Review Report

October 15, 2021
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	Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 120 mg, Opdivo Intravenous Infusion 240 mg
Non-proprietary Name	Nivolumab (Genetical Recombination) (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	December 10, 2020, February 18, 2021[1)]
Dosage Form/Strength	Injection: Each vial of 2, 10, 12, or 24 mL contains 20, 100, 120, or 240 mg of nivolumab (genetical recombination), respectively.
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in (i) the treatment of unresectable, advanced or recurrent gastric cancer and (ii) the adjuvant therapy of esophageal cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition.

Indications

- ○ Treatment of malignant melanoma
- ○ Treatment of unresectable, advanced or recurrent non-small cell lung cancer
- ○ Treatment of unresectable or metastatic renal cell carcinoma
- ○ Treatment of relapsed or refractory classical Hodgkin lymphoma
- ○ Treatment of recurrent or metastatic head and neck cancer

1) (i) A partial change application for a new indication and a new dosage concerning unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy and (ii) a partial change application for a new indication and a new dosage concerning adjuvant therapy of esophageal cancer were submitted on (i) December 10, 2020 and (ii) February 18, 2021, respectively.

- ○ Treatment of unresectable, advanced or recurrent gastric cancer ~~that has progressed after cancer chemotherapy~~
- ○ Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma ~~that has progressed after cancer chemotherapy~~
- ○ Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy
- ○ Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy
- ○ Adjuvant therapy of esophageal cancer

(Underline denotes additions. Strikethrough denotes deletions.
Double line denotes changes made as of May 27, 2021 after submission of the present applications.)

Dosage and Administration

Treatment of malignant melanoma

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months.

In combination therapy with ipilimumab (genetical recombination) for unresectable malignant melanoma, the usual adult dosage of nivolumab (genetical recombination) is 80 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

Treatment of unresectable, advanced or recurrent non-small cell lung cancer, unresectable, advanced or recurrent gastric cancer ~~that has progressed after cancer chemotherapy~~

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

When administered in combination with other antineoplastic drugs, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 360 mg administered as an intravenous infusion every 3 weeks.

Treatment of unresectable or metastatic renal cell carcinoma

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

When administered in combination with cabozantinib, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

When administered in combination with ipilimumab (genetical recombination) to chemotherapy-naïve patients with unresectable or metastatic renal cell carcinoma, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

Treatment of relapsed or refractory classical Hodgkin lymphoma

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

The usual pediatric dosage of nivolumab (genetical recombination) is 3 mg/kg (body weight) administered as an intravenous infusion every 2 weeks. For pediatric patients weighing >40 kg, nivolumab (genetical recombination) may be administered as an intravenous infusion at 240 mg every 2 weeks or at 480 mg every 4 weeks.

Treatment of recurrent or metastatic head and neck cancer

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma ~~that has progressed after cancer chemotherapy~~

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

When administered in combination with ipilimumab (genetical recombination), the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 360 mg administered as an intravenous infusion every 3 weeks.

Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

When administered in combination with ipilimumab (genetical recombination), the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy, adjuvant therapy of esophageal cancer

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of esophageal cancer, the maximum duration of treatment is 12 months.

~~Treatment of relapsed or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, unresectable advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy, unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy]~~

~~The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.~~

(Underline denotes additions. Strikethrough denotes deletions. Double line denotes changes made as of May 27, 2021, August 25, 2021, or September 27, 2021 after submission of the present applications.)

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

September 7, 2021

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	Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 120 mg, Opdivo Intravenous Infusion 240 mg
Non-proprietary Name	Nivolumab (Genetical Recombination)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	December 10, 2020, February 18, 2021[2)]
Dosage Form/Strength	Injection: Each vial of 2, 10, 12, or 24 mL contains 20, 100, 120, or 240 mg of nivolumab (genetical recombination), respectively.

Proposed Indications

- Treatment of malignant melanoma
- Treatment of unresectable, advanced or recurrent non-small cell lung cancer
- Treatment of unresectable or metastatic renal cell carcinoma
- Treatment of relapsed or refractory classical Hodgkin lymphoma
- Treatment of recurrent or metastatic head and neck cancer
- Treatment of unresectable, advanced or recurrent gastric cancer ~~that has progressed after cancer chemotherapy~~
- Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy
- Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy
- Treatment of ~~unresectable, advanced or recurrent~~ esophageal cancer ~~that has progressed after cancer chemotherapy~~

(Strikethrough denotes deletions.)

Proposed Dosage and Administration

Treatment of malignant melanoma

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months.

2) (i) A partial change application for a new indication and a new dosage concerning unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy and (ii) a partial change application for a new indication and a new dosage concerning adjuvant therapy of esophageal cancer were submitted on (i) December 10, 2020 and (ii) February 18, 2021, respectively.

In combination therapy with ipilimumab (genetical recombination) for unresectable malignant melanoma, the usual adult dosage of nivolumab (genetical recombination) is 80 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

Treatment of unresectable, advanced or recurrent non-small cell lung cancer
The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.
When administered in combination with other antineoplastic drugs, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 360 mg administered as an intravenous infusion every 3 weeks.

Treatment of unresectable or metastatic renal cell carcinoma
The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.
When administered in combination with ipilimumab (genetical recombination) to chemotherapy-naïve patients with unresectable or metastatic renal cell carcinoma, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

Treatment of unresectable, advanced or recurrent gastric cancer
The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.
When administered in combination with other antineoplastic drugs, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 360 mg administered as an intravenous infusion every 3 weeks.

Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy
The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.
When administered in combination with ipilimumab (genetical recombination), the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

Treatment of esophageal cancer
The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of esophageal cancer, the maximum duration of treatment is 12 months.

Treatment of relapsed or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, ~~unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy,~~ unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy~~,~~ ~~unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy~~

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

(Underline denotes additions. Strikethrough denotes deletions.)

Table of Contents

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

Nivolumab (genetical recombination) is a human monoclonal antibody against human programmed cell death-1 (PD-1) belonging to the immunoglobulin (Ig) G4 subclass, discovered by Ono Pharmaceutical Co., Ltd. and Medarex, Inc., the US (currently known as Bristol-Myers Squibb). Nivolumab binds to the extracellular domain of PD-1 (PD-1 ligand binding site) and blocks the interaction between PD-1 and PD-1 ligands, thereby enhancing the activation of cancer antigen-specific T cells, etc. to inhibit tumor growth.

In Japan, nivolumab was approved for the indications of (a) "unresectable malignant melanoma" in July 2014, (b) "unresectable, advanced or recurrent non-small cell lung cancer (NSCLC)" in December 2015, (c) "unresectable or metastatic renal cell carcinoma (RCC)" in August 2016, (d) "relapsed or refractory classical Hodgkin lymphoma (cHL)" in December 2016, (e) "recurrent or metastatic head and neck cancer" in March 2017, (f) "unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy" in September 2017, (g) "unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy" in August 2018, and (h) "unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy" and "unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy" in February 2020. In addition, the above indication (a) was modified to "malignant melanoma" in August 2018. After the present partial change applications were filed, the above indication (g) was modified to "unresectable, advanced or recurrent malignant pleural mesothelioma" in May 2021.

The applicant submitted (i) a partial change application for a new indication and a new dosage concerning unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy and (ii) a partial change application for a new indication and a new dosage concerning adjuvant therapy of esophageal cancer, at around the same time, though different dates on (i) December 10, 2020 and (ii) February 18, 2021, respectively. Thus, this review report summarizes the reviews of both applications.

1.2 Development history etc.

1.2.1 Unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy [see Section 7.1 for an outline of the review of (i) in Section 1.1]

The applicant initiated Part 1 and Part 2 of a global phase II/III study in patients with unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy (Study 37) in April 2016 and March 2017, respectively. The applicant and Bristol-Myers Squibb initiated a global phase III study in these patients etc. (Study 44) in October 2016.

US and EU applications were filed based mainly on the results from Study 44 in November 2020. In the US, nivolumab was approved for the following indication in April 2021: "OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma." The EU application is under review.

As of July 2021, nivolumab has been approved for the indication of unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy in [redacted] countries.

In Japan, patient enrollment in Part 1 and Part 2 of Study 37 and Study 44 began in [redacted] 20[redacted], [redacted] 20[redacted], and [redacted] 20[redacted], respectively.

The applicant has filed a partial change application for a new indication and a new dosage concerning unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy, based mainly on the results from Studies 44 and 37.

1.2.2 Adjuvant therapy of esophageal cancer [see Section 7.2 for an outline of the review of (ii) in Section 1.1]

The applicant and Bristol-Myers Squibb initiated a global phase III study in patients with resected esophageal cancer (Study 43) in July 2016.

US and EU applications were filed based mainly on the results from Study 43 in November 2020. In the US, nivolumab was approved for the following indication in May 2021: "OPDIVO is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy (CRT)." In the EU, nivolumab was approved for the following indication in July 2021: "OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy."

As of July 2021, nivolumab has been approved for the indication of adjuvant therapy of esophageal cancer in [redacted] countries or regions.

In Japan, patient enrollment in Study 43 began in [redacted] 20[redacted].

The applicant has filed a partial change application for a new indication and a new dosage concerning adjuvant therapy of esophageal cancer, based mainly on the results from Study 43.

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

Because the present applications are intended for new indications and new dosages, no new data on quality have been submitted.

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

Although the present applications are intended for new indications and new dosages, no new data on non-clinical pharmacology have been submitted. The non-clinical pharmacology of nivolumab was evaluated during the review for the initial approval.

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

Although the present applications are intended for new indications and new dosages, no new data on non-clinical pharmacokinetics have been submitted. The non-clinical pharmacokinetics of nivolumab were evaluated during the review for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present applications are intended for new indications and new dosages, no new data on toxicity 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 applications are intended for new indications and new dosages, no new data on biopharmaceutic studies and associated analytical methods have been submitted. The biopharmaceutic studies and associated analytical methods were evaluated during the review for the initial approval etc.

6.1 Clinical pharmacology

The applicant submitted the results of PPK analyses etc. based on the data from Study 44 etc. for gastric cancer and based on the data from Study 43 etc. for esophageal cancer, as clinical pharmacology data. On the basis of the data submitted, PMDA concluded that the applicant's discussion on the PK of nivolumab in patients with gastric cancer based on the data from Study 44 etc. is not different from the content evaluated during the review for the initial approval etc.

6.1.1 PPK analysis

A PPK analysis (software used, NONMEM Version 7.4) was performed using the PK data for nivolumab obtained from a Japanese clinical study (Study 07), global studies (Studies 473 and 43), and foreign clinical studies (Studies 001, 003, 017, and 057) (1,493 subjects, 8,312 sampling points). The PK parameters of (a) nivolumab 240 mg Q2W, (b) nivolumab 240 mg Q2W for 8 doses followed by nivolumab 480 mg Q4W, or (c) nivolumab 480 mg Q4W in patients with resected esophageal cancer enrolled in Study 43[3)] (494 patients) were predicted from the PPK analysis. The predicted PK parameters are shown in Table 1.

The applicant's explanation about nivolumab exposure in patients with resected esophageal cancer, based on the predicted PK parameters:

- Nivolumab exposure at steady state was predicted to be similar between nivolumab 240 mg Q2W for 8 doses followed by nivolumab 480 mg Q4W and nivolumab 480 mg Q4W.
- The C_{max} values after the first dose of nivolumab 480 mg Q4W and at steady state were predicted to be

3) Patients who received nivolumab and had evaluable PK data etc.

lower than the C_{max}[4)] at steady state after nivolumab monotherapy (10 mg/kg Q2W) that has been demonstrated to be tolerable in Japanese patients (see "Review Report on Opdivo Intravenous Infusion 20 mg and Opdivo Intravenous Infusion 100 mg, dated June 18, 2014").

Table 1. Predicted PK parameters of nivolumab in patients with resected esophageal cancer

Dosing regimen	After the first dose			At steady state		
	C_{max}*1 (μg/mL)	C_{avg}*2 (μg/mL)	C_{min}*3 (μg/mL)	C_{max} (μg/mL)	C_{avg} (μg/mL)	C_{min} (μg/mL)
240 mg Q2W	60.6 (24.8)	38.3 (20.8)	33.6 (22.7)	156 (25.0)	115 (27.1)	94.5 (29.7)
240 mg Q2W (8 doses) followed by 480 mg Q4W	60.6 (24.8)	38.3 (20.8)	33.6 (22.7)	202 (24.2)	114 (26.8)	79.2 (31.8)
480 mg Q4W	121 (24.8)	46.3 (21.1)	25.8 (24.2)	202 (24.1)	114 (26.8)	79.2 (31.7)

Geometric mean (CV %); *1, Maximum serum concentration after the first dose; *2, Average serum concentration over 28 days after the first dose; *3, Minimum serum concentration at 28 days after the first dose

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 nivolumab is acceptable.

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

7.1 Data concerning unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from a total of 2 studies presented in Table 2: 1 global phase II/III study and 1 global phase III study.

Table 2. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study identifier	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Global	Study 37	II/III	Patients with unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy	Part 1 40 (a) 21 (b) 19 Part 2 724 (a) 362 (b) 362	Part 1 Nivolumab 360 mg Q3W intravenously in combination with (a) SOX or (b) CAPOX Part 2 (a) Nivolumab 360 mg or (b) placebo Q3W intravenously in combination with SOX or CAPOX	Efficacy Safety
		Study 44	III	Patients with unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy	1,581 (a) 789 (b) 792	(a) Nivolumab 240 mg Q2W intravenously in combination with FOLFOX, or nivolumab 360 mg Q3W intravenously in combination with CAPOX (b) FOLFOX or CAPOX	Efficacy Safety

The clinical studies are summarized below. Unless otherwise specified, the dosing regimens of other antineoplastic drugs used in the clinical studies are shown in Table 3. The main adverse events other than deaths observed in the clinical studies are described in Section "7.3.1 Adverse events etc. observed in clinical

4) The C_{max} (geometric mean [CV %]) at steady state after nivolumab 10 mg/kg Q2W in Japanese patients predicted from the PPK analysis using the PK data for nivolumab obtained from clinical studies in patients with malignant melanoma etc. (3,939 subjects, 21,098 sampling points) was 412 μg/mL (16.8) (see "Review Report on Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, and Opdivo Intravenous Infusion 240 mg, dated August 26, 2020").

studies in patients with unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy."

Table 3. Listing of dosing regimens of other antineoplastic drugs used in clinical studies

	Dosing regimen
CAPOX	OX 130 mg/m^2 intravenously on Day 1 and Cape 1,000 mg/m^2 BID orally on Days 1-14 of a 3-week cycle
FOLFOX	OX 85 mg/m^2 and LV 400 mg/m^2 intravenously and 5-FU 400 mg/m^2 IV bolus on Day 1 followed by 5-FU 2,400 mg/m^2 intravenously over Days 1-2 of a 2-week cycle
SOX	OX 130 mg/m^2 intravenously on Day 1 and S-1 40 mg/m^2 BID orally on Days 1-14 of a 3-week cycle

7.1.1 Evaluation data

7.1.1.1 Global studies

7.1.1.1.1 Global phase II/III study (CTD 5.3.5.1-2, 5.3.5.1-3, 5.3.5.1-4; Study 37 [ongoing since April 2016 (in Part 2, data cutoff on October 31, 2018 for interim analysis of PFS and data cutoff on January 31, 2020 for final analysis of OS and safety)])

A randomized, open-label study was conducted at 13 sites in 2 countries including Japan to evaluate the tolerability, safety, etc. of nivolumab in combination with SOX (a combination of tegafur, gimeracil, oteracil potassium, and oxaliplatin) or CAPOX (a combination of capecitabine and oxaliplatin)[5)] in patients with human epidermal growth factor receptor type 2 (HER2)-negative,[6)] unresectable, advanced or recurrent gastric cancer[7)] previously untreated with chemotherapy[8)] (Part 1). A randomized, double-blind, placebo-controlled study was conducted at 130 sites in 3 countries or regions including Japan to evaluate the efficacy and safety of nivolumab plus investigator's choice (IC) (SOX or CAPOX)[9)] compared with placebo plus IC (Part 2) (target sample size, 30 subjects in Part 1, 650 subjects in Part 2).

Subjects in Part 1 were to receive nivolumab 360 mg Q3W intravenously in combination with SOX or CAPOX. Subjects in Part 2 were to receive nivolumab 360 mg or placebo Q3W intravenously in combination with SOX or CAPOX. Treatment was to be continued until disease progression or any withdrawal criterion was met.

Among 40 subjects who were enrolled and randomized in Part 1 (21 in the nivolumab/SOX group, 19 in the nivolumab/CAPOX group), 39 subjects (21 in the nivolumab/SOX group, 18 in the nivolumab/CAPOX group) after excluding 1 subject in the nivolumab/CAPOX group who did not receive study drug were included in the safety population (including 10 Japanese patients in the nivolumab/SOX group and 10 Japanese patients in the nivolumab/CAPOX group). Moreover, 38 subjects (21 in the nivolumab/SOX group, 17 in the nivolumab/CAPOX group) after excluding 1 subject in the nivolumab/CAPOX group previously treated with nivolumab were included in the full analysis set (FAS), which was used as the efficacy population (including 10 Japanese patients in the nivolumab/SOX group and 9 Japanese patients in the nivolumab/CAPOX group). If

5) In Part 1, subjects were randomized to receive SOX or CAPOX.
6) HER2-positive patients (HER2 status was to be assessed using local laboratory criteria. If there is no local laboratory criteria, rough indication for positive was 3+ by immunohistochemistry [IHC], or 2+ by IHC and positive by *in situ* hybridization [ISH]), and patients with indeterminate or undetermined HER2 status were excluded.
7) Patients with gastroesophageal junction (Siewert type I to III) adenocarcinoma were also allowed to be enrolled in the study.
8) In the case of recurrent disease, patients with the last regimen of neoadjuvant or adjuvant chemotherapy (including chemoradiotherapy) completed ≥180 days before recurrence were allowed to be enrolled in the study.
9) In Part 2, the investigator or subinvestigator was to choose SOX or CAPOX.

the pre-specified criteria for starting Part 2[10] were met, Part 2 was to be started (Unless otherwise specified, this review report describes the results from Part 2 of Study 37).

All of 724 subjects who were enrolled in Part 2 and randomized (362 in the nivolumab/IC group, 362 in the placebo/IC group) were included in the intention-to-treat (ITT) population, which was used as the efficacy population (including 198 Japanese patients in the nivolumab/IC group and 197 Japanese patients in the placebo/IC group). After excluding 3 subjects in the nivolumab/IC group and 4 subjects in the placebo/IC group who did not receive study drug from the ITT population, 717 subjects (359 in the nivolumab/IC group, 358 in the placebo/IC group) were included in the safety population (including 195 Japanese patients in the nivolumab/IC group and 194 Japanese patients in the placebo/IC group).

The primary endpoints of Part 2 were initially progression-free survival (PFS) and overall survival (OS) as assessed by the Blinded Independent Review Committee (BIRC) per Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1, and 1 interim analysis of PFS for efficacy evaluation was to be conducted when [redacted] PFS events had occurred (Protocol Amendment Version [redacted], dated [redacted], 20[redacted]).

Then, as [redacted], the assumed hazard ratio of PFS in Part 2 was changed from [redacted] to 0.68. Along with this change, the number of PFS events required for the final analysis of PFS was changed from [redacted] to 430, and the interim analysis of PFS was to take place when 323 PFS events had occurred. If the interim or final analysis of PFS demonstrated statistically significant prolongation of PFS, [redacted] was to be conducted when [redacted] OS events had been observed (Protocol Amendment Version [redacted], dated [redacted], 20[redacted]).

Furthermore, from the results of [redacted],[11] since [redacted] etc., [redacted], also after the PFS analysis, the study was to be continued while maintaining blindness, and the final analysis of OS was to be conducted when 464 OS events had occurred (Protocol Amendment Version [redacted], dated [redacted], 20[redacted]).

In order to adjust for the multiplicity of multiple primary endpoints, a two-sided alpha of 0.04 and a two-sided alpha of 0.01 were allocated to PFS and OS, respectively, to control the overall type I error rate of Part 2 at a two-sided alpha level of 0.05. Lan-DeMets α spending function with O'Brien-Fleming boundaries was used to control the type I error rate for an interim analysis.

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10) If both of the following criteria (a) and (b) were met, Part 2 was to be started. In Part 1, the tolerable safety profile of nivolumab/IC was confirmed, and the objective response rates in the nivolumab/SOX group and the nivolumab/CAPOX group were 57.1% (12 of 21 subjects) and 76.5% (13 of 17 subjects), respectively.
(a) The tolerable safety profile of nivolumab/IC was confirmed by the Independent Data Monitoring Committee.
(b) ≥2 of 15 patients achieved an objective response (CR or PR) as assessed by the BIRC per RECIST ver.1.1.

11) [redacted]

Regarding efficacy in Part 2, Table 4 and Figure 1 show the results of the interim analysis of the dual primary endpoint of PFS as assessed by the BIRC per RECIST ver.1.1 (data cutoff on October 31, 2018) and the Kaplan-Meier curves, respectively. The superiority of nivolumab/IC over placebo/IC was demonstrated.

Table 4. Results of interim analysis of PFS (BIRC assessment, ITT population, data cutoff on October 31, 2018)

	Nivolumab/IC	Placebo/IC
N	362	362
No. of events (%)	141 (39.0)	184 (50.8)
Median [95% CI] (months)	10.45 [8.44, 14.75]	8.34 [6.97, 9.40]
Hazard ratio [95% CI]*1	0.68 [0.54, 0.85]*2	
P-value (two-sided)*3	0.0007	

*1 Stratified Cox proportional hazards model stratified by PD-L1 status[12] (TPS) (≥1% vs. <1% or indeterminate), ECOG PS (0 vs. 1), disease status (newly diagnosed vs. recurrent), and country (Japan vs. others)
*2 The 98.51% CI corresponding to the significance level for the interim analysis was [0.51, 0.90].
*3 Stratified log-rank test (the same stratification factors as the Cox proportional hazards model), two-sided significance level of 0.0149

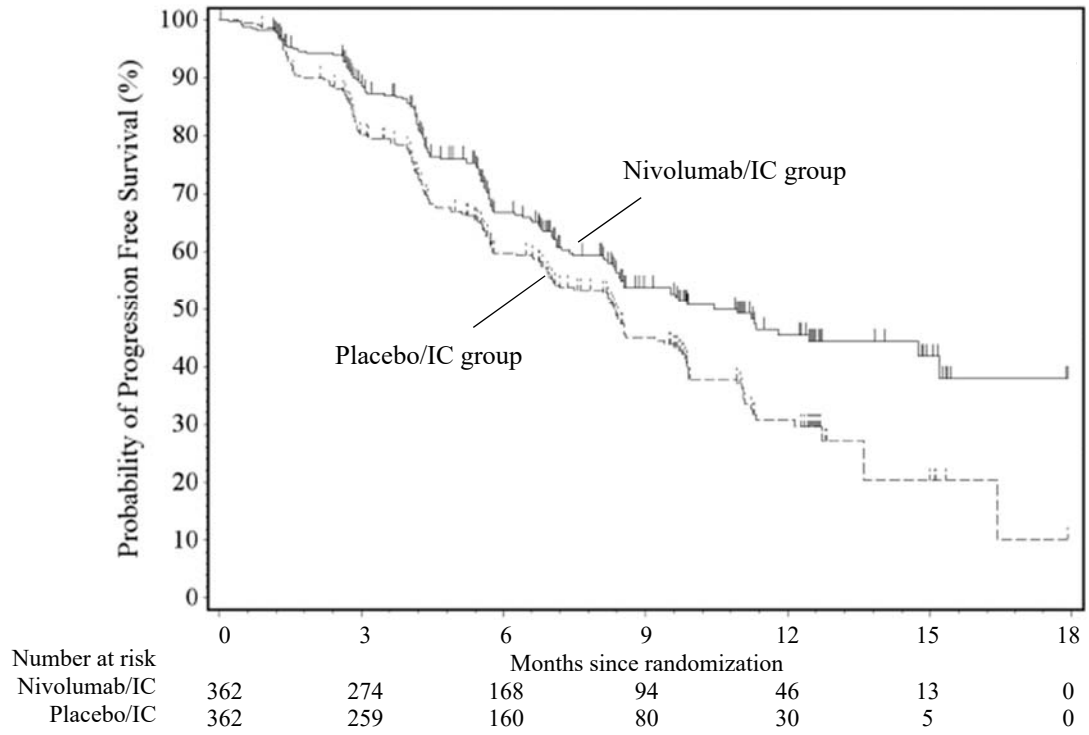

Figure 1. Kaplan-Meier curves for PFS at the time of interim analysis (BIRC assessment, ITT population, data cutoff on October 31, 2018)

Table 5 and Figure 2 show the results of the final analysis of the other dual primary endpoint of OS (data cutoff on January 31, 2020) and the Kaplan-Meier curves, respectively. The superiority of nivolumab/IC over placebo/IC was not demonstrated.

[12] PD-L1 status was determined by assay using the PD-L1 IHC 28-8 pharmDX (Dako) at a central laboratory.

Table 5. Results of final analysis of OS (ITT population, data cutoff on January 31, 2020)

	Nivolumab/IC	Placebo/IC
N	362	362
No. of events (%)	230 (63.5)	245 (67.7)
Median [95% CI] (months)	17.45 [15.67, 20.83]	17.15 [15.18, 19.65]
Hazard ratio [95% CI]*1	0.90 [0.75, 1.08]	
P-value (two-sided)*2	0.257	

*1 Stratified Cox proportional hazards model stratified by PD-L1 status[12] (TPS) (≥1% vs. <1% or indeterminate), ECOG PS (0 vs. 1), disease status (newly diagnosed vs. recurrent), and country (Japan vs. others)

*2 Stratified log-rank test (the same stratification factors as the Cox proportional hazards model), two-sided significance level of 0.05

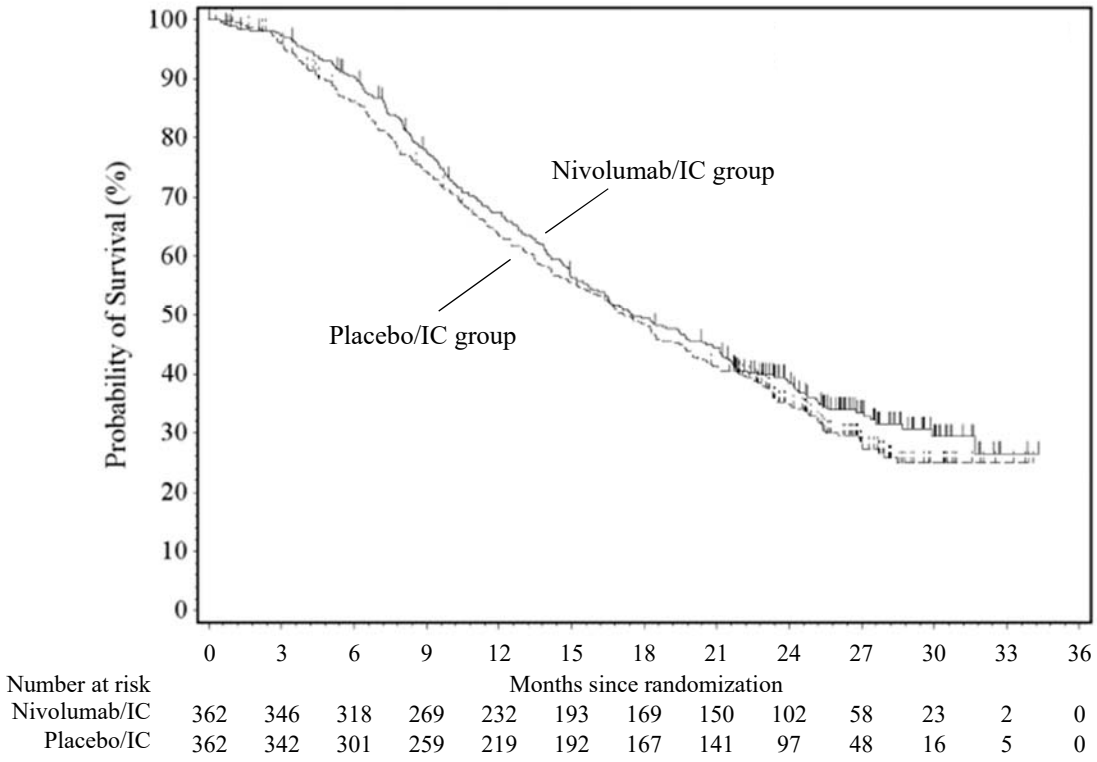

Figure 2. Kaplan-Meier curves for OS at the time of final analysis (ITT population, data cutoff on January 31, 2020)

Regarding safety, 15 of 359 subjects (4.2%) in the nivolumab/IC group and 20 of 358 subjects (5.6%) in the placebo/IC group died during the study treatment period or within 28 days after the last dose of study drug in Part 2 (including 7 Japanese patients in the nivolumab/IC group and 3 Japanese patients in the placebo/IC group). The causes of deaths other than disease progression (6 in the nivolumab/IC group, 13 in the placebo/IC group) were shock haemorrhagic; febrile neutropenia; subdural haematoma; sudden death; hepatic failure; disseminated intravascular coagulation; death; pneumonia; and meningitis (1 subject each) in the nivolumab/IC group and pneumonia (2 subjects); sepsis; cerebrovascular accident; respiratory failure; completed suicide; and haemolytic anaemia (1 subject each) in the placebo/IC group. A causal relationship to study drug could not be ruled out for febrile neutropenia; sudden death; and hepatic failure (1 subject each) in the nivolumab/IC group and sepsis; respiratory failure; and haemolytic anaemia (1 subject each) in the placebo/IC group (In Japanese patients who died due to adverse events, the causes of deaths were shock haemorrhagic; febrile neutropenia; subdural haematoma; and sudden death [1 subject each] in the nivolumab/IC group and sepsis in the placebo/IC group, and a causal relationship to study drug could not be ruled out for febrile neutropenia; and sudden death [1 subject each] in the nivolumab/IC group and sepsis in

the placebo/IC group). There were no deaths during the study treatment period or within 28 days after the last dose of study drug in Part 1.

7.1.1.1.2 Global phase III study (CTD 5.3.5.1-1, Study 44 [ongoing since October 2016 (data cutoff on May 27, 2020)])

A randomized, open-label study was conducted at 175 sites in 29 countries or regions including Japan to evaluate the efficacy and safety of nivolumab/IC[13] compared with IC in patients with HER2-negative,[14] unresectable, advanced or recurrent gastric cancer[15] previously untreated with chemotherapy[16] (target sample size, 2,005 subjects[17]). Although this study was initially a 2-arm study to evaluate the efficacy and safety of nivolumab/ipilimumab (IPI) compared with IC, as the results of Study CA209012[18] and the KEYNOTE-059 study[19] indicated that the efficacy of nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy is expected, the study design was modified to a 3-arm study including the nivolumab/IC group (Protocol Amendment Version 02, dated December 7, 2016). Then, in accordance with the Independent Data Monitoring Committee's recommendation based on [redacted], enrollment in the nivolumab/IPI group was closed on June 5, 2018[20] (Protocol Amendment Version [redacted], dated [redacted], 20[redacted]) (Unless otherwise specified, this review report describes the results from the nivolumab/IC and IC groups of Study 44).

Subjects in the nivolumab/IC group were to receive nivolumab 240 mg Q2W intravenously plus FOLFOX (fluorouracil + leucovorin + oxaliplatin) or nivolumab 360 mg Q3W intravenously plus CAPOX for a maximum of 24 months. Subjects in the IC group were to receive FOLFOX or CAPOX. Treatment was to be continued until disease progression or any withdrawal criterion was met.

All of 1,581 subjects who were enrolled in the study and randomized (789 in the nivolumab/IC group, 792 in the IC group) were included in the ITT population, which was used as the efficacy population (including 57 Japanese patients in the nivolumab/IC group and 52 Japanese patients in the IC group). After excluding 7 subjects in the nivolumab/IC group and 25 subjects in the IC group who did not receive study drug from the ITT population, 1,549 subjects (782 in the nivolumab/IC group, 767 in the IC group) were included in the safety population (including 57 Japanese patients in the nivolumab/IC group and 52 Japanese patients in the IC group).

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13) The investigator or subinvestigator was to choose FOLFOX or CAPOX.
14) HER2-positive patients (HER2 status was to be assessed using local laboratory criteria, local clinical practice guidelines, etc.) were excluded. Patients with indeterminate or undetermined HER2 status were allowed to be enrolled in the study.
15) Patients with gastroesophageal junction (Siewert type I-III) adenocarcinoma and patients with adenocarcinoma with epicenter in the esophagus were also allowed to be enrolled in the study.
16) In the case of recurrent disease, patients with the last regimen of neoadjuvant or adjuvant chemotherapy (including chemoradiotherapy or radiotherapy) completed ≥6 months before randomization were allowed to be enrolled in the study.
17) The total number of subjects in the nivolumab/IC, IC, and nivolumab/IPI groups combined
18) A foreign phase I/II study to evaluate the efficacy, safety. etc. of nivolumab/chemotherapy in chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC
19) A global phase II study to evaluate the efficacy and safety of pembrolizumab alone or in combination with chemotherapy (5-FU/CDDP or Cape/CDDP) in patients with unresectable, advanced or recurrent gastric cancer
20) By June 5, 2018, 409 patients had been enrolled in the nivolumab/IPI group.

The primary endpoint of the study was initially [redacted] in [redacted] population. Then, given that [redacted] showed [redacted] etc., PFS and the objective response rate as assessed by the BIRC per RECIST ver.1.1 were added as primary endpoints, and the primary analysis population was changed from [redacted] to [redacted] (Protocol Amendment Version 04, dated January 5, 2018). Since Study CA209032[21)] showed a trend towards higher efficacy in patients with a combined positive score (CPS) ≥5, etc., [redacted][22)] [redacted] as [redacted], taking account of [redacted], the target sample size was changed to [redacted][17)] (Protocol Amendment Version [redacted], dated [redacted], 20[redacted]). Then, since the results of the KEYNOTE-059 study, the KEYNOTE-061 study, etc. suggested that PD-L1 CPS may be better associated with the efficacy of nivolumab than tumor proportion score (TPS), the primary endpoints of the study were amended to PFS and OS in PD-L1 positive patients with CPS ≥5, and PFS and OS in CPS ≥1 patients and the ITT population, etc., were changed to secondary endpoints (Protocol Amendment Version 07, dated September 14, 2018). As [redacted], the target sample size was changed from [redacted] to 2,005[17)] (Protocol Amendment Version [redacted], dated [redacted], 20[redacted]). Moreover, since the results of the KEYNOTE-062 study[11)] etc. indicated that a longer follow-up is needed to evaluate the efficacy of nivolumab, the timing of analysis for PFS and OS was changed. For efficacy evaluation, the primary analysis of PFS and 1 interim analysis of OS were to be conducted when the last enrolled patient had been followed up for ≥12 months, and the final analysis of OS was to be conducted when the last enrolled patient had been followed up for ≥24 months (Protocol Amendment Version 09, dated September 16, 2019).

In order to adjust for the multiplicity of multiple endpoints and analysis populations, a two-sided alpha of 0.02 and a two-sided alpha of 0.03 were allocated to PFS and OS in the CPS ≥5 population, respectively, and the Bonferroni-based graphical approach was used to control the overall type I error rate of the study at a two-sided alpha level of 0.05 (Figure 3). Lan-DeMets α spending function with O'Brien-Fleming boundaries was used to control the type I error rate for an interim analysis.

21) A foreign phase I/II study to evaluate the efficacy, safety, etc. of nivolumab/IPI in patients with advanced solid tumors
22) [redacted]

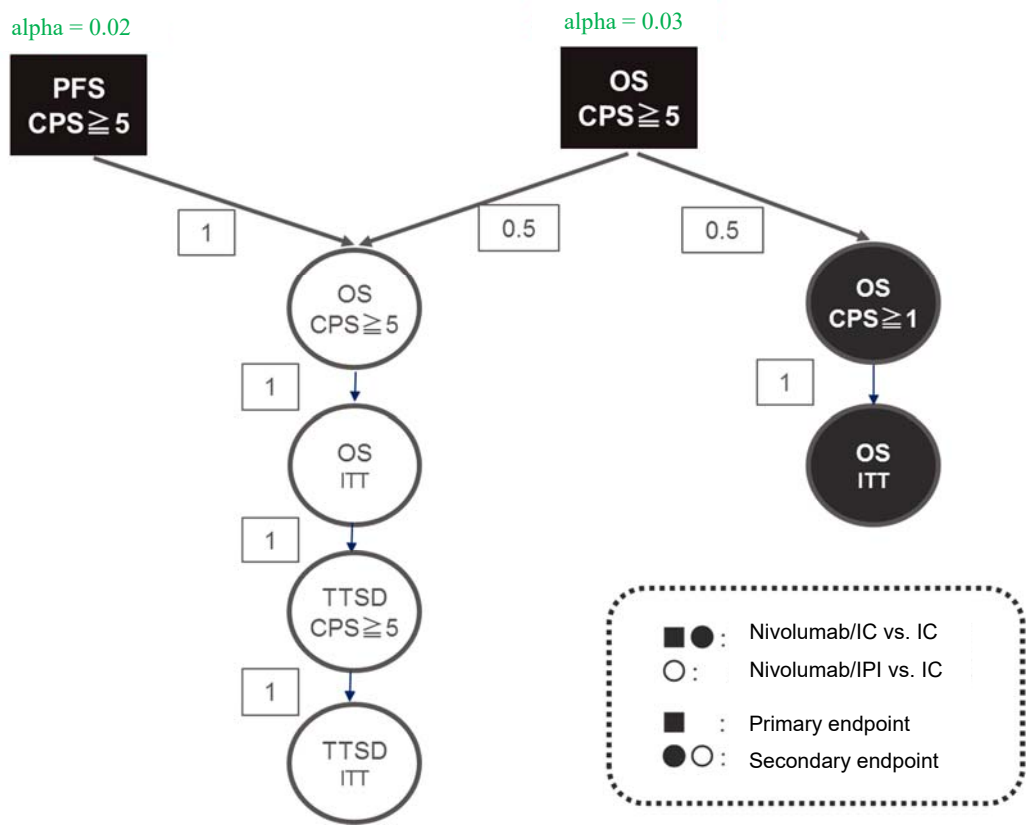

Figure 3. Testing procedure for OS and PFS and allocation of two-sided alpha

Regarding efficacy, Table 6 and Figure 4 show the results of the primary analysis of the dual primary endpoint of PFS as assessed by the BIRC per RECIST ver.1.1 in the CPS ≥5 population (data cutoff on May 27, 2020) and the Kaplan-Meier curves, respectively. The superiority of nivolumab/IC over IC was demonstrated.

Table 6. Results of primary analysis of PFS (BIRC assessment, CPS ≥5 population, data cutoff on May 27, 2020)

	Nivolumab/IC	IC
N	473	482
No. of events (%)	328 (69.3)	350 (72.6)
Median [95% CI] (months)	7.69 [7.03, 9.17]	6.05 [5.55, 6.90]
Hazard ratio [95% CI][*1]	0.68 [0.58, 0.79][*2]	
P-value (two-sided)[*3]	<0.0001	

*1, Stratified Cox proportional hazards model stratified by PD-L1 status[12)] (TPS) (≥1% vs. <1% or indeterminate), ECOG PS (0 vs. 1), IC (FOLFOX vs. CAPOX), and region (Asia vs. US/Canada vs. the rest of the world); *2, The 98% CI corresponding to the significance level for the interim analysis was [0.56, 0.81]. *3, Stratified log-rank test (the same stratification factors as the Cox proportional hazards model), two-sided significance level of 0.02

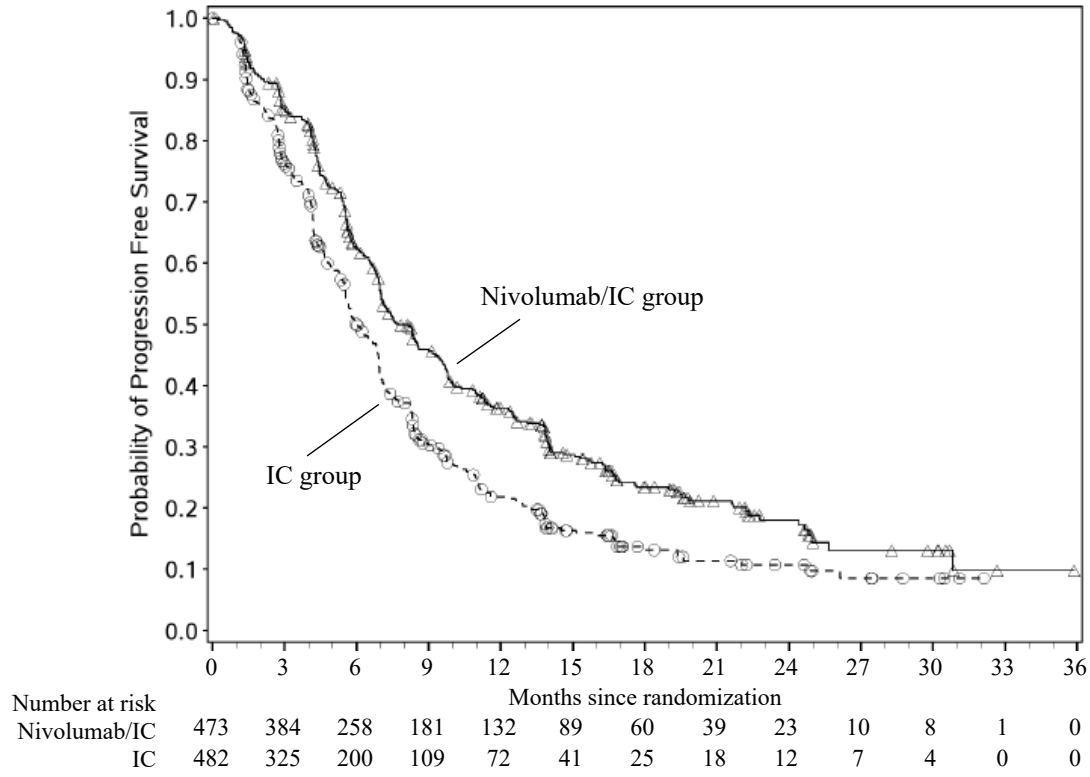

Figure 4. Kaplan-Meier curves for PFS at the time of primary analysis (BIRC assessment, CPS ≥5 population, data cutoff on May 27, 2020)

Table 7 and Figure 5 show the results of the interim analysis of the other dual primary endpoint of OS in the CPS ≥5 population (data cutoff on May 27, 2020) and the Kaplan-Meier curves, respectively. The superiority of nivolumab/IC over IC was demonstrated. In addition, when tested in accordance with the procedure and allocation of alpha presented in Figure 3, nivolumab/IC demonstrated a statistically significant improvement in OS in the CPS ≥1 population and in the ITT population versus IC (Table 7 and Figures 6 and 7).

Table 7. Results of interim analysis of OS (data cutoff on May 27, 2020)

Population	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio [95% CI]*1	*P*-value (two-sided)*5
CPS ≥5	Nivolumab/IC	473	309 (65.3)	14.39 [13.11, 16.23]	0.71 [0.61, 0.83]*2	<0.0001*6
	IC	482	362 (75.1)	11.10 [10.02, 12.09]		
CPS ≥1	Nivolumab/IC	641	434 (67.7)	13.96 [12.55, 14.98]	0.77 [0.68, 0.88]*3	<0.0001*7
	IC	655	492 (75.1)	11.33 [10.64, 12.25]		
ITT	Nivolumab/IC	789	544 (68.9)	13.83 [12.55, 14.55]	0.80 [0.71, 0.90]*4	0.0002*7
	IC	792	591 (74.6)	11.56 [10.87, 12.48]		

*1 Stratified Cox proportional hazards model stratified by PD-L1 status[12] (TPS) (≥1% vs. <1% or indeterminate), ECOG PS (0 vs. 1), IC (FOLFOX vs. CAPOX), and region (Asia vs. US/Canada vs. the rest of the world)
*2 The 98.4% CI corresponding to the significance level for the interim analysis was [0.59, 0.86].
*3 The 99.3% CI corresponding to the significance level for the interim analysis was [0.64, 0.92].
*4 The 99.3% CI corresponding to the significance level for the interim analysis was [0.68, 0.94].
*5 Stratified log-rank test (the same stratification factors as the Cox proportional hazards model)
*6 Two-sided significance level of 0.016
*7 Two-sided significance level of 0.007

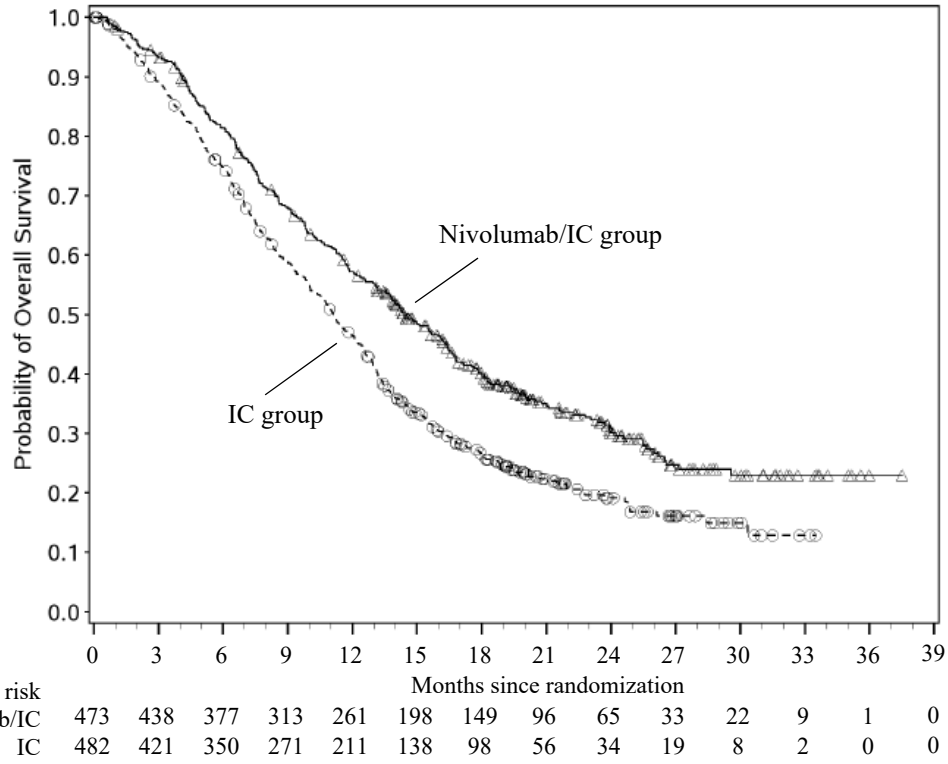

Figure 5. Kaplan-Meier curves for OS at the time of interim analysis (CPS ≥5 population, data cutoff on May 27, 2020)

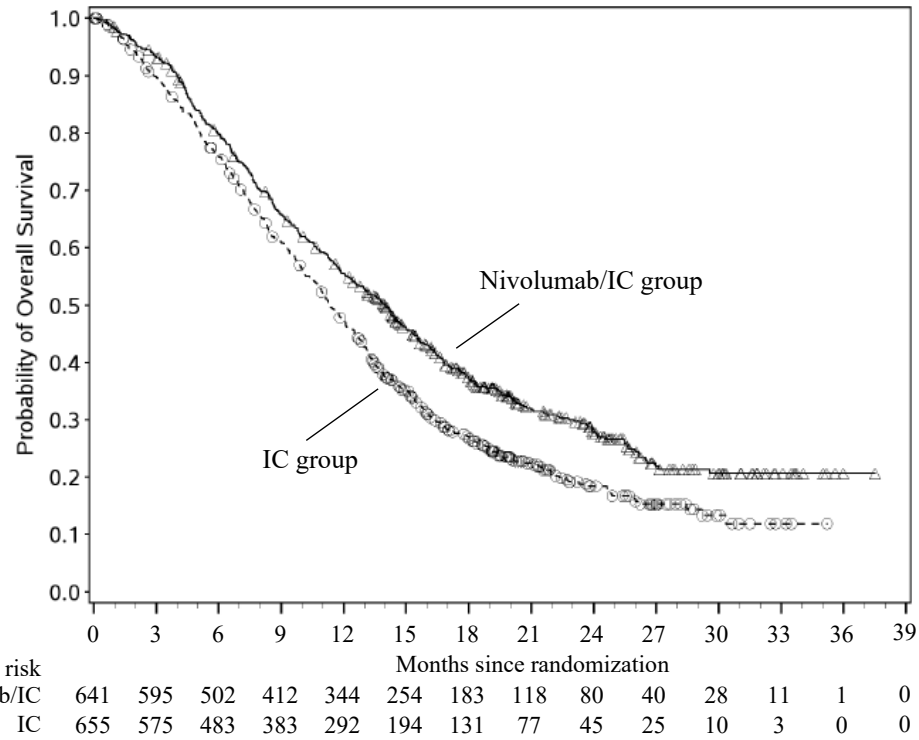

Figure 6. Kaplan-Meier curves for OS at the time of interim analysis (CPS ≥1 population, data cutoff on May 27, 2020)

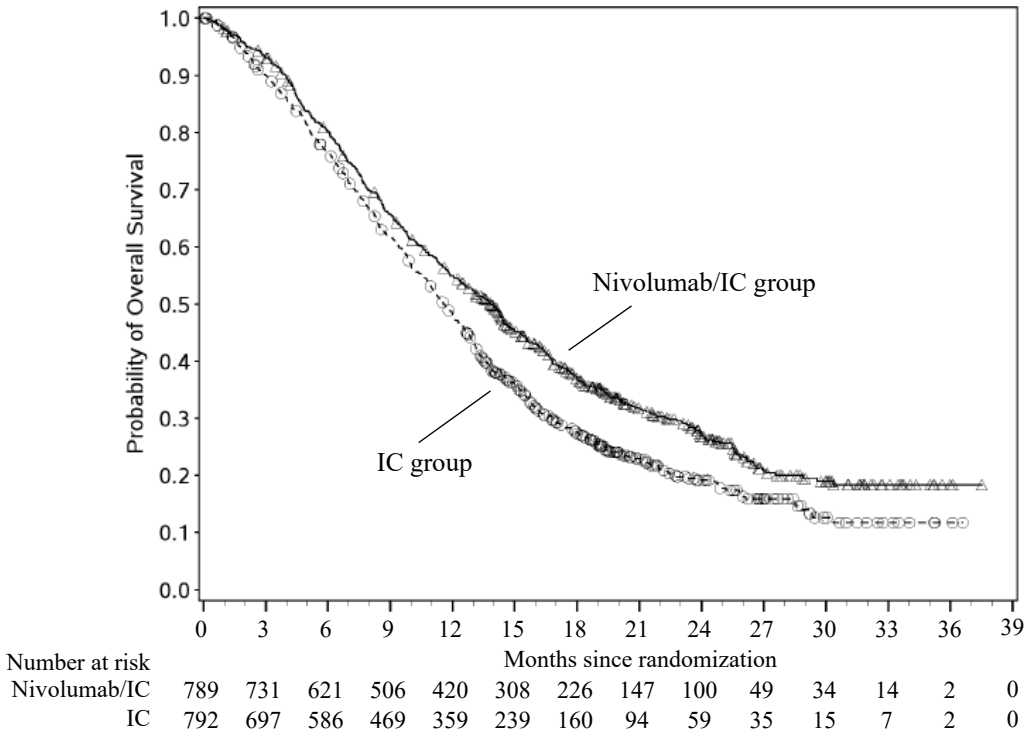

Figure 7. Kaplan-Meier curves for OS at the time of interim analysis (ITT population, data cutoff on May 27, 2020)

Regarding safety, 103 of 782 subjects (13.2%) in the nivolumab/IC group and 89 of 767 subjects (11.6%) in the IC group died during the study treatment period or within 30 days after the last dose of study drug (No Japanese patients died). The causes of deaths other than disease progression (67 in the nivolumab/IC group, 62 in the IC group) were malignant neoplasm progression; and pneumonia (3 subjects each); gastrointestinal haemorrhage; sudden death; cerebral infarction; febrile neutropenia; and myocardial infarction (2 subjects each); and sepsis and abdominal infection; lower respiratory tract infection and pulmonary embolism; intestinal lung disease (ILD); respiratory failure; thrombosis mesenteric vessel; pulmonary hypertension; diarrhoea; respiratory tract infection; hypovolaemic shock; embolism; intestinal perforation; acute myocardial infarction; septic shock; arrhythmia; pneumonia aspiration; pulmonary embolism; gastrointestinal inflammation; cerebrovascular accident; cardiac arrest; and pneumonitis (1 subject each) in the nivolumab/IC group and myocardial infarction (4 subjects); and asthenia and decreased appetite; gastric haemorrhage and ischaemic stroke; shock haemorrhagic; intracranial pressure increased; diarrhoea; arrhythmia; sudden death; chronic obstructive pulmonary disease; sepsis; venous thrombosis; cardio-respiratory arrest; acute cardiac failure; thrombotic microangiopathy; renal failure; cardiac arrest; diabetic metabolic decompensation; pulmonary embolism; malignant neoplasm progression; ILD; metastases to meninges; euthanasia; acute respiratory failure; and unknown (1 subject each) in the IC group. A causal relationship to study drug could not be ruled out for febrile neutropenia (2 subjects); and pneumonia; gastrointestinal haemorrhage; cerebral infarction; ILD; thrombosis mesenteric vessel; diarrhoea; septic shock; gastrointestinal inflammation; cerebrovascular accident; and pneumonitis (1 subject each) in the nivolumab/IC group and asthenia and decreased appetite; diarrhoea; pulmonary embolism; and ILD (1 subject each) in the IC group.

7.1.R Outline of the review conducted by PMDA

7.1.R.1 Review strategy

PMDA decided to focus its efficacy and safety reviews on the results from Studies 44 and 37 and evaluate the efficacy of nivolumab in Japanese patients systematically, based on Study 44, Study 37, etc., in accordance with "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Basic Principles on Global Clinical Trials (Reference Cases)" (PFSB/ELD 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), etc.

7.1.R.2 Efficacy

On the basis of the following considerations, PMDA concluded that the efficacy of nivolumab/IC was demonstrated in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy.

7.1.R.2.1 Choice of control group

The applicant's explanation about choice of a control group in Studies 44 and 37:

For the following reasons etc., either FOLFOX or CAPOX was chosen as a control group in Study 44, and either SOX or CAPOX was chosen as a control group in Study 37.

- The NCCN guidelines (gastric cancer) (v.3.2015) at the time of planning Studies 44 and 37 recommended fluoropyrimidine- and platinum-containing chemotherapy (5-FU/cisplatin [CDDP], capecitabine [Cape]/CDDP, FOLFOX, and CAPOX) as first-line treatment in patients with unresectable, advanced or recurrent gastric cancer.
- The Japanese clinical practice guidelines (gastric cancer) (2014, prompt report in May 2015) at the time of planning Studies 44 and 37 recommended S-1/CDDP, Cape/CDDP, SOX, and CAPOX as first-line treatment in patients with unresectable, advanced or recurrent gastric cancer.
- Multiple phase III clinical studies, meta-analysis, etc. reported no clear differences in PFS, OS, etc. between oxaliplatin (OX) plus a fluoropyrimidine and CDDP plus a fluoropyrimidine and a trend towards less hematologic toxicity with OX plus a fluoropyrimidine (*Ann Oncol*. 2015;26:141-8, *Gastric Cancer.* 2011;14:50-5, etc.).

PMDA accepted the applicant's explanation.

7.1.R.2.2 Efficacy endpoint and evaluation results

The applicant's explanation about the primary endpoints for Studies 44 and 37:

In multiple clinical studies that demonstrated improved PFS in patients with unresectable, advanced or recurrent gastric cancer, worsening of clinical symptoms and deterioration of quality of life (QOL) associated with disease progression were delayed (*J Clin Oncol.* 2007;25:3210-6, etc.). Thus, improved PFS in these patients is expected to preserve their QOL etc. and is considered clinically relevant. In addition, these patients are treated with the expectation of survival benefit. Given these points, PFS and OS were selected as the primary endpoints for Studies 44 and 37.

The applicant's explanation about the results of efficacy assessment of nivolumab/IC in Studies 44 and 37:

Study 44

The study demonstrated the superiority of nivolumab/IC over IC in the dual primary endpoint of PFS as assessed by the BIRC per RECIST ver.1.1 in the CPS ≥5 population [see Section 7.1.1.1.2].

The study demonstrated the superiority of nivolumab/IC over IC in the other dual primary endpoint of OS in the CPS ≥5 population. When tested in accordance with the pre-specified procedure and allocation of alpha (Figure 3), nivolumab/IC demonstrated a statistically significant improvement in OS also in the CPS ≥1 population and in the ITT population versus IC [see Section 7.1.1.1.2].

The hazard ratios [95% CI] of PFS for nivolumab/IC vs. IC by chemotherapy regimen in the control group of (a) FOLFOX or (b) CAPOX were (a) 0.67 [0.54, 0.83] and (b) 0.71 [0.57, 0.88] in the CPS ≥5 population. The hazard ratios [95% CI] of OS were (a) 0.71 [0.57, 0.88] and (b) 0.69 [0.55, 0.85] in the CPS ≥5 population, (a) 0.77 [0.64, 0.92] and (b) 0.75 [0.62, 0.90] in the CPS ≥1 population, and (a) 0.78 [0.66, 0.91] and (b) 0.81 [0.68, 0.96] in the ITT population (data cutoff on May 27, 2020). There were no differences affecting the assessment of efficacy of nivolumab/IC between FOLFOX and CAPOX chosen for the IC group.

In the Japanese subgroup of Study 44, Table 8 and Figure 8 show the results of the primary analysis of PFS and the Kaplan-Meier curves, respectively. Table 9 and Figures 9 to 11 show the results of the interim analysis of OS and the Kaplan-Meier curves, respectively.

Table 8. Study 44: Results of primary analysis of PFS in Japanese subgroup (BIRC assessment, CPS ≥5 population, data cutoff on May 27, 2020)

	Nivolumab/IC	IC
N	27	19
No. of events (%)	17 (63.0)	12 (63.2)
Median [95% CI] (months)	8.41 [5.39, 16.79]	10.87 [5.75, 13.77]
Hazard ratio [95% CI]*	1.13 [0.54, 2.37]	

* Unstratified Cox proportional hazards model

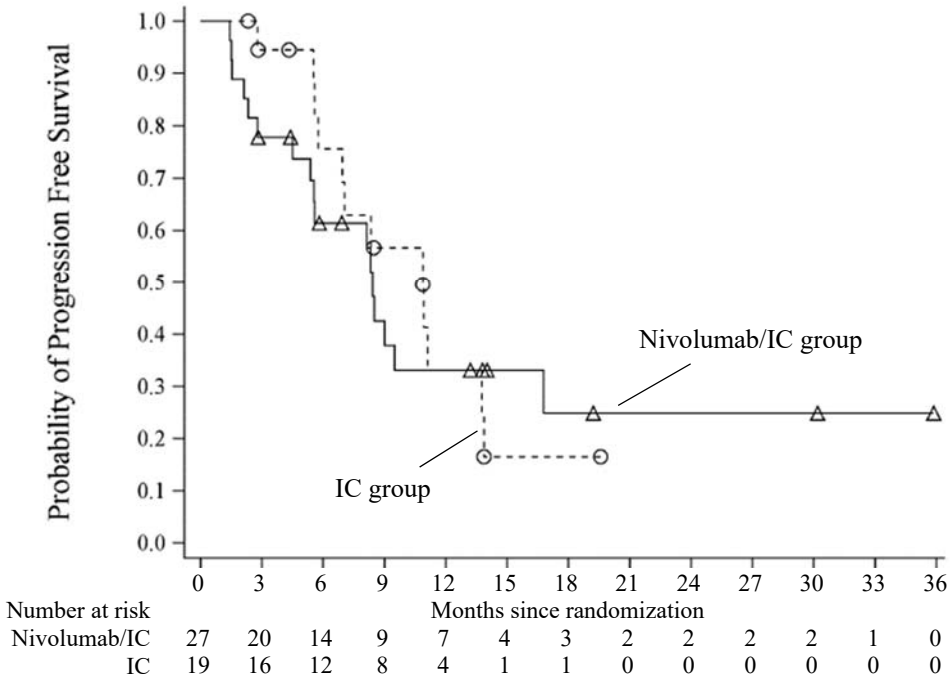

Figure 8. Study 44: Kaplan-Meier curves for PFS at the time of primary analysis in Japanese subgroup (BIRC assessment, CPS ≥5 population, data cutoff on May 27, 2020)

Table 9. Study 44: Results of interim analysis of OS in Japanese subgroup (data cutoff on May 27, 2020)

Population	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio [95% CI]*
CPS ≥5	Nivolumab/IC	27	19 (70.4)	16.10 [8.97, 23.95]	1.08 [0.52, 2.24]
	IC	19	12 (63.2)	16.23 [10.12, 21.06]	
CPS ≥1	Nivolumab/IC	41	29 (70.7)	16.13 [11.56, 20.21]	1.14 [0.64, 2.03]
	IC	33	19 (57.6)	16.23 [12.25, 21.06]	
ITT	Nivolumab/IC	57	37 (64.9)	17.02 [15.01, 23.95]	1.26 [0.76, 2.09]
	IC	52	26 (50.0)	17.05 [13.93, —]	

—, Not estimable; *, Unstratified Cox proportional hazards model

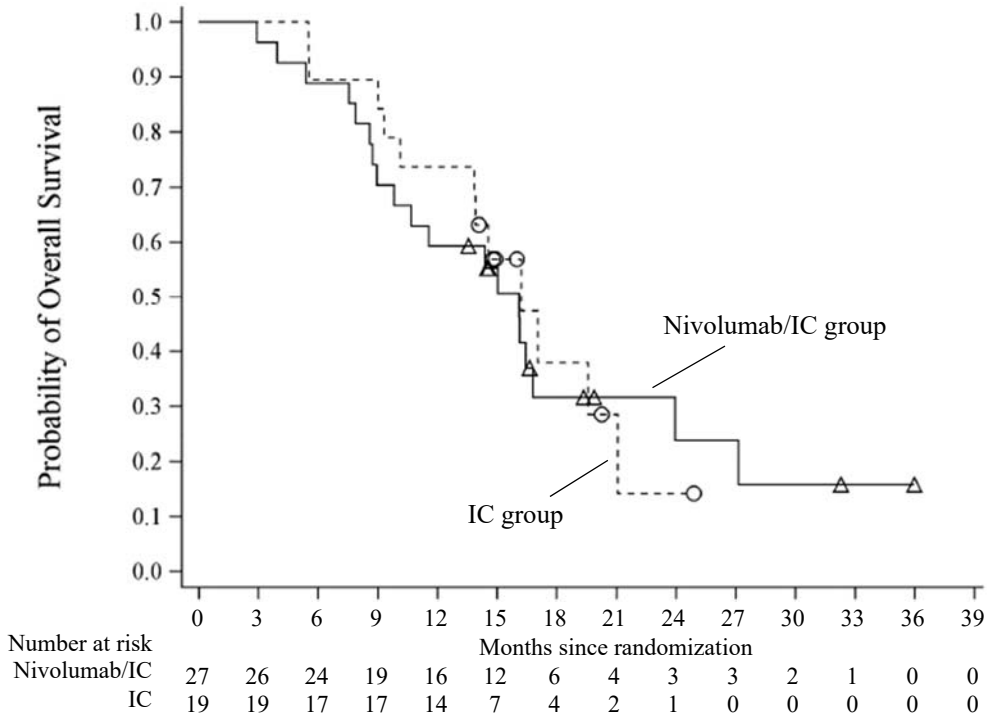

Figure 9. Study 44: Kaplan-Meier curves for OS at the time of interim analysis in Japanese subgroup (CPS ≥5 population, data cutoff on May 27, 2020)

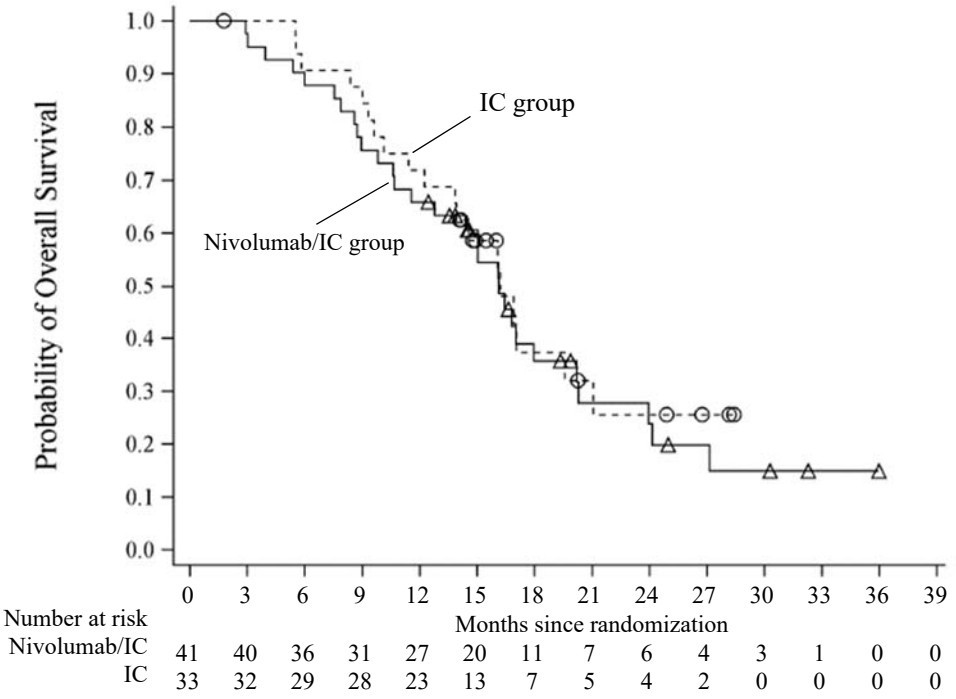

Figure 10. Study 44: Kaplan-Meier curves for OS at the time of interim analysis in Japanese subgroup (CPS ≥1 population, data cutoff on May 27, 2020)

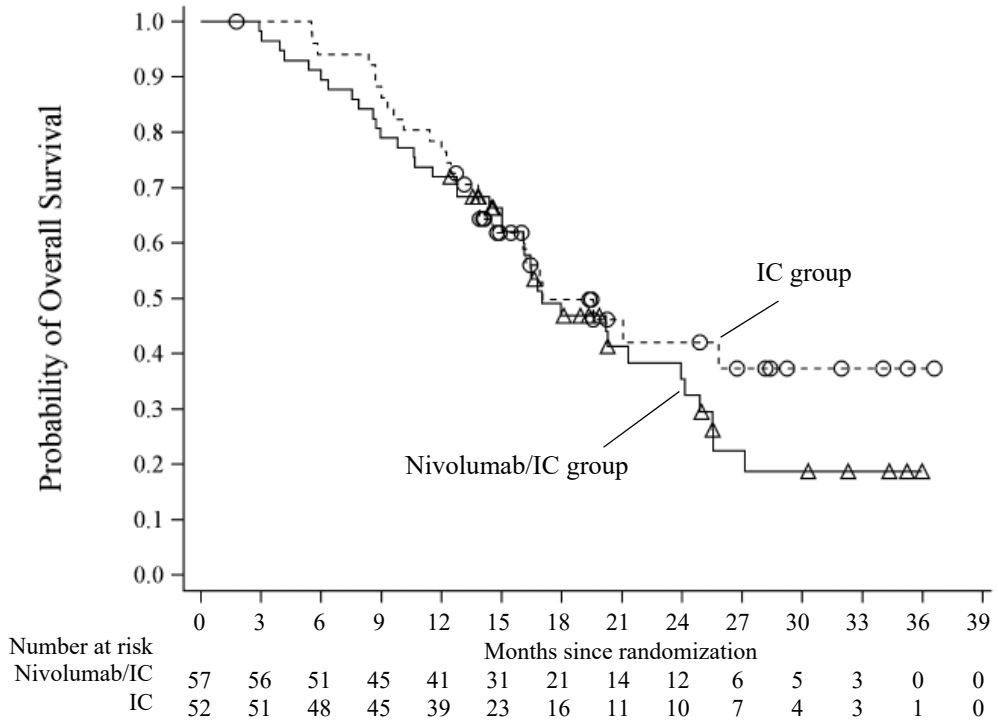

Figure 11. Study 44: Kaplan-Meier curves for OS at the time of interim analysis in Japanese subgroup (ITT population, data cutoff on May 27, 2020)

Study 37

The study demonstrated the superiority of nivolumab/IC over placebo/IC in the dual primary endpoint of PFS as assessed by the BIRC per RECIST ver.1.1 [see Section 7.1.1.1.1]. The hazard ratios [95% CI] of PFS for nivolumab/IC vs. placebo/IC by chemotherapy regimen in the control group (a) SOX or (b) CAPOX were (a) 0.68 [0.51, 0.90] and (b) 0.69 [0.47, 1.01] (data cutoff on October 31, 2018). There were no differences affecting the assessment of efficacy of nivolumab/IC between SOX and CAPOX chosen for the placebo/IC group.

There was no statistically significant improvement in the other dual primary endpoint of OS with nivolumab/IC compared with placebo/IC [see Section 7.1.1.1.1].

In the Japanese subgroup of Study 37, Table 10 and Figure 12 show the results of the interim analysis of PFS and the Kaplan-Meier curves, respectively. Table 11 and Figure 13 show the results of the final analysis of OS and the Kaplan-Meier curves, respectively.

Table 10. Study 37: Results of interim analysis of PFS in Japanese subgroup (BIRC assessment, ITT population, data cutoff on October 31, 2018)

	Nivolumab/IC	Placebo/IC
N	198	197
No. of events (%)	79 (39.9)	94 (47.7)
Median [95% CI] (months)	9.89 [8.11, —]	8.54 [7.06, 9.89]
Hazard ratio [95% CI]*	0.83 [0.62, 1.13]	

—, Not estimable; *, Unstratified Cox proportional hazards model

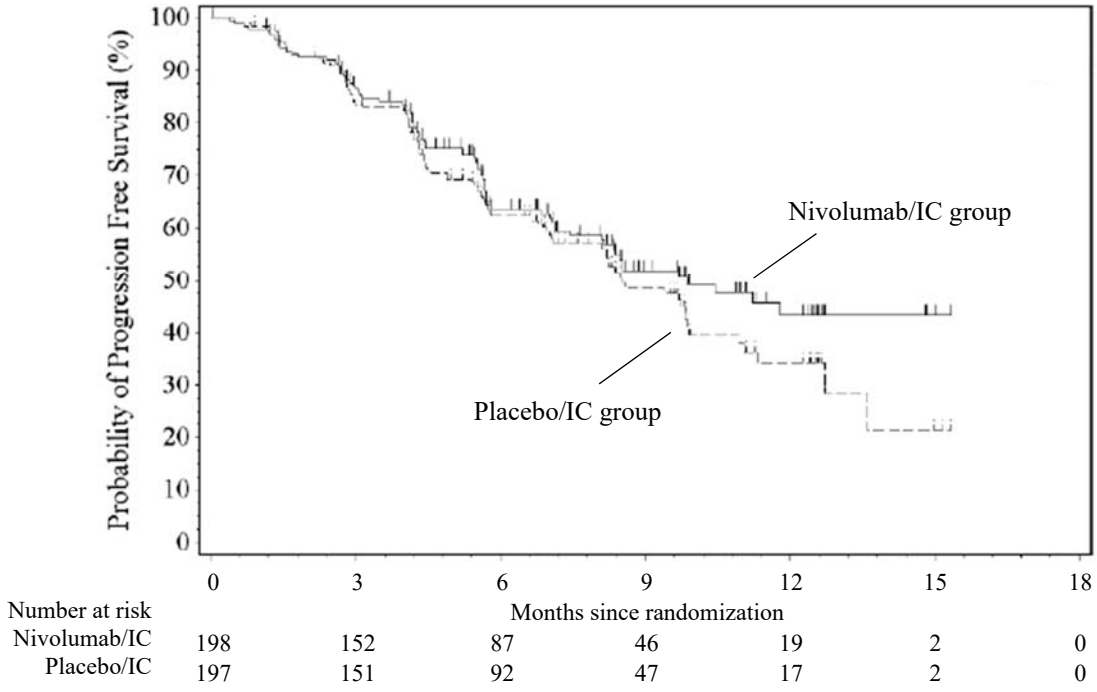

Figure 12. Study 37: Kaplan-Meier curves for PFS at the time of interim analysis in Japanese subgroup (BIRC assessment, ITT population, data cutoff on October 31, 2018)

Table 11. Study 37: Results of final analysis of OS in Japanese subgroup (ITT population, data cutoff on January 31, 2020)

	Nivolumab/IC	Placebo/IC
N	198	197
No. of events (%)	130 (65.7)	129 (65.5)
Median [95% CI] (months)	16.53 [14.65, 20.40]	19.12 [16.76, 22.54]
Hazard ratio [95% CI]*	1.04 [0.81, 1.32]	

* Unstratified Cox proportional hazards model

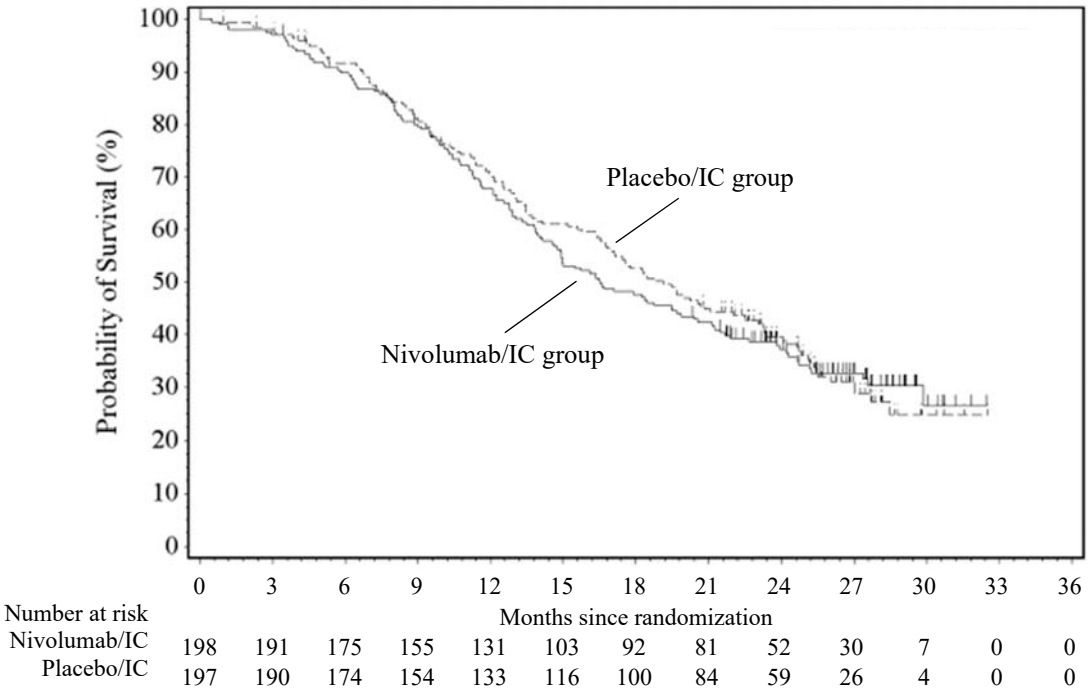

Figure 13. Study 37: Kaplan-Meier curves for OS at the time of final analysis in Japanese subgroup (ITT population, data cutoff on January 31, 2020)

The applicant's explanation about (a) the consistency of the results of OS between Studies 44 and 37, (b) the consistency of the results between the Japanese subgroup and the entire study population, and (c) the efficacy of nivolumab/IC in the patient population of Studies 44 and 37:

(a) Consistency of the results of OS between Studies 44 and 37

With respect to the dual primary endpoint of OS of Studies 44 and 37, Study 44 demonstrated a statistically significant improvement in OS for the nivolumab/IC group compared with the control group, but Study 37 did not. The applicant's view on its reason is described below.

In Study 44, 31.9% of patients received subsequent therapy, while 65.3% of patients received subsequent therapy in Study 37 (Tables 12 and 13). In the treatment of patients with unresectable, advanced or recurrent gastric cancer, an increase in the proportion of patients receiving subsequent therapies after disease progression has been reported to be associated with prolongation of post-progression survival (*Cancer Chemother Pharmacol*. 2018;81:981-9). In fact, the median OS was 17.45 months in the nivolumab/IC group and 17.15 months in the control group in Study 37 and 13.83 months in the nivolumab/IC group and 11.56 months in the control group in Study 44, showing a trend towards longer OS in Study 37 than in Study 44. It has been reported that in efficacy evaluation based on an OS benefit, as post-progression survival increases, the power for detecting an experimental treatment effect as a statistically significant difference in OS between treatment arms tends to decrease (*J Natl Cancer Inst.* 2009;101:1642-9). Taking also account of this finding, it seems that nivolumab/IC did not lead to a statistically significant improvement in OS compared with placebo/IC in Study 37 due to a higher proportion of patients receiving subsequent therapy in Study 37 than in Study 44, etc.

As to subsequent therapies, the Japanese and foreign clinical practice guidelines recommend paclitaxel and ramucirumab (PTX/RAM) as second-line treatment in patients with unresectable, advanced or recurrent gastric cancer (*Lancet Oncol*. 2014;15:1224-35), and nivolumab monotherapy has been approved as third- or later-line treatment in [redacted] countries or regions[23)] including Japan. The efficacy of these therapies has been demonstrated based on an OS benefit. Thus, it seems that receipt of subsequent therapies including nivolumab monotherapy made it difficult to detect an OS benefit of first-line nivolumab/IC.

Table 12. Study 44: Proportion of patients receiving subsequent therapy

	Entire population		Japanese patients		Non-Japanese patients	
	Nivolumab/IC N = 789	IC N = 792	Nivolumab/IC N = 57	IC N = 52	Nivolumab/IC N = 732	IC N = 740
Patients who received second-line therapy	235 (29.8)	269 (34.0)	41 (71.9)	35 (67.3)	194 (26.5)	234 (31.6)
Patients who received third-line therapy	64 (8.1)	91 (11.5)	15 (26.3)	16 (30.8)	49 (6.7)	75 (10.1)
Subsequent therapies received						
Nivolumab	6 (0.8)	28 (3.5)	2 (3.5)	14 (26.9)	4 (0.5)	14 (1.9)
Other immune checkpoint inhibitors	7 (0.9)	38 (4.8)	0	3 (5.8)	7 (1.0)	35 (4.7)

Table 13. Study 37: Proportion of patients receiving subsequent therapy

	Entire population		Japanese patients		Non-Japanese patients	
	Nivolumab/IC N = 362	Placebo/IC N = 362	Nivolumab/IC N = 198	Placebo/IC N = 197	Nivolumab/IC N = 164	Placebo/IC N = 165
Patients who received second-line therapy	232 (64.1)	241 (66.6)	141 (71.2)	150 (76.1)	91 (55.5)	91 (55.2)
Patients who received third-line therapy	102 (28.2)	140 (38.7)	63 (31.8)	103 (52.3)	39 (23.8)	37 (22.4)
Subsequent therapies received						
Nivolumab	39 (10.8)	92 (25.4)	31 (15.7)	83 (42.1)	8 (4.9)	9 (5.5)
Other immune checkpoint inhibitors	8 (2.2)	8 (2.2)	0	1 (0.5)	8 (4.9)	7 (4.2)

(b) Consistency of results between Japanese subgroup and entire study population

The applicant's view on the reasons for not obtaining consistent results of (i) OS or (ii) PFS between the entire population and the Japanese subgroup in Study 44:

(i) OS

Since the impact of the proportion of patients receiving subsequent therapy on OS is as described in the above (a), no consistent results between the entire population and the Japanese subgroup were obtained due to a higher proportion of patients receiving subsequent therapy in the Japanese subgroup than in the non-Japanese subgroup (Table 12).

(ii) PFS

In the Japanese subgroup (CPS ≥5 patients) of Study 44, while the hazard ratio [95% CI] of PFS as assessed by the BIRC was 1.13 [0.54, 2.37], the hazard ratio [95% CI] of PFS as assessed by the investigator was 0.76 [0.39, 1.49], which was consistent with the hazard ratio of PFS as assessed by the BIRC in the entire population

23) Nivolumab monotherapy has been approved as third- or later-line treatment in patients with unresectable, advanced or recurrent gastric cancer in the following countries or regions (Date of approval): Japan (September 2017), [redacted].

(CPS ≥5 patients) (0.68). Thus, differences in the assessment of disease progression between the BIRC and the investigator in the Japanese subgroup may have affected the consistency of the results between the Japanese subgroup and the entire population. In the PFS assessment in Study 44, the proportion of patients who started subsequent therapy before assessed as progressive disease (PD) by the BIRC and were thus censored was calculated. There were no clear differences between the nivolumab/IC and IC groups in the entire population (58 of 473 patients [12.3%] and 59 of 482 patients [12.2%], respectively). On the other hand, the proportion of such patients was higher in the IC group than in the nivolumab/IC group in the Japanese subgroup (5 of 19 patients [26.3%] and 5 of 27 patients [18.5%], respectively). It seems that these censored patients started subsequent therapy because disease progression was determined by the investigator (sub-investigator) based on clinical symptoms etc. before PD on the image was detected. The possibility of informative censoring (censoring potentially related to a PFS event) cannot be ruled out, and PFS in the IC group in the Japanese subgroup of Study 44 is potentially overestimated. When (A) these cases were handled as events at this time point or (B) these cases were not handled as events or censorings at this time point, the hazard ratios [95% CI] of PFS in the Japanese subgroup (CPS ≥5 patients) were (A) 1.01 [0.54, 1.91] and (B) 1.14 [0.58, 2.21].

(c) Efficacy of nivolumab/IC in the patient population of Studies 44 and 37

Given the following points etc. in addition to the above content in (a) and (b), the efficacy of nivolumab/IC is expected in the patient population of Studies 44 and 37 including Japanese patients.

- In the entire population of Study 44, nivolumab/IC demonstrated a statistically significant improvement in OS versus IC.
- In the entire population of Study 37, although there was no statistically significant improvement in OS with nivolumab/IC compared with placebo/IC, the hazard ratio was <1, showing a trend towards prolongation of OS.
- Though nivolumab monotherapy is a third-line option in Japan, improved PFS in the first-line treatment leads to the most favorable state of clinical symptoms of gastric cancer and contributes to preservation of the patient's QOL. The magnitude of the PFS benefit observed in the ITT population of Study 37 and in the CPS ≥5 population of Study 44 was clinically relevant.
- There were no clear differences in the PK and efficacy of nivolumab in the approved indications including unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, between Japanese and non-Japanese populations (see "Review Report on Opdivo Intravenous Infusion 20 mg and Opdivo Intravenous Infusion 100 mg, dated August 22, 2017" etc.).

PMDA's discussion:

As patients with unresectable, advanced or recurrent gastric cancer are treated with the expectation of survival benefit, demonstration of the OS benefit of nivolumab/IC in Study 44 is important for evaluating the efficacy of nivolumab/IC in the first-line treatment of these patients.

On the other hand, no consistent results of OS between the Japanese subgroup and the entire population in Study 44 were obtained, and it is difficult to conclude that nivolumab/IC led to an improvement in OS compared with placebo/IC in Study 37 in which Japanese patients accounted for 54.6% of the entire study

population. However, given that there were no clear differences in the PK and efficacy of nivolumab in the approved indications including unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy between Japanese and non-Japanese populations (see "Review Report on Opdivo Intravenous Infusion 20 mg and Opdivo Intravenous Infusion 100 mg, dated August 22, 2017" etc.), etc., the applicant's explanation (differences in the results of OS between the Japanese subgroup and the entire population of Study 44 and between the entire population of Study 37 and the entire population of Study 44 may have resulted from differences in the proportion of patients receiving subsequent therapy including nivolumab monotherapy that has demonstrated an OS benefit in the third-line or beyond) is understandable to a certain extent.

Under the situation where third-line nivolumab monotherapy has demonstrated an OS benefit, the applicant's explanation about the clinical relevance of administering nivolumab/IC with the expectation of a PFS benefit in the first-line treatment is also understandable to a certain extent, and PMDA decided to evaluate the efficacy of first-line nivolumab/IC, taking also account of the magnitude of the effect on PFS. With regard to PFS in Study 44, given the above analysis results after changing the handling of cases with possible informative censoring, etc., there are limitations to explaining the reason for not obtaining consistent results between the Japanese subgroup and the entire population, based only on differences in the distribution of these cases with censoring. Meanwhile, taking also into account that Study 37 showed consistent PFS results between the Japanese subgroup and the entire population, etc., PMDA concluded, based on the following points, that the results of Studies 44 and 37 showed the efficacy of nivolumab/IC in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy, including Japanese patients.

- Study 44 confirmed the efficacy of nivolumab/IC based on an OS benefit.
- Studies 37 and 44 demonstrated the superiority of nivolumab/IC over the control group (placebo/IC or IC) in terms of PFS, and the magnitude of the observed effects was clinically relevant to a certain extent [see Sections 7.1.1.1.1 and 7.1.1.1.2].
- Nivolumab/IC was not shown to be clearly inferior to the control group (placebo/IC or IC) in terms of OS in the entire population of Study 37 or in the Japanese subgroup of Study 44.

However, as Study 44 showed that the efficacy of nivolumab/IC tended to differ according to PD-L1 expression [see Section 7.1.1.1.2, Table 7 and Figures 5-7, etc.], the clinical positioning of nivolumab/IC by PD-L1 expression will be further discussed in Section "7.1.R.4.2 Clinical positioning of nivolumab and target population."

7.1.R.3 Safety [for adverse events, see Section "7.3.1 Adverse events etc. observed in clinical studies in patients with unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy"]

PMDA's conclusion:

On the basis of the following considerations, adverse events that require particular attention following administration of nivolumab/IC in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy are the events that were considered to require attention during

the review etc. of the applications for the approved indications.[24)] Attention should be paid to the possible occurrence of these adverse events during treatment with nivolumab.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with nivolumab, nivolumab/IC is tolerable in patients with gastric cancer as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and interruption of nivolumab and the concomitant antineoplastic drugs.

7.1.R.3.1 Safety profile of nivolumab

The applicant's explanation about the safety profile of nivolumab/IC based on safety information from Studies 44 and 37:

Table 14 summarizes safety data from Studies 44 and 37.

Table 14. Summary of safety data (Studies 44 and 37)

	n (%)			
	Study 44		Study 37	
	Nivolumab/IC N = 782	IC N = 767	Nivolumab/IC N = 359	Placebo/IC N = 358
All adverse events	776 (99.2)	752 (98.0)	358 (99.7)	357 (99.7)
Grade ≥3 adverse events	621 (79.4)	519 (67.7)	257 (71.6)	232 (64.8)
Adverse events leading to death	137 (17.5)	111 (14.5)	10 (2.8)	8 (2.2)
Serious adverse events	423 (54.1)	335 (43.7)	135 (37.6)	120 (33.5)
Adverse events leading to treatment discontinuation*1	371 (47.4)	251 (32.7)	130 (36.2)	93 (26.0)
Nivolumab or placebo	—	—	63 (17.5)	33 (9.2)
S-1, Cape, 5-FU, LV, or OX	—	—	115 (32.0)	87 (24.3)
Adverse events leading to dose interruption*1	513 (65.6)	380 (49.5)	297 (82.7)	284 (79.3)
Nivolumab or placebo	—	—	134 (37.3)	122 (34.1)
S-1, Cape, 5-FU, LV, or OX	—	—	296 (82.5)	282 (78.8)
Adverse events leading to dose reduction*2	317 (40.5)	296 (38.6)	125 (34.8)	121 (33.8)

—, Unknown because information by drug was not collected in Study 44; *1, Adverse events leading to discontinuation or interruption of any study drug; *2, Adverse events leading to dose reduction of S-1, Cape, 5-FU, LV, or OX

In Study 44, there were no adverse events of any grade reported at a ≥10% higher incidence in the nivolumab/IC group than in the IC group. Grade ≥3 adverse events reported at a ≥3% higher incidence in the nivolumab/IC group than in the IC group were neutropenia (132 subjects [16.9%] in the nivolumab/IC group, 100 subjects [13.0%] in the IC group), anaemia (86 subjects [11.0%], 56 subjects [7.3%]), and lipase increased (55 subjects [7.0%], 28 subjects [3.7%]). Adverse events leading to study drug interruption reported at a ≥3% higher incidence in the nivolumab/IC group than in the IC group were neutropenia (132 subjects [16.9%], 98 subjects [12.8%]), neutrophil count decreased (84 subjects [10.7%], 53 subjects [6.9%]), and thrombocytopenia (64 subjects [8.2%], 38 subjects [5.0%]). There were no adverse events leading to death, serious adverse events, adverse events leading to study drug discontinuation, or adverse events leading to dose

[24)] ILD; hepatic function disorder; abnormal thyroid function; pituitary dysfunction; infusion reaction; skin disorder; colitis, enteritis, and severe diarrhoea; myasthenia gravis, myocarditis, rhabdomyolysis, and myositis; neurological disorder; renal disorder; venous thromboembolism; adrenal disorder; encephalitis; type 1 diabetes mellitus; serious blood disorder; cardiac disorder; tuberculosis, and pancreatitis (see "Review Report on Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 120 mg, and Opdivo Intravenous Infusion 240 mg, dated July 13, 2021" etc.)

reduction of study drug that were reported at a ≥3% higher incidence in the nivolumab/IC group than in the IC group.

In Study 37, adverse events of any grade reported at a ≥10% higher incidence in the nivolumab/IC group than in the placebo/IC group were rash (61 subjects [17.0%] in the nivolumab/IC group, 21 subjects [5.9%] in the placebo/IC group) and pruritus (60 subjects [16.7%], 20 subjects [5.6%]). Grade ≥3 adverse events reported at a ≥3% higher incidence in the nivolumab/IC group than in the placebo/IC group were neutrophil count decreased (71 subjects [19.8%], 58 subjects [16.2%]). Adverse events leading to study drug interruption reported at a ≥3% higher incidence in the nivolumab/IC group than in the placebo/IC group were neutrophil count decreased (137 subjects [38.2%], 119 subjects [33.2%]), decreased appetite (62 subjects [17.3%], 43 subjects [12.0%]), and pneumonia (18 subjects [5.0%], 7 subjects [2.0%]). Adverse events leading to dose reduction of study drug reported at a ≥3% higher incidence in the nivolumab/IC group than in the placebo/IC group were nausea (21 subjects [5.8%], 9 subjects [2.5%]). There were no adverse events leading to death, serious adverse events, or adverse events leading to study drug discontinuation that were reported at a ≥3% higher incidence in the nivolumab/IC group than in the placebo/IC group.

The applicant's explanation about differences in safety profile between Studies 44 and 37 and chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC (Part 1b[25)] of Study 227 and Study 9LA[26)]) (the previously approved indication for which nivolumab [360 mg Q3W] was administered in combination with other antineoplastic drugs, as in Studies 44 and 37):
Table 15 shows the results of comparison of the incidence of adverse events among the nivolumab/IC groups of Studies 44 and 37, the nivolumab/chemotherapy [27)] group of Study 227, and the nivolumab/IPI/chemotherapy[28)] group of Study 9LA.

Table 15. Summary of safety data (Studies 44, 37, 227, and 9LA)

	n (%)			
	Gastric cancer (Study 44)	Gastric cancer (Study 37)	NSCLC (Study 227)	NSCLC (Study 9LA)
	Nivolumab/IC N = 782	Nivolumab/IC N = 359	Nivolumab/chemotherapy N = 172	Nivolumab/IPI/chemotherapy N = 358
All adverse events	776 (99.2)	358 (99.7)	172 (100)	355 (99.2)
Grade ≥3 adverse events	621 (79.4)	257 (71.6)	130 (75.6)	249 (69.6)
Adverse events leading to death	137 (17.5)	10 (2.8)	25 (14.5)	51 (14.2)
Serious adverse events	423 (54.1)	135 (37.6)	91 (52.9)	203 (56.7)
Adverse events leading to treatment discontinuation*	371 (47.4)	130 (36.2)	42 (24.4)	100 (27.9)
Adverse events leading to dose interruption*	513 (65.6)	297 (82.7)	106 (61.6)	194 (54.2)

* Adverse events leading to discontinuation or interruption of any study drug because information by drug was not collected in Studies 44, 227, and 9LA.

Adverse events of any grade reported at a ≥10% higher incidence in both Studies 44 and 37 than in both Studies 227 and 9LA were diarrhoea (308 subjects [39.4%] in Study 44, 144 subjects [40.1%] in Study 37, 38 subjects

25) The PD-L1-negative cohort of a global phase III study to evaluate the efficacy and safety of nivolumab/chemotherapy vs. chemotherapy alone, etc., in chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC
26) A global phase III study to compare the efficacy and safety of nivolumab/IPI/chemotherapy vs. chemotherapy alone in chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC
27) (a) CBDCA/GEM or CDDP/GEM, or (b) CBDCA/PEM or CDDP/PEM
28) (a) CBDCA/PTX, or (b) CBDCA/PEM or CDDP/PEM

[22.1%] in Study 227, 105 subjects [29.3%] in Study 9LA), peripheral neuropathy (232 subjects [29.7%], 51 subjects [14.2%], 4 subjects [2.3%], 12 subjects [3.4%]), AST increased (157 subjects [20.1%], 69 subjects [19.2%], 15 subjects [8.7%], 23 subjects [6.4%]), abdominal pain (151 subjects [19.3%], 61 subjects [17.0%], 10 subjects [5.8%], 24 subjects [6.7%]), peripheral sensory neuropathy (143 subjects [18.3%], 201 subjects [56.0%], 5 subjects [2.9%], 6 subjects [1.7%]), and palmar-plantar erythrodysaesthesia syndrome (103 subjects [13.2%], 53 subjects [14.8%], 0 subjects, 0 subjects). There were no Grade ≥3 adverse events, adverse events leading to death, or serious adverse events that were reported at a ≥3% higher incidence in both Studies 44 and 37 than in both Studies 227 and 9LA. There were no adverse events leading to discontinuation or interruption of study drug that were reported at a ≥5% higher incidence in both Studies 44 and 37 than in both Studies 227 and 9LA.

PMDA's discussion:
Although the incidences of some adverse events were higher in the nivolumab/IC group than in the control group (the IC group or the placebo/IC group) in Studies 44 and 37, all those events were known adverse events associated with nivolumab or IC. Although the incidences of some adverse events were higher in patients with gastric cancer than in NSCLC patients, all those events were known adverse events associated with nivolumab or the concomitant antineoplastic drugs, and there were no clear differences in the incidence of serious adverse events. Given these findings etc., nivolumab/IC is tolerable in patients with gastric cancer as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and interruption of nivolumab and the concomitant antineoplastic drugs.

7.1.R.3.2 Differences in safety between Japanese and non-Japanese populations

The applicant's explanation about differences in the safety of nivolumab/IC between Japanese and non-Japanese populations, based on safety information from Studies 44 and 37:

Table 16 summarizes safety data from Japanese and non-Japanese patients in the nivolumab/IC groups of Studies 44 and 37.

Table 16. Summary of safety data (nivolumab/IC groups of Studies 44 and 37)

	n (%)			
	Study 44		Study 37	
	Japanese patients N = 57	Non-Japanese patients N = 725	Japanese patients N = 195	Non-Japanese patients N = 164
All adverse events	57 (100)	719 (99.2)	195 (100)	163 (99.4)
Grade ≥3 adverse events	33 (57.9)	588 (81.1)	133 (68.2)	124 (75.6)
Adverse events leading to death	0	137 (18.9)	4 (2.1)	6 (3.7)
Serious adverse events	23 (40.4)	400 (55.2)	72 (36.9)	63 (38.4)
Adverse events leading to treatment discontinuation*1	26 (45.6)	345 (47.6)	65 (33.3)	65 (39.6)
Nivolumab or placebo	—	—	36 (18.5)	27 (16.5)
S-1, Cape, 5-FU, LV, or OX	—	—	54 (27.7)	61 (37.2)
Adverse events leading to dose interruption*1	39 (68.4)	474 (65.4)	173 (88.7)	124 (75.6)
Nivolumab or placebo	—	—	77 (39.5)	57 (34.8)
S-1, Cape, 5-FU, LV, or OX	—	—	173 (88.7)	123 (75.0)
Adverse events leading to dose reduction*2	45 (78.9)	272 (37.5)	66 (33.8)	59 (36.0)

—, Unknown because information by drug was not collected in Study 44; *1, Adverse events leading to discontinuation or interruption of any study drug; *2, Adverse events leading to dose reduction of S-1, Cape, 5-FU, LV, or OX

In Study 44, adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were peripheral sensory neuropathy (37 subjects [64.9%] in the Japanese subgroup, 106 subjects [14.6%] in the non-Japanese subgroup), decreased appetite (35 subjects [61.4%], 189 subjects [26.1%]), neutrophil count decreased (26 subjects [45.6%], 144 subjects [19.9%]), platelet count decreased (20 subjects [35.1%], 148 subjects [20.4%]), palmar-plantar erythrodysaesthesia syndrome (19 subjects [33.3%], 84 subjects [11.6%]), malaise (13 subjects [22.8%], 39 subjects [5.4%]), peripheral oedema (12 subjects [21.1%], 74 subjects [10.2%]), nasopharyngitis (8 subjects [14.0%], 22 subjects [3.0%]), and liver disorder (6 subjects [10.5%], 0 subjects). Grade ≥3 adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (15 subjects [26.3%], 75 subjects [10.3%]). Serious adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were overdose (4 subjects [7.0%], 7 subjects [1.0%]) and enterocolitis (3 subjects [5.3%], 1 subject [0.1%]). Adverse events leading to study drug discontinuation reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were peripheral sensory neuropathy (12 subjects [21.1%], 23 subjects [3.2%]). Adverse events leading to study drug interruption reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (13 subjects [22.8%], 71 subjects [9.8%]), diarrhoea (7 subjects [12.3%], 32 subjects [4.4%]), peripheral sensory neuropathy (4 subjects [7.0%], 5 subjects [0.7%]), enterocolitis (3 subjects [5.3%], 1 subject [0.1%]), and nasopharyngitis (3 subjects [5.3%], 0 subjects). Adverse events leading to dose reduction of study drug reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (16 subjects [28.1%], 32 subjects [4.4%]), decreased appetite (14 subjects [24.6%], 2 subjects [0.3%]), platelet count decreased (11 subjects [19.3%], 31 subjects [4.3%]), palmar-plantar erythrodysaesthesia syndrome (10 subjects [17.5%], 19 subjects [2.6%]), diarrhoea (9 subjects [15.8%], 20 subjects [2.8%]), nausea (7 subjects [12.3%], 13 subjects [1.8%]), and peripheral sensory neuropathy (6 subjects [10.5%], 14 subjects [1.9%]). There were no adverse events leading to death reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

In Study 37, adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were peripheral sensory neuropathy (148 subjects [75.9%] in the Japanese subgroup, 53 subjects [32.3%] in the non-Japanese subgroup), decreased appetite (131 subjects [67.2%], 78 subjects [47.6%]), platelet count decreased (99 subjects [50.8%], 51 subjects [31.1%]), neutrophil count decreased (98 subjects [50.3%], 59 subjects [36.0%]), constipation (80 subjects [41.0%], 40 subjects [24.4%]), malaise (61 subjects [31.3%], 0 subjects), dysgeusia (58 subjects [29.7%], 1 subject [0.6%]), white blood cell count decreased (58 subjects [29.7%], 20 subjects [12.2%]), hiccups (32 subjects [16.4%], 4 subjects [2.4%]), dry skin (24 subjects [12.3%], 3 subjects [1.8%]), and vascular pain (22 subjects [11.3%], 1 subject [0.6%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were decreased appetite (25 subjects [12.8%], 4 subjects [2.4%]). Serious adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were decreased appetite (18 subjects [9.2%], 1 subject [0.6%]). Adverse events leading to study drug interruption reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (88 subjects [45.1%], 49 subjects [29.9%]), platelet count decreased (59 subjects [30.3%], 32 subjects [19.5%]), decreased appetite (54 subjects [27.7%], 8 subjects [4.9%]), diarrhoea (34 subjects [17.4%], 9 subjects [5.5%]), nausea (33 subjects [16.9%], 9 subjects [5.5%]), white blood cell count decreased (26 subjects [13.3%], 5 subjects [3.0%]), peripheral sensory neuropathy (24 subjects [12.3%], 9 subjects [5.5%]), and malaise (13 subjects [6.7%], 0 subjects). Adverse events leading to dose reduction of study drug reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were decreased appetite (25 subjects [12.8%], 3 subjects [1.8%]). There were no adverse events leading to death or study drug discontinuation that were reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

PMDA's discussion:

Although the incidences of some adverse events were higher in Japanese patients than in non-Japanese patients in Studies 44 and 37, given the following points etc., nivolumab/IC is tolerable also in Japanese patients as long as appropriate measures, e.g. interruption of nivolumab and the concomitant antineoplastic drugs, are taken.

- All of the adverse events reported at a higher incidence in Japanese patients than in non-Japanese patients were known adverse events associated with nivolumab or the concomitant antineoplastic drugs.
- There was no trend towards clearly higher incidences of adverse events leading to death and serious adverse events in Japanese patients than in non-Japanese patients.

7.1.R.4 Clinical positioning and dosage and administration

In the present partial change application for gastric cancer, the proposed dosage and administration was "The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. <u>When administered in combination with other antineoplastic drugs, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 360 mg administered as an intravenous infusion every 3 weeks."</u> (Underline denotes additions to the approved content.). The following statements

were included in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section of the proposed package insert.

- Opdivo should be intravenously infused over at least 30 minutes (the same as the approved content).
- The efficacy and safety of Opdivo monotherapy have not been established in first- or second-line treatment.
- When Opdivo is administered in combination with other antineoplastic drugs, other antineoplastic drugs to be combined should be selected based on a careful review of the content of the "CLINICAL STUDIES" section.

On the basis of Sections "7.1.R.2 Efficacy" and "7.1.R.3 Safety" and the considerations in the following section, PMDA concluded that the following statements should be included in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section, and then the proposed dosage and administration is appropriate.

- Opdivo should be intravenously infused over at least 30 minutes (the same as the approved content).
- The efficacy and safety of Opdivo monotherapy have not been established in first- or second-line treatment.
- When administered in combination with other antineoplastic drugs, Opdivo should be used in HER2-negative patients.
- The efficacy of Opdivo in combination with other antineoplastic drugs tends to differ according to the percentage of PD-L1 expression (CPS). The necessity of the addition of Opdivo should be carefully determined based on a careful review of the content of the "CLINICAL STUDIES" section, particularly regarding CPS, and a thorough understanding of the efficacy and safety of Opdivo.
- When administered in combination with other antineoplastic drugs, other antineoplastic drugs to be combined should be selected based on a careful review of the content of the "CLINICAL STUDIES" section.

7.1.R.4.1 Dosage and administration of nivolumab

The applicant's explanation about the dosing rationale for nivolumab in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy:

Since Studies 44 and 37 in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy demonstrated the clinical usefulness of nivolumab 240 mg Q2W or 360 mg Q3W in combination with IC [see Sections 7.1.R.2 and 7.1.R.3], the dosing regimen in the present partial change application was selected based on these 2 studies. The "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section will advise that other antineoplastic drugs to be combined with Opdivo should be selected based on a careful review of the content of the "CLINICAL STUDIES" section.

On the basis of the above, the following statements were included in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section of the proposed package insert, and then the dosage and administration statement was proposed as follows: "The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. When administered in combination with other antineoplastic drugs, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 360 mg administered as an intravenous infusion every 3 weeks."

- Opdivo should be intravenously infused over at least 30 minutes (the same as the approved content).
- When Opdivo is administered in combination with other antineoplastic drugs, other antineoplastic drugs to be combined should be selected based on a careful review of the content of the "CLINICAL STUDIES" section.

PMDA's discussion:
PMDA largely accepted the above explanation by the applicant and concluded that the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section should be modified as follows, and then the proposed dosage and administration statement is appropriate.

- Opdivo should be intravenously infused over at least 30 minutes (the same as the approved content).
- When administered in combination with other antineoplastic drugs, other antineoplastic drugs to be combined should be selected based on a careful review of the content of the "CLINICAL STUDIES" section.

7.1.R.4.2 Clinical positioning of nivolumab and target population

Nivolumab for patients with unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy is described as follows in the major Japanese/foreign clinical practice guidelines and textbook of clinical oncology.

Clinical practice guidelines

- NCCN guidelines (gastric cancer) (v.4.2021)
  - Nivolumab plus fluoropyrimidine (5-FU or Cape) and OX is strongly recommended as first-line treatment in patients with HER2-negative, unresectable, advanced gastric cancer with PD-L1 CPS ≥5 (Category 1).
  - Nivolumab plus fluoropyrimidine (5-FU or Cape) and OX is a first-line treatment option for patients with HER2-negative, unresectable, advanced gastric cancer with PD-L1 CPS 1 to 4 (Category 2B).
- Japanese clinical practice guidelines (gastric cancer) (2021)
  The results of comparative studies showing the usefulness of nivolumab/chemotherapy for the first-line treatment of unresectable, advanced or recurrent gastric cancer (Studies 44 and 37) have been reported.

The applicant's explanation about the clinical poisoning of nivolumab and the target population:
Since Studies 44 and 37 in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy demonstrated the following results etc., nivolumab/IC is recommended as first-line treatment in these patients.

- Study 44 demonstrated the superiority of nivolumab/IC over IC in the dual primary endpoint of PFS in the CPS ≥5 population. The study demonstrated the superiority of nivolumab/IC over IC in the other dual primary endpoint of OS in the CPS ≥5 population. Nivolumab/IC demonstrated a statistically significant improvement in OS also in the CPS ≥1 population and in the ITT population versus IC, based on the pre-specified multiplicity adjustment procedure.
- Study 37 demonstrated the superiority of nivolumab/IC over placebo/IC in the dual primary endpoint of

PFS in the ITT population. As to the other dual primary endpoint of OS in the ITT population, there was a trend towards prolongation of OS in the nivolumab/IC group compared with the placebo/IC group.

However, HER2-positive patients were excluded from Studies 44 and 37, and no clinical studies have evaluated the clinical usefulness of nivolumab/IC in HER2-positive patients. Trastuzumab plus fluoropyrimidine and platinum is recommended as the standard of care for patients with HER2-positive, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy. Thus, nivolumab/IC is not recommended for these patients. In order to advise that nivolumab/IC is recommended for HER2-negative patients, the "CLINICAL STUDIES" section of the package insert will contain information on the HER2 status of patients enrolled in clinical studies, and the "PRECAUTIONS CONCERNING INDICATIONS" section will advise that eligible patients must be selected based on a careful review of the relevant content of the "CLINICAL STUDIES" section and a thorough understanding of the efficacy and safety of Opdivo.

At the time of approval of nivolumab monotherapy as third- or later-line treatment in patients with unresectable, advanced or recurrent gastric cancer, the "PRECAUTIONS CONCERNING INDICATIONS" section advised that the efficacy and safety of Opdivo monotherapy have not been established in first- or second-line treatment. Along with the present partial change application, this statement will be moved to the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section.

On the basis of the above, the following statement will be included in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section.

- The efficacy and safety of Opdivo monotherapy have not been established in first- or second-line treatment.

Since Study 44 showed that the efficacy of nivolumab/IC tended to differ according to PD-L1 expression [see Table 7 and Figure 5-7, etc. in Section 7.1.1.1.2] etc., PMDA asked the applicant to explain the efficacy and safety of nivolumab/IC by PD-L1 CPS (at the cutoffs of 1 and 5) and the target population for nivolumab/IC.

The applicant's response[29]:

(a) Efficacy

Tables 17 and 18 and Figure 14 show the results of OS and PFS by PD-L1 CPS (at the cutoffs of 1 and 5) in Study 44 (data cutoff on May 27, 2020).

Although the add-on effect of nivolumab to chemotherapy tended to be smaller in patients with lower CPS than in patients with higher CPS, given the following point etc., it is difficult to draw a definitive conclusion that PD-L1 expression is a predictive factor for response to nivolumab/IC. Thus, the efficacy of nivolumab/IC is considered to be expected, regardless of PD-L1 expression.

- Study 44 demonstrated a statistically significant improvement in OS with nivolumab/IC compared with IC also in the ITT population, based on the pre-specified multiplicity adjustment procedure. Analyses of

[29] In Study 37, information on PD-L1 CPS was not collected.

CPS <1 and CPS 1 to <5 patients (Tables 17 and 18) were post-hoc exploratory analyses, e.g., the randomization was not stratified by PD-L1 CPS in Study 44. Thus, interpretation of the results has limitations.

Table 17. Study 44: OS by PD-L1 expression (ITT population, data cutoff on May 27, 2020)

PD-L1 expression	Treatment group	N	OS		
			Median [95% CI] (months)	Hazard ratio*1 [95% CI]	*P*-value for interaction*2
CPS <1	Nivolumab/IC	140	13.08 [9.82, 16.66]	0.92 [0.70, 1.23]	0.0345
	IC	125	12.48 [10.12, 13.83]		
CPS ≥1 and <5	Nivolumab/IC	168	12.29 [9.63, 14.26]	0.97 [0.76, 1.24]	
	IC	173	11.99 [10.87, 13.90]		
CPS ≥5	Nivolumab/IC	473	14.39 [13.11, 16.23]	0.70 [0.60, 0.81]	
	IC	482	11.10 [10.02, 12.09]		

*1, Unstratified Cox proportional hazards model; *2, Unstratified Cox proportional hazards model with (a) treatment, (b) PD-L1 level, and (c) treatment by PD-L1 level interaction as covariates

Table 18. Study 44: PFS by PD-L1 expression (BIRC assessment, ITT population, data cutoff on May 27, 2020)

PD-L1 expression	Treatment group	N	PFS		
			Median [95% CI] (months)	Hazard ratio*1 [95% CI]	*P*-value for interaction*2
CPS <1	Nivolumab/IC	140	8.67 [6.93, 9.69]	0.93 [0.69, 1.26]	0.0257
	IC	125	8.11 [6.87, 9.82]		
CPS ≥1 and <5	Nivolumab/IC	168	7.16 [6.83, 8.38]	0.93 [0.73, 1.20]	
	IC	173	8.15 [7.03, 9.07]		
CPS ≥5	Nivolumab/IC	473	7.69 [7.03, 9.17]	0.69 [0.59, 0.80]	
	IC	482	6.05 [5.55, 6.90]		

*1, Unstratified Cox proportional hazards model; *2, Unstratified Cox proportional hazards model with (a) treatment, (b) PD-L1 level, and (c) treatment by PD-L1 level interaction as covariates

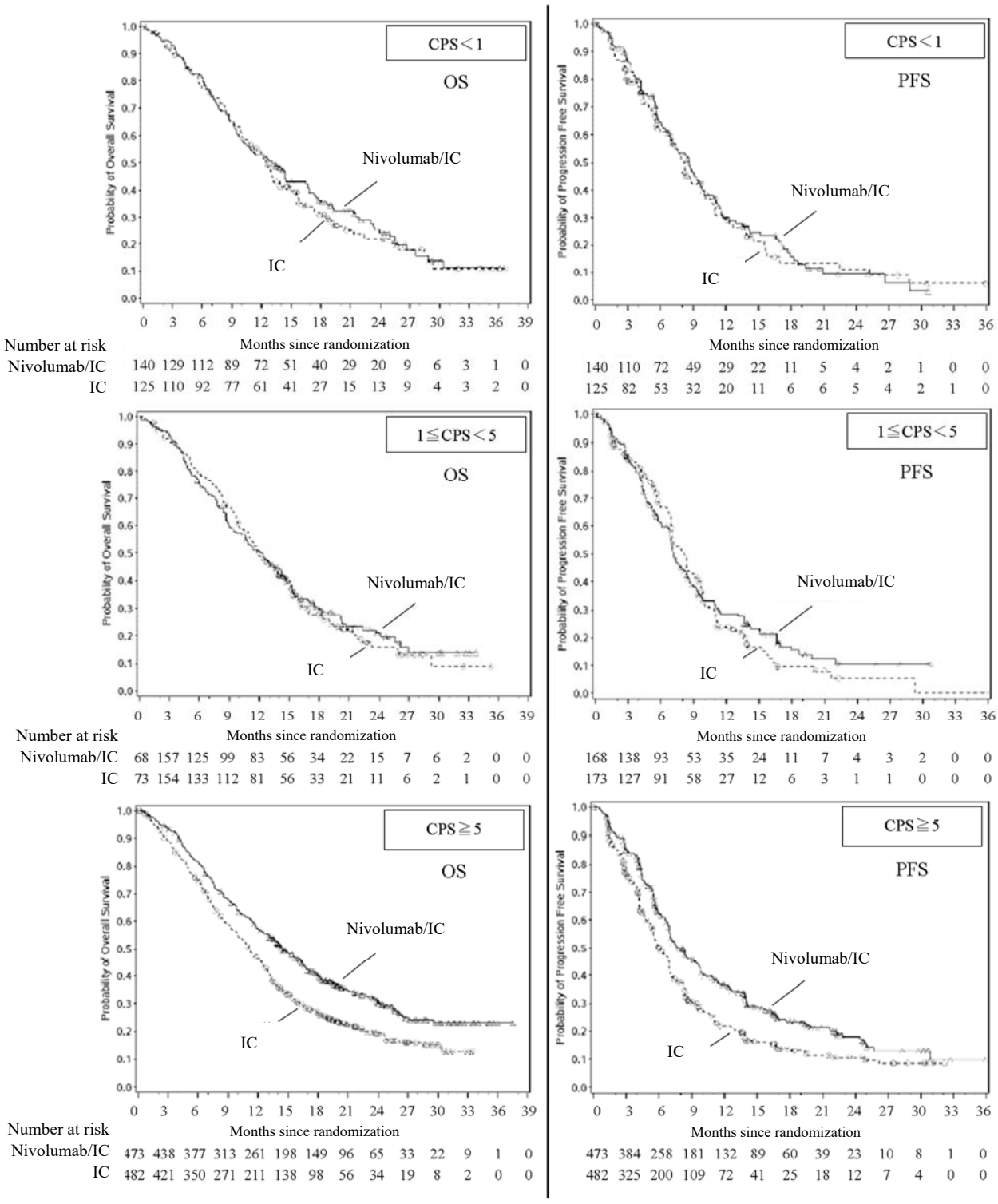

Figure 14. Study 44: Kaplan-Meier curves for PFS and OS by PD-L1 expression (data cutoff on May 27, 2020)
(OS [on the left]: Top, CPS <1; Middle, CPS ≥1 and <5; Bottom, CPS ≥5)
(PFS [on the right]: Top, CPS <1; Middle, CPS ≥1 and <5; Bottom, CPS ≥5)

(b) Safety

Among subjects in the nivolumab/IC group of Study 44, the incidences of adverse events of any grade in the CPS <1, CPS 1 to <5, and CPS ≥5 subgroups were 98.6%, 98.8%, and 99.6%, respectively. The incidences of

Grade ≥3 adverse events were 76.3%, 83.8%, and 78.8%, respectively, and the incidences of serious adverse events were 51.1%, 59.3%, and 53.4%, respectively. Since there were no clear differences in the safety of nivolumab/IC according to PD-L1 expression, nivolumab/IC is considered tolerable, regardless of PD-L1 expression.

On the basis of the above findings (a) and (b), nivolumab/IC is recommended, regardless of PD-L1 expression, for patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy.

PMDA's discussion:
Taking account of review etc. in Section "7.1.R.2 Efficacy," the efficacy of nivolumab/IC was demonstrated in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy. However, given the following points etc., it is difficult to conclude that a favorable balance of risks and benefits of nivolumab/IC was shown in the CPS <5 population. Thus, the necessity of the addition of nivolumab to chemotherapy, the standard of care for these patients, should be determined carefully, taking also account of PD-L1 expression.

- Since it was suggested that PD-L1 CPS may be a predictive factor for response to nivolumab, patients with CPS ≥5 were defined as the primary population for Study 44 [see Section 7.1.1.1.2]. Then, the efficacy of nivolumab/IC tended to differ according to PD-L1 expression (the CPS ≥5 population, the CPS ≥1 population, the ITT population) [see Table 7 and Figures 5-7, etc. in Section 7.1.1.1.2]. Analyses of CPS ≥5, CPS 1 to <5, and CPS <1 subgroups showed that the add-on effect of nivolumab to chemotherapy (OS and PFS) tended to be smaller in other subgroups than in the CPS ≥5 subgroup.
- In Studies 44 and 37, the incidence of adverse events tended to be higher in the nivolumab/IC group than in the control group (the IC group or placebo/IC group) [see Section 7.1.R.3.1].

Thus, the efficacy of nivolumab/IC by PD-L1 expression in Study 44 should be described in the "CLINICAL STUDIES" section of the package insert, and then the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section should advise that prior to administration of nivolumab/IC, the necessity of the addition of nivolumab should be determined carefully, taking account of the percentage of PD-L1 expression (CPS). Nivolumab/IC is recommended for HER2-negative patients, which is important information for administering nivolumab/IC. This information should be specified in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section.

On the basis of the above, the following statements should be included in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section.

- The efficacy and safety of Opdivo monotherapy have not been established in first- or second-line treatment.
- When administered in combination with other antineoplastic drugs, Opdivo should be used in HER2-negative patients.
- The efficacy of Opdivo in combination with other antineoplastic drugs tends to differ according to the percentage of PD-L1 expression (CPS). The necessity of the addition of Opdivo should be carefully

determined based on a careful review of the content of the “CLINICAL STUDIES” section, particularly regarding CPS, and a thorough understanding of the efficacy and safety of Opdivo.

7.1.R.5 Indication

The present partial change application for gastric cancer seeks to amend the approved indication of “unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy” to “unresectable, advanced or recurrent gastric cancer.” After the submission of the present application, the applicant explained that the “PRECAUTIONS CONCERNING INDICATIONS” section will be amended as follows.

- The efficacy and safety of Opdivo in adjuvant therapy have not been established (the same as the approved content).
- Eligible patients must be selected based on a careful review of the “CLINICAL STUDIES” section, particularly regarding the HER2 status of patients enrolled in clinical studies, and a thorough understanding of the efficacy and safety of Opdivo.

PMDA’s conclusion:

On the basis of the considerations in Sections “7.1.R.2 Efficacy,” “7.1.R.3 Safety,” and “7.1.R.4 Clinical positioning and dosage and administration,” the following statement should be included in the “PRECAUTIONS CONCERNING INDICATIONS” section, and then the proposed indication is appropriate. The “PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION” section should advise about the HER2 status of patients for whom nivolumab/IC is recommended [see Section 7.1.R.4.2].

- The efficacy and safety of Opdivo in adjuvant therapy have not been established (the same as the approved content).

7.1.R.6 Post-marketing investigations

Post-marketing investigations for the treatment of unresectable, advanced or recurrent gastric cancer will be described in Section 7.2.R.6, with those for the adjuvant therapy of esophageal cancer.

7.2 Data concerning adjuvant therapy of esophageal cancer and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from 1 global phase III study presented in Table 19.

Table 19. Listing of efficacy and safety clinical study

Data category	Geographical location	Study identifier	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Global	Study 43	III	Patients with resected esophageal cancer who had not achieved pCR following neoadjuvant chemoradiotherapy	794 (a) 532 (b) 262	(a) Nivolumab 240 mg Q2W for 8 doses followed by nivolumab 480 mg Q4W intravenously (b) Placebo Q2W for 8 doses followed by placebo Q4W intravenously	Efficacy Safety

The clinical study is summarized below. The main adverse events other than deaths observed in the clinical study are described in Section "7.3.2 Adverse events etc. observed in clinical study in the adjuvant therapy of esophageal cancer."

7.2.1 Evaluation data

7.2.1.1 Global study

7.2.1.1.1 Global phase III study (CTD 5.3.5.1-1, Study 43 [ongoing since July 2016 (data cutoff on May 12, 2020)])

A randomized, double-blind study was conducted at 170 sites in 29 countries or regions including Japan to compare the efficacy and safety of nivolumab vs. placebo in patients with resected[30] esophageal cancer[31] who had not achieved a pathological complete response (pCR)[32] following neoadjuvant chemoradiotherapy[33] (target sample size, 760 subjects).

Subjects in the nivolumab group were to receive nivolumab 240 mg Q2W for 8 doses followed by 480 mg Q4W intravenously. Subjects in the placebo group were to receive placebo Q2W for 8 doses followed by placebo Q4W intravenously. Treatment was to be continued until disease progression or any withdrawal criterion was met, or for up to 12 months.

All of 794 subjects who were enrolled in the study and randomized (532 in the nivolumab group, 262 in the placebo group) were included in the ITT population, which was used as the efficacy population (including 50 Japanese patients in the nivolumab group and 13 Japanese patients in the placebo group). After excluding 2 subjects in the placebo group who did not receive study drug from the ITT population, 792 subjects (532 in the

30) Patients with completely resected tumors were enrolled.
31) Patients who had stage II or III esophageal (excluding cervical esophageal) or gastroesophageal junction cancer (as defined in the 7th edition of the Cancer Staging Manual of the American Joint Committee on Cancer [AJCC]) and histologically confirmed predominant squamous-cell carcinoma or adenocarcinoma, at the initial diagnosis, were enrolled.
32) Defined as at least ypT1 or ypN1 (per AJCC 7th edition) listed in the pathology report of resected specimens
33) Chemotherapy and radiation regimens were to follow local standards of care per NCCN or ESMO guidelines. Platinum based chemotherapy was to be used.

nivolumab group, 260 in the placebo group) were included in the safety population (including 50 Japanese patients in the nivolumab group and 13 Japanese patients in the placebo group).

At the time of initiating the study, disease-free survival (DFS)[34] per investigator assessment and OS were co-primary endpoints of the study, and 1 interim analysis of OS for efficacy evaluation was planned. (a) The primary analysis of DFS, (b) the interim analysis of OS, and (c) the final analysis of OS were to be performed when (a) 455 DFS events, (b) 330 OS events, and (c) 440 OS events had been observed. However, since the results of the CROSS study[35] etc. indicated that a longer follow-up is needed to evaluate the efficacy of nivolumab, etc., OS was changed from the co-primary endpoint to the secondary endpoint. OS was to be tested upon demonstration of a statistically significant improvement in DFS. The first interim analysis of DFS and the second interim analysis of OS were added, which were to occur at the following timing (Protocol Amendment Version 4, dated June 6, 2019). Lan-DeMets α spending function with O'Brien-Fleming boundaries was used to control the type I error rate for interim analyses.

- The interim analysis of DFS (the first interim analysis of OS): when 374 DFS events had been observed.
- The final analysis of DFS (the second interim analysis of OS): when 440 DFS events had been observed.
- The final analysis of OS: when 460 OS events had been observed.

Regarding efficacy, Table 20 and Figure 15 show the results of the interim analysis of DFS (data cutoff on May 12, 2020) and the Kaplan-Meier curves, respectively. The superiority of nivolumab over placebo was demonstrated.

Table 20. Results of interim analysis of DFS (Investigator assessment, ITT population, data cutoff on May 12, 2020)

	Nivolumab	Placebo
N	532	262
No. of events (%)	241 (45.3)	155 (59.2)
Median [95% CI] (months)	22.41 [16.62, 34.00]	11.04 [8.34, 14.32]
Hazard ratio [95% CI]*1	0.69 [0.56, 0.85]*2	
P-value (two-sided)*3	0.0003	

*1, Stratified Cox proportional hazards model stratified by PD-L1 status[12] (TPS) (≥1% vs. <1% or indeterminate or non-evaluable), pathological lymph node status (positive vs. negative), and histologic type (squamous vs. adenocarcinoma); *2, The 96.4% CI corresponding to the significance level for the interim analysis was [0.56, 0.86]; *3, Stratified log-rank test (the same stratification factors as the Cox proportional hazards model), two-sided significance level of 0.036

34) Defined as the time between date of randomization and first date of recurrence (the appearance of new lesions [local, regional, or distant in location from the primary resected site]) or death, whichever occurred first

35) A foreign phase III study to compare the efficacy and safety of neoadjuvant therapy plus surgery vs. surgery alone in patients with squamous-cell carcinoma or adenocarcinoma of the esophagus or gastroesophageal junction

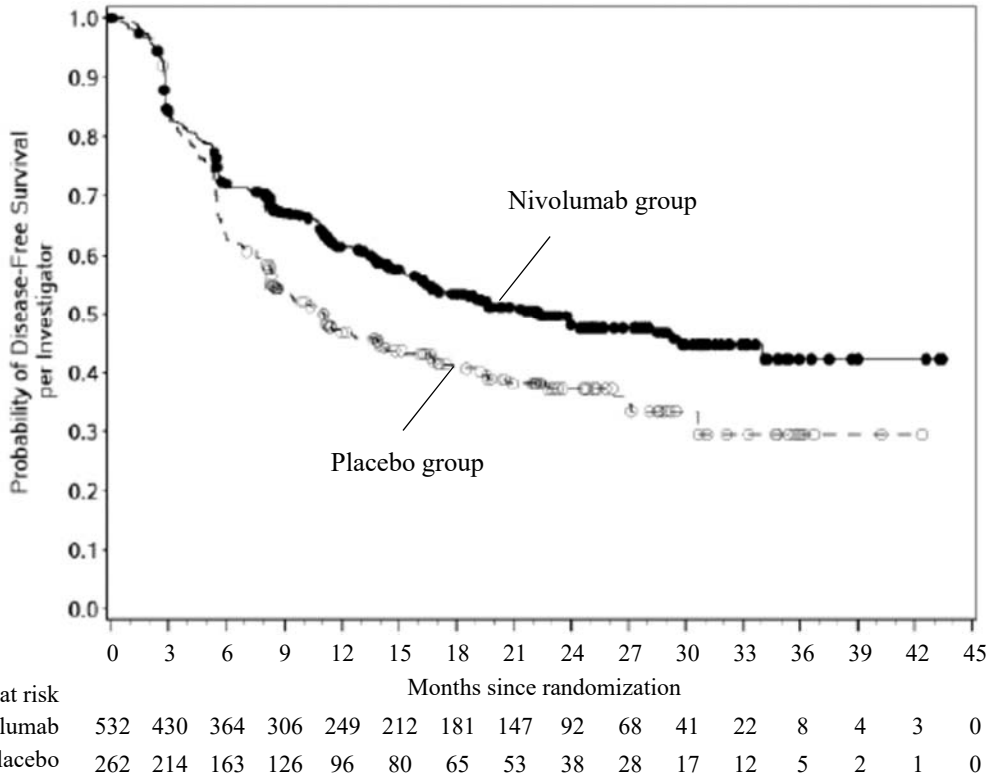

Figure 15. Kaplan-Meier curves for DFS at the time of interim analysis (Investigator assessment, ITT population, data cutoff on May 12, 2020)

Regarding safety, 7 of 532 subjects (1.3%) in the nivolumab group and 4 of 260 subjects (1.5%) in the placebo group died during the study treatment period or within 30 days after the last dose of study drug (no Japanese patients died). The causes of deaths other than disease progression (2 in the nivolumab group, 2 in the placebo group) were haemorrhage intracranial and malignant neoplasm progression; completed suicide; cardiac arrest; pneumonia aspiration; and myocardial infarction (1 subject each) in the nivolumab group and pneumothorax; and subacute endocarditis (1 subject each) in the placebo group. A causal relationship to study drug could not be ruled out for 1 case of cardiac arrest in the nivolumab group.[36)]

7.2.R Outline of the review conducted by PMDA

7.2.R.1 Review strategy

PMDA decided to focus its efficacy and safety reviews on the results from Study 43 and evaluate the efficacy of nivolumab in Japanese patients systematically, based on Study 43 etc., in accordance with "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Basic Principles on Global Clinical Trials (Reference Cases)" (PFSB/ELD 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), etc.

36) Its causal relationship to study drug was denied by the investigator after database lock.

7.2.R.2 Efficacy

On the basis of the following considerations, PMDA concluded that the efficacy of nivolumab was demonstrated in patients with resected esophageal cancer who had not achieved pCR following neoadjuvant chemoradiotherapy.

7.2.R.2.1 Choice of control group

The applicant's explanation about the reason for choosing placebo as a control group in Study 43:
Since the NCCN guidelines (esophageal cancer) (v.3.2015) at the time of planning Study 43 recommended no adjuvant therapy for the patient population of Study 43, etc., placebo was chosen as a control group in Study 43.

PMDA accepted the applicant's explanation.

7.2.R.2.2 Efficacy endpoint and evaluation results

The applicant's explanation about the primary endpoint of Study 43 and the efficacy of nivolumab in the patient population of this study:
Improved DFS in patients with resected esophageal cancer who have not achieved pCR following neoadjuvant chemoradiotherapy is expected to delay worsening of clinical symptoms, deterioration of QOL, etc., associated with disease progression by prolonging the time to disease progression, and is considered clinically relevant. Thus, DFS was selected as the primary endpoint of Study 43.

Study 43 demonstrated the superiority of nivolumab over placebo in the primary endpoint of DFS per investigator assessment [see Section 7.2.1.1.1]. Table 21 and Figure 16 show the results of the first interim analysis of the secondary endpoint of OS (data cutoff on May 12, 2020) and the Kaplan-Meier curves, respectively.

Table 21. Results of first interim analysis of OS (ITT population, data cutoff on May 12, 2020)

	Nivolumab	Placebo
N	532	262
No. of events (%)	[redacted]	[redacted]
Median [95% CI] (months)	[redacted]	[redacted]
Hazard ratio [95% CI][*1]	[redacted]	
P-value (two-sided)[*2]	[redacted]	

[redacted], *1, Stratified Cox proportional hazards model stratified by PD-L1 status[12)] (TPS) (≥1% vs. <1% or indeterminate or non-evaluable), pathological lymph node status (positive vs. negative), and histologic type (squamous vs. adenocarcinoma); *2, Stratified log-rank test (the same stratification factors as the Cox proportional hazards model), two-sided significance level of [redacted]

Figure 16. Kaplan-Meier curves for OS at the time of first interim analysis (ITT population, data cutoff on May 12, 2020)

In the Japanese subgroup of Study 43, Table 22 and Figure 17 show the results of the interim analysis of DFS (data cutoff on May 12, 2020) and the Kaplan-Meier curves, respectively.

Table 22. Results of interim analysis of DFS in Japanese subgroup (Investigator assessment, ITT population, data cutoff on May 12, 2020)

	Nivolumab	Placebo
N	50	13
No. of events (%)	26 (52.0)	6 (46.2)
Median [95% CI] (months)	23.98 [8.38, —]	27.04 [8.38, —]
Hazard ratio [95% CI]*	1.36 [0.56, 3.32]	

—, Not estimable; *, Unstratified Cox proportional hazards model

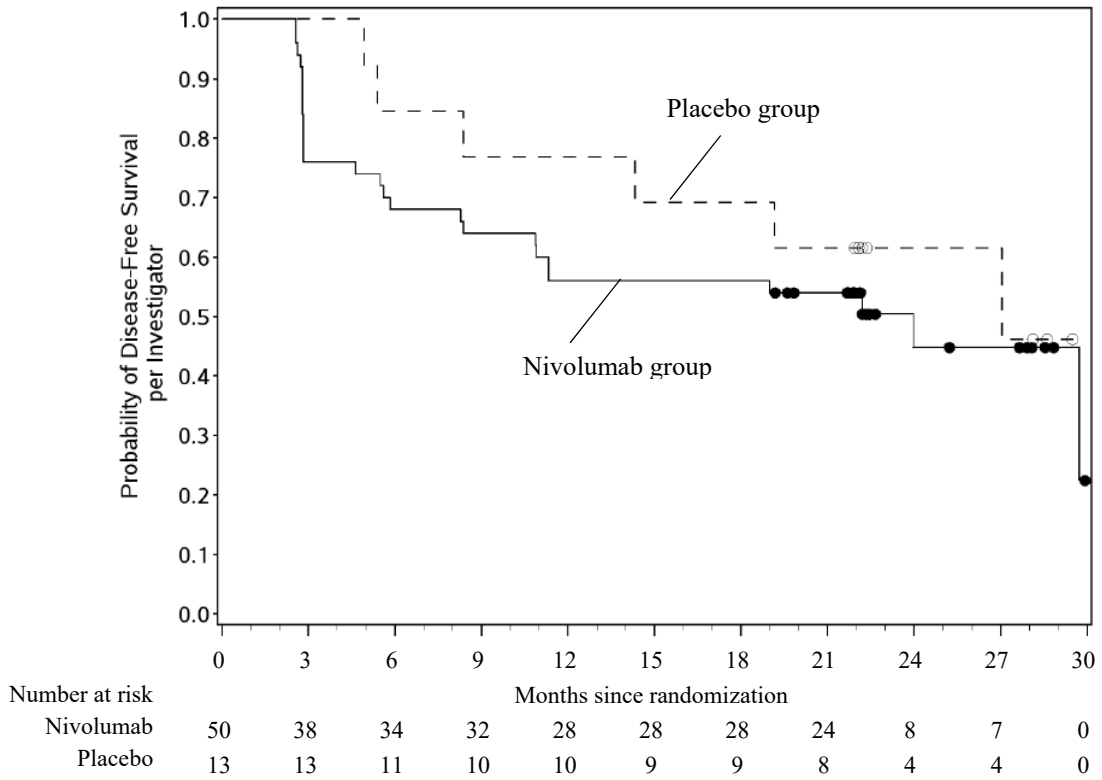

Figure 17. Kaplan-Meier curves for DFS at the time of interim analysis in the Japanese subgroup (Investigator assessment, ITT population, data cutoff on May 12, 2020)

The applicant's explanation about the efficacy of nivolumab in Japanese patients, based on the above results of DFS in the Japanese subgroup of Study 43:

Supplemental analyses were performed, taking account of the possibility that imbalances between the treatment groups in the Japanese subgroup in terms of the distribution of patients with pathological lymph node positive status (31 of 50 subjects [62.0%] in the nivolumab group, 3 of 13 subjects [23.1%] in the placebo group) etc. led to differences in the results of DFS. The results of these analyses are shown below.

- An adjusted analysis was performed in the Japanese subgroup using the unstratified Cox proportional hazards model with pathological lymph node status (positive vs. negative) as a covariate. The hazard ratio [95% CI] of DFS for nivolumab vs. placebo was 0.77 [0.29, 2.00].
- An adjusted analysis was performed using the unstratified Cox proportional hazards model with pathological lymph node status (positive vs. negative), ECOG PS (0 vs. 1), disease stage at the initial diagnosis (stage II vs. stage III), and the grade of histologic differentiation (G1 or G2 vs. G3 or G4) (these have been reported as prognostic factors in patients with resected esophageal cancer in the publications [*World J Surg*. 2018;42:1496-505, *Anticancer Res.* 2017;37:3301-6, *Int Surg.* 2013;98:234-40, etc.] etc.) as covariates. The hazard ratio [95% CI] of DFS for nivolumab vs. placebo in the Japanese subgroup was 0.82 [0.24, 2.80].
- Subjects were selected by stratified random sampling from the entire population so that the obtained sample had the same joint distribution of pathological lymph node status, ECOG PS, disease stage at the initial diagnosis, and the grade of histologic differentiation and the same size as the Japanese subgroup (repeated 10,000 times), and the hazard ratio [95% CI] of DFS for nivolumab vs. placebo was estimated.

The estimated hazard ratio [95% CI] of DFS (mean) was 1.11 [0.42, 2.87], which was different from the hazard ratio in the entire population.

Though these were post-hoc analyses, and the results should be interpreted carefully, the above indicated that imbalances between the treatment groups in terms of multiple prognostic factors including pathological lymph node status may have affected the results of DFS in the Japanese subgroup of Study 43. Given the results of the adjusted analyses of these prognostic factors etc., the efficacy of nivolumab is expected also in Japanese patients.

PMDA's discussion:
The applicant's explanation that imbalances between the treatment groups in terms of multiple prognostic factors including pathological lymph node status may have affected the results of DFS in the Japanese subgroup of Study 43 is understandable to a certain extent. Taking also account of the following points etc., PMDA concluded that the efficacy of nivolumab was demonstrated in the patient population of Study 43, including Japanese patients.

- Study 43 demonstrated the superiority of nivolumab over placebo in the primary endpoint of DFS in the entire population, and the magnitude of the observed effects was clinically relevant.
- In the entire population of Study 43, a secondary endpoint of OS, [redacted].
- There were no clear differences in the efficacy of nivolumab between Japanese and non-Japanese populations in the approved indications including unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy (see "Review Report on Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, and Opdivo Intravenous Infusion 240 mg, dated January 9, 2020" etc.).
- There are no clear differences in the PK of nivolumab and the diagnosis of and treatment paradigm for esophageal cancer between Japanese and non-Japanese populations.

7.2.R.3 Safety [for adverse events, see Section "7.3.2 Adverse events etc. observed in clinical study in the adjuvant therapy of esophageal cancer"]
PMDA's conclusion:
On the basis of the following considerations, adverse events that require particular attention following administration of nivolumab in patients with resected esophageal cancer are the events that were considered to require attention during the review etc. of the applications for the approved indications.[24)] Attention should be paid to the possible occurrence of these adverse events during treatment with nivolumab.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with nivolumab, nivolumab is tolerable also in patients with resected esophageal cancer as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and interruption of nivolumab.

7.2.R.3.1 Safety profile

The applicant's explanation about the safety profile of nivolumab based on safety information from Study 43:
Table 23 summarizes safety data from Study 43.

Table 23. Summary of safety data (Study 43)

	n (%)	
	Nivolumab N = 532	Placebo N = 260
All adverse events	510 (95.9)	243 (93.5)
Grade ≥3 adverse events	192 (36.1)	90 (34.6)
Adverse events leading to death	13 (2.4)	11 (4.2)
Serious adverse events	158 (29.7)	78 (30.0)
Adverse events leading to treatment discontinuation	68 (12.8)	20 (7.7)
Adverse events leading to dose interruption	148 (27.8)	62 (23.8)

In Study 43, adverse events of any grade reported at a ≥5% higher incidence in the nivolumab group than in the placebo group were pruritus (68 subjects [12.8%] in the nivolumab group, 16 subjects [6.2%] in the placebo group), rash (63 subjects [11.8%], 17 subjects [6.5%]), hypothyroidism (56 subjects [10.5%], 4 subjects [1.5%]), and hyperthyroidism (41 subjects [7.7%], 1 subject [0.4%]). There were no Grade ≥3 adverse events, adverse events leading to death, serious adverse events, adverse events leading to treatment discontinuation, or adverse events leading to dose interruption that were reported at a ≥2% higher incidence in the nivolumab group than in the placebo group.

The applicant's explanation about differences in safety profile between Study 43 and a global phase III study of nivolumab monotherapy in patients with unresectable, advanced or recurrent esophageal cancer previously treated with chemotherapy (Study 473):
Table 24 shows the results of comparison of the incidence of adverse events in the nivolumab group between Studies 43 and 473.

Table 24. Summary of safety data (Studies 43 and 473)

	n (%)	
	Study 43*1 N = 532	Study 473*2 N = 192
All adverse events	510 (95.9)	172 (89.6)
Grade ≥3 adverse events	192 (36.1)	77 (40.1)
Adverse events leading to death	13 (2.4)	5 (2.6)
Serious adverse events	158 (29.7)	57 (29.7)
Adverse events leading to treatment discontinuation	68 (12.8)	24 (12.5)
Adverse events leading to dose interruption	148 (27.8)	49 (25.5)

*1, Nivolumab 240 mg Q2W for 8 doses followed by nivolumab 480 mg Q4W intravenously; *2, Nivolumab 240 mg Q2W intravenously

Adverse events of any grade reported at a ≥10% higher incidence in Study 43 than in Study 473 were diarrhoea (155 subjects [29.1%] in Study 43, 33 subjects [17.2%] in Study 473), fatigue (144 subjects [27.1%], 18 subjects [9.4%]), nausea (121 subjects [22.7%], 21 subjects [10.9%]), and vomiting (80 subjects [15.0%], 9 subjects [4.7%]). There were no Grade ≥3 adverse events, adverse events leading to death, serious adverse

events, adverse events leading to treatment discontinuation, or adverse events leading to dose interruption that were reported at a ≥3% higher incidence in Study 43 than in Study 473.

PMDA's discussion:
Although the incidences of some adverse events were higher in the nivolumab group than in the placebo group in Study 43, and the incidences of some adverse events were higher in patients with resected esophageal cancer than in patients with the approved indication, given that all those events were known adverse events associated with nivolumab, and that those events were also potentially associated with the primary disease or surgery, etc., nivolumab is tolerable also in patients with resected esophageal cancer as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and interruption of nivolumab.

7.2.R.3.2 Differences in safety between Japanese and non-Japanese populations

The applicant's explanation about differences in the safety of nivolumab between Japanese and non-Japanese populations, based on safety information from Study 43:
Table 25 summarizes safety data from Japanese and non-Japanese patients in the nivolumab group of Study 43.

Table 251. Summary of safety data from Japanese and non-Japanese patients (nivolumab group of Study 43)

	n (%)	
	Japanese patients N = 50	Non-Japanese patients N = 482
All adverse events	46 (92.0)	464 (96.3)
Grade ≥3 adverse events	21 (42.0)	171 (35.5)
Adverse events leading to death	0	13 (2.7)
Serious adverse events	15 (30.0)	143 (29.7)
Adverse events leading to treatment discontinuation	5 (10.0)	63 (13.1)
Adverse events leading to dose interruption	21 (42.0)	127 (26.3)

In the nivolumab group of Study 43, adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were pneumonia (8 subjects [16.0%] in the Japanese subgroup, 28 subjects [5.8%] in the non-Japanese subgroup), pneumonia aspiration (6 subjects [12.0%], 4 subjects [0.8%]), and dermatitis (6 subjects [12.0%], 1 subject [0.2%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were pneumonia (4 subjects [8.0%], 10 subjects [2.1%]) and pneumonia aspiration (3 subjects [6.0%], 3 subjects [0.6%]). Serious adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were pneumonia (4 subjects [8.0%], 12 subjects [2.5%]) and pneumonia aspiration (3 subjects [6.0%], 4 subjects [0.8%]). Adverse events leading to dose interruption reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were pneumonia aspiration (3 subjects [6.0%], 1 subject [0.2%]). There were no adverse events leading to death or treatment discontinuation that were reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

PMDA's discussion:

Although the number of Japanese patients included in Study 43 was limited, and there are limitations to rigorous comparison of the safety of nivolumab between the Japanese and non-Japanese subgroups, given that the results were possibly influenced by the differences in the distribution of the primary tumor location in Study 43,[37] and that there was no trend towards clearly higher incidences of Grade ≥3 adverse events and serious adverse events in Japanese patients than in non-Japanese patients, etc., nivolumab is tolerable also in Japanese patients as long as appropriate measures, e.g. interruption of nivolumab, are taken.

7.2.R.4 Clinical positioning and indications

The proposed indication concerning esophageal cancer in the present partial change application is shown in the table below (Strikethrough denotes deletions from the approved content). After the submission of the present application, the applicant explained that the "PRECAUTIONS CONCERNING INDICATIONS" section will be amended as shown in the table below (Underline denotes additions to the approved content. Strikethrough denotes deletions.).

Indication	Precautions concerning indication
~~Unresectable, advanced or recurrent~~ esophageal cancer ~~that has progressed after cancer chemotherapy~~	• The efficacy and safety of Opdivo as a first-line treatment have not been established. • The efficacy and safety of Opdivo in ~~adjuvant or~~ neoadjuvant therapy have not been established. • Eligible patients must be selected based on a careful review of the content of the "CLINICAL STUDIES" section, particularly regarding the pathological lymph node status of patients with resected esophageal cancer with residual tumor confined to the epithelium enrolled in the clinical study, and a thorough understanding of the efficacy and safety of Opdivo.

On the basis of Sections "7.2.R.2 Efficacy" and "7.2.R.3 Safety" and the considerations in the section below, PMDA concluded that the appropriate indications and statements in the "PRECAUTIONS CONCERNING INDICATIONS" section for esophageal cancer are as shown in the table below (Underline denotes additions to the approved content. Strikethrough denotes deletions.).

Indications	Precautions concerning indications
Unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy	• The efficacy and safety of Opdivo as a first-line treatment have not been established. • ~~The efficacy and safety of Opdivo in adjuvant or neoadjuvant therapy have not been established.~~ • Eligible patients must be selected based on a careful review of the content of the "CLINICAL STUDIES" section and a thorough understanding of the efficacy and safety of Opdivo.
Adjuvant therapy of esophageal cancer	• Opdivo should be administered to patients who have not achieved a pathological complete response (pCR) following neoadjuvant therapy. • The efficacy and safety of Opdivo in neoadjuvant therapy have not been established. • Eligible patients must be selected based on a careful review of the content of the "CLINICAL STUDIES" section, particularly regarding prior therapies of patients enrolled in the clinical study, the definition of pCR, etc., and a thorough understanding of the efficacy and safety of Opdivo.

[37] In the nivolumab group, (a) 88.0% of Japanese patients and 57.3% of non-Japanese patients had esophageal cancer (excluding cervical esophageal cancer) and (b) 12.0% of Japanese patients and 42.7% of non-Japanese patients had gastroesophageal junction cancer.

7.2.R.4.1 Clinical positioning of nivolumab and target population

Nivolumab for the adjuvant therapy of esophageal cancer is described as follows in the major Japanese/foreign clinical practice guidelines and textbook of clinical oncology.

Clinical practice guidelines

- NCCN guidelines (esophageal cancer) (v.4.2021)
  Nivolumab is recommended for the adjuvant therapy of patients with resected esophageal cancer who had not achieved pCR following neoadjuvant chemoradiotherapy.

The applicant's explanation about the clinical positioning of nivolumab and the target population:

Since Study 43 in patients with resected esophageal cancer who had not achieved pCR following neoadjuvant chemoradiotherapy demonstrated the superiority of nivolumab over placebo in the primary endpoint of DFS, etc., nivolumab is recommended in these patients. On the other hand, as no clinical studies have evaluated the clinical usefulness of nivolumab in chemotherapy-naïve patients with unresectable, advanced or recurrent esophageal cancer or the clinical usefulness of nivolumab as neoadjuvant therapy in patients with resectable esophageal cancer, nivolumab is not recommended in these patients.

The applicant's view on the use of nivolumab in (a) patients with pCR following neoadjuvant therapy, (b) patients who have received neoadjuvant therapy with chemotherapy alone, and (c) patients with cervical esophageal cancer (these patients were not eligible for Study 43):

(a) Compared with patients with pCR after neoadjuvant chemoradiotherapy, those without pCR were reported to have poor prognosis (*Int J Radiat Oncol Biol Phys*. 2011;80:996-1001, etc.) etc., thus patients without pCR were enrolled in Study 43. However, given that a certain proportion of patients with pCR after neoadjuvant chemoradiotherapy have been reported to have recurrence (*Ann Surg Oncol*. 2021;28:3034-43, etc.) etc., nivolumab will become a treatment option for these patients. Meanwhile, as patients with residual tumor confined to the epithelium were regarded as patients with pCR and excluded from Study 43, this information will be included in the "CLINICAL STUDIES" section of the package insert, and then the relevant statement will be included in the "PRECAUTIONS CONCERNING INDICATIONS" section.

(b) When to use chemoradiotherapy and when to use chemotherapy as neoadjuvant therapy for esophageal cancer are unclear at present. Study 473 in patients with unresectable, advanced or recurrent esophageal cancer previously treated with chemotherapy showed no clear differences in the efficacy[38)] and safety[39)]

38) According to the subgroup analysis of Study 473 by prior radiotherapy status, the hazard ratios [95% CI] of OS for nivolumab vs. control group (DTX and PTX) were 0.83 [0.63, 1.08] in the subgroup with prior radiotherapy and 0.68 [0.45, 1.03] in the subgroup without prior radiotherapy. The objective response rates in the subgroup with prior radiotherapy and the subgroup without prior radiotherapy were 15.44% (21 of 136 subjects) and 19.30% (11 of 57 subjects), respectively.

39) In the nivolumab group of Study 473, the incidences of adverse events of any grade in 135 patients with prior radiotherapy and 57 patients without prior radiotherapy were 91.1% and 86.0%, respectively. The incidences of Grade ≥3 adverse events were 41.5% and 36.8%, respectively, the incidences of adverse events leading to death were 1.5% and 5.3%, respectively, the incidences of serious adverse events were 32.6% and 22.8%, respectively, the incidences of adverse events leading to treatment discontinuation were 12.6% and 12.3%, respectively, and the incidences of adverse events leading to dose interruption were 26.7% and 22.8%, respectively.

of nivolumab according to prior radiotherapy status. Taking account of these points etc., the use of nivolumab is recommended in patients who have received neoadjuvant therapy with chemotherapy alone.

(c) The Japanese clinical practice guidelines (esophageal cancer) (2017) recommend surgery after neoadjuvant chemoradiotherapy as a treatment option for cervical esophageal cancer. Study 473 in patients with unresectable, advanced or recurrent esophageal cancer previously treated with chemotherapy showed no clear differences in the efficacy[40)] and safety[41)] of nivolumab between the entire population and the subgroup of patients with cervical esophageal cancer. Given these findings etc., the use of nivolumab is recommended in patients with cervical esophageal cancer.

On the basis of the above, the following statements were included in the "PRECAUTIONS CONCERNING INDICATIONS" section of the proposed package insert, and then the approved indication of "unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy" was amended to "esophageal cancer."

- The efficacy and safety of Opdivo as a first-line treatment have not been established (the same as the approved content).
- The efficacy and safety of Opdivo in neoadjuvant therapy have not been established.
- Eligible patients must be selected based on a careful review of the content of the "CLINICAL STUDIES" section, particularly regarding the pathological lymph node status of patients with resected esophageal cancer with residual tumor confined to the epithelium enrolled in the clinical study, and a thorough understanding of the efficacy and safety of Opdivo.

PMDA's discussion:

Given that the risk of recurrence after neoadjuvant therapy and surgery is considered different between patients with pCR and patients without pCR, i.e., the patient population of Study 43, and that no clinical studies have evaluated the clinical usefulness of nivolumab in patients with pCR, the target population for nivolumab is patients without pCR following neoadjuvant therapy. As the use of nivolumab is recommended in the patient population of Study 43, the "CLINICAL STUDIES" section of the package insert should include information regarding prior therapies of patients enrolled in Study 43, the definition of pCR, etc., and then the relevant statement should be included in the "PRECAUTIONS CONCERNING INDICATIONS" section. In addition, given that no clinical studies have evaluated the clinical usefulness of nivolumab in chemotherapy-naïve patients with unresectable, advanced or recurrent esophageal cancer, etc., the present partial change application should seek approval to add a new indication separately from the previously approved indication.

40) The hazard ratios [95% CI] of OS for nivolumab vs. control group (DTX and PTX) in the entire population and the subgroup of patients with cervical esophageal cancer of Study 473 were 0.79 [0.63, 0.99] and 0.59 [0.22, 1.61], respectively.

41) In 7 patients with cervical esophageal cancer enrolled in the nivolumab group of Study 473, the incidence of adverse events of any grade was 100%, the incidence of Grade ≥3 adverse events was 57.1%, the incidence of serious adverse events was 57.1%, the incidence of adverse events leading to treatment discontinuation was 28.6%, and the incidence of adverse events leading to dose interruption was 28.6%. No adverse events leading to death were reported [for adverse events observed in all subjects in the nivolumab group of Study 473, see Section 7.2.R.3.1].

On the basis of the above, the following statements should be included in the "PRECAUTIONS CONCERNING INDICATIONS" section, and then the appropriate indication should be "adjuvant therapy of esophageal cancer."

- Opdivo should be administered to patients who have not achieved a pathological complete response (pCR) following neoadjuvant therapy.
- The efficacy and safety of Opdivo in neoadjuvant therapy have not been established.
- Eligible patients must be selected based on a careful review of the content of the "CLINICAL STUDIES" section, particularly regarding prior therapies of patients enrolled in the clinical study, the definition of pCR, etc., and a thorough understanding of the efficacy and safety of Opdivo.

7.2.R.4.2 Efficacy and safety of nivolumab by PD-L1 expression and target population

As nivolumab is an antibody drug directed against human PD-1, PMDA asked the applicant to explain the efficacy and safety of nivolumab by PD-L1 (a ligand of PD-1) expression and the target population.

The applicant's response:

In Study 43, tumor-cell PD-L1 expression was evaluated using the PD-L1 IHC 28-8 PharmDX assay (Dako). In patients with quantifiable tumor PD-L1 expression (TPS), (a) the efficacy and (b) safety of nivolumab were analyzed by PD-L1 expression.

(a) Efficacy

Table 26 and Figure 18 show the results of the interim DFS analysis (data cutoff on May 12, 2020) by PD-L1 expression (at the cutoffs of 1%, 5%, and 10%) and the Kaplan-Meier curves, respectively.

At any cutoff, the study demonstrated an improvement in DFS with nivolumab compared with placebo in both the PD-L1 positive and negative subgroups. Thus, the efficacy of nivolumab is considered to be expected, regardless of PD-L1 expression.

Table 26. Results of DFS by PD-L1 expression (Study 43, data cutoff on May 12, 2020)

PD-L1 expression	Treatment group	N	DFS		
			Median [95% CI] (months)	Hazard ratio*1 [95% CI]	*P*-value for interaction*2
<1%	Nivolumab	374	21.26 [16.30, 34.00]	0.73 [0.57, 0.92]	0.9306
	Placebo	196	11.10 [8.25, 15.21]		
≥1%	Nivolumab	89	19.65 [11.33, —]	0.75 [0.45, 1.24]	
	Placebo	40	14.13 [5.49, 22.80]		
<5%	Nivolumab	403	19.65 [15.93, 34.00]	0.75 [0.60, 0.94]	0.4774
	Placebo	208	11.14 [8.34, 16.66]		
≥5%	Nivolumab	60	28.32 [13.27, —]	0.60 [0.33, 1.10]	
	Placebo	28	9.23 [3.25, 27.04]		
<10%	Nivolumab	416	19.65 [15.93, 34.00]	0.76 [0.61, 0.95]	0.2737
	Placebo	212	11.14 [8.34, 16.66]		
≥10%	Nivolumab	47	28.32 [13.27, —]	0.51 [0.27, 0.99]	
	Placebo	24	8.31 [2.99, 22.80]		

—, Not estimable; *1, Unstratified Cox proportional hazards model; *2, Unstratified Cox proportional hazards model with (a) treatment, (b) PD-L1 status, and (c) treatment by PD-L1 status interaction as covariates

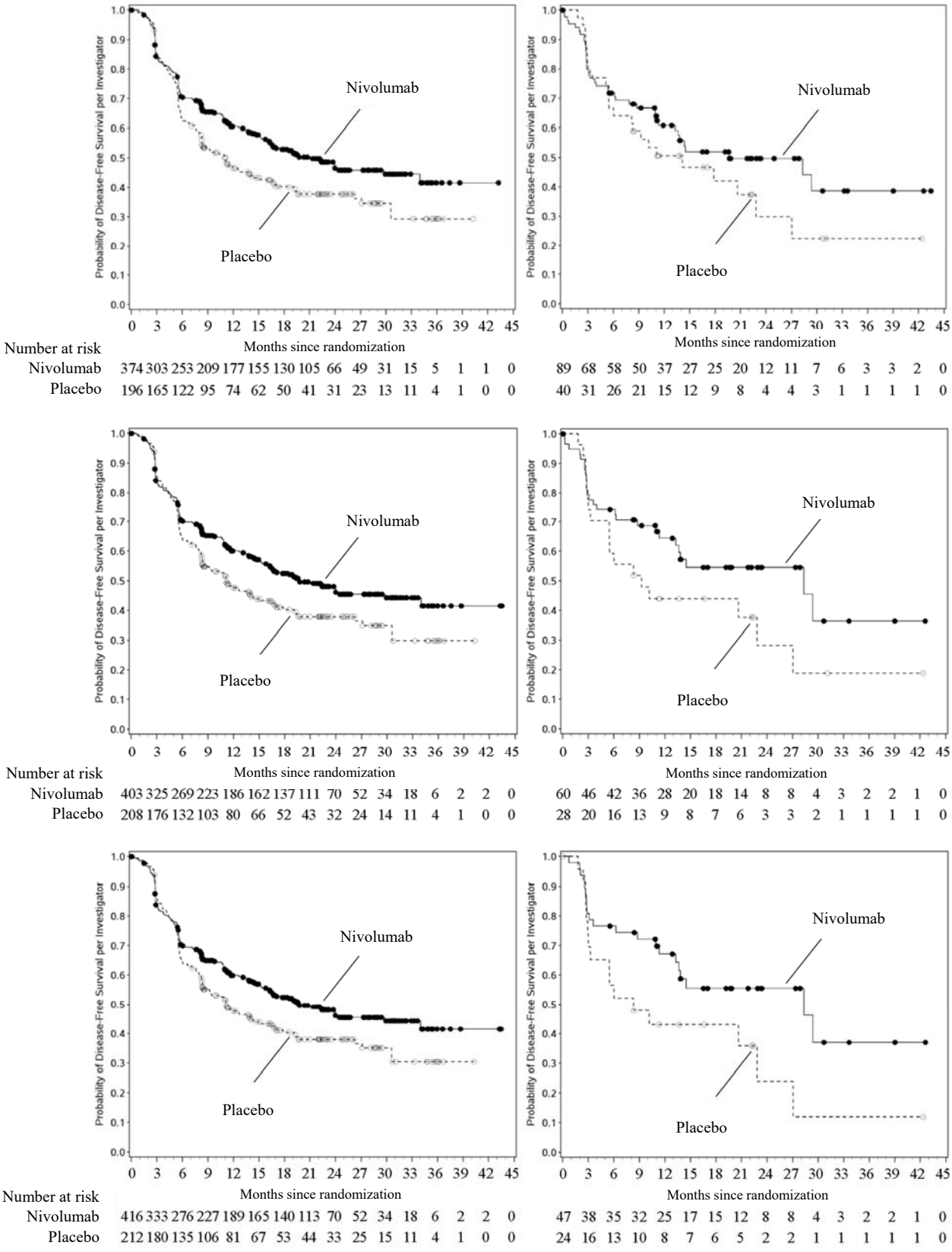

Figure 18. Kaplan-Meier curves for DFS by PD-L1 expression
(ITT population, Investigator assessment, data cutoff on May 12, 2020)
(Left top figure, <1%; Right top figure, ≥1%; Left middle figure, <5%; Right middle figure, ≥5%; Left bottom figure, <10%; Right bottom figure, ≥10%)

(b) Safety

In the nivolumab group of Study 43, the incidences of adverse events of any grade in the PD-L1 <1% and ≥1% subgroups were 97.1% and 94.4%, respectively, the incidences of Grade ≥3 adverse events were 35.0% and 33.7%, respectively, and the incidences of serious adverse events were 29.1% and 27.0%, respectively. The incidences of adverse events of any grade in the PD-L1 <5% and ≥5% subgroups were 96.5% and 96.7%, respectively, the incidences of Grade ≥3 adverse events were 35.5% and 30.0%, respectively, and the incidences of serious adverse events were 29.8% and 21.7%, respectively. The incidences of adverse events of any grade in the PD-L1 <10% and ≥10% subgroups were 96.4% and 97.9%, respectively, the incidences of Grade ≥3 adverse events were 35.6% and 27.7%, respectively, and the incidences of serious adverse events were 29.6% and 21.3%, respectively.

Regarding the safety of nivolumab by PD-L1 expression, at any cutoff, there were no clear differences in the safety of nivolumab between the PD-L1 positive and negative subgroups. Thus, nivolumab is tolerable, regardless of PD-L1 expression.

On the basis of the above analysis results (a) and (b), nivolumab is recommended in patients with resected esophageal cancer, regardless of PD-L1 expression.

PMDA's discussion:

PMDA largely accepted the above explanation by the applicant. It is necessary to continue to collect information on the predictive factors for response to nivolumab, including factors other than PD-L1, and appropriately provide any new information to healthcare professionals in clinical practice.

7.2.R.5 Dosage and administration

The proposed dosage and administration for esophageal cancer in the present partial change application was "The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of esophageal cancer, the maximum duration of treatment is 12 months." (Underline denotes additions to the approved content.). The following statements were included in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section of the proposed package insert (the same as the approved content).

- Opdivo should be intravenously infused over at least 30 minutes.
- The efficacy and safety of Opdivo in combination with other antineoplastic drugs have not been established.

As a result of the review on Sections "7.2.R.2 Efficacy" and "7.2.R.3 Safety" and the considerations in the section below etc., PMDA concluded that the "DOSAGE AND ADMINISTRATION" and "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" sections as proposed by the applicant are appropriate.

7.2.R.5.1 Dosage and administration of nivolumab

The applicant's explanation about the dosing rationale for nivolumab in patients with esophageal cancer:

On the basis of the following points etc., the dosing regimen of nivolumab in the present partial change application was selected.

- Study 43 in patients with resected esophageal cancer who had not achieved pCR following neoadjuvant chemoradiotherapy demonstrated the clinical usefulness of nivolumab 240 mg Q2W for 8 doses[42)] followed by nivolumab 480 mg Q4W (for up to 12 months) [see Sections 7.2.R.2 and 7.2.R.3].
- In light of the results of simulations using the PPK model etc., no clear differences in the efficacy and safety of nivolumab were expected between the 240 mg Q2W and 480 mg Q4W dosing regimens. The 480 mg Q4W dosing regimen has been approved for all indications in Japan based on this point etc. (see "Review Report on Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, and Opdivo Intravenous Infusion 240 mg, dated August 26, 2020").

PMDA accepted the applicant's explanation.

7.2.R.6 Post-marketing investigations

The applicant explained that there is no need to conduct post-marketing surveillance associated with the present partial change applications for (a) gastric cancer and (b) esophageal cancer, immediately after obtaining approval, for the following reasons etc.

- As to the above (a), although the incidences of some adverse events were higher in the nivolumab/IC group than in the control group (the IC or placebo/IC group) in Studies 44 and 37, all those events were known adverse events associated with nivolumab or IC, and there were no clear differences in safety profile between nivolumab/IC in Studies 44 and 37 and nivolumab/chemotherapy etc. in the approved indication. Given these findings etc., no new safety concerns about nivolumab have been identified [see Section 7.1.R.3.1].
- As to the above (b), although the incidences of some adverse events were higher in the nivolumab group than in the placebo group in Study 43, all those events were known adverse events associated with nivolumab etc., and there were no clear differences in the safety profile of nivolumab between Study 43 and the previously approved indication concerning esophageal cancer. Given these findings etc., no new safety concerns about nivolumab have been identified [see Section 7.2.R.3.1].
- Post-marketing surveillance for the previously approved indications has been conducted, and a certain amount of nivolumab safety information from Japanese patients is available. A review of this safety information from Japanese patients obtained to date has identified no new safety concerns.

PMDA accepted the applicant's explanation.

42) Given that simulations using the PPK model predicted that serum nivolumab concentrations reach a steady state after 8 doses of 240 mg Q2W, and taking account of the clinical convenience of less frequent dosing, etc., subjects were to be switched from 240 mg Q2W to 480 mg Q4W after 8 doses of 240 mg Q2W.

7.3 Adverse events etc. observed in clinical studies

Among clinical study data submitted for safety evaluation, deaths are described in Sections 7.1.1 and 7.2.1 "Evaluation data." The main adverse events other than deaths are described below.

7.3.1 Adverse events etc. observed in clinical studies in patients with unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy

7.3.1.1 Global phase II/III study (Study 37)

7.3.1.1.1 Part 1

Adverse events occurred in 21 of 21 subjects (100%) in the nivolumab/SOX group and 18 of 18 subjects (100%) in the nivolumab/CAPOX group, and a causal relationship to study drug could not be ruled out for all those events. Adverse events reported by ≥50% of subjects in the nivolumab/SOX group were diarrhoea (16 subjects [76.2%]); decreased appetite (14 subjects [66.7%]); and nausea; and peripheral sensory neuropathy (12 subjects each [57.1%]). Those reported by ≥50% of subjects in the nivolumab/CAPOX group were decreased appetite (14 subjects [77.8%]); peripheral sensory neuropathy (12 subjects [66.7%]); neutrophil count decreased (10 subjects [55.6%]); and nausea (9 subjects [50.0%]).

Serious adverse events occurred in 5 of 21 subjects (23.8%) in the nivolumab/SOX group and 8 of 18 subjects (44.4%) in the nivolumab/CAPOX group. Those reported by ≥2 subjects in the nivolumab/CAPOX group were decreased appetite; and type 1 diabetes mellitus (2 subjects each [11.1%]). A causal relationship to study drug could not be ruled out for all those events.

Adverse events leading to study drug discontinuation occurred in 6 of 21 subjects (28.6%) in the nivolumab/SOX group and 4 of 18 subjects (22.2%) in the nivolumab/CAPOX group. Those reported by ≥2 subjects in the nivolumab/SOX group were peripheral sensory neuropathy (2 subjects [9.5%]). Those reported by ≥2 subjects in the nivolumab/CAPOX group were peripheral sensory neuropathy (2 subjects [11.1%]). A causal relationship to study drug could not be ruled out for all those events.

7.3.1.1.2 Part 2

Adverse events occurred in 358 of 359 subjects (99.7%) in the nivolumab/IC group and 357 of 358 subjects (99.7%) in the placebo/IC group, and those for which a causal relationship to study drug could not be ruled out occurred in 351 of 359 subjects (97.8%) in the nivolumab/IC group and 349 of 358 subjects (97.5%) in the placebo/IC group. Adverse events reported by ≥20% of subjects in either group are shown in Table 27.

Table 27. Adverse events reported by ≥20% of subjects in either group

SOC PT (MedDRA ver.22.1)	n (%)			
	Nivolumab/IC N = 359		Placebo/IC N = 358	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	358 (99.7)	257 (71.6)	357 (99.7)	232 (64.8)
Gastrointestinal disorders				
Nausea	192 (53.5)	11 (3.1)	191 (53.4)	12 (3.4)
Diarrhoea	144 (40.1)	16 (4.5)	139 (38.8)	15 (4.2)
Constipation	120 (33.4)	1 (0.3)	86 (24.0)	0
Vomiting	91 (25.3)	6 (1.7)	89 (24.9)	4 (1.1)
Nervous system disorders				
Peripheral sensory neuropathy	201 (56.0)	14 (3.9)	189 (52.8)	8 (2.2)
Investigations				
Neutrophil count decreased	157 (43.7)	71 (19.8)	136 (38.0)	58 (16.2)
Platelet count decreased	150 (41.8)	38 (10.6)	161 (45.0)	34 (9.5)
White blood cell count decreased	78 (21.7)	10 (2.8)	60 (16.8)	9 (2.5)
Metabolism and nutrition disorders				
Decreased appetite	209 (58.2)	29 (8.1)	212 (59.2)	28 (7.8)
General disorders and administration site conditions				
Pyrexia	87 (24.2)	2 (0.6)	62 (17.3)	2 (0.6)
Fatigue	82 (22.8)	6 (1.7)	78 (21.8)	3 (0.8)
Blood and lymphatic system disorders				
Anaemia	93 (25.9)	45 (12.5)	102 (28.5)	45 (12.6)

Serious adverse events occurred in 135 of 359 subjects (37.6%) in the nivolumab/IC group and 120 of 358 subjects (33.5%) in the placebo/IC group. Those reported by ≥5 subjects in the nivolumab/IC group were decreased appetite (19 subjects [5.3%]); pneumonia (14 subjects [3.9%]); pyrexia (8 subjects [2.2%]); asthenia (7 subjects [1.9%]); and diarrhoea; ileus; nausea; and ILD (5 subjects each [1.4%]). Those reported by ≥5 subjects in the placebo/IC group were decreased appetite (12 subjects [3.4%]); abdominal pain (10 subjects [2.8%]); pneumonia; and cholangitis (7 subjects each [2.0%]); diarrhoea; obstruction gastric; pyrexia; and pyloric stenosis (6 subjects each [1.7%]); and malaise (5 subjects [1.4%]). A causal relationship to study drug could not be ruled out for decreased appetite (18 subjects); diarrhoea; and ILD (5 subjects each); pneumonia; asthenia; and nausea (4 subjects each); pyrexia (3 subjects); and ileus (1 subject) in the nivolumab/IC group and decreased appetite (10 subjects); diarrhoea (6 subjects); malaise (4 subjects); abdominal pain; and pneumonia (2 subjects each); and pyrexia; and pyloric stenosis (1 subject each) in the placebo/IC group.

Adverse events leading to study drug discontinuation occurred in 130 of 359 subjects (36.2%) in the nivolumab/IC group and 93 of 358 subjects (26.0%) in the placebo/IC group. Those reported by ≥5 subjects in the nivolumab/IC group were peripheral sensory neuropathy (37 subjects [10.3%]); peripheral neuropathy; and infusion related reaction (11 subjects each [3.1%]); ILD (7 subjects [1.9%]); and platelet count decreased; and decreased appetite (5 subjects each [1.4%]). Those reported by ≥5 subjects in the placebo/IC group were peripheral sensory neuropathy (32 subjects [8.9%]); peripheral neuropathy (8 subjects [2.2%]); and platelet count decreased; and hypersensitivity (5 subjects each [1.4%]). A causal relationship to study drug could not be ruled out for peripheral sensory neuropathy (37 subjects); peripheral neuropathy; and infusion-related reaction (11 subjects each); ILD (7 subjects); and platelet count decreased; and decreased appetite (4 subjects each) in the nivolumab/IC group and peripheral sensory neuropathy (32 subjects); peripheral neuropathy (8 subjects); and platelet count decreased; and hypersensitivity (5 subjects each) in the placebo/IC group.

7.3.1.2 Global phase III study (Study 44)

Adverse events occurred in 776 of 782 subjects (99.2%) in the nivolumab/IC group and 752 of 767 subjects (98.0%) in the IC group, and those for which a causal relationship to study drug could not be ruled out occurred in 738 of 782 subjects (94.4%) in the nivolumab/IC group and 679 of 767 subjects (88.5%) in the IC group. Adverse events reported by ≥20% of subjects in either group are shown in Table 28.

Table 28. Adverse events reported by ≥20% of subjects in either group

SOC PT (MedDRA ver.23.0)	n (%)			
	Nivolumab/IC N = 782		IC N = 767	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	776 (99.2)	621 (79.4)	752 (98.0)	519 (67.7)
Gastrointestinal disorders				
Nausea	372 (47.6)	25 (3.2)	334 (43.5)	28 (3.7)
Diarrhoea	308 (39.4)	40 (5.1)	258 (33.6)	28 (3.7)
Vomiting	245 (31.3)	33 (4.2)	221 (28.8)	32 (4.2)
Constipation	193 (24.7)	5 (0.6)	160 (20.9)	3 (0.4)
Nervous system disorders				
Peripheral neuropathy	232 (29.7)	34 (4.3)	201 (26.2)	23 (3.0)
General disorders and administration site conditions				
Fatigue	257 (32.9)	41 (5.2)	219 (28.6)	25 (3.3)
Investigations				
Neutrophil count decreased	170 (21.7)	90 (11.5)	124 (16.2)	70 (9.1)
Platelet count decreased	168 (21.5)	22 (2.8)	122 (15.9)	20 (2.6)
AST increased	157 (20.1)	19 (2.4)	96 (12.5)	9 (1.2)
Blood and lymphatic system disorders				
Anaemia	299 (38.2)	86 (11.0)	254 (33.1)	56 (7.3)
Neutropenia	214 (27.4)	132 (16.9)	192 (25.0)	100 (13.0)
Thrombocytopenia	171 (21.9)	22 (2.8)	152 (19.8)	16 (2.1)
Metabolism and nutrition disorders				
Decreased appetite	224 (28.6)	28 (3.6)	203 (26.5)	19 (2.5)

Serious adverse events occurred in 423 of 782 subjects (54.1%) in the nivolumab/IC group and 335 of 767 subjects (43.7%) in the IC group. Those reported by ≥10 subjects in the nivolumab/IC group were malignant neoplasm progression (109 subjects [13.9%]); vomiting (25 subjects [3.2%]); anaemia (24 subjects [3.1%]); pneumonia (22 subjects [2.8%]); pyrexia (20 subjects [2.6%]); diarrhoea (19 subjects [2.4%]); febrile neutropenia (18 subjects [2.3%]); pneumonitis (17 subjects [2.2%]); upper gastrointestinal haemorrhage (15 subjects [1.9%]); ascites (13 subjects [1.7%]); gastrointestinal haemorrhage (12 subjects [1.5%]); overdose; and pulmonary embolism (11 subjects each [1.4%]); and dysphagia; and sepsis (10 subjects each [1.3%]). Those reported by ≥10 subjects in the IC group were malignant neoplasm progression (90 subjects [11.7%]); vomiting (24 subjects [3.1%]); dysphagia (16 subjects [2.1%]); pulmonary embolism (13 subjects [1.7%]); diarrhoea (12 subjects [1.6%]); and pneumonia; and pyrexia (10 subjects each [1.3%]). A causal relationship to study drug could not be ruled out for diarrhoea; and pneumonitis (17 subjects each); febrile neutropenia (16 subjects); vomiting (12 subjects); anaemia (11 subjects); pyrexia (8 subjects); pneumonia (4 subjects); gastrointestinal haemorrhage; and sepsis (2 subjects each); and pulmonary embolism; upper gastrointestinal haemorrhage; and ascites (1 subject each) in the nivolumab/IC group; and vomiting (18

subjects); diarrhoea (10 subjects); decreased appetite (8 subjects); pyrexia (3 subjects); and pulmonary embolism; and pneumonia (2 subjects each) in the IC group.

Adverse events leading to study drug discontinuation occurred in 371 of 782 subjects (47.4%) in the nivolumab/IC group and 251 of 767 subjects (32.7%) in the IC group. Those reported by ≥10 subjects in the nivolumab/IC group were peripheral neuropathy (61 subjects [7.8%]); malignant neoplasm progression (37 subjects [4.7%]); peripheral sensory neuropathy (35 subjects [4.5%]); diarrhoea (16 subjects [2.0%]); platelet count decreased; and infusion related reaction (15 subjects each [1.9%]); thrombocytopenia; and pneumonitis (13 subjects each [1.7%]); and neutrophil count decreased (11 subjects [1.4%]). Those reported by ≥10 subjects in the IC group were peripheral neuropathy (41 subjects [5.3%]); peripheral sensory neuropathy (36 subjects [4.7%]); malignant neoplasm progression (28 subjects [3.7%]); thrombocytopenia (12 subjects [1.6%]); neutrophil count decreased (11 subjects [1.4%]); and platelet count decreased (10 subjects [1.3%]). A causal relationship to study drug could not be ruled out for peripheral neuropathy (59 subjects); peripheral sensory neuropathy (35 subjects); diarrhoea (15 subjects); infusion related reaction (14 subjects); platelet count decreased; thrombocytopenia; and pneumonitis (13 subjects each); and neutrophil count decreased (10 subjects) in the nivolumab/IC group and peripheral neuropathy (40 subjects); peripheral sensory neuropathy (36 subjects); thrombocytopenia (12 subjects); and platelet count decreased; and neutrophil count decreased (10 subjects each) in the IC group.

7.3.2 Adverse events etc. observed in clinical study in the adjuvant therapy of esophageal cancer

7.3.2.1 Global phase III study (Study 43)

Adverse events occurred in 510 of 532 subjects (95.9%) in the nivolumab group and 243 of 260 subjects (93.5%) in the placebo group, and those for which a causal relationship to study drug could not be ruled out occurred in 376 of 532 subjects (70.7%) in the nivolumab group and 119 of 260 subjects (45.8%) in the placebo group. Adverse events reported by ≥10% of subjects in either group are shown in Table 29.

Table 29. Adverse events reported by ≥10% of subjects in either group

SOC PT (MedDRA ver.23.0)	n (%)			
	Nivolumab N = 532		Placebo N = 260	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	510 (95.9)	192 (36.1)	243 (93.5)	90 (34.6)
Gastrointestinal disorders				
Diarrhoea	155 (29.1)	5 (0.9)	76 (29.2)	2 (0.8)
Nausea	121 (22.7)	4 (0.8)	55 (21.2)	0
Vomiting	80 (15.0)	3 (0.6)	42 (16.2)	3 (1.2)
Dysphagia	69 (13.0)	4 (0.8)	43 (16.5)	9 (3.5)
Abdominal pain	62 (11.7)	3 (0.6)	37 (14.2)	3 (1.2)
Constipation	61 (11.5)	0	32 (12.3)	0
Gastrooesophageal reflux disease	41 (7.7)	1 (0.2)	34 (13.1)	0
General disorders and administration site conditions				
Fatigue	144 (27.1)	7 (1.3)	63 (24.2)	3 (1.2)
Respiratory, thoracic and mediastinal disorders				
Cough	98 (18.4)	1 (0.2)	48 (18.5)	1 (0.4)
Dyspnoea	54 (10.2)	3 (0.6)	27 (10.4)	1 (0.4)
Skin and subcutaneous tissue disorders				
Pruritus	68 (12.8)	2 (0.4)	16 (6.2)	0
Rash	63 (11.8)	4 (0.8)	17 (6.5)	1 (0.4)
Investigations				
Weight decreased	69 (13.0)	2 (0.4)	23 (8.8)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	53 (10.0)	1 (0.2)	21 (8.1)	0
Metabolism and nutrition disorders				
Decreased appetite	79 (14.8)	5 (0.9)	26 (10.0)	2 (0.8)
Nervous system disorders				
Headache	41 (7.7)	1 (0.2)	29 (11.2)	0
Endocrine disorders				
Hypothyroidism	56 (10.5)	0	4 (1.5)	0

Serious adverse events occurred in 158 of 532 subjects (29.7%) in the nivolumab group and 78 of 260 subjects (30.0%) in the placebo group. Those reported by ≥5 subjects in the nivolumab group were pneumonia (16 subjects [3.0%]); malignant neoplasm progression (12 subjects [2.3%]); pneumonia aspiration (7 subjects [1.3%]); dysphagia; and pneumonitis (6 subjects each [1.1%]); and pleural effusion (5 subjects [0.9%]). Those reported by ≥5 subjects in the placebo group were malignant neoplasm progression (8 subjects [3.1%]); and pneumonia; and dysphagia (5 subjects each [1.9%]). A causal relationship to study drug could not be ruled out for 6 cases of pneumonitis and 2 cases of pneumonia in the nivolumab group.

Adverse events leading to study drug discontinuation occurred in 68 of 532 subjects (12.8%) in the nivolumab group and 20 of 260 subjects (7.7%) in the placebo group. Those reported by ≥3 subjects in the nivolumab group were pneumonitis (10 subjects [1.9%]); malignant neoplasm progression (5 subjects [0.9%]); and myocarditis; and rash (3 subjects each [0.6%]). Those reported by ≥3 subjects in the placebo group were malignant neoplasm progression (4 subjects [1.5%]). A causal relationship to study drug could not be ruled out for 10 cases of pneumonitis, 3 cases of myocarditis, and 3 cases of rash in the nivolumab group.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that as the application data as a whole were collected and generated in accordance with the reliability criteria, there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding in CTD 5.3.5.1-1 (esophageal cancer), although the finding had no significant impact on the overall assessment of the studies. The applicant was notified of this matter and asked for a corrective action.

Finding requiring corrective action

Sponsor

- A clinical study report was prepared using case report forms containing some data that had not been reviewed by the investigator.

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

The new drug application data (CTD 5.3.5.1-1, CTD 5.3.5.1-2, CTD 5.3.5.1-4 [gastric cancer], CTD 5.3.5.1-1 [esophageal cancer]) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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 nivolumab has efficacy in (i) the treatment of unresectable, advanced or recurrent gastric cancer and (ii) the adjuvant therapy of esophageal cancer, and that nivolumab has acceptable safety in view of its benefits. Thus, nivolumab is clinically meaningful because it offers a treatment option.

PMDA considers that the indications, dosage and administration, etc., need to be further discussed.

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

Review Report (2)

October 15, 2021

Product Submitted for Approval

Brand Name	Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 120 mg, Opdivo Intravenous Infusion 240 mg
Non-proprietary Name	Nivolumab (Genetical Recombination)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	December 10, 2020, February 18, 2021[43)]

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

In view of the discussions presented in Sections "7.1.R.2 Efficacy" and "7.2.R.2 Efficacy" in the Review Report (1), PMDA concluded as follows regarding the efficacy of (i) nivolumab/IC in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy and (ii) nivolumab in patients with resected esophageal cancer who have not achieved pCR following neoadjuvant chemoradiotherapy.

(i) Since a global phase III study (Study 44) and a global phase II/III study (Study 37) in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy etc. produced the following results, etc., the efficacy of nivolumab was demonstrated in these patients.

- Study 44 demonstrated the superiority of nivolumab/IC over IC in the dual primary endpoint of OS in the CPS ≥5 population. When secondary endpoints were tested in accordance with the pre-specified procedure and allocation of alpha, nivolumab/IC demonstrated a statistically significant improvement in OS in the CPS ≥1 population and in the ITT population versus IC.

43) (i) A partial change application for a new indication and a new dosage concerning unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy and (ii) a partial change application for a new indication and a new dosage concerning adjuvant therapy of esophageal cancer were submitted on(i) December 10, 2020 and (ii) February 18, 2021, respectively.

- Study 37 demonstrated the superiority of nivolumab/IC over placebo/IC in the dual primary endpoint of PFS.

(ii) Since a global phase III study in patients with resected esophageal cancer who had not achieved pCR following neoadjuvant chemoradiotherapy (Study 43) demonstrated the superiority of nivolumab over placebo in the primary endpoint of DFS, etc., the efficacy of nivolumab was demonstrated in these patients.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.2 Safety

PMDA's conclusion:

In view of the discussions presented in Sections "7.1.R.3 Safety" and "7.2.R.3 Safety" in the Review Report (1), adverse events that require attention following administration of (i) nivolumab/IC in patients with HER2-negative, unresectable, advanced or recurrent gastric cancer previously untreated with chemotherapy and (ii) nivolumab in patients with resected esophageal cancer are the events that were considered to require attention at the time of approval etc. of the applications for the approved indications.[44)] As with use in the approved indications, attention should be paid to the possible occurrence of these adverse events during treatment with nivolumab.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with nivolumab, nivolumab is tolerable also in the above cases (i) and (ii) as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and interruption of nivolumab and the concomitant antineoplastic drugs.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.3 Indications etc.

PMDA's conclusion:

In view of the discussions presented in Sections "7.1.R.5 Indication" and "7.2.R.4 Clinical positioning and indications" in the Review Report (1), the appropriate statements in the "INDICATIONS" and "PRECAUTIONS CONCERNING INDICATIONS" sections for (i) unresectable, advanced or recurrent gastric cancer and (ii) adjuvant therapy of esophageal cancer are as shown in the table below.

44) ILD; hepatic function disorder; abnormal thyroid function; pituitary dysfunction; infusion reaction; skin disorder; colitis, enteritis, and severe diarrhoea; myasthenia gravis, myocarditis, rhabdomyolysis, and myositis; neurological disorder; renal disorder; venous thromboembolism; adrenal disorder; encephalitis; type 1 diabetes mellitus; serious blood disorder; cardiac disorder; tuberculosis; and pancreatitis (see "Review Report on Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 120 mg, and Opdivo Intravenous Infusion 240 mg, dated July 13, 2021" etc.)

	Indications	Precautions concerning indications
(i)	Unresectable, advanced or recurrent gastric cancer	• The efficacy and safety of Opdivo in adjuvant therapy have not been established.
(ii)	Adjuvant therapy of esophageal cancer	• Opdivo should be administered to patients who have not achieved a pathological complete response (pCR) following neoadjuvant therapy. • The efficacy and safety of Opdivo in neoadjuvant therapy have not been established. • Eligible patients must be selected based on a careful review of the content of the "CLINICAL STUDIES" section, particularly regarding prior therapies of patients enrolled in the clinical study, the definition of pCR, etc., and a thorough understanding of the efficacy and safety of Opdivo.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

On the basis of the above, PMDA instructed the applicant to revise the "INDICATIONS" and "PRECAUTIONS CONCERNING INDICATIONS" sections as shown above. The applicant agreed.

1.4 Dosage and administration etc.

PMDA's conclusion:

In view of the discussions presented in Sections "7.1.R.4 Clinical positioning and dosage and administration" and "7.2.R.5 Dosage and administration" in the Review Report (1), the appropriate statements in the "DOSAGE AND ADMINISTRATION" and "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" sections for (i) unresectable, advanced or recurrent gastric cancer and (ii) adjuvant therapy of esophageal cancer are as shown in the table below.

	Dosage and administration	Precautions concerning dosage and administration
(i)	The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. When administered in combination with other antineoplastic drugs, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 360 mg administered as an intravenous infusion every 3 weeks.	• Opdivo should be intravenously infused over at least 30 minutes. • The efficacy and safety of Opdivo monotherapy have not been established in first- or second-line treatment. • When administered in combination with other antineoplastic drugs, Opdivo should be used in HER2-negative patients. • The efficacy of Opdivo in combination with other antineoplastic drugs tends to differ according to the percentage of PD-L1 expression (CPS). The necessity of the addition of Opdivo should be carefully determined based on a careful review of the content of the "CLINICAL STUDIES" section, particularly regarding CPS, and a thorough understanding of the efficacy and safety of Opdivo. • When administered in combination with other antineoplastic drugs, other antineoplastic drugs to be combined should be selected based on a careful review of the content of the "CLINICAL STUDIES" section.
(ii)	The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of esophageal cancer, the maximum duration of treatment is 12 months.	• Opdivo should be intravenously infused over at least 30 minutes. • The efficacy and safety of Opdivo in combination with other antineoplastic drugs have not been established.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

On the basis of the above, PMDA instructed the applicant to revise 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 Sections "7.1.R.6 Post-marketing investigations" and "7.2.R.6 Post-marketing investigations" in the Review Report (1), PMDA concluded that at present, there is little need to conduct post-marketing surveillance in patients with (i) gastric cancer or (ii) esophageal cancer, immediately after obtaining approval, and that the applicant may collect safety information through routine pharmacovigilance practices.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for nivolumab should include the safety and efficacy specifications presented in Table 30, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 31.

Table 30. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Myasthenia gravis, myocarditis, myositis, rhabdomyolysis • Colitis, enteritis, severe diarrhoea • Type 1 diabetes mellitus • Hepatitis fulminant, hepatic failure, hepatic function disorder, hepatitis, cholangitis sclerosing • Endocrine disorder (thyroid dysfunction, pituitary dysfunction, adrenal disorder) • Neurological disorder • Renal disorder • Encephalitis • Severe skin disorder • Venous thromboembolism • Infusion reaction • Serious blood disorder • Haemophagocytic syndrome • Tuberculosis • Pancreatitis • Use of nivolumab in patients with a history of organ transplant (including haematopoietic stem cell transplant)	• Excessive immunisation reaction • Embryonic/fetal toxicity • Cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles, etc.) • Aplasia pure red cell • Tumor haemorrhage • Fistula • Increased risk of severe complication associated with allogeneic haematopoietic stem cell transplant after nivolumab therapy (haematopoietic neoplasm)	None
Efficacy specification		
• Efficacy in patients with unresectable malignant melanoma in clinical practice • Efficacy in adult patients with relapsed or refractory cHL in clinical practice • Efficacy in patients with unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy in clinical practice		

No changes have been made for the present partial change applications.

Table 31. 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, nivolumab monotherapy) • Specified use-results survey in adult patients with relapsed or refractory cHL (all-case surveillance) • Specified use-results survey in patients with unresectable malignant melanoma (nivolumab/IPI therapy) • Specified use-results survey in patients with unresectable or metastatic RCC (nivolumab/IPI therapy) • Use-results survey in patients with unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy (nivolumab monotherapy) • Specified use-results survey in pediatric patients with relapsed or refractory cHL (all-case surveillance) • Post-marketing clinical studies in the approved indications[*1]	• Use-results survey in patients with unresectable malignant melanoma (all-case surveillance, nivolumab monotherapy) • Specified use-results survey in adult patients with relapsed or refractory cHL (all-case surveillance) • Post-marketing clinical studies in the approved indications[*2]	• Organize and disseminate information materials for healthcare professionals. • Organize and disseminate information materials for patients.

Underline denotes activities to be performed for the additional indications and dosage regimens. Wavy line denotes activities added after the present partial change applications were submitted. *1: 11 studies are ongoing. *2: 5 studies are ongoing.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below with the following condition, provided that the necessary precautions 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 properly used under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy, at medical institutions capable of emergency response.

Indications (Underline denotes additions. Strikethrough denotes deletions. Double line denotes changes made as of May 27, 2021 after submission of the present partial change applications.)

- ○ Treatment of malignant melanoma
- ○ Treatment of unresectable, advanced or recurrent non-small cell lung cancer
- ○ Treatment of unresectable or metastatic renal cell carcinoma
- ○ Treatment of relapsed or refractory classical Hodgkin lymphoma
- ○ Treatment of recurrent or metastatic head and neck cancer
- ○ Treatment of unresectable, advanced or recurrent gastric cancer ~~that has progressed after cancer chemotherapy~~
- ○ Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma ~~that has progressed after cancer chemotherapy~~
- ○ Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy
- ○ Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy

○ Adjuvant therapy of esophageal cancer

Dosage and administration (Underline denotes additions. Strikethrough denotes deletions. Double line denotes changes made as of May 27, 2021, August 25, 2021, or September 27, 2021 after submission of the present applications.)

Treatment of malignant melanoma
The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months.
In combination therapy with ipilimumab (genetical recombination) for unresectable malignant melanoma, the usual adult dosage of nivolumab (genetical recombination) is 80 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

Treatment of unresectable, advanced or recurrent non-small cell lung cancer, unresectable, advanced or recurrent gastric cancer ~~that has progressed after cancer chemotherapy~~
The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.
When administered in combination with other antineoplastic drugs, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 360 mg administered as an intravenous infusion every 3 weeks.

Treatment of unresectable or metastatic renal cell carcinoma
The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.
When administered in combination with cabozantinib, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.
When administered in combination with ipilimumab (genetical recombination) to chemotherapy-naïve patients with unresectable or metastatic renal cell carcinoma, the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

Treatment of relapsed or refractory classical Hodgkin lymphoma
The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.
The usual pediatric dosage of nivolumab (genetical recombination) is 3 mg/kg (body weight) administered as an intravenous infusion every 2 weeks. For pediatric patients weighing ≥40 kg, nivolumab (genetical

recombination) may be administered as an intravenous infusion at 240 mg every 2 weeks or at 480 mg every 4 weeks.

Treatment of recurrent or metastatic head and neck cancer

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma ~~that has progressed after cancer chemotherapy~~

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

When administered in combination with ipilimumab (genetical recombination), the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 360 mg administered as an intravenous infusion every 3 weeks.

Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

When administered in combination with ipilimumab (genetical recombination), the usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy, adjuvant therapy of esophageal cancer

The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of esophageal cancer, the maximum duration of treatment is 12 months.

~~**Treatment of relapsed or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy, unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy**~~

~~The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.~~

Approval Condition

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

Warnings (No change)

1. Opdivo should be administered only to patients who are considered eligible for its use under the supervision of physicians with sufficient knowledge of and experience with cancer chemotherapy at medical institutions with adequate facilities to respond to emergencies. Prior to the start of therapy, the benefits and risks of the therapy should be thoroughly explained to the patient or his/her family members and consent must be obtained.
2. There have been reports of patients who died after experiencing interstitial lung disease. Patients should be closely monitored for initial symptoms (e.g., shortness of breath, dyspnoea, coughing, and fatigue) and examined by chest X-ray. In the event of an abnormality being found, the administration of Opdivo should be discontinued and appropriate actions such as the introduction of corticosteroid therapy should be taken.

Contraindication (No change)

Patients with a history of hypersensitivity to the ingredients of Opdivo

Precautions Concerning Indications (Underline denotes additions. Strikethrough denotes deletions. Double line denotes changes made as of May 27, 2021 or August 25, 2021 after submission of the present applications.)

Malignant melanoma

1. Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of Opdivo presented in the "CLINICAL STUDIES" section.

Unresectable, advanced or recurrent non-small cell lung cancer

2. Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of Opdivo presented in the "CLINICAL STUDIES" section, particularly regarding the characteristics, such as presence or absence of *EGFR* mutations or *ALK* rearrangements of patients enrolled in the clinical study.
3. The efficacy and safety of Opdivo in adjuvant therapy have not been established.

Unresectable or metastatic renal cell carcinoma

4. The use of Opdivo <u>in combination with ipilimumab (genetical recombination)</u> for the treatment of chemotherapy-naïve patients should be limited to IMDC[Note)] intermediate- or poor-risk patients.
5. The efficacy and safety of Opdivo in adjuvant therapy have not been established.
6. Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of Opdivo presented in the "CLINICAL STUDIES" section.

Relapsed or refractory classical Hodgkin lymphoma

7. Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of Opdivo presented in the "CLINICAL STUDIES" section.

Recurrent or metastatic head and neck cancer

8. The efficacy and safety of Opdivo have not been established in platinum-based chemotherapy-naïve patients.
9. The efficacy and safety of Opdivo in adjuvant therapy have not been established.

10. Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of Opdivo presented in the "CLINICAL STUDIES" section.

Unresectable, advanced or recurrent gastric cancer ~~that has progressed after cancer chemotherapy~~

~~11. The efficacy and safety of Opdivo have not been established in first- or second-line treatment.~~

11. ~~12~~.The efficacy and safety of Opdivo in adjuvant therapy have not been established.

Unresectable, advanced or recurrent malignant pleural mesothelioma ~~that has progressed after cancer chemotherapy~~

~~13. The efficacy and safety of Opdivo as a first-line treatment have not been established.~~

12. ~~14~~. The efficacy and safety of Opdivo in adjuvant or neoadjuvant therapy have not been established.

Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy

13. ~~15~~. The efficacy and safety of Opdivo have not been established in patients who have not received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan hydrochloride hydrate.
14. ~~16~~. Opdivo should be administered to patients who have been demonstrated to have a MSI-High cancer by a highly experienced pathologist or at a laboratory facility using the approved *in vitro* diagnostic or medical device.
15. ~~17~~. Eligible patients must be selected by physicians with adequate knowledge in the efficacy and safety of Opdivo, after fully understanding the "CLINICAL STUDIES" section, and carefully considering the choice of alternative therapies.
16. ~~18~~. The efficacy and safety of Opdivo in adjuvant therapy have not been established.

Unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy

17. ~~19~~. The efficacy and safety of Opdivo as a first-line treatment have not been established.

~~20. The efficacy and safety of Opdivo in adjuvant or neoadjuvant therapy have not been established.~~

18. ~~21~~. Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of Opdivo presented in the "CLINICAL STUDIES" section.

Adjuvant therapy of esophageal cancer

19. Opdivo should be administered to patients who have not achieved a pathological complete response (pCR) following neoadjuvant therapy.
20. The efficacy and safety of Opdivo in neoadjuvant therapy have not been established.
21. Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of Opdivo presented in the "CLINICAL STUDIES" section, particularly regarding the characteristics, such as prior therapies of patients enrolled in the clinical study and the definition of pCR.

Note) International Metastatic RCC Database Consortium

Precautions Concerning Dosage and Administration (Underline denotes additions. Strikethrough denotes deletions. Double line denotes changes made as of May 27, 2021 after submission of the present applications.)

All indications

1. Opdivo should be intravenously infused over at least 30 minutes.

Malignant melanoma

2. When administered in combination with ipilimumab (genetical recombination) to patients with unresectable malignant melanoma, the necessity of the combination therapy should be carefully determined based on a careful review of the content of the "CLINICAL STUDIES" section, particularly regarding the characteristics, such as prior treatments, of patients enrolled in clinical studies, and a thorough understanding of the efficacy and safety of Opdivo. The add-on effect of ipilimumab (genetical recombination) to Opdivo on survival prolongation tends to differ according to the percentage of tumor cells expressing PD-L1 (PD-L1 expression rate). In patients who have been confirmed to have a high PD-L1 expression rate, Opdivo monotherapy should also be carefully considered before initiating Opdivo/ipilimumab (genetical recombination) therapy.

Unresectable, advanced or recurrent non-small cell lung cancer

3. The efficacy and safety of Opdivo monotherapy have not been established in chemotherapy-naïve patients.
4. When administered in combination with other antineoplastic drugs, other antineoplastic drugs to be combined should be selected based on a careful review of the content of the "CLINICAL STUDIES" section, after taking account of the PD-L1 expression rate of patients included in clinical studies.

Unresectable or metastatic renal cell carcinoma

5. The efficacy and safety of Opdivo monotherapy have not been established in chemotherapy-naïve patients or patients who have received cytokine therapy as the only prior treatment.

Relapsed or refractory classical Hodgkin lymphoma

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

Recurrent or metastatic head and neck cancer

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

Unresectable, advanced or recurrent gastric cancer ~~that has progressed after cancer chemotherapy~~

8. The efficacy and safety of Opdivo monotherapy ~~in combination with other antineoplastic drugs~~ have not been established in first- or second-line treatment.
9. When administered in combination with other antineoplastic drugs, Opdivo should be used in HER2-negative patients.
10. The efficacy of Opdivo in combination with other antineoplastic drugs tends to differ according to the percentage of PD-L1 expression (CPS). The necessity of the addition of Opdivo should be carefully determined based on a careful review of the content of the "CLINICAL STUDIES" section, particularly regarding CPS, and a thorough understanding of the efficacy and safety of Opdivo.
11. When administered in combination with other antineoplastic drugs, other antineoplastic drugs to be combined should be selected based on a careful review of the content of the "CLINICAL STUDIES" section.

Unresectable, advanced or recurrent malignant pleural mesothelioma ~~that has progressed after cancer chemotherapy~~

129. The efficacy and safety of Opdivo monotherapy ~~in combination with other antineoplastic drugs~~ have not been established in chemotherapy-naïve patients.

Unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy

13~~10~~. The efficacy and safety of Opdivo in combination with other antineoplastic drugs have not been established.

Adjuvant therapy of esophageal cancer

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

Appendix

List of Abbreviations

AJCC	American Joint Committee on Cancer
AST	aspartate aminotransferase
BID	bis in die
BIRC	blinded independent review committee
Cape	capecitabine
Cape/CDDP	a combination of Cape and CDDP
CAPOX	a combination of Cape and OX
CBDCA	carboplatin
CBDCA/GEM	a combination of CBDCA and GEM
CBDCA/PEM	a combination of CBDCA and PEM
CBDCA/PTX	a combination of CBDCA and PTX
CDDP	cisplatin
CDDP/GEM	a combination of CDDP and GEM
CDDP/PEM	a combination of CDDP and PEM
cHL	classical Hodgkin lymphoma
CI	confidence interval
CPS	combined positive score: the number of PD-L1 stained cells (tumor cells, macrophages, and lymphocytes) divided by the total number of viable tumor cells and multiplied by 100
CR	complete response
DFS	disease-free survival
DTX	docetaxel hydrate
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
FAS	full analysis set
FOLFOX	a combination of 5-FU, LV, and OX
5-FU	fluorouracil
5-FU/CDDP	a combination of 5-FU and CDDP
GEM	gemcitabine hydrochloride
HER2	human epidermal growth factor receptor type 2
IC	investigator's choice
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
IPI	ipilimumab (genetical recombination)
ISH	*in situ* hybridization
ITT	intention-to-treat
Japanese clinical practice guidelines (esophageal cancer)	Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus, edited by the Japan Esophageal Society
Japanese clinical practice guidelines (gastric cancer)	Japanese Gastric Cancer Treatment Guidelines, edited by the Japanese Gastric Cancer Association
LV	leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCCN guidelines (esophageal cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Esophageal and Esophagogastric Junction Cancers
NCCN guidelines (gastric cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Gastric Cancer
nivolumab	nivolumab (genetical recombination)
nivolumab/CAPOX	a combination of nivolumab and CAPOX

nivolumab/chemotherapy	a combination of nivolumab and chemotherapy
nivolumab/IC	a combination of nivolumab and IC
nivolumab/IPI	a combination of nivolumab and IPI
nivolumab/IPI/chemotherapy	a combination of nivolumab, IPI, and chemotherapy
nivolumab/SOX	a combination of nivolumab and SOX
NSCLC	non-small cell lung cancer
OS	overall survival
OX	oxaliplatin
Partial change application	application for partial change of marketing approval
pCR	pathological CR
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PEM	pemetrexed sodium hydrate
pembrolizumab	pembrolizumab (genetical recombination)
PFS	progression free survival
PK	pharmacokinetics
Placebo/IC	a combination of placebo and IC
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
PTX	paclitaxel
PTX/RAM	a combination of PTX and RAM
QOL	quality of life
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
Q4W	quaque 4 weeks
RAM	ramucirumab (genetical recombination)
RECIST	Response Evaluation Criteria in Solid Tumors
S-1	a combination formulation of tegafur, gimeracil, and oteracil potassium
S-1/CDDP	a combination of S-1 and CDDP
SOC	system organ class
SOX	a combination of S-1 and OX
Study 001	Study CA209001
Study 003	Study CA209003
Study 017	Study CA209017
Study 057	Study CA209057
Study 07	Study ONO-4538-07
Study 227	Study ONO-4538-27/CA209227
Study 37	Study ONO-4538-37
Study 43	Study ONO-4538-43/CA209577
Study 44	Study ONO-4538-44/CA209649
Study 473	Study ONO-4538-24/BMS CA209473
Study 9LA	Study ONO-4538-77/CA2099LA
trastuzumab	trastuzumab (genetical recombination)
TPS	tumor proportion score: the percentage of PD-L1 positive tumor cells relative to all viable tumor cells present
TTSD	time to symptom deterioration