigator's choice of any of the following treatments: • PTX 80-100 mg/m^2 intravenously on Days 1, 8, and 15 of each 4-week cycle • DTX 75 mg/m^2 intravenously every 3 weeks • CPT-11 180 mg/m^2 intravenously every 2 weeks	Efficacy Safety
Reference	Global	Study 028	Ib	[Cohort A4] Patients with radically unresectable, advanced or recurrent PD-L1 positive esophageal cancer	23	Pembrolizumab 10 mg/kg intravenously every 2 weeks	Efficacy Safety

*1 The global cohort comprises patients, including Chinese patients, enrolled during the global enrollment period.
*2 The Chinese cohort comprises Chinese patients enrolled during the global enrollment period or the extension period (the Chinese enrollment period).

A summary of the clinical studies is presented below. Major adverse events other than deaths reported in the studies are detailed in Section "7.3 Adverse events reported in clinical studies."

7.1 Evaluation data

7.1.1 Global clinical studies

7.1.1.1 Global phase II study (CTD 5.3.5.2.2, Study 180, ongoing since [redacted], 20[redacted] [data cutoff on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 43 sites in 10 countries, including Japan, to evaluate the efficacy and safety of pembrolizumab in chemotherapy-treated[5)] patients with radically unresectable, advanced or recurrent esophageal cancer[6)] (target sample size, 100 patients).

Patients received pembrolizumab 200 mg intravenously every 3 weeks for up to 35 doses, or until disease progression or a withdrawal criterion was met.

All 121 enrolled and treated patients (including 30 Japanese patients) were included in the All-Subjects-as-Treated (ASaT) population, and the ASaT population was used for the efficacy analyses. The ASaT population was also used for safety analyses.

The primary endpoint was response rate, as assessed by blinded independent central review (BICR) using RECIST ver. 1.1. The primary analysis was conducted in (a) the ASaT population, (b) patients with an intermediate or high gene expression profile (GEP) score,[7)] and (c) patients with a high GEP score. Study 180 involved no statistical hypothesis tests for the efficacy evaluation.

Table 4 shows the efficacy results based on the primary endpoint, response rate, as assessed by BICR using RECIST ver. 1.1 (data cutoff on [redacted], 20[redacted]).

Table 4. Best overall response and response rate (Study 180)
(RECIST ver. 1.1, efficacy analysis set, BICR assessment, data cutoff on [redacted], 20[redacted])

Best overall response	n (%)		
	ASaT population N = 121	Patients with intermediate or high GEP N = 51	Patients with high GEP N = 24
CR	2 (1.7)	0	0
PR	10 (8.3)	7 (13.7)	5 (20.8)
SD	25 (20.7)	11 (21.6)	6 (25.0)
PD	71 (58.7)	29 (56.9)	11 (45.8)
NE	13 (10.7)	4 (7.8)	2 (8.3)
Response (CR + PR) (Response rate [95% CI*] [%])	12 (9.9 [5.2, 16.7])	7 (13.7 [5.7, 26.3])	5 (20.8 [7.1, 42.2])

* Exact test

5) Patients participating in Study 180 must have experienced disease progression after 2 prior lines of standard therapy. Patients with HER2 positive adenocarcinoma of the esophagogastric junction were also required to have documentation of disease progression after treatment containing trastuzumab. A chemotherapy or chemoradiotherapy as a neoadjuvant or adjuvant therapy, or a chemoradiotherapy with curative intent was counted as 1 line of chemotherapy, if disease progression occurred within 6 months of cessation of the treatment.

6) Patients who had an adenocarcinoma or squamous cell carcinoma of the esophagus or an adenocarcinoma of the esophagogastric junction (defined as an adenocarcinoma of the lower esophagus with the center of carcinoma located within 1 to 5 cm above the esophagogastric junction) were enrolled.

7) An index defined based on the tumor mRNA expression levels of 18 genes that were considered to be associated with immunity. Cutoff values were set to classify tumors into "low," "intermediate," and "high" groups, based on findings including the results of Study 028.

The safety analysis revealed deaths, during the treatment period or within 90 days after the last dose, of 7 (including no Japanese patients) of 121 patients (5.8%). The causes of death were pneumonia aspiration in 2 patients, cerebrovascular accident, chronic obstructive pulmonary disease, pneumonia, pneumonitis, and tumour necrosis in 1 patient each. A causal relationship to pembrolizumab could not be ruled out for the pneumonitis in 1 patient.

7.1.1.2 Global phase III study (CTD 5.3.5.1.1, 5.3.5.1.2, Study 181, ongoing since [redacted], 20[redacted] [data cutoff on October 15, 2018])

The global cohort[8)]of an open-label, randomized study was conducted at 154 sites in 32 countries and regions, including Japan, to compare the efficacy and safety of pembrolizumab versus investigator's choice of therapy (IC), in chemotherapy-treated[9)] patients with radically unresectable, advanced or recurrent esophageal cancer[7)] (target sample size, 600 subjects).

Patients in the pembrolizumab group received pembrolizumab 200 mg intravenously every 3 weeks for up to 35 doses. Patients in the IC group received any of the following treatments: paclitaxel (PTX) 80 to 100 mg/m^2 intravenously administered on Days 1, 8, and 15 of each 4-week cycle, docetaxel hydrate (DTX) 75 mg/m^2 intravenously administered every 3 weeks, or irinotecan hydrochloride hydrate (CPT-11) 180 mg/m^2 intravenously administered every 2 weeks. The treatment continued until disease progression or a withdrawal criterion was met.

In the global cohort, 628 enrolled and randomized patients (314 in the pembrolizumab group and 314 in the IC group, including 77 and 75 Japanese patients, respectively) were included in the intention-to-treat (ITT) population and used for the efficacy analyses. Of these 628 patients, 18 in the IC group did not receive the study drug, and the remaining 610 (314 in the pembrolizumab group and 296 in the IC group, including 77 and 74 Japanese patients, respectively) were included in the safety analysis set.

In the Chinese cohort, 123 enrolled and randomized patients (62 in the pembrolizumab group and 61 in the IC group) were included in the ITT population and used for efficacy analyses. Of these 123 patients, 2 in the IC group did not receive the study drug, and the remaining 121 patients (62 in the pembrolizumab group and 59 in the IC group) were included in the safety analysis set.

At the start of the study, the primary endpoints in the global cohort were progression-free survival (PFS) and OS, as assessed by central imaging review using RECIST ver. 1.1. The primary analyses were originally

8) China was also included in the global cohort. Patient enrollment in the Chinese cohort, which was limited to Chinese patients, was extended beyond the end of patient enrollment in the global cohort. Eleven Chinese patients enrolled into the global cohort were also included in the Chinese cohort.

9) Patients participating in Study 181 must have experienced disease progression after 1 prior line of standard therapy. Patients with HER2 positive adenocarcinoma of the esophagogastric junction were also required to receive trastuzumab in the prior line of standard therapy. A chemotherapy or chemoradiotherapy as a neoadjuvant or adjuvant therapy, or a chemoradiotherapy with curative intent was counted as 1 line of chemotherapy, if disease progression occurred within 6 months after the treatment.

planned to be conducted in patients with high GEP scores[10] and the ITT population, along with an interim analysis for efficacy evaluation. The primary PFS analysis and the interim OS analysis were to be conducted when 240 PFS events had occurred in patients with high GEP scores, and the final OS analysis was to be conducted when 251 OS events had occurred in patients with high GEP scores.

However, the results of Study 180 suggested that OS could be a more appropriate efficacy endpoint for pembrolizumab, and that pembrolizumab was expected to show superior efficacy, particularly in patients with PD-L1 positive tumors or patients with squamous cell carcinoma. Therefore, the study protocol was amended to specify OS as the sole primary endpoint, and to perform the primary analysis in the following 3 populations: (a) patients with a PD-L1 CPS ≥10,[11] (b) patients with squamous cell carcinoma, and (c) the ITT population. With the protocol amendment, the interim OS analysis was to be conducted in (a) patients with PD-L1 CPS ≥10 and (b) patients with squamous cell carcinoma, when 251 and 385 OS events had occurred, respectively, and the final OS analysis was to be conducted in (b) patients with squamous cell carcinoma and (c) the ITT population when 310 and 473 OS events had occurred, respectively (Clinical Study Protocol ver. [redacted], dated [redacted], 20[redacted]).

Multiplicity arising from the setting of multiple primary analysis sets was adjusted by controlling the overall type-1 error rate at a 1-sided α of 2.5%, with use of the graphical method of Maurer and Bretz (*Stat Biopharm Res.* 2013;5:311-20) (Figure 6). The Lan-DeMets O'Brien-Fleming α-spending function was used to control the type 1 error rate associated with the interim analysis.

10) An index defined based on the tumor mRNA expression levels of multiple genes considered to be associated with immunity. Cutoff values were set to classify tumors into "low" and "high" groups, based on the results of Study 180.

11) PD-L1 levels were determined using the "PD-L1 IHC 22C3 pharmDx 'Dako'," of Dako Japan Co., Ltd. The PD-L1 CPS was defined as the number of PD-L1 positive cells (tumor cells, macrophages, and lymphocytes) divided by the total number of tumor cells, followed by multiplication by 100. Patients with PD-L1 CPS ≥10 represent patients who had a CPS of ≥10.

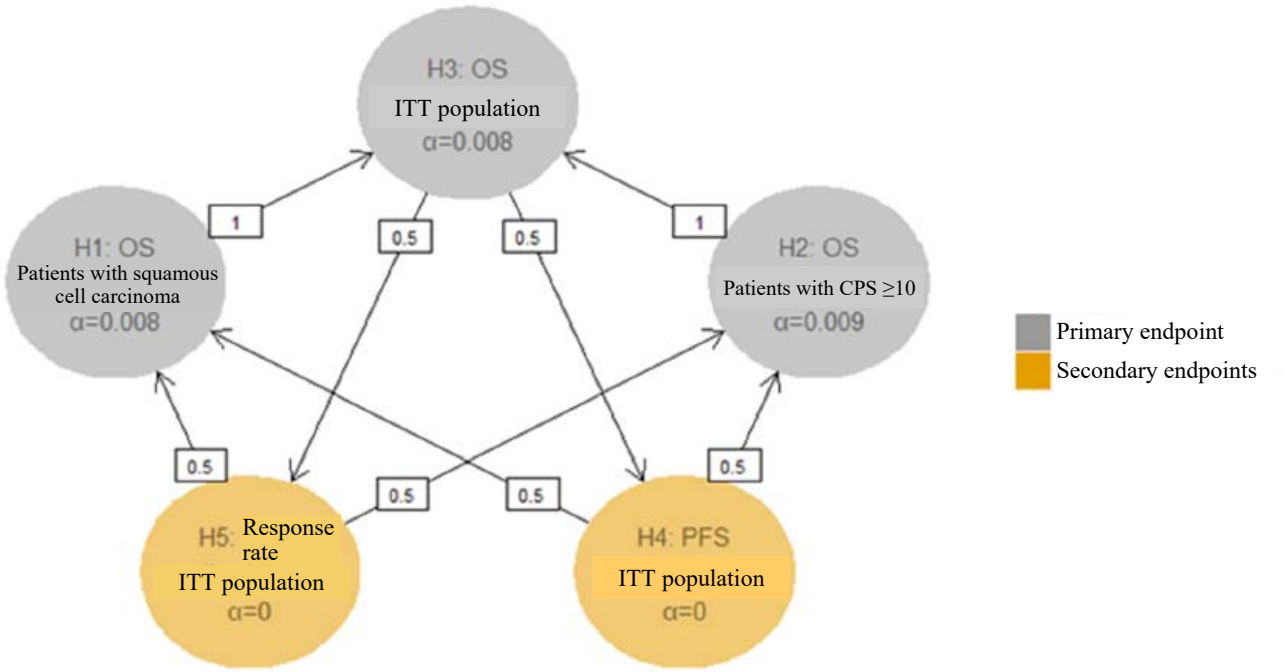

Figure 6. Statistical test procedure and significance level (1-sided) allocation for OS, PFS, and response rate

The final analysis of OS, which was the primary endpoint, initially showed a statistically significant increase in OS in patients with PD-L1 CPS ≥10;[12] however, 2 deaths were subsequently found to have been handled as censored cases.[13] The reanalysis was therefore conducted, with the 2 deaths correctly handled. The results of the reanalysis (Table 5) and the Kaplan-Meier curves of OS (Figures 7 to 9) are shown below. The OS results from the reanalysis failed to meet the prespecified criteria, in all of the analysis sets.

Table 5. OS reanalysis (data cutoff on October 15, 2018)

Patient population	Treatment group	N	Number of events (%)	Median [95% CI] (months)	Hazard ratio [95% CI]	*P*-value (1-sided)
CPS ≥10	Pembrolizumab	107	88 (82.2)	9.3 [6.6, 12.5]	0.70 [0.52, 0.94]*1	0.00855*2
	IC	115	103 (89.6)	6.7 [5.1, 8.2]		
Squamous cell carcinoma	Pembrolizumab	198	166 (83.8)	8.2 [6.7, 10.3]	0.77 [0.63, 0.96]*3	0.00894*4
	IC	203	182 (89.7)	7.1 [6.1, 8.2]		
ITT	Pembrolizumab	314	271 (86.3)	7.1 [6.2, 8.1]	0.89 [0.75, 1.05]*1	0.08431*5
	IC	314	284 (90.4)	7.1 [6.3, 8.0]		

*1 Cox regression stratified by geographic region (Asia versus non-Asia) and histology (squamous cell carcinoma versus adenocarcinoma);
*2 Log-rank test stratified by geographic region (Asia versus non-Asia) and histology (squamous cell carcinoma versus adenocarcinoma) with a 1-sided significance level of 0.00853;
*3 Cox regression stratified by geographic region (Asia versus non-Asia);
*4 Log-rank test stratified by geographic region (Asia versus non-Asia) with a 1-sided significance level of 0.00766;
*5 Maximum weighted log-rank test stratified by geographic region (Asia versus non-Asia) and histology (squamous cell carcinoma versus adenocarcinoma) with a 1-sided significance level of 0.00772.

12) The hazard ratio [95% CI] of OS for the pembrolizumab group versus the IC group was 0.69 [0.52, 0.93] (1-sided *P*-value, 0.0074; 1-sided significance level, 0.0085).
13) This data mishandling was discovered during the conduct of an additional analysis requested by an overseas regulatory agency. The applicant rechecked all of the death events occurring in Studies 180 and 181 for consistency and accuracy between the analysis data and descriptions of case report forms, and confirmed that no similar mistakes had been made. The applicant also took appropriate measures to ensure data accuracy for their ongoing clinical studies.

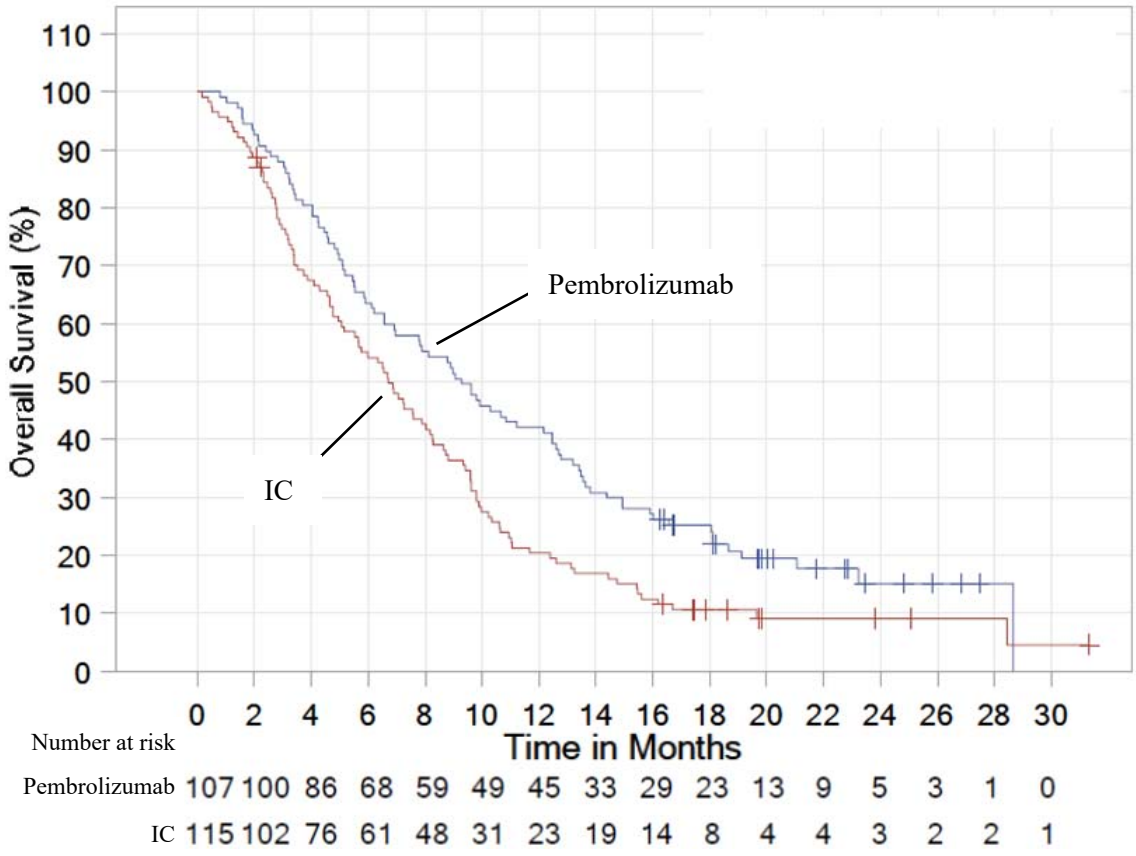

Figure 7. Kaplan Meier curves of OS (patients with PD-L1 CPS ≥10, data cutoff on October 15, 2018)

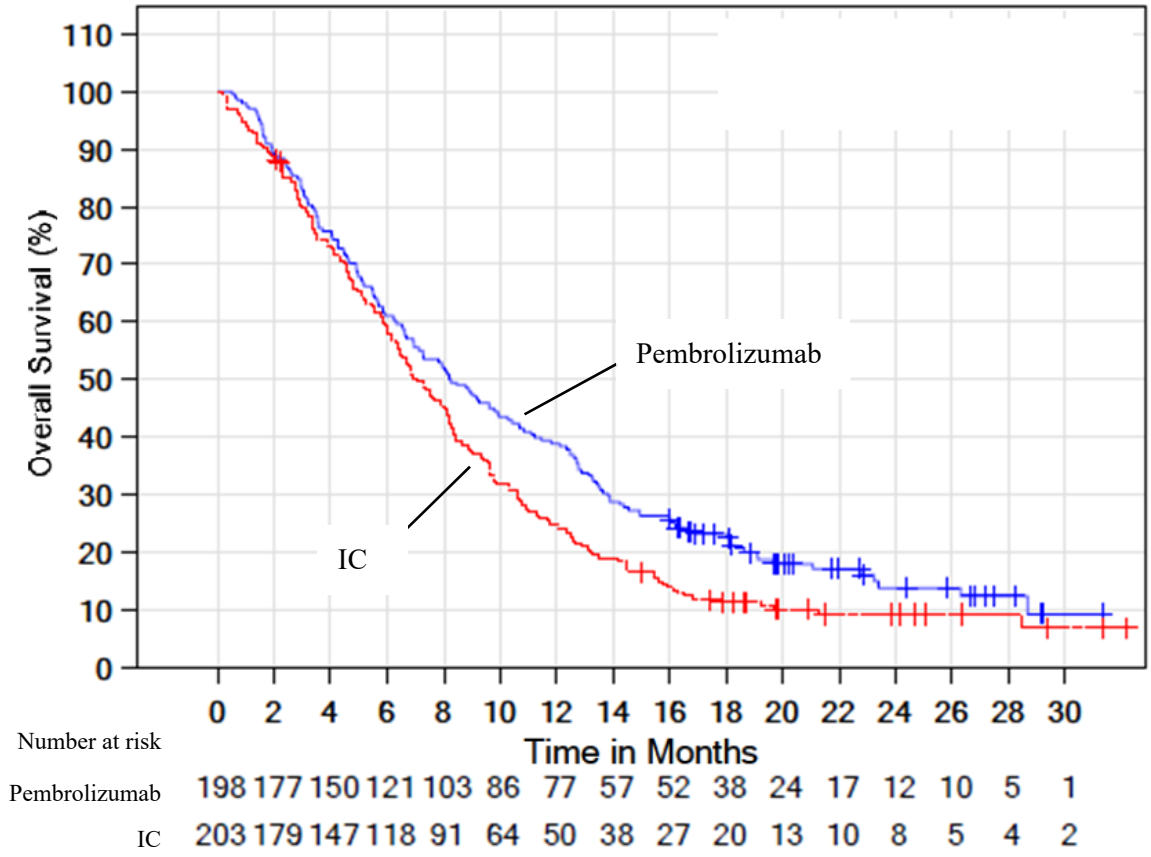

Figure 8. Kaplan Meier curves of OS (patients with squamous cell carcinoma, data cutoff on October 15, 2018)

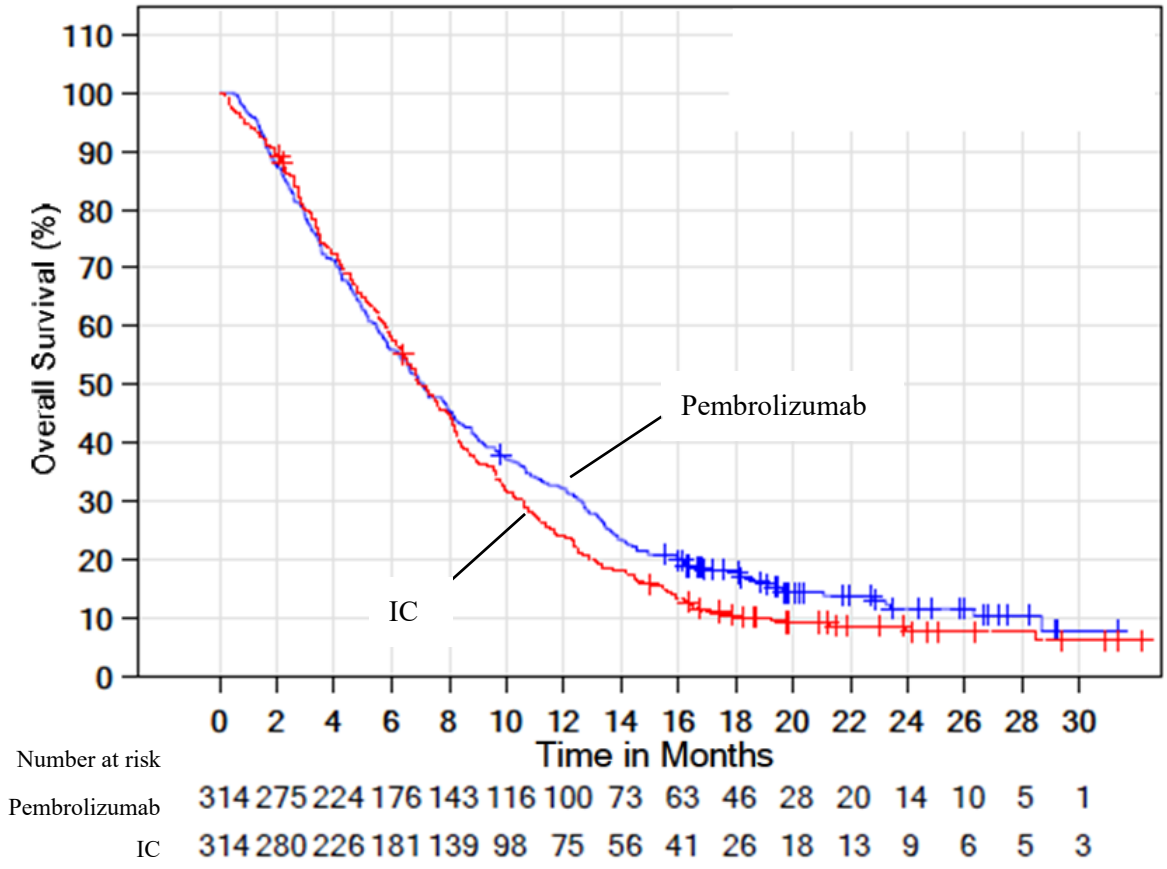

Figure 9. Kaplan Meier curves of OS (ITT population, data cutoff on October 15, 2018)

In the Chinese cohort, the hazard ratios [95% CIs] of OS (ITT population, data cutoff on February 13, 2019), which was the primary endpoint of the cohort, for the pembrolizumab group versus the IC group in the primacy analysis sets were 0.34 [0.17, 0.69] in patients with PD-L1 CPS ≥10, 0.55 [0.37, 0.83] in patients with squamous cell carcinoma, and 0.55 [0.36, 0.82] in the ITT population.

In the global cohort of Study 181, the safety analysis revealed deaths, during the treatment period or within 90 days after the last dose, of 30 of 314 patients (9.6%) in the pembrolizumab group and 32 of 296 patients (10.8%) in the IC group (including 3 of 77 and 3 of 74 Japanese patients, respectively). The causes of death, other than disease progression (0 patients in the pembrolizumab group, 1 patient in the IC group) were death in 5 patients, oesophageal haemorrhage and pneumonia aspiration in 4 patients each, pneumonia in 3 patients, completed suicide, gastrointestinal haemorrhage, and pneumonitis in 2 patients each, and acute respiratory failure, cardio-respiratory arrest, cerebrovascular accident, haemoptysis, liver injury, myocarditis, peritonitis, and sepsis in 1 patient each in the pembrolizumab group; and death in 10 patients, pneumonia in 5 patients, upper gastrointestinal haemorrhage in 2 patients, and acute respiratory failure, cerebellar stroke, gastrointestinal haemorrhage, haematemesis, haemorrhage, haemorrhage intracranial, hepatic failure, mediastinitis, pneumonia aspiration, respiratory failure, sepsis, septic shock, shock haemorrhagic, and neutrophil count decreased/white blood cell count decreased in 1 patient each in the IC group. A causal relationship to the study drug could not be ruled out for the pneumonitis in 2 patients, and death, myocarditis, and oesophageal haemorrhage in 1 patient each in the pembrolizumab group, and the pneumonia, pneumonia aspiration, sepsis, shock haemorrhagic, and

neutrophil count decreased/white blood cell count decreased in 1 patient each in the IC group. (The causes of death in Japanese patients were pneumonia aspiration in 2 patients and pneumonitis in 1 patient in the pembrolizumab group, and pneumonia, death, and pneumonia aspiration in 1 patient each in the IC group. A causal relationship to the study drug could not be ruled out for the pneumonitis in 1 patient in the pembrolizumab group and the pneumonia aspiration in 1 patient in the IC group.)

In the Chinese cohort of Study 181, the safety analysis revealed deaths, during the treatment period or within 90 days after the last dose, of 6 of 62 patients (9.7%) in the pembrolizumab group and 5 of 59 patients (8.5%) in the IC group. The causes of death were death in 2 patients, and cardiopulmonary failure, liver injury,[14] oesophageal fistula, and upper respiratory tract infection in 1 patient each in the pembrolizumab group, and gastrointestinal haemorrhage in 2 patients,[15] and acquired tracheo-oesophageal fistula, neutrophil count decreased/white blood cell count decreased,[15] and upper gastrointestinal haemorrhage in 1 patient each in the IC group. A causal relationship to the study drug could not be ruled out for the cardiopulmonary failure in 1 patient in the pembrolizumab group and the neutrophil count decreased/white blood cell count decreased in 1 patient in the IC group.

7.2 Reference data

7.2.1 Global clinical study

7.2.1.1 Global phase Ib study (CTD 5.3.5.2.1, Study 028, ongoing since [redacted], 20[redacted] [data cutoff on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 9 sites in 6 countries, including Japan, to evaluate the efficacy, safety, and other aspects of pembrolizumab in patients with various cancer types.[16] This multicohort study included cohort A4 comprising patients with radically unresectable, advanced or recurrent PD-L1 positive[17] esophageal cancer[18] (target sample size, 22 patients). (This review report describes only cohort A4 for Study 028.)

Patients in cohort A4 received pembrolizumab 10 mg/kg intravenously every 2 weeks for up to 24 months, or until disease progression or a withdrawal criterion was met.

All 23 enrolled and treated patients (including 10 Japanese patients) were included in efficacy and safety analyses.

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14) This patient was also counted in the global cohort.
15) One of the patients was also counted in the global cohort.
16) Each cohort of Study 028 enrolled patients with the following PD-L1 positive cancers: Cohort A1, colorectal cancer; cohort A2, anal canal cancer; cohort A3, pancreatic carcinoma; cohort A4, squamous cell carcinoma or adenocarcinoma of the esophagus or gastroesophageal junction; cohort A5, biliary cancer; cohort A6, carcinoid tumors; cohort A7, neuroendocrine tumors; cohort B1, breast cancer; cohort B2, ovarian cancer; cohort B3, endometrial cancer; cohort B4, cervical cancer; cohort B5, vulvar cancer; cohort C1, small cell lung cancer; cohort C2, malignant pleural mesothelioma; cohort D1, thyroid cancer; cohort D2, salivary gland cancer; cohort D3, head and neck cancer; cohort E1, glioblastoma; cohort E2, leiomyosarcoma; and, cohort E3, prostate cancer.
17) PD-L1 expression was assessed using an immunohistochemical assay (QualTek, Goleta). PD-L1 positivity was defined as PD-L1 expression in the tumor tissue stroma or in ≥1% of the tumor cells.
18) Patients with esophageal cancer that was refractory to the standard therapy, or for which no standard therapy is available or the standard therapy was not appropriate, were eligible.

The primary endpoint was response rate, as assessed by investigator using RECIST ver. 1.1.

Table 6 shows the efficacy results based on the primary endpoint, response rate as assessed by investigator using RECIST ver. 1.1. The observed response rate met the prespecified criteria.[19)]

Table 6. Best overall response and response rate (Study 028)
(RECIST ver. 1.1, efficacy analysis set, investigator assessment, data cutoff on [redacted], 20[redacted])

Best overall response	n (%)
	N = 23
CR	0
PR	7 (30.4)
SD	2 (8.7)
PD	13 (56.5)
NE	1 (4.3)
Response (CR + PR) (Response rate [95% CI*] [%])	7 (30.4 [13.2, 52.9])

* Exact test

The safety analysis revealed deaths, during the treatment period or within 90 days after the last dose, of 2 (including no Japanese patients) of 23 patients (8.7%). The causes of death were complication associated with device and haemorrhage in 1 patient each. A causal relationship to the study drug was denied for both of these events.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review and efficacy

PMDA's view:

Among the evaluation data submitted, the global phase III study in chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer (Study 181) is important in evaluating the efficacy and safety of pembrolizumab. In the study, the result for OS, which was the primary endpoint, failed to meet the prespecified criteria. However, as a result of the review of the submitted data, mainly the results of Study 181, PMDA concluded that pembrolizumab has demonstrated a certain level of efficacy in the treatment of chemotherapy-treated patients with radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma. Efficacy in Japanese patients is to be evaluated from the viewpoint of consistency between the entire study population and the Japanese subpopulation of Study 181, according to "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007), "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice, dated September 5, 2012), "Guidelines on General Principles for Planning and Design of Multi-Regional Clinical Trials" (PSEHB/PED Notification No. 0612-1, dated June 12, 2018), and other relevant regulations. This review report describes the results from the reanalysis of OS [see Section 7.1.1.2] as the results of Study 181.

19) If ≥1 of the first 6 enrolled patients responded to pembrolizumab, patient enrollment was continued until the sample size reached roughly 22 patients. Pembrolizumab was determined to be effective if ≥6 of 22 patients, ≥7 of 23 to 26 patients, or ≥8 of 27 to 30 patients responded to pembrolizumab.

7.R.1.1 Selection of efficacy endpoints and the control group

In Study 181, OS was selected as the primary endpoint.

The applicant's explanation about the rationale for the control group selected in Study 181:
At the time of planning Study 181, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN guidelines) (esophageal and esophagogastric junction cancers) (v.2.2015) recommended the use of PTX, DTX, and CPT-11, based on reports that these drugs had been demonstrated to be highly effective in the target patient population of Study 181 *(Lancet Oncol.* 2014;15:78-86, *Ann Oncol.* 2007;18:898-902, and *J Clin Oncol.* 2013;31:4438-44). In view of this recommendation and other findings, any of PTX, DTX, or CPT-11 was to be chosen by each investigator as the control in Study 181.

PMDA asked the applicant to explain the appropriateness of the dose of DTX selected for Study 181 (75 mg/m^2), which differed from the dose approved for the treatment of esophageal cancer in Japan (70 mg/m^2).

The applicant's explanation:
The dose of DTX selected for Study 181 (75 mg/m^2) was appropriate for the following reasons.

- The NCCN guidelines (esophageal and esophagogastric junction cancers) (v.2.2015) recommended the use of DTX at a dose of 75 to 100 mg/m^2 for chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer.
- The efficacy of DTX did not clearly differ between the doses of 75 mg/m^2 and 70 mg/m^2 in clinical studies in patients with esophageal cancer (*Invest New Drugs.* 2002;20:95-9 and *Ann Oncol.* 2004; 15:955-9).
- The results of the post-marketing use-results survey for DTX in Japan showed that the safety profile of DTX administered at a dose of 75 mg/m^2 did not clearly differ from that at 70 mg/m^2 (see "Review Report for Taxotere Intravenous Infusion 20 mg, Taxotere Intravenous Infusion 80 mg, dated September 28, 2010").

PMDA's view:
PMDA accepted the applicant's explanation in general. However, the possibility that the choice among the 3 different control drugs may affect the efficacy evaluation for pembrolizumab should be assessed separately [see Section 7.R.1.2].

7.R.1.2 Efficacy evaluation results

In Study 181, the results for OS, which was the primary endpoint, failed to meet the prespecified criteria. However, the OS in the pembrolizumab group tended to be longer than that in the IC group in 2 primary analysis sets: (a) patients with PD-L1 CPS ≥10 and (b) patients with squamous cell carcinoma, and the result for OS in these analysis sets appeared to differ from the result in the ITT population [see Section 7.1.1.2]. PMDA further reviewed the efficacy of pembrolizumab by PD-L1 expression status and by histology in subsections (a) and (b).

(a) Efficacy of pembrolizumab by PD-L1 expression status

The applicant's explanation about the efficacy of pembrolizumab by PD-L1 expression status, based on the results of Study 181:

In Study 181, the efficacy of pembrolizumab was assessed by PD-L1 expression status in patients who were evaluable for PD-L1 expression in tissue samples, using the "PD-L1 IHC 22C3 pharmDx assay 'Dako' (Dako Japan Co., Ltd.)."

Table 7 and Figure 10 present the OS results by PD-L1 expression status in Study 181 (cutoff values, CPS 1, CPS 10) (data cutoff on October 15, 2018).

Table 7. OS results by PD-L1 expression status (Study 181, ITT population, data cutoff on October 15, 2018)

PD-L1 expression	Treatment group	n	Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
CPS <1	Pembrolizumab	69	5.2 [3.7, 6.8]	1.34 [0.93, 1.93]	0.0098
	IC	69	8.0 [6.1, 8.6]		
CPS ≥1	Pembrolizumab	239	8.1 [6.6, 9.6]	0.78 [0.64, 0.94]	
	IC	242	6.8 [5.9, 7.9]		
CPS <10	Pembrolizumab	201	6.6 [5.4, 7.3]	1.01 [0.82, 1.24]	0.0364
	IC	196	7.4 [6.3, 8.2]		
CPS ≥10	Pembrolizumab	107	9.3 [6.6, 12.5]	0.70 [0.52, 0.94]	
	IC	115	6.7 [5.1, 8.2]		

* Cox regression stratified by geographic region (Asia vs. non-Asia)

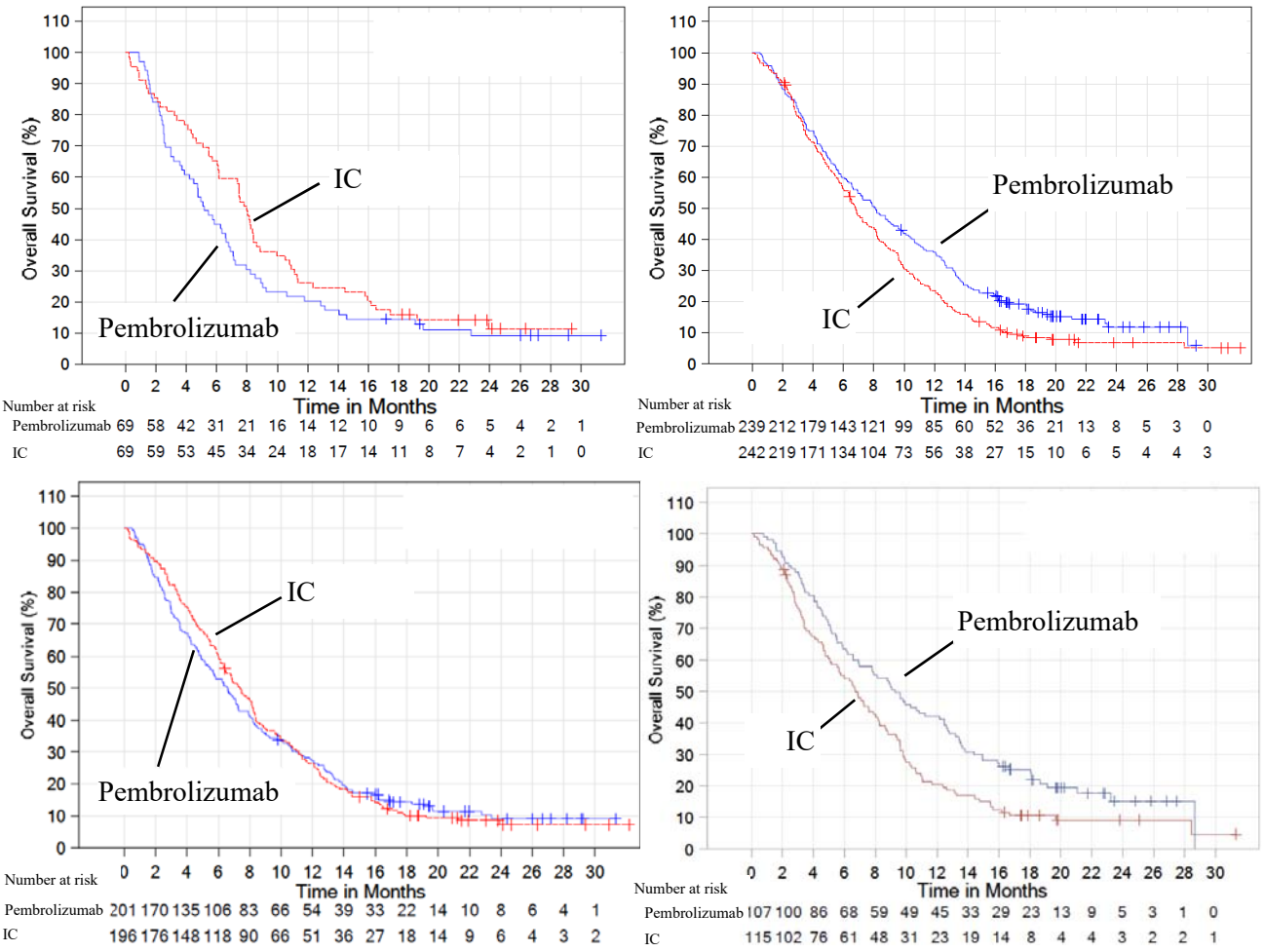

Figure 10. Kaplan-Meier curves of OS by PD-L1 expression status
(ITT population, data cutoff on October 15, 2018)
(Top left, CPS <1; top right, CPS ≥1; bottom left, CPS <10; bottom right, CPS ≥10)

Because the adjustment factors for the treatment assignment in Study 181 did not include PD-L1 expression status at a cutoff value of CPS 10 (CPS ≥10, CPS <10), the frequencies of some patient characteristics that may have affected patient prognosis, including race (Asian vs. non-Asian), ECOG PS (0 vs. 1), and prior taxane therapy (yes vs. no),[20)] had a bias of around ≥10% between the pembrolizumab group and the IC group within the PD-L1 CPS ≥10 subpopulation. Considering the possible effects of these biases on the OS results, a sensitivity analysis stratified by these patient characteristics was conducted. The sensitivity analysis provided a hazard ratio [95% CI] of 0.70 [0.52, 0.94] for the pembrolizumab group versus the IC group within the PD-L1 CPS ≥10 subpopulation, which was comparable to the result of the protocol-specified analysis.

The above results and other data indicated that PD-L1 expression status is a possible predictor of response to pembrolizumab in patients with esophageal cancer, and a patient characteristic of "PD-L1 CPS ≥10" is expected to be helpful in selecting patients who are more likely to respond to pembrolizumab.

20) The assessed patient characteristics included sex, age, race, ECOG PS, geographic region, metastasis to the brain, metastasis, histology, MSI, HER2 expression, neoadjuvant or adjuvant therapy, number of prior therapies, and the prior use of an anthracycline, an antibody drug, CPT-11, a platinum, a fluoropyrimidine, or a taxane.

(b) Efficacy of pembrolizumab by histology

The applicant's explanation about the efficacy of pembrolizumab by histology, based on the results of Study 181:

Table 8 and Figure 11 present the OS results by histology (squamous cell carcinoma, adenocarcinoma) in Study 181 (data cutoff on October 15, 2018).

Table 8. OS results by histology (Study 181, ITT population, data cutoff on October 15, 2018

Histology	Treatment group	N	Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
Adenocarcinoma	Pembrolizumab	116	5.6 [4.2, 7.1]	1.12 [0.85, 1.47]	0.0286
	IC	111	6.9 [5.7, 8.2]		
Squamous cell carcinoma	Pembrolizumab	198	8.2 [6.7, 10.3]	0.77 [0.63, 0.96]	
	IC	203	7.1 [6.1, 8.2]		

* Cox regression stratified by geographic region (Asia vs. non-Asia)

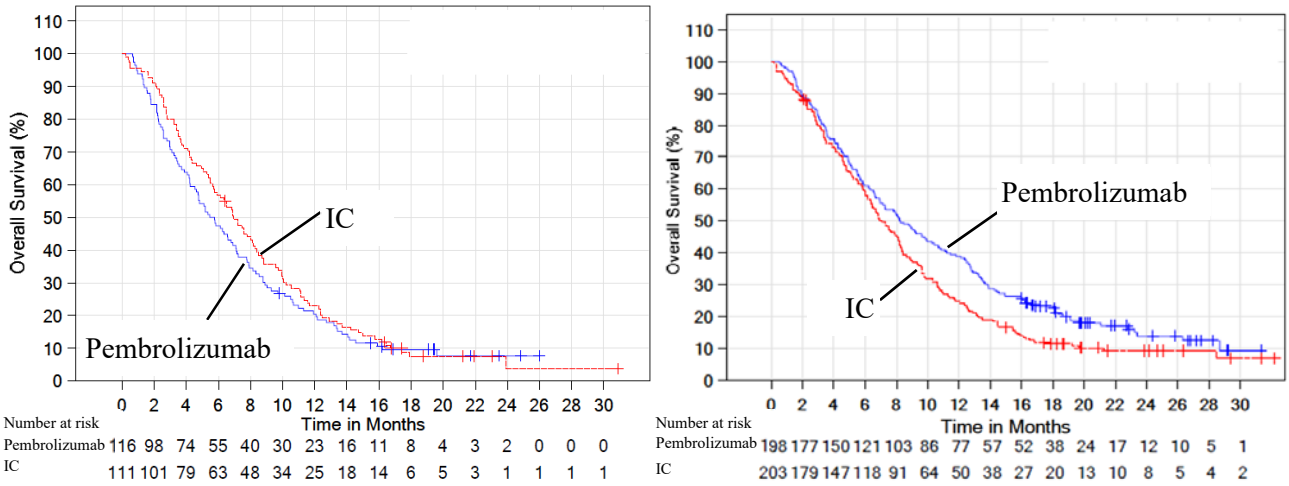

Figure 11. Kaplan-Meier curves of OS by histology (ITT population, data cutoff on October 15, 2018) (Left, adenocarcinoma; right, squamous cell carcinoma)

Taking account of the results of assessment (a) and assessment (b), the efficacy of pembrolizumab was further assessed by histology (squamous cell carcinoma, adenocarcinoma) in patients with PD-L1 CPS ≥10. The OS results are presented in Table 9 and Figure 12 (data cutoff on October 15, 2018).

Table 9. OS results by histology (Study 181, patients with PD-L1 CPS ≥10, data cutoff on October 15, 2018)

Histology	Treatment group	N	Median [95% CI] (months)	Hazard ratio* [95% CI]	P-value for interaction
Adenocarcinoma	Pembrolizumab	22	6.3 [3.4, 9.3]	0.93 [0.52, 1.65]	0.2774
	IC	33	6.9 [3.7, 8.7]		
Squamous cell carcinoma	Pembrolizumab	85	10.3 [7.0, 13.5]	0.64 [0.46, 0.90]	
	IC	82	6.7 [4.8, 8.6]		

* Cox regression stratified by geographic region (Asia vs. non-Asia)

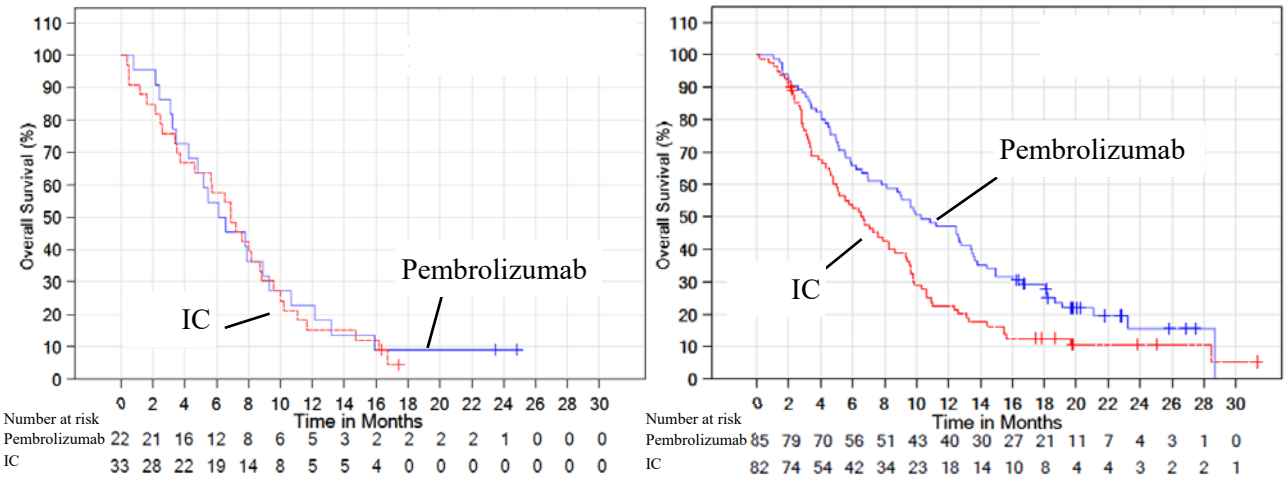

Figure 12. Kaplan-Meier curves of OS by histology (patients with PD-L1 CPS ≥10, data cutoff on October 15, 2018) (Left, adenocarcinoma; right, squamous cell carcinoma)

Among the characteristics of patients with PD-L1 CPS ≥10 squamous cell carcinoma in Study 181, which might affect patient prognosis,[21)] the frequency of the prior use of a taxane (yes vs. no) had a bias of around ≥10% between the pembrolizumab group and the IC group. Considering the possible effects of this bias on the OS results, a sensitivity analysis stratified by the prior use of a taxane was conducted. The sensitivity analysis provided a hazard ratio [95% CI] of 0.64 [0.46, 0.90] for the pembrolizumab group versus the IC group. This was comparable to the above result.

The available findings, including the results of the above assessments (a) and (b), show that pembrolizumab is expected to have efficacy in a specific subpopulation of patients enrolled in Study 181, namely, patients with PD-L1 CPS ≥10 esophageal squamous cell carcinoma, despite not being a protocol-specified efficacy analysis set. Currently, nivolumab, an anti-PD-1 antibody similar to pembrolizumab, is the only antineoplastic drug that has been demonstrated to prolong OS in chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer. In a global phase III study of nivolumab in the same patient population as that of Study 181 (Study ONO-4538-24/BMS CA209473), the hazard ratio [95% CI] of OS for the nivolumab group versus the IC group[21)] was 0.79 [0.63, 0.99] (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg, dated January 9, 2020"). In view of the results of the nivolumab study and other data, the OS result from patients with PD-L1 CPS ≥10 esophageal squamous cell carcinoma in Study 181 is clinically significant.

In patients with PD-L1 CPS ≥10 esophageal squamous cell carcinoma in Study 181, the hazard ratios [95% CIs] of OS for pembrolizumab versus each drug (PTX, DTX, or CPT-11) used in the IC group were 0.80 [0.54, 1.18], 0.39 [0.23, 0.68], and 0.37 [0.20, 0.68], respectively. There were no apparent differences in the choice among the 3 different control drugs that affect the efficacy evaluation for pembrolizumab.

21) PTX or DTX was chosen at the discretion of the investigator.

PMDA asked the applicant to explain the efficacy of pembrolizumab in Japanese patients.

The applicant's explanation:

Table 10 presents the OS results in the Japanese subpopulation of Study 181.

Table 10. OS results in Japanese patients (data cutoff on October 15, 2018)

Patient population	Treatment group	N	Number of events (%)	Median [95% CI] (months)	Hazard ratio* [95% CI]
CPS ≥10	Pembrolizumab	41	34 (82.9)	12.5 [6.6, 14.4]	0.70 [0.43, 1.13]
	IC	38	33 (86.8)	8.4 [4.8, 10.2]	
Squamous cell carcinoma	Pembrolizumab	76	62 (81.6)	11.9 [8.0, 13.5]	0.68 [0.48, 0.97]
	IC	73	64 (87.7)	8.2 [5.2, 9.8]	
ITT	Pembrolizumab	77	63 (81.8)	11.5 [8.0, 13.4]	0.68 [0.48, 0.96]
	IC	75	66 (88.0)	8.2 [5.7, 9.8]	

* Non-stratified Cox regression model

Table 11 and Figure 13 present the OS results in the Japanese patients with PD-L1 CPS ≥10 esophageal squamous cell carcinoma enrolled in Study 181.

Table 11. OS results in Japanese patients (patients with PD-L1 CPS ≥10 esophageal squamous cell carcinoma, data cutoff on October 15, 2018)

	Pembrolizumab	IC
N	40	37
Number of events (%)	33 (82.5)	32 (86.5)
Median [95% CI] (months)	12.6 [6.9, 14.4]	8.2 [4.8, 10.3]
Hazard ratio [95% CI]*	0.69 [0.42, 1.12]	

* Stratified Cox regression model including treatment as a covariate

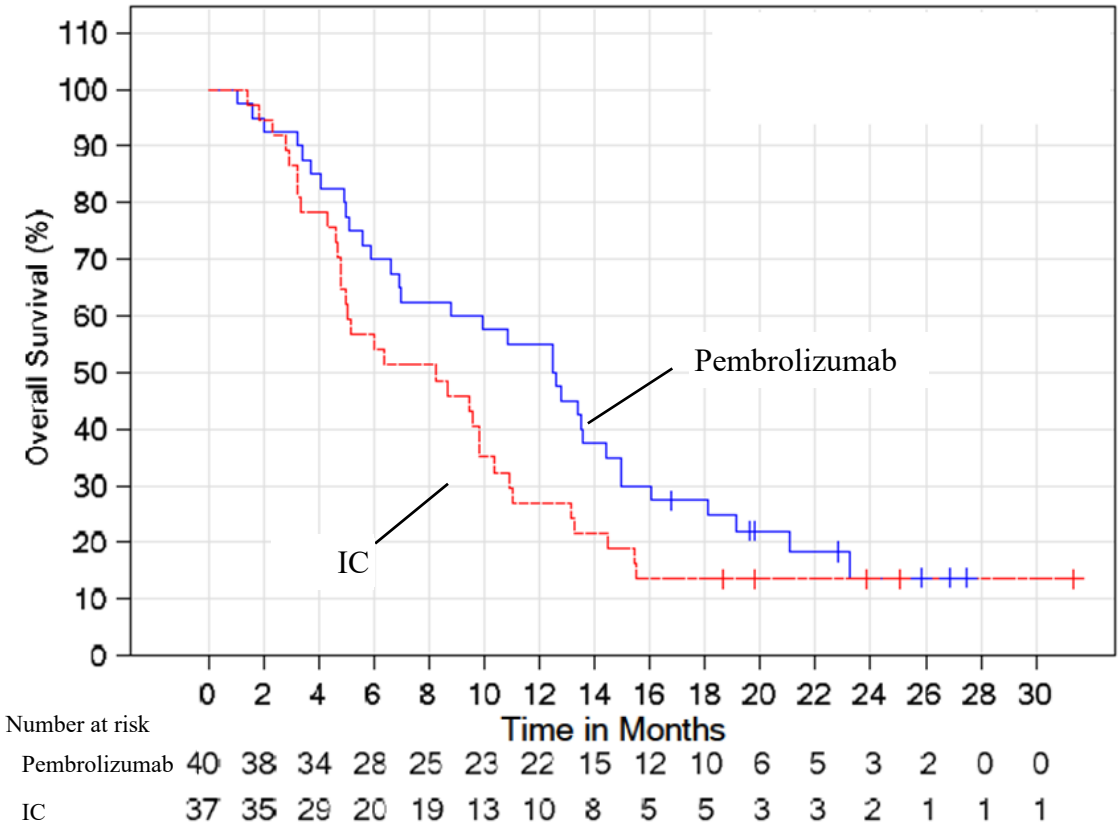

Figure 13. Kaplan-Meier curves of OS in Japanese patients
(patients with PD-L1 CPS ≥10 esophageal squamous cell carcinoma, data cutoff on October 15, 2018)

PMDA's view:

The currently available findings are insufficient to definitely conclude whether PD-L1 expression status is a predictor of response to pembrolizumab in patients with esophageal cancer. In addition, the OS results from Study 181 failed to meet the prespecified efficacy criteria, and the population comprising patients with PD-L1 CPS ≥10 squamous cell carcinoma is not a prespecified efficacy analysis set. Accordingly, the analysis results from the patient population should be interpreted carefully.

In contrast to the above, the applicant's explanation about the efficacy of pembrolizumab is understandable. In addition, in view of the findings, including that the efficacy results from the Japanese subpopulation with PD-L1 CPS ≥10 squamous cell carcinoma in Study 181 tended to be comparable to those from the entire population with PD-L1 CPS ≥10 squamous cell carcinoma, pembrolizumab has demonstrated a certain level of efficacy in the treatment of patients with PD-L1 CPS ≥10 squamous cell carcinoma, among chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer.

7.R.2 Safety [For adverse events, see Section "7.3. Adverse events, etc. reported in clinical studies."]

PMDA's view:

As a result of the following review, the use of pembrolizumab in chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer requires particular attention to the onset of the adverse

events identified as requiring attention at the regulatory reviews for the approved indications.[22)] Patients should be closely monitored for these events, when pembrolizumab is administered for the treatment of chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer, as well as for the approved indications.

Although the use of pembrolizumab requires attention to the above-mentioned adverse events, pembrolizumab is tolerable in patients with esophageal cancer as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through appropriate measures such as monitoring of adverse events, differential diagnosis and management of excessive immune-mediated adverse drug reactions, and interruption of pembrolizumab.

7.R.2.1 Safety profile, and safety differences between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of pembrolizumab, based on the safety data from Study 181:

Table 12 presents a summary of the safety data from Study 181.

Table 12. Safety summary (Study 181)

	n (%)	
	Pembrolizumab N = 314	IC N = 296
All adverse events	300 (95.5)	288 (97.3)
Grade ≥3 adverse events	170 (54.1)	183 (61.8)
Adverse events leading to death	30 (9.6)	32 (10.8)
Serious adverse events	124 (39.5)	121 (40.9)
Adverse events leading to drug discontinuation	40 (12.7)	42 (14.2)
Adverse events leading to drug interruption	84 (26.8)	111 (37.5)
Adverse events leading to dose reduction	—	59 (19.9)

In Study 181, adverse events of any grade reported with a ≥5% higher incidence in the pembrolizumab group than in the IC group were dysphagia (49 patients [15.6%] in the pembrolizumab group, 28 patients [9.5%] in the IC group) and hypothyroidism (36 patients [11.5%], 7 patients [2.4%]). The Grade ≥3 adverse event reported with a ≥2% higher incidence in the pembrolizumab group than in the IC group was dysphagia (15 patients [4.8%], 8 patients [2.7%]). Serious adverse events reported with a ≥2% higher incidence in the pembrolizumab group than in the IC group were dysphagia (11 patients [3.5%], 1 patient [0.3%]) and pneumonitis (7 patients [2.2%], 0 patients). The adverse event that led to drug interruption with a ≥2% higher incidence in the pembrolizumab group than in the IC group was AST increased (10 patients [3.2%], 2 patients [0.7%]). There were no adverse events leading to death or drug discontinuation, with a ≥2% higher incidence in the pembrolizumab group than in the IC group.

22) Gastrointestinal disorders, skin disorders, neurological disorders, hepatic function disorder, cholangitis sclerosing, eye disorders, endocrine disorders, renal impairment, interstitial lung disease (ILD), infusion reaction, pancreatitis, myositis, rhabdomyolysis, encephalitis and meningitis, myasthenia gravis, myocarditis, serious blood disorders, haemophagocytic syndrome, tuberculosis, and anaphylaxis (see "Review Report for Keytruda Injection 20 mg, Keytruda Injection 100 mg, dated November 12, 2019," etc.)

The applicant's explanation about the differences in the safety profile of pembrolizumab between Study 181 and clinical studies reviewed for the approved indications in which pembrolizumab was administered as a monotherapy, as in Study 181:
Table 13 presents the incidences of adverse events in clinical studies (a) to (g), below:

(a) A global phase III study in chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer (Study 181)
(b) A foreign phase II study and a foreign phase III study in patients with unresectable malignant melanoma (Studies 002 and 006, respectively), and a global phase III study in patients with completely resected malignant melanoma (Study 054)
(c) A global phase II/III study in platinum-based chemotherapy-treated patients with unresectable, advanced or recurrent PD-L1 positive (tumor proportion score [TPS] ≥1) NSCLC (Study 010), a global phase III study in chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥50) NSCLC (Study 024), and a global phase III study in chemotherapy-naïve patients with unresectable, advanced or recurrent PD-L1 positive (TPS ≥1) NSCLC (Study 042)
(d) A global phase II study in patients with cHL (Study 087)
(e) A global phase III study in patients with radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy (Study 045)
(f) A global phase II study in patients with MSI-High colorectal cancer (Study 164 [Cohort A])
(g) A global phase III study in chemotherapy-naïve patients with recurrent or metastatic head and neck squamous cell carcinoma (Study 048)

Table 13. Safety summary by cancer type*

	n (%)						
	(a) N = 314	(b) N = 1421	(c) N = 1472	(d) N = 210	(e) N = 266	(f) N = 61	(g) N = 300
All adverse events	300 (95.5)	1,366 (96.1)	1,419 (96.4)	202 (96.2)	248 (93.2)	60 (98.4)	290 (96.7)
Grade ≥3 adverse events	170 (54.1)	583 (41.0)	714 (48.5)	53 (25.2)	139 (52.3)	36 (59.0)	162 (54.0)
Adverse events leading to death	30 (9.6)	40 (2.8)	122 (8.3)	2 (1.0)	13 (4.9)	1 (1.6)	25 (8.3)
Serious adverse events	124 (39.5)	469 (33.0)	573 (38.9)	34 (16.2)	104 (39.1)	29 (47.5)	121 (40.3)
Adverse events leading to drug discontinuation	40 (12.7)	185 (13.0)	190 (12.9)	11 (5.2)	22 (8.3)	4 (6.6)	36 (12.0)
Adverse events leading to drug interruption	84 (26.8)	309 (21.7)	421 (28.6)	54 (25.7)	54 (20.3)	17 (27.9)	92 (30.7)

* Pembrolizumab was administered as an intravenous dose of 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks, or 10 mg/kg every 3 weeks in patients with unresectable malignant melanoma; as an intravenous dose of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, or 200 mg every 3 weeks in patients with PD-L1 positive NSCLC; or as an intravenous dose of 200 mg every 3 weeks in other patients.

The adverse event of any grade reported with a ≥5% higher incidence in patients with esophageal cancer than in those with any other type of cancer was dysphagia (15.6% in patients with esophageal cancer, 0.9% in patients with malignant melanoma, 2.4% in patients with NSCLC, 0% in patients with cHL, 0.8% in patients with urothelial carcinoma, 0% in patients with MSI-High colorectal cancer, and 8.0% in patients with head and

neck cancer). The Grade ≥3 adverse event reported with a ≥2% higher incidence in patients with esophageal cancer than in those with any other type of cancer was dysphagia (4.8%, 0.1%, 0.3%, 0%, 0%, 0%, and 2.3%). The serious adverse event reported with a ≥2% higher incidence in patients with esophageal cancer than in those with any other type of cancer was dysphagia (3.5%, 0.1%, 0.2%, 0%, 0%, 0%, and 1.3%). There were no adverse events leading to death, drug discontinuation, or interruption with a ≥2% higher incidence in patients with esophageal cancer than in those with any other type of cancer.

As described above, dysphagia was more frequently reported in patients with esophageal cancer than in patients treated for any of the approved indications. However, no clear differences were noted in the incidences of adverse events, including those leading to death or drug discontinuation. In addition, in view of the possible effects of the primary disease, the safety profile of pembrolizumab does not clearly differ between patients with radically unresectable, advanced or recurrent esophageal cancer and those treated for the approved indications.

The applicant's explanation about the differences in the safety of pembrolizumab between Japanese patients and non-Japanese patients, based on the safety data from Study 181:
Table 14 presents a summary of the safety data from Japanese and non-Japanese patients receiving pembrolizumab in Study 181.

Table 14. Safety summary (Study 181)

	n (%)	
	Japanese	Non-Japanese
	Pembrolizumab N = 77	Pembrolizumab N = 237
All adverse events	71 (92.2)	229 (96.6)
Grade ≥3 adverse events	29 (37.7)	141 (59.5)
Adverse events leading to death	3 (3.9)	27 (11.4)
Serious adverse events	19 (24.7)	105 (44.3)
Adverse events leading to drug discontinuation	7 (7.1)	33 (13.9)
Adverse events leading to drug interruption	16 (20.8)	68 (28.7)

In the pembrolizumab group, the adverse event of any grade reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients was malaise (12 patients [15.6%] in the Japanese subpopulation, 3 patients [1.3%] in the non-Japanese subpopulation). There were no Grade ≥3 adverse events or serious adverse events, or adverse events leading to death, drug discontinuation, or interruption, with a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

In the pembrolizumab group, the incidences of adverse events of any grade in patients with PD-L1 CPS <1 (N = 69) and patients with CPS ≥1 (N = 239) were 100% and 94.6%, those of Grade ≥3 adverse events were 59.4% and 52.3%, and those of serious adverse events were 46.4% and 37.2%, respectively. The incidences of adverse events of any grade in patients with CPS <10 (N = 201) and patients with CPS ≥10 (N = 107) were 95.5% and 96.3%, those of Grade ≥3 adverse events were 52.2% and 57.0%, and those of serious adverse events were

36.8% and 43.9%, respectively. The available data, including the above, indicated no clear differences in the safety of pembrolizumab between PD-L1 positive patients and negative patients.

PMDA asked the applicant to explain the differences in the incidences of adverse events (a) between patients with and without prior radiotherapy, and (b) between patients with and without the involvement of an artery, the trachea, etc.

The applicant's explanation was as follows:
In the pembrolizumab group of Study 181, the incidences of adverse events of any grade in patients with prior radiotherapy (N = 185) and patients without prior radiotherapy (N = 129) were 95.1% and 96.1%, those of Grade ≥3 adverse events were 57.3% and 49.6%, those of adverse events leading to death were 11.9% and 6.2%, and those of serious adverse events were 44.9% and 31.8%, respectively. The incidence of adverse events leading to death and serious adverse events tended to be higher in patients with prior radiotherapy than in those without prior radiotherapy. Nevertheless, pembrolizumab is tolerable regardless of prior radiotherapy, in view of the incidence of adverse events leading to death and serious adverse events in patients with prior radiotherapy in the IC group of Study 181 (N = 168) were 11.3% and 47.0%, respectively, being comparable to those in patients with prior radiotherapy in the pembrolizumab group.

In the pembrolizumab group of Study 181, the incidences of adverse events of any grade in patients with the involvement of an artery, the trachea, etc. (N = 13) and patients without such involvement (N = 301) were 100% and 95.3%, those of Grade ≥3 adverse events were 46.2% and 54.5%, those of adverse events leading to death were 15.4% and 9.3%, and those of serious adverse events were 38.5% and 39.5%, respectively. The incidence of adverse events leading to death tended to be higher in patients with the involvement of an artery, the trachea, etc. than in those without such involvement. Nevertheless, pembrolizumab is tolerable regardless of the involvement of an artery, the trachea, etc., in view of the incidence of adverse events leading to death in patients with such involvement in the IC group of Study 181 (N = 16) was 18.8%, being comparable to that in patients with such involvement in the pembrolizumab group.

PMDA's view:
In Study 181, most of the adverse events reported more frequently in the pembrolizumab group than in the IC group were known adverse events of pembrolizumab. Patients with esophageal cancer reported some serious adverse events that had not been identified in patients treated for the approved indications. However, most of these events were attributable to the primary disease. Pembrolizumab is thus tolerable in patients with esophageal cancer as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through appropriate measures such as monitoring of adverse events, differential diagnosis and management of excessive immune-mediated adverse drug reactions, and interruption of pembrolizumab.

In the same study, the incidences of adverse events leading to death or other notable adverse events tended to be higher in (a) patients with prior radiotherapy and in (b) patients with the involvement of an artery, the trachea,

etc. However, pembrolizumab is tolerable in such patients (a) and (b) as well, in view of the findings, including that there were no trend towards a clearly higher incidence of serious adverse events or other notable adverse events in the pembrolizumab group than in the IC group, within both patient populations (a) and (b), and that pembrolizumab is intended to be administered by physicians with sufficient knowledge and experience in chemotherapy for esophageal cancer.

7.R.2.2 Others

During the review of approval for nivolumab, an anti-PD-1 antibody similar to pembrolizumab for the treatment of esophageal cancer, (a) tumour haemorrhage and (b) fistula were included as new important potential risks in the safety specifications in the risk management plan. PMDA asked the applicant to explain the incidences of (a) tumour haemorrhage and (b) fistula in patients with esophageal cancer receiving pembrolizumab.

The applicant's explanation:

(a) Tumour haemorrhage

As tumour haemorrhage-related events, events coded as the following MedDRA preferred terms (PTs) were counted: "tumour haemorrhage," "intracranial tumour haemorrhage," "haemorrhagic tumour necrosis," "skin neoplasm bleeding," "oesophageal haemorrhage," and "upper gastrointestinal haemorrhage."

Table 15 shows the incidences of tumour haemorrhage in Study 181.

Table 15. Incidences of tumour haemorrhage (Study 181)

PT (MedDRA ver. 21.0)	n (%)			
	Pembrolizumab N = 314		IC N = 296	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Tumour haemorrhage	7 (2.2)	5 (1.6)	5 (1.7)	3 (1.0)
Oesophageal haemorrhage	6 (1.9)	5 (1.6)	4 (1.4)	3 (1.0)
Upper gastrointestinal haemorrhage	1 (0.3)	0	1 (0.3)	0

In Study 181, tumour haemorrhage led to death in 4 patients (1.3%) in the pembrolizumab group and 2 patients (0.7%) in the IC group. A causal relationship to the study drug could not be ruled out in 1 patient in the pembrolizumab group, who had undergone stent implantation and received only 1 dose of pembrolizumab. Serious tumour haemorrhage were reported in 4 patients (1.3%) in the pembrolizumab group and 3 patients (1.0%) in the IC group. A causal relationship to the study drug could not be ruled out in the 1 patient in the pembrolizumab group. Tumour haemorrhage led to drug discontinuation in 4 patients (1.3%) in the pembrolizumab group and 2 patients (0.7%) in the IC group. No patients interrupted the study drug due to tumour haemorrhage.

The median time (range) to the first onset of tumour haemorrhage was 18 (9-142) days in the pembrolizumab group and 88 (8-243) days in the IC group. In the pembrolizumab group, 5 of 7 patients with tumour

haemorrhage had received prior radiotherapy, whereas 4 of 5 patients with tumour haemorrhage had received prior radiotherapy in the IC group.

(b) Fistula

As fistula-related adverse events, events coded as the following MedDRA High Level Term (HLT) were counted: "gastrointestinal fistulae."

Table 16 shows the incidence of fistula in Study 181.

Table 16. Incidence of fistula (Study 181)

PT (MedDRA/J ver. 21.0)	n (%)			
	Pembrolizumab N = 314		IC N = 296	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Fistula	5 (1.6)	3 (1.0)	3 (1.0)	1 (0.3)
Tracheo-oesophageal fistula	2 (0.6)	1 (0.3)	2 (0.7)	1 (0.3)
Oesophageal fistula	3 (1.0)	2 (0.6)	1 (0.3)	0

In Study 181, serious fistula were reported in 3 patients (1.0%; oesophageal fistula in 2 patients and tracheo-oesophageal fistula in 1 patient) in the pembrolizumab group and no patients in the IC group. A causal relationship to pembrolizumab could not be ruled out in 1 patient (0.3%, tracheo-oesophageal fistula) who started steroid therapy after the last dose of pembrolizumab (Day 64), and experienced a Grade 3 tracheo-oesophageal fistula 26 days after the last dose of pembrolizumab (Day 90) during the steroid therapy. Fistula led to drug interruption in 4 patients (1.3%; oesophageal fistula in 3 patients and oesophagobronchial fistula in 1 patient) in the pembrolizumab group and 1 patient (0.3%; tracheo-oesophageal fistula) in the IC group. No fistula led to death or drug discontinuation.

The median time (range) to the first onset of fistula was 90 (21-231) days in the pembrolizumab group and 61 (35-78) days in the IC group. In the pembrolizumab group, 3 of 5 patients experiencing fistula had received prior radiotherapy, whereas 2 of 3 patients with fistula had received prior radiotherapy in the IC group.

PMDA's view:

In Study 181, a serious tumour haemorrhage and fistula for which a causal relationship to pembrolizumab could not be ruled out occurred in 1 patient each. Due to the limited number of patients experiencing such events, the presence of other possible factors, such as stent implantation, as well as the absence of a clear tendency toward higher incidences of the events in the pembrolizumab group than in the IC group, etc., no particular caution regarding tumour haemorrhage or fistula is considered to be necessary at this time. However, even though tumour haemorrhage and fistula can be attributable to the primary disease, so that definitely relating such events to pembrolizumab may be difficult in patients with esophageal cancer, the applicant should continue to collect relevant information in the post-marketing setting, and appropriately communicate new findings to healthcare professionals.

7.R.3 Clinical positioning and indication

In the present partial change application, the applicant initially proposed that the indication for esophageal cancer be "unresectable, advanced or recurrent esophageal cancer," and that the "Precautions Concerning Indications" section include a precautionary statement regarding PD-L1 expression status only for patients with esophageal adenocarcinoma, who would receive pembrolizumab as a second-line treatment. However, after filing the application, the applicant proposed that the following statements be included in the "Precautions Concerning Indications" section.

- The efficacy and safety of pembrolizumab as the first-line therapy have not been established.
- Pembrolizumab should be administered to patients who have been demonstrated to have a tumor with PD-L1 expression by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic, after carefully reading the "Clinical Studies" section to understand CPS.

PMDA's view:

As a result of the discussions described in Sections "7.R.1 Data for review and efficacy," "7.R.2 Safety," and the subsection below, the indication should be "radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy," and the following statements should be included in the "Precautions Concerning Indications" section.

- The efficacy and safety of pembrolizumab as the first-line therapy have not been established.
- The efficacy and safety of pembrolizumab in neoadjuvant or adjuvant therapy have not been established.
- Pembrolizumab should be administered to patients who have been demonstrated to have a tumor with PD-L1 expression by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic or medical device, after carefully reading the "Clinical Studies" section to understand the percentage of PD-L1 positive cells (CPS).

7.R.3.1 Clinical positioning and indication of pembrolizumab

Representative clinical practice guidelines and leading clinical oncology textbooks in and outside of Japan currently describe pembrolizumab therapy for esophageal cancer as follows. The US National Cancer Institute Physician Data Query (NCI-PDQ) (version dated January 22, 2020) has no description regarding pembrolizumab therapy for esophageal cancer.

Clinical practice guidelines

- NCCN guidelines (esophageal and esophagogastric junction cancers) (v.4, 2019):
  The use of pembrolizumab is strongly recommended for chemotherapy-treated patients with PD-L1 positive (CPS ≥10) esophageal squamous cell carcinoma.

The applicant's explanation about the clinical positioning and indication of pembrolizumab:

In Study 181 in chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer, OS, which was the primary endpoint, tended to be prolonged in the following 2 primary analysis sets: patients with PD-L1 CPS ≥10 and patients with squamous cell carcinoma [see Section 7.1.1.2]. In addition, pembrolizumab showed a clinically relevant increase in OS in patients with PD-L1 CPS ≥10 squamous cell

carcinoma, as compared with the existing treatments, DTX and PTX [see Section 7.R.1.2], despite that group having not been a prespecified analysis set. The available data, including the above, support the use of pembrolizumab as a recommended therapy for patients with PD-L1 CPS ≥10 esophageal squamous cell carcinoma. However, Study 181, involving chemotherapy-treated patients, provided no clinical study data supporting the clinical usefulness of pembrolizumab in chemotherapy-naïve patients with esophageal cancer, and the administration of pembrolizumab to chemotherapy-naïve patients with esophageal cancer is thus not recommended.

In view of the above, the use of pembrolizumab can be recommended for the treatment of chemotherapy-treated patients with radically unresectable, advanced or recurrent PD-L1 positive (CPS ≥10) esophageal squamous cell carcinoma. In Study 181, PD-L1 expression status in tumor tissue was determined using the "PD-L1 IHC 22C3 pharmDx assay 'Dako' (Dako Japan Co., Ltd.)." The same diagnostic kit should also be used in the post-marketing setting to select patients who are appropriate for pembrolizumab therapy. This will be stated in the "Precautions Concerning Indications" section.

There have been no clinical study data comparing pembrolizumab with nivolumab, which has been approved for the treatment of chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer; therefore, which drug should be preferred first is unclear, at present. Pembrolizumab is expected to offer an additional treatment option to patients with PD-L1 positive esophageal squamous cell carcinoma among the intended patient population of nivolumab.

As described above, the proposed indication is "unresectable, advanced or recurrent esophageal cancer," and the following statements are to be included in the proposed "Precautions Concerning Indications" section.

- The efficacy and safety of pembrolizumab as the first-line therapy have not been established.
- Pembrolizumab should be administered to patients who have been demonstrated to have a tumor with PD-L1 expression by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic, after carefully reading the "Clinical Studies" section to understand CPS.

PMDA's view:

PMDA accepted the applicant's explanation in general. However, in consideration of the following points, the "Indications" section should clearly specify that pembrolizumab is intended for patients who have received prior chemotherapies and have PD-L1 positive esophageal squamous cell carcinoma: (a) there have been no clinical study results supporting the clinical usefulness of pembrolizumab in chemotherapy-naïve patients with radically unresectable, advanced or recurrent esophageal cancer, and (b) the information that the patients with PD-L1 positive esophageal squamous cell carcinoma are expected to respond to pembrolizumab is important for selecting appropriate patients for pembrolizumab therapy.

The efficacy and safety of pembrolizumab as neoadjuvant or adjuvant therapy have not been demonstrated. A precautionary statement that the efficacy and safety of pembrolizumab in neoadjuvant or adjuvant therapy have not been established should thus be included in the "Precautions Concerning Indications" section.

The proposed indication of pembrolizumab used the expression, "unresectable, advanced or recurrent." However, "unresectable, advanced or recurrent" is synonymous with "radically unresectable, advanced or recurrent" in esophageal cancer. In view of the indication of nivolumab, an anti-PD-1 antibody similar to pembrolizumab, which has been approved for the treatment of esophageal cancer, use of the expression "radically unresectable, advanced or recurrent" is more appropriate than the proposed "unresectable, advanced or recurrent."

On the basis of the above, the indication should be "radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy," and the following statements should be included in the "Precautions Concerning Indications" section.

- The efficacy and safety of pembrolizumab as the first-line therapy have not been established.
- The efficacy and safety of pembrolizumab in neoadjuvant or adjuvant therapy have not been established.
- Pembrolizumab should be administered to patients who have been demonstrated to have a tumor with PD-L1 expression by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic or medical device, after carefully reading the "Clinical Studies" section to understand the percentage of PD-L1 positive cells (CPS).

7.R.4 Dosage and administration

On the basis of the data related to the clinical pharmacology of pembrolizumab and esophageal cancer submitted for the present application, the applicant has proposed the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as presented in the table below (underline denotes additions or changes made for the present partial change application).

Dosage and Administration	Precautions Concerning Dosage and Administration
[Malignant melanoma] • The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. [Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments), recurrent or metastatic head and neck cancer, or unresectable, advanced or recurrent esophageal cancer] • The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes. [Radically unresectable or metastatic RCC] • In combination with axitinib, the usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes.	[Unresectable, advanced or recurrent NSCLC] • When pembrolizumab (genetical recombination) is used with other antineoplastic drugs, the "Clinical Studies" section should be understood sufficiently before selecting concomitant antineoplastic drugs. [Recurrent or metastatic head and neck cancer] • The dosage regimen of pembrolizumab (genetical recombination) should be selected based on a good understanding of the efficacy and safety of pembrolizumab (genetical recombination), after carefully reading the "Clinical Studies" section. [Malignant melanoma, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments), or unresectable, advanced or recurrent esophageal cancer] • The efficacy and safety of pembrolizumab (genetical recombination) in combination with other antineoplastic drugs have not been established. [All indications] • Dose adjustment criteria in case of adverse drug reactions

PMDA's view:

On the basis of the review described in Sections "7.R.1 Data for review and efficacy," "7.R.2 Safety," and "7.R.3 Clinical positioning and indication," as well as the subsection, the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be set or modified as presented in the table below (underline denotes changes from the above table).

Dosage and Administration	Precautions Concerning Dosage and Administration
[Malignant melanoma] • The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. [Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments), recurrent or metastatic head and neck cancer, or radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy] • The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes. [Radically unresectable or metastatic RCC] • In combination with axitinib, the usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes.	[Unresectable, advanced or recurrent NSCLC] • When pembrolizumab (genetical recombination) is used with other antineoplastic drugs, the "Clinical Studies" section should be understood sufficiently before selecting concomitant antineoplastic drugs. [Recurrent or metastatic head and neck cancer] • The dosage regimen of pembrolizumab (genetical recombination) should be selected based on a good understanding of the efficacy and safety of pembrolizumab (genetical recombination), after carefully reading the "Clinical Studies" section. [Malignant melanoma, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments), or radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy] • The efficacy and safety of pembrolizumab (genetical recombination) in combination with other antineoplastic drugs have not been established. [All indications] • Dose adjustment criteria in case of adverse drug reactions

7.R.4.1 Dosage and administration of pembrolizumab

The applicant's explanation about the dosage and administration of pembrolizumab:

In view of the following points and other findings, the dosage and administration of pembrolizumab for the approved indications, including esophageal cancer, should be updated to add a regimen of 400 mg every 6 weeks to the approved 200 mg every 3 weeks regimen.

- The available data, including the results of simulations using PPK models for pembrolizumab, predicted no clear differences in the efficacy or safety of pembrolizumab between the 400 mg every 6 weeks regimen and the approved 200 mg every 3 weeks regimen [see Section 6.1].
- The results of a foreign phase I/II study evaluating the safety, tolerability, and other aspects of pembrolizumab administered in combination with other chemotherapies (e.g., CBDCA) in chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC, etc. (Study 021) showed no clear differences in the incidences of adverse events between the 2 mg/kg every 3 weeks regimen and the 10 mg/kg every 3 weeks regimen (Table 17).
- No clear differences have been noticed in the incidences of adverse events across cancer types [see Section 7.R.2.1]. This suggests that pembrolizumab, also when administered at a dose of 400 mg every 6 weeks, is unlikely to provide any clear difference in the incidence of adverse events across cancer types.

- There have been no clear differences in the pharmacokinetics of pembrolizumab, between in and outside of Japan (see "Review Report for Keytruda Injection 20 mg, Keytruda Injection 100 mg, dated August 30, 2016").
- A reduced dosing frequency of pembrolizumab is expected to offer clinical benefits, such as a possible reduction in burdens on the patients or health professionals.

Table 17. Summary of the safety of pembrolizumab administered at a dose of 2 or 10 mg/kg every 3 weeks in combination with other antineoplastic drugs* (Study 021)

	n (%)					
	Cohort A (Pembrolizumab + CBDCA + PTX)		Cohort B (Pembrolizumab + CBDCA + PTX + BV)		Cohort C (Pembrolizumab + CBDCA + PEM)	
	2 mg/kg N = 13	10 mg/kg N = 12	2 mg/kg N = 11	10 mg/kg N = 13	2 mg/kg N = 12	10 mg/kg N = 12
All adverse events	13 (100)	12 (100)	11 (100)	13 (100)	12 (100)	12 (100)
Grade ≥3 adverse events	8 (61.5)	7 (58.3)	8 (72.7)	9 (69.2)	7 (58.3)	9 (75.0)
Study drug-related Grade ≥3 adverse events	7 (53.8)	3 (25.0)	4 (36.4)	6 (46.2)	4 (33.3)	7 (58.3)
Adverse events leading to death	0	0	1 (9.1)	1 (7.7)	0	2 (16.7)
Study drug-related adverse events leading to death	0	0	0	0	0	0
Serious adverse events	7 (53.8)	5 (41.7)	8 (72.7)	8 (61.5)	6 (50.0)	7 (58.3)
Study drug-related serious adverse events	5 (38.5)	2 (16.7)	4 (36.4)	5 (38.5)	4 (33.3)	3 (25.0)
Adverse events leading to drug interruption	2 (15.4)	1 (8.3)	2 (18.2)	4 (30.8)	4 (33.3)	3 (25.0)
Study drug-related adverse events leading to drug interruption	1 (7.7)	0	2 (18.2)	3 (23.1)	3 (25.0)	3 (25.0)

* The study drugs were administered every 3 weeks. CBDCA was intravenously administered at an AUC of 6 mg·min/mL in cohorts A and B, or an AUC of 5 mg·min/mL in cohort C. Paclitaxel (PTX) was intravenously administered at a dose of 175 or 200 mg/m^2, bevacizumab (genetical recombination) (BV) was intravenously administered at a dose of 15 mg/kg, and pemetrexed sodium hydrate (PEM) was intravenously administered at a dose of 500 mg/m^2.

After the present partial change application, preliminary results were obtained from the cohort B of a foreign phase I study evaluating the efficacy and safety of pembrolizumab administered at a dose of 400 mg every 6 weeks in patients with unresectable malignant melanoma (Study 555).[23)] The efficacy of pembrolizumab, demonstrated as a response rate [95% CI], as assessed by BICR using RECIST v. 1.1, of 38.6 [24.4, 54.5]%, was comparable to that observed in clinical studies in which pembrolizumab was intravenously administered to patients with unresectable malignant melanoma at a dose of 2 or 10 mg/kg every 3 weeks. The safety analysis in Study 555 provided an incidence of adverse events of any grade of 97.7%, an incidence of Grade ≥3 adverse events of 25.0%, and an incidence of serious adverse events of 15.9%, with no adverse events leading to death. These incidences did not tend to be clearly higher than those observed in patients who received pembrolizumab for unresectable malignant melanoma at a dose of 2 or 10 mg/kg every 2 or 3 weeks [see Section 7.R.2.1].

PMDA's view:

PMDA accepted the applicant's explanation in general. However, the proposed statements regarding esophageal cancer should be changed based on the discussion described in Section "7.R.3.1 Clinical positioning and indication of pembrolizumab."

23) The preliminary results were from 44 patients who could be followed up for at least 3 months.

As described above, the following statements should be included in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections for the present partial change application.

- Dosage and administration
  - [Malignant melanoma]
    The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab infused intravenously over 30 minutes. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months.
  - [Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments), recurrent or metastatic head and neck cancer, or radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy]
    The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab infused intravenously over 30 minutes.
  - [Radically unresectable or metastatic renal cell carcinoma]
    In combination with axitinib, the usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab infused intravenously over 30 minutes.

Precautions Concerning Dosage and Administration

- [Unresectable, advanced or recurrent NSCLC]
  When pembrolizumab is used with other antineoplastic drugs, the "Clinical Studies" section should be understood sufficiently before selecting concomitant antineoplastic drugs.
- [Recurrent or metastatic head and neck cancer]
  The dosage regimen of pembrolizumab should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section.
- [Malignant melanoma, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments), or radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy]
  The efficacy and safety of pembrolizumab in combination with other antineoplastic drugs have not been established.
- [All indications]
  Dose adjustment criteria in case of adverse drug reactions

7.R.5 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plans for (a) a new indication of esophageal cancer and (b) a new dosage regimen of 400 mg every 6 weeks:

(a) In view of the available data, including those described below, no new safety concerns have been identified for the present application. Thus, conducting new post-marketing surveillance immediately after the approval in patients receiving pembrolizumab for esophageal cancer will not be necessary.

- Dysphagia was more frequently reported in patients receiving pembrolizumab for esophageal cancer in Study 181 than in those treated for the approved indications, and oesophageal haemorrhage was newly identified as a serious adverse event of pembrolizumab in Study 181. However, these adverse events were likely to be attributable to the primary disease. This indicates that the safety profile of pembrolizumab observed in Study 181 does not clearly differ from that in patients treated for the approved indications [see Section 7.R.2.1].
- In Study 181, the safety profile of pembrolizumab did not clearly differ between Japanese and non-Japanese patients. Accordingly, no new safety concerns have been identified in Japanese patients with esophageal cancer [see Section 7.R.2.1].
- A certain amount of data regarding the safety of pembrolizumab in Japanese patients have been collected through the ongoing post-marketing surveillance for the approved indications. In addition, no new concerns regarding the safety of pembrolizumab have been raised, thus far by the surveillance.

(b) In view of the available data, including the results of PPK analyses [see Section 6.1] which indicated no clear differences in the safety profile of pembrolizumab across the approved cancer types [see Section 7.R.2.1], the safety profile of pembrolizumab administered with the 400 mg every 6 weeks regimen does not clearly differ from that with the approved 200 mg every 3 weeks regimen across all of the approved indications. Therefore, safety information on the use of pembrolizumab administered at a dose of 400 mg every 6 weeks will be collected through the ongoing post-marketing surveillance for the approved indications.

PMDA's view:

PMDA has concluded as follows as to the above (a) and (b).

(a) As a result of the discussion described in Section "7.R.2 Safety," there is little necessity to conduct post-marketing surveillance covering patients receiving pembrolizumab for esophageal cancer immediately after the approval, and safety information may be collected through routine pharmacovigilance activities, in view of the available data, including the point that no new safety concerns have been identified for the present partial change application.

(b) Safety information regarding the use of pembrolizumab administered at a dose of 400 mg every 6 weeks may be collected through the ongoing post-marketing surveillance, as proposed by the applicant.

7.3 Adverse events reported in clinical studies

Among the clinical study results submitted for the safety evaluation, death-related results are presented in Sections "7.1 Evaluation data" and "7.2 Reference data," whereas other major adverse events are detailed below.

7.3.1 Global phase II study (Study 180)

Adverse events were reported in 116 of 121 patients (95.9%). Adverse events for which a causal relationship to pembrolizumab could not be ruled out were reported in 70 of 121 patients (57.9%). The adverse events reported with a ≥10% incidence were fatigue in 34 patients (28.1%), cough and decreased appetite in 24 patients (19.8%) each, constipation and nausea in 23 patients (19.0%) each, vomiting in 20 patients (16.5%), diarrhoea in 19 patients (15.7%), anaemia in 18 patients (14.9%), pneumonia in 17 patients (14.0%), dyspnoea in 16 patients (13.2%), and AST increased and pruritus in 13 patients (10.7%) each.

Serious adverse events were reported in 47 of 121 patients (38.8%). The serious adverse events reported by ≥2 patients were pneumonia in 13 patients (10.7%), pneumonia aspiration in 5 patients (4.1%), acute kidney injury in 4 patients (3.3%), lung infection and pneumonitis in 3 patients (2.5%) each, and atrial fibrillation, delirium, diabetic ketoacidosis, hypopituitarism, and oesophageal stenosis in 2 patients (1.7%) each. A causal relationship to pembrolizumab could not be ruled out for the pneumonitis in 3 patients, diabetic ketoacidosis and hypopituitarism in 2 patients each, and pneumonia in 1 patient.

Adverse events led to drug discontinuation in 13 of 121 patients (10.7%). The adverse events that led to drug discontinuation were pneumonitis in 4 patients (3.3%), and ALT increased, blood bilirubin increased, cerebrovascular accident, chronic obstructive pulmonary disease, colitis, interstitial lung disease, pneumonia, pneumonia aspiration, and tumour necrosis in 1 patient (0.8%) each. A causal relationship to pembrolizumab could not be ruled out for the pneumonitis in 4 patients, and ALT increased, colitis, and interstitial lung disease in 1 patient each.

7.3.2 Global phase III study (Study 181)

7.3.2.1 Global cohort

Adverse events were reported in 300 of 314 patients (95.5%) in the pembrolizumab group and 288 of 296 patients (97.3%) in the control group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 202 of 314 patients (64.3%) in the pembrolizumab group and 255 of 296 patients (86.1%) in the control group. Table 18 shows the adverse events reported with a ≥10% incidence in either treatment group.

Table 18. Adverse events reported with a ≥10% incidence in either treatment group

SOC PT (MedDRA ver. 21.0)	n (%)			
	Pembrolizumab N = 314		IC N = 296	
	Any grade	Grade ≥3	Any grade	Grade ≥3
All adverse events	300 (95.5)	170 (54.1)	288 (97.3)	183 (61.8)
Blood and lymphatic system disorders				
Anaemia	53 (16.9)	19 (6.1)	85 (28.7)	31 (10.5)
Neutropenia	0	0	39 (13.2)	26 (8.8)
Endocrine disorders				
Hypothyroidism	36 (11.5)	0	7 (2.4)	0
Gastrointestinal disorders				
Nausea	60 (19.1)	3 (1.0)	84 (28.4)	9 (3.0)
Constipation	57 (18.2)	3 (1.0)	56 (18.9)	1 (0.3)
Dysphagia	49 (15.6)	15 (4.8)	28 (9.5)	8 (2.7)
Diarrhoea	39 (12.4)	3 (1.0)	83 (28.0)	9 (3.0)
Vomiting	39 (12.4)	5 (1.6)	55 (18.6)	9 (3.0)
Abdominal pain	37 (11.8)	6 (1.9)	29 (9.8)	4 (1.4)
General disorders and administration site conditions				
Fatigue	70 (22.3)	5 (1.6)	89 (30.1)	6 (2.0)
Asthenia	45 (14.3)	8 (2.5)	43 (14.5)	6 (2.0)
Pyrexia	33 (10.5)	1 (0.3)	50 (16.9)	0
Laboratory tests				
White blood cell count decreased	2 (0.6)	1 (0.3)	53 (17.9)	31 (10.5)
Neutrophil count decreased	3 (1.0)	2 (0.6)	52 (17.6)	30 (10.1)
Weight decreased	40 (12.7)	6 (1.9)	34 (11.5)	0
Metabolism and nutrition disorders				
Decreased appetite	78 (24.8)	9 (2.9)	76 (25.7)	7 (2.4)
Musculoskeletal and connective tissue disorders				
Back pain	37 (11.8)	5 (1.6)	24 (8.1)	1 (0.3)
Nervous system disorders				
Peripheral sensory neuropathy	3 (1.0)	0	52 (17.6)	1 (0.3)
Respiratory, thoracic, and mediastinal disorders				
Cough	40 (12.7)	1 (0.3)	30 (10.1)	0
Skin and subcutaneous tissue disorders				
Alopecia	4 (1.3)	0	88 (29.7)	1 (0.3)

Serious adverse events were reported in 124 of 314 patients (39.5%) in the pembrolizumab group and 121 of 296 patients (40.9%) in the IC group. The serious adverse events reported by ≥3 patients in each treatment group were pneumonia in 14 patients (4.5%), dysphagia and pneumonia aspiration in 11 patients (3.5%) each, pneumonitis in 7 patients (2.2%), death in 5 patients (1.6%), autoimmune hepatitis, oesophageal haemorrhage, and pyrexia in 4 patients (1.3%) each, and abdominal pain, colitis, hypercalcaemia, oesophageal obstruction, pulmonary embolism, respiratory tract infection, and sepsis in 3 patients (1.0%) each in the pembrolizumab group; and febrile neutropenia in 22 patients (7.4%), pneumonia in 20 patients (6.8%), death in 10 patients (3.4%), anaemia, diarrhoea, pneumonia aspiration, pyrexia, and vomiting in 5 patients (1.7%) each, dehydration, gastrointestinal haemorrhage, and neutropenia in 4 patients (1.4%) each, and nausea, neutrophil count decreased, sepsis, and upper gastrointestinal haemorrhage in 3 patients (1.0%) each in the IC group. A causal relationship to the study drug could not be ruled out for the pneumonitis in 7 patients, autoimmune hepatitis, colitis, and pneumonia in 3 patients each, pyrexia in 2 patients, and death, dysphagia, oesophageal haemorrhage, and pneumonia aspiration in 1 patient each in the pembrolizumab group; and the febrile neutropenia in 21 patients, pneumonia in 8 patients, diarrhoea, pyrexia, and vomiting in 4 patients each,

anaemia, nausea, neutropenia, and neutrophil count decreased in 3 patients each, sepsis in 2 patients, and dehydration and pneumonia aspiration in 1 patient each in the IC group.

Adverse events led to drug discontinuation in 40 of 314 patients (12.7%) in the pembrolizumab group and 42 of 296 patients in the IC group. The adverse events that led to drug discontinuation in ≥2 patients were autoimmune hepatitis in 5 patients (1.6%), death and oesophageal haemorrhage in 4 patients (1.3%) each, pneumonia and pneumonitis in 3 patients (1.0%), and gastrointestinal haemorrhage in 2 patients (0.6%) in the pembrolizumab group; and pneumonia in 5 patients (1.7%), death in 4 patients (1.4%), neuropathy peripheral in 3 patients (1.0%), and dehydration, dysphagia, malaise, oesophageal perforation, and upper gastrointestinal haemorrhage in 2 patients (0.7%) each in the IC group. A causal relationship to the study drug could not be ruled out for the autoimmune hepatitis in 5 patients, pneumonitis in 3 patients, and death and oesophageal haemorrhage in 1 patient each in the pembrolizumab group, and the neuropathy peripheral in 3 patients, malaise and pneumonia in 2 patients each, and dehydration in 1 patient in the IC group.

7.3.2.2 Chinese cohort

Adverse events were reported in 62 of 62 patients (100.0%) in the pembrolizumab group and 56 of 59 patients (94.9%) in the IC group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 47 of 62 patients (75.8%) in the pembrolizumab group and 49 of 59 patients (83.1%) in the IC group. Table 19 shows the adverse events reported with a ≥10% incidence in either treatment group.

Table 19. Adverse events reported with a ≥10% incidence in either treatment group

SOC PT (MedDRA ver. 21.1)	n (%)			
	Pembrolizumab N = 62		IC N = 59	
	Any grade	Grade ≥3	Any grade	Grade ≥3
All adverse events	62 (100)	33 (53.2)	56 (94.9)	40 (67.8)
Blood and lymphatic system disorders				
Anaemia	15 (24.2)	3 (4.8)	30 (50.8)	4 (6.8)
Leukopenia	0	0	7 (11.9)	1 (1.7)
Endocrine disorders				
Hypothyroidism	12 (19.4)	0	2 (3.4)	0
Gastrointestinal disorders				
Constipation	11 (17.7)	1 (1.6)	10 (16.9)	0
Diarrhoea	7 (11.3)	0	19 (32.2)	4 (6.8)
Vomiting	5 (8.1)	1 (1.6)	19 (32.2)	4 (6.8)
Nausea	6 (9.7)	0	16 (27.1)	2 (3.4)
Gastroesophageal reflux disease	6 (9.7)	0	6 (10.2)	0
General disorders and administration site conditions				
Asthenia	12 (19.4)	1 (1.6)	4 (6.8)	0
Fatigue	3 (4.8)	0	10 (16.9)	2 (3.4)
Pyrexia	4 (6.5)	0	10 (16.9)	0
Malaise	2 (3.2)	0	6 (10.2)	1 (1.7)
Infections and infestations				
Pneumonia	7 (11.3)	3 (4.8)	5 (8.5)	0
Laboratory tests				
ALT increased	12 (19.4)	0	4 (6.8)	0
Weight decreased	12 (19.4)	1 (1.6)	16 (27.1)	0
Gamma-glutamyltransferase increased	7 (11.3)	0	4 (6.8)	0
White blood cell count decreased	4 (6.5)	0	30 (50.8)	13 (22.0)
Neutrophil count decreased	2 (3.2)	0	18 (30.5)	9 (15.3)
Lymphocyte count decreased	1 (1.6)	0	8 (13.6)	3 (5.1)
Metabolism and nutrition disorders				
Hypoalbuminaemia	14 (22.6)	0	11 (18.6)	0
Decreased appetite	11 (17.7)	0	11 (18.6)	2 (3.4)
Hypokalaemia	5 (8.1)	1 (1.6)	11 (18.6)	3 (5.1)
Musculoskeletal and connective tissue disorders				
Back pain	7 (11.3)	0	1 (1.7)	0
Respiratory, thoracic, and mediastinal disorders				
Cough	11 (17.7)	0	7 (11.9)	0
Productive cough	3 (4.8)	0	7 (11.9)	0
Skin and subcutaneous tissue disorders				
Alopecia	0	0	7 (11.9)	0

Serious adverse events were reported in 22 of 62 patients (35.5%) in the pembrolizumab group and 22 of 59 patients (37.3%) in the IC group. The serious adverse events reported by ≥2 patients in each group were death, oesophageal obstruction, pneumonia, and upper respiratory tract infection in 2 patients (3.2%) each in the pembrolizumab group, and diarrhoea in 3 patients (5.1%), and bone marrow failure, gastrointestinal haemorrhage, haemoptysis, oesophageal fistula, pneumonia, pyrexia, suicide attempt, and white blood cell count decreased in 2 patients (3.4%) each in the IC group. A causal relationship to the study drug could not be ruled out for the pneumonia in 1 patient in the pembrolizumab group, and the diarrhoea in 3 patients, bone marrow failure and white blood cell count decreased in 2 patients each, and haemoptysis and pyrexia in 1 patient each in the IC group.

Adverse events led to drug discontinuation in 10 of 62 patients (16.1%) in the pembrolizumab group and 9 of 59 patients (15.3%) in the IC group. The adverse events that led to drug discontinuation in ≥2 patients in each group were death and pneumonia in 2 patients (3.2%) each in the pembrolizumab group, and fatigue in 2 patients (3.4%) in the IC group. A causal relationship to the study drug could not be ruled out for the pneumonia in 2 patients in the pembrolizumab group and fatigue in 2 patients in the IC group.

7.3.3 Global phase II study (Study 028)

Adverse events were reported in 21 of 23 patients (91.3%), and adverse events for which a causal relationship to pembrolizumab could not be ruled out were reported in 9 of 23 patients (39.1%). The adverse events reported with a ≥10% incidence were decreased appetite in 7 patients (30.4%), anaemia and fatigue in 6 patients (26.1%) each, cancer pain and constipation in 5 patients (21.7%) each, nausea in 4 patients (17.4%), and anxiety, dehydration, diarrhoea, dry skin, dysphagia, nasopharyngitis, and pyrexia in 3 patients (13.0%) each.

Serious adverse events were reported in 9 of 23 patients (39.1%). The serious adverse events reported were anaemia, complication associated with device, decreased appetite, enterocolitis, gastrointestinal haemorrhage, haemorrhage, hypercalcaemia of malignancy, ischaemic stroke, liver disorder, pemphigoid, and peritonitis in 1 patient (4.3%) each. A causal relationship to pembrolizumab could not be ruled out for the decreased appetite, liver disorder, and pemphigoid in 1 patient each.

Adverse events led to drug discontinuation in 2 of 23 patients (8.7%). The adverse events that led to drug discontinuation were complication associated with device and liver disorder in 1 patient (4.3%). A causal relationship to pembrolizumab could not be ruled out for the liver disorder.

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

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

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

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

The new drug application data (CTD 5.3.5.1.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals, Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that pembrolizumab has a certain level of efficacy in the treatment of radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy, and that pembrolizumab has acceptable safety in view of its benefits. Pembrolizumab offers a new therapeutic option for chemotherapy-treated patients with radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma, which is of clinical significance. The efficacy, indication, dosage and administration, post-marketing investigations, etc. of pembrolizumab should be further evaluated.

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)

July 6, 2020

Product Submitted for Approval	
Brand Name	Keytruda Injection 100 mg
Non-proprietary Name	Pembrolizumab (Genetical Recombination)
Applicant	MSD K.K.
Date of Application	November 8, 2019

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

As a result of its review described in Section "7.R.1 Data for review and efficacy" of the Review Report (1), PMDA has concluded that the results of a global phase III study in chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer (Study 181) demonstrated a certain level of efficacy of pembrolizumab in the treatment of chemotherapy-treated patients with radically unresectable, advanced or recurrent PD-L1 positive (combined positive score [CPS] ≥10) esophageal squamous cell carcinoma, although the result for overall survival (OS), which was the primary endpoint, failed to meet the prespecified criteria.

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

1.2 Safety

As a result of its review described in Section "7.R.2 Safety" of the Review Report (1), PMDA has concluded that the administration of pembrolizumab to chemotherapy-treated patients with radically unresectable, advanced or recurrent esophageal cancer requires particular attention to the onset of the following adverse events, which have been identified as requiring attention at the regulatory reviews for the approved indications: gastrointestinal disorders, skin disorders, neurological disorders, hepatic function disorder, cholangitis sclerosing, eye disorders, endocrine disorders, renal impairment, interstitial lung disease (ILD), infusion reaction, pancreatitis, myositis, rhabdomyolysis, encephalitis and meningitis, myasthenia gravis, myocarditis, serious blood disorders, haemophagocytosis, tuberculosis, and anaphylaxis.

PMDA has also concluded that, although the use of pembrolizumab requires attention to the above-mentioned adverse events, pembrolizumab therapy is tolerable in patients with esophageal cancer as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through appropriate measures such as monitoring of adverse events, differential diagnosis and management of excessive immune-mediated adverse drug reactions, and interruption of pembrolizumab.

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

1.3 Clinical positioning and indication

As a result of its review described in Section "7.R.3 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the indication of pembrolizumab should be "radically unresectable, advanced or recurrent esophageal squamous cell carcinoma that has progressed after cancer chemotherapy," and that the percentages of PD-L1 positive cells (CPS) in patients who responded to pembrolizumab therapy in Study 181 should be stated in the "Clinical Studies" section of the package insert, and the following cautionary statements should be contained in the "Precautions Concerning Indications" section.

[Precautions Concerning Indications]

- The efficacy and safety of pembrolizumab as the first-line therapy have not been established.
- The efficacy and safety of pembrolizumab in neoadjuvant or adjuvant therapy have not been established.
- Pembrolizumab should be administered to patients who have been demonstrated to have a tumor with PD-L1 expression by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic or medical device, after carefully reading the "Clinical Studies" section to understand the percentage of PD-L1 positive cells (CPS).

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

In view of the above, PMDA instructed the applicant to modify the "Indications" and "Precautions Concerning Indications" sections as shown above. The applicant agreed.

1.4 Dosage and administration

As a result of its review described in Section "7.R.4 Dosage and administration" of the Review Report (1), PMDA has concluded that the statements presented in the table below should be contained in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections (underline denotes changes for the present partial change application).

Dosage and Administration	Precautions Concerning Dosage and Administration
[Malignant melanoma] • The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. [Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments), recurrent or metastatic head and neck cancer, or radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy] • The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes. [Radically unresectable or metastatic renal cell carcinoma] • In combination with axitinib, the usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes.	[Unresectable, advanced or recurrent NSCLC] • When pembrolizumab (genetical recombination) is used with other antineoplastic drugs, the "Clinical Studies" section should be understood sufficiently before selecting concomitant antineoplastic drugs. [Recurrent or metastatic head and neck cancer] • The dosage regimen of pembrolizumab (genetical recombination) should be selected based on a good understanding of the efficacy and safety of pembrolizumab (genetical recombination), after carefully reading the "Clinical Studies" section. [Malignant melanoma, relapsed or refractory cHL, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent MSI-High solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments), or radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy] • The efficacy and safety of pembrolizumab (genetical recombination) in combination with other antineoplastic drugs have not been established. [All indications] • Dose adjustment criteria in case of adverse drug reactions

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

In view of the above, PMDA instructed the applicant to modify the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as shown above. The applicant agreed.

1.5 Risk management plan (draft)

In view of the discussions presented in Section "7.R.5 Post-marketing investigations" of the Review Report (1), PMDA has concluded that (a) safety information regarding the new indication of esophageal cancer may be collected through routine pharmacovigilance activities, and that (b) safety information regarding the new dosage regimen of 400 mg every 6 weeks for all of the approved indications may be collected through the ongoing post-marketing surveillance or other activities for the approved indications, as proposed by the applicant.

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

In view of the discussion above, PMDA has concluded that the risk management plans (draft) for pembrolizumab should include the safety specifications presented in Table 20, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 21.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Colitis, enteritis, and severe diarrhoea • Hepatic function disorder and cholangitis sclerosing • Renal impairment (tubulointerstitial nephritis, etc.) • Endocrine disorders (pituitary dysfunction, thyroid dysfunction, and adrenal dysfunction) • Type 1 diabetes mellitus • Uveitis • Myositis and rhabdomyolysis • Pancreatitis • Neurological disorders (Guillain-Barre syndrome, etc.) • Severe skin disorders (toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, pemphigoid, etc.) • Encephalitis and meningitis • Myasthenia gravis • Myocarditis • Serious blood disorders (immune thrombocytopenic purpura, haemolytic anaemia, aplasia pure red-cell, agranulocytosis, etc.) • Haemophagocytic syndrome • Infusion reaction • Use in patients with a history of organ transplantation (including hematopoietic stem cell transplantation) • Tuberculosis	• An increased risk of severe comorbidities associated with allogenic hematopoietic stem cell transplantation after pembrolizumab therapy (hematological malignancies) • Embryonic/fetal toxicities	None
Efficacy specification (for the present partial change application)		
None		

No changes are made for the present partial change application. Dotted line denotes important identified risks added after the present partial change application.

Table 21. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Use-results survey in patients with unresectable, advanced or recurrent PD-L1 positive NSCLC (all-case surveillance) • Use-results survey in patients with relapsed or refractory cHL (all-case surveillance) • Use-results survey in patients with radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy (all-case surveillance) • Use-results survey in patients with MSI-High solid tumors (except colorectal cancer) • Use-results survey in patients with radically unresectable or metastatic renal cell carcinoma • Post-marketing clinical studies (extension studies of Studies 010, 024, 087, 204, 045, 189, 407, 042, 054, 252, 426, 048, 587, and 180)	• Use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Use-results survey in patients with unresectable, advanced or recurrent PD-L1 positive NSCLC (all-case surveillance) • Use-results survey in patients with relapsed or refractory cHL (all-case surveillance) • Use-results survey in patients with radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy (all-case surveillance) • Use-results survey in patients with MSI-High solid tumors (except colorectal cancer) • Post-marketing clinical studies (extension studies of Studies 010, 024, 087, 204, and 045)	• Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients

Single underline denotes activities to be performed after the new indication is added. Dotted line denotes activities added after the present partial change application.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indications and dosage and administration shown below, with the following approval condition, provided that the necessary precautionary statements are included in the package insert and information regarding the proper use of the product is properly disseminated after the market launch, and provided that the product is used under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions capable of emergency response. The re-examination period is the remainder of the ongoing re-examination period (until October 18, 2022).

Indications (Single underline denotes additions. Double-underline denotes additions made as of December 20, 2019 after the present partial change application.)

Malignant melanoma

Unresectable, advanced or recurrent non-small cell lung cancer

Relapsed or refractory classical Hodgkin lymphoma

Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy

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

Radically unresectable or metastatic renal cell carcinoma

Recurrent or metastatic head and neck cancer

Radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy

Dosage and Administration (Single underline denotes additions. Double-underline denotes additions made as of December 20, 2019 after the present partial change application.)

[Malignant melanoma]

The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months.

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

The usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes.

[Radically unresectable or metastatic renal cell carcinoma]

In combination with axitinib, the usual adult dosage is 200 mg every 3 weeks or 400 mg every 6 weeks of pembrolizumab (genetical recombination) infused intravenously over 30 minutes.

Approval Conditions

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

Warnings (No change)

1. Pembrolizumab should be administered only to patients considered appropriate to receive pembrolizumab therapy by a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution that can provide adequate emergency medical care. Inform the patient or their family members of the effectiveness and risks of pembrolizumab and obtain their consent before the start of treatment.
2. There have been reports of patients who died after experiencing interstitial lung disease. Patients should be closely monitored for initial symptoms (shortness of breath, dyspnoea, cough, etc.) and examined by chest X-rays. If any abnormalities are observed, discontinue pembrolizumab and take appropriate measures such as treatment with corticosteroids.

Contraindication (No change)

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

Precautions Concerning Indications (Single underline denotes additions. Single strikethrough denotes deletions. Double-underline denotes additions made as of December 20, 2019 after the partial change

application. Double-strikethrough denotes deletions made as of December 20, 2019 after the partial change application.)

[Malignant melanoma]

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

[Unresectable, advanced or recurrent non-small cell lung cancer]

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

[Relapsed or refractory classical Hodgkin lymphoma]

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

[Radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy]

1. The efficacy and safety of pembrolizumab as the first-line therapy have not been established
2. Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section to understand particularly for the characteristics (e.g., prior treatments) of patients enrolled in the clinical studies.
3. The efficacy and safety of pembrolizumab in neoadjuvant or adjuvant therapy have not been established.

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

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

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

[Radically unresectable or metastatic renal cell carcinoma]
The efficacy and safety of pembrolizumab in adjuvant therapy have not been established.

[Recurrent or metastatic head and neck cancer]
1. The efficacy and safety of pembrolizumab in adjuvant therapy have not been established.
2. The survival benefit of pembrolizumab as monotherapy tends to differ according to ~~the percentage of tumor cells and immune cells (macrophages and lymphocytes) expressing PD-L1,~~ the percentage of PD-L1 positive cells (combined positive score [CPS]). The "Clinical Studies" section should be carefully read to understand CPS and appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab.
3. Appropriate patients should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section.

[Radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy]
1. The efficacy and safety of pembrolizumab as the first-line therapy have not been established
2. The efficacy and safety of pembrolizumab in neoadjuvant or adjuvant therapy have not been established.
3. Pembrolizumab should be administered to patients who have been demonstrated to have a tumor with PD-L1 expression by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic or medical device, after carefully reading the "Clinical Studies" section to understand the percentage of PD-L1 positive cells (CPS).

Precautions Concerning Dosage and Administration (Single underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of December 20, 2019, after the present partial change applications. Double-strikethrough denotes deletions made as of December 20, 2019, after the present partial change application.)

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

[Recurrent or metastatic head and neck cancer]
The dosage regimen of pembrolizumab should be selected based on a good understanding of the efficacy and safety of pembrolizumab, after carefully reading the "Clinical Studies" section.

[Malignant melanoma, relapsed or refractory classical Hodgkin lymphoma, radically unresectable urothelial carcinoma that has progressed after cancer chemotherapy, advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after cancer chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments), or radically unresectable, advanced or recurrent PD-L1 positive esophageal squamous cell carcinoma that has progressed after cancer chemotherapy]
The efficacy and safety of pembrolizumab in combination with other antineoplastic drugs have not been established.

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

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

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

Appendix

List of Abbreviations

AEOSI	adverse events of special interest
ALT	alanine aminotransferase
ASaT	all subject as treated
AST	aspartate aminotransferase
AUC_{wk6}	area under the concentration-time curve over a 6-week interval at treatment initiation
$AUC_{wk6,ss}$	area under the concentration-time curve over a 6-week interval at steady state
BID	bis in die
BIRC	blinded independent review committee
BV	bevacizumab (genetical recombination)
C_{avg}	average serum concentration at treatment initiation
$C_{avg,ss}$	average serum concentration at steady state
CBDCA	carboplatin
CDDP	cisplatin
cHL	classical Hodgkin lymphoma
CI	confidence interval
C_{max}	maximum serum concentration at treatment initiation
$C_{max,ss}$	maximum serum concentration at steady state
C_{min}	minimum serum concentration at treatment initiation
$C_{min,ss}$	minimum serum concentration at steady state
CPS	combined positive score
CPT-11	irinotecan hydrochloride hydrate
CR	complete response
DTX	docetaxel hydrate
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
GEP	gene expression profile
HLT	high level term
IC	investigator's choice
ITT	intention-to-treat
Japanese clinical practice guidelines (esophageal cancer)	Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus 2017, edited by the Japan Esophageal Society
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MSI-High	microsatellite instability-high
NCCN guidelines (Esophageal and esophagogastric junction cancers)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Esophageal and Esophagogastric Junction Cancers
NE	not evaluable
nivolumab	nivolumab (genetical recombination)
NSCLC	non-small cell lung cancer

NSQ	non-squamous
OS	overall survival
partial change application	application for partial change approval
PD	progressive disease
PD-1	programmed cell death-1
PD-L	programmed cell death-ligand
PEM	pemetrexed sodium hydrate
pembrolizumab	pembrolizumab (genetical recombination)
pembrolizumab + CBDCA + PEM	a combination of pembrolizumab, CBDCA, and PEM
pembrolizumab + CBDCA + PTX + BV	a combination of pembrolizumab, CBDCA, PTX, and BV
pembrolizumab + CBDCA PTX	a combination of pembrolizumab, CBDCA, and PTX
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PT	preferred term
PTX	paclitaxel
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
Q6W	quaque 6 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
Study 001	the KEYNOTE-001 study
Study 002	the KEYNOTE-002 study
Study 006	the KEYNOTE-006 study
Study 010	the KEYNOTE-010 study
Study 012	the KEYNOTE-012 study
Study 013	the KEYNOTE-013 study
Study 021	the KEYNOTE-021 study
Study 024	the KEYNOTE-024 study
Study 028	the KEYNOTE-028 study
Study 040	the KEYNOTE-040 study
Study 042	the KEYNOTE-042 study
Study 045	the KEYNOTE-045 study
Study 048	the KEYNOTE-048 study
Study 052	the KEYNOTE-052 study
Study 054	the KEYNOTE-054 study
Study 055	the KEYNOTE-055 study
Study 087	the KEYNOTE-087 study
Study 158	the KEYNOTE-158 study
Study 164	the KEYNOTE-164 study
Study 180	the KEYNOTE-180 study
Study 181	the KEYNOTE-181 study

Study 189	the KEYNOTE-189 study
Study 204	the KEYNOTE-204 study
Study 252	the KEYNOTE-252 study
Study 407	the KEYNOTE-407 study
Study 426	the KEYNOTE-426 study
Study 555	the KEYNOTE-555 study
Study 587	the KEYNOTE-587 study
TPS	tumor proportion score
trastuzumab	trastuzumab (genetical recombination)
5-FU	5-fluorouracil