Review Report

January 9, 2020
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg
Non-proprietary Name	Nivolumab (Genetical Recombination) (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	March 28, 2019, May 30, 2019[1)]
Dosage Form/Strength	Injection: Each vial of 2, 10, or 24 mL contains 20, 100, or 240 mg of nivolumab (genetical recombination)
Application Classification	Prescription drug, (4) Drug with new indications
Items Warranting Special Mention	Priority review (PSEHB/PED Notification No. 0725-2 dated July 25, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has (a) a certain level of efficacy in the treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy, and (b) efficacy in the treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy, and that the product has acceptable safety in view of its benefits (see the Attachment).

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

Indications

1. Treatment of malignant melanoma
2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer

1) Applications for partial change in new indications for (a) MSI-High colorectal cancer and (b) esophageal cancer were filed on (a) March 28, 2019 and (b) May 30, 2019, respectively.

3. Treatment of unresectable or metastatic renal cell carcinoma
4. Treatment of relapsed or refractory classical Hodgkin lymphoma
5. Treatment of recurrent or metastatic head and neck cancer
6. Treatment of unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy
7. Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy
8. Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy
9. Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy

(Underline denotes additions.)

Dosage and Administration

1. Treatment of malignant melanoma

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

   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.
3. Treatment of unresectable, advanced or recurrent non-small cell lung cancer, 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 microsatellite instability-high (MSI-High) colorectal cancer that has

progressed after cancer chemotherapy, or 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.

(Underline denotes additions.)

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

December 6, 2019

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 240 mg
Non-proprietary Name	Nivolumab (Genetical Recombination)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	March 28, 2019, May 30, 2019[2)]
Dosage Form/Strength	Injection: Each vial of 2, 10, or 24 mL contains 20, 100, or 240 mg of nivolumab (genetical recombination).
Proposed Indications	1. Treatment of malignant melanoma 2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer 3. Treatment of unresectable or metastatic renal cell carcinoma 4. Treatment of relapsed or refractory classical Hodgkin lymphoma 5. Treatment of recurrent or metastatic head and neck cancer 6. Treatment of unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy 7. Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy 8. Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy 9. Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy (Underline denotes additions.)
Proposed Dosage and Administration	1. Treatment of malignant melanoma The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks.

2) Applications for partial change in new indications for (a) MSI-High colorectal cancer and (b) esophageal cancer were filed on (a) March 28, 2019 and (b) May 30, 2019, respectively.

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.

2. 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.

   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.

3. Treatment of unresectable, advanced or recurrent non-small cell lung cancer, 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 microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy, or 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.

(Underline denotes additions.)

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), a human monoclonal antibody against human programmed cell death-1 (PD-1) belonging to the immunoglobulin (Ig) G4 subclass, was developed by Ono Pharmaceutical Co., Ltd. and by Medarex in the US (currently known as Bristol-Myers Squibb). Nivolumab is considered to bind to the extracellular domain of PD-1 (PD-1 ligand binding site) and block the interaction between PD-1 and PD-1 ligands, thereby enhancing the activation of cancer antigen-specific T cells and cytotoxic activation against cancer cells, 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, and (g) "unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy" in August 2018. The above indication (a) was modified to "malignant melanoma" in August 2018.

Recently, the applicant submitted the following applications for partial change in new indications for (i) microsatellite instability-high (MSI-High) colorectal cancer and (ii) esophageal cancer, on different days in a short period (i.e., (i) March 28, 2019 and (ii) May 30, 2019, respectively). This review report summarizes the reviews of both applications. In this review report, "MSI-High patients" are expressed as (a) "MSI-High patients," when the term refers to patients in whom a deficiency of the DNA mismatch repair system was detected via either polymerase chain reaction (PCR) or immunohistochemistry (IHC) assay (broad term), and as (b) "MSI-High (PCR) patients," when the term refers to patients in whom a deficiency of the DNA mismatch repair system was detected specifically via PCR (narrow term).

1.2 Development history etc.

1.2.1 Treatment of MSI-High colorectal cancer [(i) in Section 1.1; see Section 7.1 for an outline of the review]

Outside Japan, Bristol-Myers Squibb initiated a foreign phase II study in chemotherapy-treated patients with unresectable, advanced or recurrent mismatch repair deficient (dMMR) or MSI-High colorectal cancer (Study 142) in March 2014. With the results of Study 142 serving as pivotal data, the applicant has recently filed an application for partial change for nivolumab to add an indication for MSI-High colorectal cancer.

In the US, an approval application based on the pivotal data from Study 142 was filed in February 2017, and nivolumab received accelerated approval for the following indication in July 2017: "OPDIVO is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval

based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of the clinical benefit in confirmatory trials."

As of October 2019, nivolumab has been approved for the treatment of MSI-High colorectal cancer in 3 countries and regions.

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

Outside Japan, the applicant initiated a global phase III study in patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine- and platinum-based chemotherapy (Study 473) in December 2015.

In Japan, the applicant initiated a Japanese phase II study in patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine-, platinum-, and taxane-based chemotherapy (Study 07) in February 2014. Patient enrollment in Study 473 began in Japan in [redacted] 20[redacted].

With the results of Study 473 serving as pivotal data, the applicant has now filed an application for partial change for nivolumab to add an indication for esophageal cancer.

As of October 2019, there is no country or region that has approved nivolumab for the treatment of esophageal cancer.

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

Because the present applications are intended for new indications, 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, 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, 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, no new toxicity data have been submitted.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Analytical procedures

In Study 142, (a) dMMR and (b) MSI-High were assessed using (a) an IHC assay and (b) a PCR assay, respectively. A partial change application for "MSI test kit (FALCO)," a PCR assay developed by FALCO biosystems Ltd., was submitted on November 1, 2019, as an *in vitro* diagnostics to assist assessment of patient suitability for nivolumab therapy.

6.2 Clinical pharmacology

The applicant's explanation:

The submitted results from Studies 142, 07, and 473 showed no clear differences in the pharmacokinetics of nivolumab among cancer types.

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 and other relevant properties of nivolumab was acceptable.

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

7.1 Data concerning the treatment of MSI-High colorectal cancer and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of result data from the following 6 clinical studies: a Japanese phase II study, a global phase II study, a global phase III study, a foreign phase Ib study, a foreign phase I/II study, and a foreign phase II study (Table 1).

Table 1. Clinical studies on efficacy and safety

Data type	Region	Study identifier	Phase	Study population	Number of patients*	Brief description of dosage regimen	Main endpoints
Evaluation data	Japan	Study 39	II	Chemotherapy-treated patients with unresectable, advanced or recurrent uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma	2	Nivolumab 240 mg intravenously every 2 weeks	Efficacy Safety
	Global	Study 275	II	Patients with unresectable urothelial carcinoma who previously received platinum-containing chemotherapy	2	Nivolumab 3 mg/kg intravenously every 2 weeks	Efficacy Safety
		Study 12	III	Patients with unresectable, advanced or recurrent gastric cancer who previously received ≥2 prior chemotherapies	1	Nivolumab 3 mg/kg intravenously every 2 weeks	Efficacy Safety
	Foreign	Study 009	Ib	Patients with metastatic clear-cell RCC	2	Nivolumab 0.3, 2, or 10 mg/kg intravenously every 3 weeks	Tolerability Safety
		Study 032	I/II	Gastric cancer cohort: Chemotherapy-treated patients with unresectable, advanced or recurrent gastric cancer	7	Nivolumab 3 mg/kg intravenously every 2 weeks	Efficacy Safety
		Study 142	II	Monotherapy stage: Chemotherapy-treated patients with unresectable, advanced or recurrent dMMR or MSI-High (PCR) colorectal cancer	74	Nivolumab 3 mg/kg intravenously every 2 weeks	Efficacy Safety

*, Number of patients with dMMR or MSI-High cancers who received nivolumab

A summary of each clinical study is presented below. Common adverse events other than deaths reported in these studies are detailed in Section "7.3.1 Adverse events reported in clinical studies in patients with MSI-High colorectal cancer."

7.1.1 Evaluation data

7.1.1.1 Japanese clinical study

7.1.1.1.1 Japanese phase II study (CTD 5.3.5.4-5, Study 39, ongoing since June 2016 [data cutoff on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 7 study sites in Japan to evaluate the efficacy and safety of nivolumab in chemotherapy-treated[3)] patients with unresectable, advanced or recurrent uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma (target sample size: 20 patients for each cancer type).

Patients received nivolumab 240 mg intravenously every 2 weeks, until disease progression or a withdrawal criterion was met.

Of 64 patients enrolled into this study and treated with nivolumab, 2 patients were diagnosed with MSI-High uterine corpus cancer. (This review report describes the results from these 2 patients as data from Study 39.)

The best overall response, as assessed by the investigator using RECIST ver. 1.1, was partial response (PR) in 2 patients.

3) The study enrolled patients with uterine cervical cancer or uterine corpus cancer who previously received ≥1 prior chemotherapies, and patients with soft tissue sarcoma who previously received ≥2 prior chemotherapies.

No deaths were reported during the treatment period or within 28 days after the last dose.

7.1.1.2 Global clinical studies

7.1.1.2.1 Global phase II study (CTD 5.3.5.4-3.1, Study 275, ongoing since March 2015 [data cutoff on April 15, 2016])

An open-label, uncontrolled study was conducted at 63 study sites in 11 countries including Japan to evaluate the efficacy and safety of nivolumab in patients with unresectable urothelial carcinoma who previously received platinum-containing chemotherapy (target sample size: 242 patients).

Patients received nivolumab 3 mg/kg intravenously every 2 weeks, until disease progression or a withdrawal criterion was met.

Of 270 patients enrolled into the study and received nivolumab, 2 were diagnosed with MSI-High. (This review report describes results from these 2 patients [including no Japanese patients] as data from Study 275.)

The best overall response, as assessed by the blinded independent review committee (BIRC) using RECIST ver. 1.1, was complete response (CR) in 1 patient and stable disease (SD) in 1 patient.

No deaths were reported during the treatment period or within 30 days after the last dose.

7.1.1.2.2 Global phase III study (CTD 5.3.5.4-4, Study 12, ongoing since November 2014 [data cutoff on August 13, 2016])

A double-blind, randomized, controlled study was conducted at 49 study sites in 3 countries or regions including Japan to compare the efficacy and safety of nivolumab versus placebo in patients with unresectable, advanced or recurrent gastric cancer who previously received ≥2 prior chemotherapies (target sample size: 290 to 480 patients).

Patients received nivolumab 3 mg/kg or placebo intravenously every 2 weeks, until disease progression or a withdrawal criterion was met.

Of 330 patients enrolled into the study and received nivolumab, 1 patient was diagnosed with MSI-High. (This review report describes results from this patient [a Japanese patient] as data from Study 12.)

The best overall response, as assessed by the investigator using RECIST ver. 1.1, was not evaluable (NE) in 1 patient.

No deaths were reported during the treatment period or within 28 days after the last dose.

7.1.1.3 Foreign clinical studies

7.1.1.3.1 Foreign phase Ib study (CTD 5.3.5.4-1, Study 009, ongoing since September 2011 [data cutoff on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 14 study sites outside Japan to evaluate the tolerability, safety, and other aspects of nivolumab in patients with metastatic clear-cell RCC[4] (target sample size: 80 patients).

Patients received nivolumab 0.3, 2, or 10 mg/kg intravenously every 3 weeks, until disease progression or a withdrawal criterion was met.

Of 91 patients enrolled into the study and received nivolumab, 2 were diagnosed with MSI-High. (This review report describes results from these 2 patients [1 in the 0.3 mg/kg group and 1 in the 2 mg/kg group] as data from Study 009.)

The best overall response, as assessed by the investigator using RECIST ver. 1.1, was SD in 2 patients.

No deaths were reported during the treatment period or within 30 days after the last dose.

7.1.1.3.2 Foreign phase I/II phase study (CTD 5.3.5.4-2.1 and 5.3.5.4-2.2, Study 032, December 2013 to [redacted] 20[redacted] [data cutoff on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 18 study sites outside Japan to evaluate the efficacy, safety, and other aspects of nivolumab monotherapy or in combination with ipilimumab in chemotherapy-treated patients with unresectable, advanced or recurrent solid tumors[5] (target sample size: 100 patients for each cancer type). (This review report describes results from the nivolumab monotherapy group as data from Study 032.)

Patients received nivolumab 3 mg/kg intravenously every 2 weeks, until disease progression or a withdrawal criterion was met.

Of 59 patients enrolled in the gastric cancer cohort and received nivolumab monotherapy, 7 were MSI-High. (This review report describes results from these 7 patients as data from Study 032.)

The best overall response, as assessed by the investigator using RECIST ver. 1.1, was CR in 1 patient, PR in 1 patient, SD in 3 patients, and progressive disease (PD) in 2 patients.

No deaths were reported during the treatment period or within 30 days after the last dose.

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4) Patients with a Karnofsky performance status of ≥70% were enrolled.

5) The study enrolled patients diagnosed with gastric cancer (including gastroesophageal junction cancer and adenocarcinoma arising from the lower esophagus), pancreatic carcinoma, breast cancer, small cell lung cancer, bladder cancer, and ovary cancer.

7.1.1.3.3 Foreign phase II study (CTD 5.3.5.2-1.1, 5.3.5.2-1.2, and 5.3.5.2-1.3, Study 142, ongoing since March 2014 [data cutoff on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of nivolumab monotherapy or in combination with ipilimumab in patients with unresectable, advanced or recurrent colorectal cancer. The study comprised 3 cohorts[6)] of which 1 cohort included chemotherapy-treated[7)] patients with MSI-High[8)] colorectal cancer from 31 study sites outside Japan (target sample size: 48 patients for the nivolumab monotherapy group and 48 for the nivolumab/ipilimumab group). (This review report describes results from the nivolumab monotherapy group in the MSI-High colorectal cancer cohort as data from Study 142.)

Patients in the nivolumab monotherapy group received nivolumab 3 mg/kg intravenously every 2 weeks, until disease progression or a withdrawal criterion was met.

The primary endpoint was response rate, as assessed by the investigator using RECIST ver. 1.1. Initially, this study was planned to use a Simon 2-stage design, assuming a threshold response rate of 30%[9)] and an expected response rate of 52%, with a 1-sided significance level of 0.05, and 90% power.[10)] At the time of planning the study, the efficacy analysis set was to include enrolled patients with colorectal cancer locally assessed as dMMR or MSI-High (PCR) and subsequently confirmed centrally as MSI-High (PCR). However, of the 32 patients enrolled in Stage 1 based on the local assessment, 11 patients were not centrally confirmed as having MSI-High (PCR) colorectal cancer. Therefore, the efficacy analysis set was revised to include patients who were enrolled into the study based on the local assessment. As a result of enrolling additional patients into Stage 2 to ensure that at least 48 patients with centrally confirmed MSI-High (PCR) cancer would receive study treatment,[11)] a total of 74 patients were enrolled and received nivolumab. All of these 74 patients were included in the efficacy analysis set.

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6) The study comprised 3 cohorts: a cohort of patients with MSI-High colorectal cancer after prior chemotherapy, a cohort of patients with [redacted] colorectal cancer with no [redacted], and a cohort of patients with non-microsatellite instability-high (non-MSI-High) colorectal cancer.

7) Patients who received ≥1 prior chemotherapies with (a) fluoropyrimidine and (b) L-OHP or CPT-11.

8) Eligible patients had confirmed colorectal cancer locally assessed as dMMR or MSI-H (PCR). dMMR and MSI-High (PCR) were determined as follows:
- If any of 4 mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) were not detected by IHC assay in a tumor tissue sample, the sample was determined as "dMMR."
- If 5 microsatellite markers from the DNA extracted from a tumor tissue sample were analyzed by PCR assay and an abnormal repeat size was detected in ≥2 of the 5 microsatellites, the sample was determined as "MSI-High (PCR)." Similarly, if ≥6 microsatellite markers were analyzed by PCR assay and an abnormal repeat size was detected in ≥30% of the microsatellite markers, the sample was determined as "MSI-High (PCR)."

9) The threshold response rate was determined based on response rates of 11% to 22.7%, observed in patients receiving standard second-line therapies for unresectable, advanced or recurrent colorectal cancer (i.e., treatments with fluoropyrimidines, L-OHP, CPT-11, or other antitumor drugs which were not used for the first-line therapy) *(J Clin Oncol.* 2007; 25:1539-44, etc.), and response rates of 1.0% and 1.6% with regorafenib and trifluridine/tipiracil hydrochloride, respectively, which are selected as third-line or subsequent treatments (*Lancet.* 2013; 381:303-12, *N Engl J Med.* 2015; 372:1909-19).

10) If ≥7 of 19 patients treated with nivolumab in Stage 1 had a response, Stage 2 would be initiated. In addition, if a total of ≥20 of 48 patients treated with nivolumab in Stages 1 and 2 combined had a response, nivolumab therapy was determined to have expected efficacy.

11) When 19 patients had received nivolumab in Stage 1, it was expected that up to 6 patients would be responders at Week 24, and patient enrollment in the nivolumab monotherapy group was suspended. At Week 60, an additional 1 patient had a response, resulting in a total of 7 responders. Patient enrollment in Stage 2 was then initiated to ensure that at least 48 patients with centrally confirmed MSI-High (PCR) cancer would receive study treatment.

With the above change in the efficacy analysis set, the 2-stage design was no longer used in the efficacy evaluation. Since a larger number of patients than initially planned (48 patients) were included in the efficacy analysis set, the method for calculating the 95% confidence interval (CI) for the response rate was changed from the Atkinson-Brown method to the Clopper-Pearson method. Furthermore, the efficacy of nivolumab as an immune checkpoint inhibitor was to be comprehensively evaluated based on the primary endpoint and other endpoints such as duration of response, and the planned hypothesis tests for the efficacy evaluation were not performed (Statistical Analysis Plan ver. [redacted], dated [redacted], 20[redacted])[12)]

The safety analysis set was the same as the efficacy analysis set.

Table 2 shows the efficacy results based on the primary endpoint, the response rate as assessed by the investigator using RECIST ver. 1.1 (data cutoff on [redacted], 20[redacted]).

Table 2. Best overall response and response rate
(RECIST ver. 1.1, efficacy analysis set, investigator assessment, data cutoff on [redacted], 20[redacted])

Best overall response	Number of patients (%)
	N = 74
CR	0
PR	23 (31.1)
SD	29 (39.2)
PD	18 (24.3)
NE	4 (5.4)
Response (CR + PR) (Response rate [95% CI*] [%])	23 (31.1 [20.8, 42.9])

*, Clopper-Pearson method

Deaths, during the treatment period or within 30 days after the last dose, were reported in 4 of 74 patients (5.4%). The cause of deaths, other than disease progression in 3 patients, was sudden death in 1 patient, for which a causal relationship to nivolumab could not be ruled out.

7.1.R Outline of the review conducted by PMDA for the treatment of MSI-High colorectal cancer

7.1.R.1 Data for review

Of the evaluation data submitted by the applicant, PMDA determined that the foreign phase II study in chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer (Study 142) was important in evaluating the efficacy and safety of nivolumab; therefore, the efficacy and safety of nivolumab were evaluated based primarily on the results of Study 142. The applicant had submitted no clinical study results regarding the efficacy or safety of nivolumab in Japanese patients with MSI-High colorectal cancer for the present partial change application. However, PMDA concluded that the efficacy and safety of nivolumab in Japanese patients can be evaluated based on the results of Study 142, in view of the following findings.

- No clear differences are observed in the pharmacokinetics of nivolumab between Japanese and non-Japanese patients (see “Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated June 18, 2014”).

12 The Statistical Analysis Plan was prepared before the day of database lock ([redacted], 20[redacted])

- There are no large differences in the diagnosis and treatment algorithm for unresectable, advanced or recurrent colorectal cancer, between in and outside Japan.
- No clear differences are observed in the efficacy of nivolumab for the approved indications between Japanese and non-Japanese patients (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg, dated July 26, 2018").

7.1.R.2 Efficacy

On the basis of the discussion presented below, PMDA concluded that a certain level of efficacy of nivolumab have been demonstrated in patients with unresectable, advanced or recurrent MSI-High colorectal cancer who previously received fluoropyrimidine, oxaliplatin (L-OHP), and irinotecan hydrochloride hydrate (CPT-11).

7.1.R.2.1 Efficacy endpoints and efficacy evaluation results

The applicant's explanation about the primary endpoint selected in Study 142 and the efficacy of nivolumab in patients with MSI-High colorectal cancer, taking account of the molecular pathology of MSI-High colorectal cancer:

Microsatellites are repetitive sequences of 1 to several bases located in a wide range of genomes, and are prone to be replicated incorrectly during DNA replication. MSI-High represents a state in which a loss of function of mismatch repair proteins and a subsequent deficiency in the DNA mismatch repair system cause failures to repair DNA replication errors, resulting in abnormally frequent repetitions of microsatellite sequences.

In MSI-High colorectal cancer, somatic cell mutations occur frequently due to the deficiency of DNA mismatch repair system described above. In association with the production of neoantigen that is a target for cancer antigen-specific T cells, a tumor microenvironment with increased cytotoxic T cells, which are activated in tumors, is formed. Meanwhile, immunosuppressive signaling molecules (e.g., PD-1) are highly expressed in MSI-High colorectal cancer, making the cancer cells resistant to tumor rejection (*New Eng J Med.* 2015;372:2509-20, etc.). In view of such findings, nivolumab, an immune checkpoint inhibitor, is expected to have efficacy in the treatment of MSI-High colorectal cancer.

In chemotherapy-treated patients with unresectable, advanced or recurrent colorectal cancer, achieving an objective response would lead to an improvement of the clinical symptoms associated with disease progression (*J Clin Oncol.* 2008;26:2311-9, etc.), and would thus be clinically meaningful. Therefore, Study 142 used response rate as the primary endpoint, and the results of the study showed: (a) the primary endpoint of response rate [95% CI] (%), as assessed by the investigator using RECIST ver. 1.1, was 31.1 [20.8, 42.9] [see Section 7.1.1.3.3], and (b) a secondary endpoint of response rate [95% CI] (%), as assessed by the independent radiology review committee (IRRC) using RECIST ver. 1.1, was 27.0 [17.4, 38.6]. In view of the fact that these response rates were higher than the study results with the existing treatments shown below, nivolumab has expected efficacy in the target patient population of Study 142.

- The response rates with fluoropyrimidine-based chemotherapies were 11% to 22.7% in patients with unresectable, advanced or recurrent colorectal cancer that had progressed after treatment with fluoropyrimidine, and L-OHP or CPT-11 (*J Clin Oncol.* 2007;25:1539-44, etc.).

- The investigator-assessed response rate was 1.0% in the regorafenib group of a global phase III study to evaluate the efficacy and safety of regorafenib versus placebo in patients with unresectable, advanced or recurrent colorectal cancer who had received ≥2 prior chemotherapies and had disease progression after treatment with fluoropyrimidine, L-OHP, CPT-11, and bevacizumab, and — for patients with KRAS wild-type tumors — cetuximab or panitumumab (*Lancet.* 2013;381:303-12).
- The investigator-assessed response rate was 1.6% in the trifluridine/tipiracil hydrochloride group of a global phase III study to evaluate the efficacy and safety of trifluridine/tipiracil hydrochloride versus placebo in patients with unresectable, advanced or recurrent colorectal cancer who had received ≥2 prior chemotherapies and were refractory or intolerant to fluoropyrimidine, L-OHP, CPT-11, and bevacizumab, and — for patients with KRAS wild-type tumors — cetuximab or panitumumab (*N Engl J Med.* 2015;372:1909-19).

Although Study 142 included no Japanese patients, nivolumab is expected to show efficacy in Japanese patients with MSI-High colorectal cancer based on the results of Study 142 and the following reasons.

- In the clinical studies submitted for the present partial change application, 2 of 3 Japanese and 3 of 11 non-Japanese patients with MSI-High solid tumors other than colorectal cancer achieved a response to nivolumab, indicating no clear differences in the efficacy of nivolumab between Japanese and non-Japanese patients.
- MSI-High colorectal cancer and other MSI-High solid tumors have similar tumor biological characteristics; therefore, the efficacy of nivolumab between Japanese and non-Japanese is unlikely to depend on the type of cancer.
- None of the clinical study results from the approved indications of nivolumab (malignant melanoma, NSCLC, RCC, head and neck cancer, and cHL) showed any clear differences in the efficacy of nivolumab between Japanese and non-Japanese patients (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg, dated July 26, 2018," etc.).

In Study 142, the efficacy analysis set was changed to include 74 patients with colorectal cancer locally assessed as dMMR or MSI-High (PCR), after the efficacy evaluation was conducted for Stage 1 of the Simon 2-stage design that had been planned at the start of the study. PMDA asked the applicant to explain the effects of the change in the protocol on the efficacy evaluation.

The applicant's explanation:

Study sites tested microsatellite status via standard assays that are widely used in clinical practice, at laboratories that were certificated under the Clinical Laboratory Improvement Amendments or accredited by the College of American Pathologists, or locally certificated measurement organizations. Therefore, selecting a population comprising the 74 patients with locally assessed dMMR or MSI-High (PCR) colorectal cancer as the efficacy analysis set was appropriate. Further, this change in the protocol was unlikely to influence the efficacy results for nivolumab, for the following and other reasons.

- In the 48 patients who was to comprise the efficacy analysis set as per protocol before the change, the response rate [95% CI] (%) was 33.3 [22.0, 56.6] (Atkinson-Brown method), which was comparable to that in the efficacy analysis set comprised of 74 patients as per the protocol after the amendment.

PMDA's view:
The relationship between overall survival (OS) (the true endpoint) and response rate has not been clarified in patients with unresectable, advanced or recurrent colorectal cancer, and it is thus difficult to evaluate the prolonged survival of nivolumab in such patients based on the results for response rate (the primary endpoint) from Study 142. Further, in Study 142, (a) the lower bound of the 95% CI for the response rate was below the initially-specified threshold response rate (30%), and (b) the efficacy analysis set was changed after conducting the efficacy evaluation for Stage 1 of the Simon 2-stage design. Therefore, the results of Study 142 should be interpreted carefully.

Nevertheless, the applicant's explanation about the efficacy of nivolumab is understandable. PMDA concluded that the efficacy of nivolumab can be expected in patients, including Japanese patients, with unresectable, advanced or recurrent MSI-High colorectal cancer who previously received fluoropyrimidine, L-OHP, and CPT-11.

7.1.R.3 Safety [For adverse events, see "7.3.1 Adverse events reported in the clinical studies in patients with MSI-High colorectal cancer."]

PMDA's view:
On the basis of the discussions in the subsections below, nivolumab therapy in chemotherapy-treated patients with MSI-High colorectal cancer requires particular attention to the onset of the adverse events identified as requiring attention at the regulatory reviews for the approved indications.[13)] Patients should be closely monitored for these events when nivolumab is administered for the treatment of MSI-High colorectal cancer, as well as for the approved indications.

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

7.1.R.3.1 Safety profile

The applicant's explanation about the safety profile of nivolumab in chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer, based on the safety data from Study 142:

13) Intestinal lung disease (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, and tuberculosis (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg, dated July 26, 2018," etc.)

Table 3 presents a summary of the safety data from Study 142.

Table 3. Safety summary (Study 142)

	Number of patients (%)
	N = 74
All adverse events	71 (95.9)
Grade ≥3 adverse events	41 (55.4)
Adverse events leading to death*	7 (9.5)
Serious adverse events	31 (41.9)
Adverse events leading to drug discontinuation	6 (8.1)
Adverse events leading to drug interruption	23 (31.1)

*, Adverse events which occurred or worsened, during the treatment period or within 30 days after the last dose

In Study 142, adverse events of any grade reported with ≥10% incidence were diarrhoea in 32 patients (43.2%), fatigue in 31 patients (41.9%), anaemia in 27 patients (36.5%), nausea in 25 patients (33.8%), vomiting in 21 patients (28.4%), abdominal pain and cough in 19 patients (25.7%) each, pyrexia in 18 patients (24.3%), constipation in 15 patients (20.3%), hyperglycaemia, pruritus, and arthralgia in 14 patients (18.9%) each, aspartate aminotransferase (AST) increased and headache in 12 patients (16.2%) each, asthenia, lipase increased, and back pain in 11 patients (14.9%) each, upper respiratory tract infection, alanine aminotransferase (ALT) increased, decreased appetite, and rash in 10 patients (13.5%) each, blood alkaline phosphatase increased and dizziness in 9 patients (12.2%) each, and dyspepsia and rash maculo-papular in 8 patients (10.8%) each. Grade ≥3 adverse events reported with a ≥2% incidence were lipase increased in 7 patients (9.5%), anaemia and malignant neoplasm progression in 6 patients (8.1%) each, vomiting, intestinal obstruction, fatigue, amylase increased, and weight increased in 3 patients (4.1%) each, and diarrhoea, abdominal pain, small intestinal obstruction, ALT increased, blood bilirubin increased, lymphocyte count decreased, hyperglycaemia, neutropenia, and acute kidney injury in 2 patients (2.7%) each. The adverse event that resulted in death with a ≥2% incidence was malignant neoplasm progression in 6 patients (8.1%). Serious adverse events reported with a ≥2% incidence were malignant neoplasm progression in 6 patients (8.1%), abdominal pain, intestinal obstruction, and vomiting in 3 patients (4.1%) each, and diarrhoea, small intestinal obstruction, and pyrexia in 2 patients (2.7%) each. Adverse events that led to drug interruption with a ≥2% incidence were diarrhoea in 5 patients (6.8%), and nasopharyngitis, upper respiratory tract infection, intestinal obstruction, ALT increased, AST increased, pneumonitis, and neutropenia in 2 patients (2.7%) each. No adverse events led to drug discontinuation with a ≥2% incidence.

The applicant's explanation about the differences in the safety profile of nivolumab between patients with MSI-High colorectal cancer and patients treated for the approved indications:

Table 4 presents comparisons of the incidences of adverse events in clinical studies (a) to (j) below.

(a) A foreign phase II study in patients with MSI-High colorectal cancer (Study 142)

(b) The nivolumab group of a global phase III study in patients with esophageal cancer (Study 473)

(c) The nivolumab groups of foreign phase III studies in patients with unresectable malignant melanoma (Studies 066 and 037)

(d) The nivolumab group of a global phase III study in patients with completely resected malignant melanoma (Study 238)
(e) The nivolumab groups of foreign phase III studies in patients with NSCLC (Studies 017 and 057)
(f) The nivolumab group of a global phase III study in patients with RCC (Study 025)
(g) A Japanese phase II study and a foreign phase II study in patients with cHL (Studies 15 and 205, respectively)
(h) The nivolumab group of a global phase III study in patients with head and neck cancer (Study 141)
(i) The nivolumab group of a global phase III study in patients with gastric cancer (Study 12)
(j) A Japanese phase II study in patients with malignant pleural mesothelioma (Study 41)

Table 4. Safety summary[*1] by cancer type[*2]

	Number of patients (%)									
	(a) n = 74	(b) n = 192	(c) n = 474	(d) n = 452	(e) n = 418	(f) n = 406	(g) n = 260	(h) n = 236	(i) n = 330	(j) n = 34
All adverse events	71 (95.9)	172 (89.6)	457 (96.4)	438 (96.9)	407 (97.4)	397 (97.8)	255 (98.1)	229 (97.0)	300 (90.9)	32 (94.1)
Grade ≥3 adverse events	41 (55.4)	77 (40.1)	218 (46.0)	115 (25.4)	222 (53.1)	230 (56.7)	83 (31.9)	143 (60.6)	153 (46.4)	13 (38.2)
Adverse events leading to death	7 (9.5)	5 (2.6)	48 (10.1)	1 (0.2)	67 (16.0)	24 (5.9)	5 (1.9)	56 (23.7)	35 (10.6)	0
Serious adverse events	31 (41.9)	57 (29.7)	206 (43.5)	79 (17.5)	195 (46.7)	194 (47.8)	55 (21.2)	127 (53.8)	131 (39.7)	11 (32.4)
Adverse events leading to drug discontinuation	6 (8.1)	24 (12.5)	48 (10.1)	44 (9.7)	62 (14.8)	72 (17.7)	13 (5.0)	51 (21.6)	23 (7.0)	2 (5.9)
Adverse events leading to drug interruption	23 (31.1)	49 (25.5)	146 (30.8)	128 (28.3)	118 (28.2)	177 (43.6)	85 (32.7)	56 (23.7)	63 (19.1)	11 (32.4)

*1, Patients received nivolumab 240 mg intravenously every 2 weeks in studies (b) and (j), and nivolumab 3 mg/kg intravenously every 2 weeks in other studies; *2, Adverse events which occurred during the treatment period, or within 28 days after the last dose or until the start of subsequent therapies, whichever came first, in Studies 473, 15, 12, and 41; or, adverse events which occurred or worsened during the treatment period or within 30 days after the last dose in other studies

Adverse events of any grade with a ≥10% higher incidence in patients with MSI-High colorectal cancer than in those with any other cancer type were anaemia (36.5% in the MSI-High colorectal cancer group, 16.2% in the unresectable malignant melanoma group, 13.4% in the NSCLC group, 19.2% in the RCC group, 10.8% in the cHL group, 18.6% in the head and neck cancer group, 13.0% in the gastric cancer group, 2.4% in the completely resected malignant melanoma group, and 2.9% in the malignant pleural mesothelioma group), vomiting (28.4%, 14.8%, 11.0%, 16.3%, 15.4%, 11.4%, 13.6%, 8.2%, and 5.9%), and hyperglycaemia (18.9%, 3.8%, 5.3%, 8.4%, 6.5%, 5.5%, 0.6%, 1.8%, and 0%). Grade ≥3 adverse events with a ≥3% higher incidence in patients with MSI-High colorectal cancer than in those with any other cancer type were lipase increased (9.5%, 1.7%, 0.2%, 0.7%, 4.6%, 2.1%, 0%, 4.9%, and 5.9%), intestinal obstruction (4.1%, 0%, 0%, 0%, 0%, 0%, 0.6%, 0%, and 0%), and weight increased (4.1%, 0%, 0%, 0.7%, 0%, 0%, 0.3%, 0%, and 0%). Serious adverse events with a ≥3% higher incidence in patients with MSI-High colorectal cancer than in those with any other cancer type were intestinal obstruction (4.1%, 0%, 0%, 0%, 0%, 0%, 0.6%, 0%, and 0%) and vomiting (4.1%, 0.8%, 0%, 0.2%, 0.4%, 0%, 0.9%, 0.2%, and 0%). No adverse events leading to death, or led to drug discontinuation or interruption, with a ≥3% higher incidence in patients with MSI-High colorectal cancer than in those with any other cancer type.

There were no adverse events of any grade, Grade ≥3 adverse events, serious adverse events, or adverse events that led to death, drug discontinuation or interruption, which had not been identified in patients with any other cancer type, but were newly reported by ≥2 patients in Study 142.

PMDA's view:

Some adverse events were more frequently reported in patients receiving nivolumab for unresectable, advanced or recurrent MSI-High colorectal cancer in Study 142 than in those treated for the approved indications. However, all of the adverse events were known adverse events of nivolumab. In view of such findings, PMDA concluded that nivolumab therapy is tolerable in patients with unresectable, advanced or recurrent MSI-High colorectal cancer, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through appropriate measures such as monitoring of adverse events, differential diagnosis and management of excessive immune-mediated adverse drug reactions, and interruption of nivolumab.

7.1.R.3.2 Safety differences between Japanese and non-Japanese patients

The applicant's explanation about differences in the safety of nivolumab in the treatment of colorectal cancer between Japanese and non-Japanese patients based on the submitted safety data from the clinical studies and other findings:

Table 5 presents a safety summary from Japanese and non-Japanese patients treated with nivolumab for colorectal cancer in Studies 142, 001,[14] 003,[15] and 01.[16] There were no clear differences in the incidences of adverse events between Japanese and non-Japanese patients.

Table 5. Safety summary (colorectal cancer; Japanese patients in Study 01 and non-Japanese patients in Studies 142, 001, and 003)

	Number of patients*1 (%)	
	Japanese n = 4	Non-Japanese n = 107
All adverse events	4 (100)	104 (97.2)
Grade ≥3 adverse events	2 (50.0)	65 (60.7)
Adverse events leading to death*2	0	17 (15.9)
Serious adverse events	1 (25.0)	53 (49.5)
Adverse events leading to drug discontinuation	0	12 (11.2)
Adverse events leading to drug interruption	0	26 (24.3)

*1, Patients enrolled in cohorts receiving nivolumab 1, 3, and 20 mg/kg every 2 weeks in Study 01, cohorts receiving nivolumab 0.3, 1, 3, and 10 mg/kg every 4 weeks in Study 001, or a cohort receiving nivolumab 10 mg/kg every 2 weeks in Study 003; *2, Total number of deaths in all of the studies

PMDA's view:

There are limitations to evaluating differences in the safety of nivolumab between Japanese and non-Japanese patients with MSI-High colorectal cancer based on the above results because no safety data from Japanese

14) A foreign phase I Study to evaluate the safety, tolerability, and other aspects of nivolumab in patients with solid tumors, including advanced or recurrent NSCLC and colorectal cancer

15) A foreign phase I Study to evaluate the safety, tolerability, and other aspects of nivolumab in patients with solid tumors, including advanced or recurrent NSCLC and colorectal cancer

16) A Japanese phase I study to evaluate the safety, tolerability, and other aspects of nivolumab in patients with advanced solid tumors

patients with MSI-High colorectal cancer have been submitted in the present partial change application and the number of Japanese patients who have been treated with nivolumab for colorectal cancer is small. Nevertheless, PMDA concluded that nivolumab is also tolerable in Japanese patients with MSI-High colorectal cancer, in view of the following points.

- No clear differences are observed in the safety of nivolumab between Japanese and non-Japanese patients when treated for the approved indications (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg, dated July 26, 2018," etc.).
- No clear differences are observed in the pharmacokinetics of nivolumab between Japanese and non-Japanese patients (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated June 18, 2014," etc.).

7.1.R.4 Clinical positioning and indication

The proposed indication for MSI-High colorectal cancer in the present partial change application was "treatment of unresectable, advanced or recurrent microsatellite instability high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy." The proposed "Precautions Concerning Indications" section included the following statements:

- The efficacy and safety of nivolumab in first-line treatment have not been established.
- Nivolumab should be administered to patients with a MSI-High cancer confirmed by tests performed by a thoroughly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic should be used in the test.
- The efficacy and safety of nivolumab in adjuvant chemotherapy have not been established.
- Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of nivolumab presented in the "Clinical Studies" section.

PMDA's view:

On the basis of the discussions in Sections "7.1.R.2 Efficacy" and "7.1.R.3 Safety," and the subsections below, the indication of nivolumab should be "Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy," as proposed by the applicant, with the following statements in the "Precautions Concerning Indications" section.

- The efficacy and safety of nivolumab have not been established in patients who have not received prior treatment with a fluoropyrimidine, L-OHP, and CPT-11.
- Nivolumab should be administered to patients with a MSI-High cancer confirmed by tests performed by a thoroughly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic should be used in the test.
- The efficacy and safety of nivolumab in adjuvant therapy have not been established.
- Eligible patients must be selected by physicians with adequate knowledge in the efficacy and safety of nivolumab, after fully understanding the "Clinical Studies" section, and carefully considering the choice of alternative therapies.

7.1.R.4.1 Intended patient population and indication of nivolumab

In representative clinical practice guidelines and leading clinical oncology textbooks in and outside Japan, descriptions on nivolumab in the treatment of patients with MSI-High colorectal cancer are as shown below.

Clinical practice guidelines

- NCCN guidelines (colon cancer) (v.2, 2019):
  - Nivolumab is recommended for the second- or third-line treatment of unresectable, advanced or recurrent dMMR or MSI-High colon cancer.
- NCCN guidelines (rectal cancer) (v.2, 2019):
  - Nivolumab is recommended for the second- or third-line treatment of unresectable, advanced or recurrent dMMR or MSI-High rectal cancer.
- Japanese clinical practice guidelines (large intestine carcinoma):
  - The efficacy of nivolumab has been reported in the treatment of unresectable, advanced or recurrent dMMR or MSI-High colorectal cancer.

The applicant's explanation about the intended patient population of nivolumab in the present partial change application, taking account of the results of Study 142:

Patients with ≥1 prior chemotherapies were included in Study 142. A total of 74 patients received nivolumab therapy, of whom (a) 16 had received 1 prior chemotherapy and (b) 53 had received prior treatment with a fluoropyrimidine, L-OHP, and CPT-11. The investigator-assessed response rates [95% CIs] (%) in patient populations (a) and (b) were 43.8 [19.8, 70.1] and 26.4 [15.3, 40.3], respectively, both of which were higher than the response rates with existing second-line or subsequent treatments for unresectable, advanced or recurrent colorectal cancer [see Section 7.1.1.3.3]. These results suggest that nivolumab can be recommended as a therapeutic option for the second-line or subsequent treatment for MSI-High colorectal cancer that has progressed after chemotherapy. The clinical benefit of nivolumab as a first- or second-line treatment for MSI-High colorectal cancer will continue to be investigated in an ongoing open-label, randomized, global phase IIIb study to compare the efficacy and safety of nivolumab administered alone or in combination with ipilimumab in patients with unresectable, advanced or recurrent MSI-High colorectal cancer who received no or 1 prior chemotherapy (Study CA2098HW; target sample size, 494 patients).

Because no clinical study data are available as to the efficacy and safety of nivolumab in comparison with pembrolizumab, which has been approved for the treatment of chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High solid tumors (including colorectal cancer), there are no clear standards on the choice between nivolumab and pembrolizumab, at present. The most suitable treatment option should be selected according to the conditions of individual patients upon thorough understanding of the efficacy and safety of these drugs.

Accordingly, the indication was proposed as "Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy," with the following statements included in the "Precautions Concerning Indications" section.

- The efficacy and safety of nivolumab in first-line treatment have not been established.
- The efficacy and safety of nivolumab in adjuvant chemotherapy have not been established.
- Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of nivolumab presented in the "Clinical Studies" section.

PMDA's view:
PMDA generally accepted the applicant's explanation. However, due to the absence of data from confirmatory studies of nivolumab in patients with MSI-High colorectal cancer, PMDA concluded that nivolumab is not recommended to be chosen over the standard treatment with a fluoropyrimidine, L-OHP, and CPT-11 for chemotherapy-naïve patients with unresectable, advanced or recurrent MSI-High colorectal cancer. Therefore, the "Precautions Concerning Indications" section should include a statement that the efficacy and safety of nivolumab have not been established in patients who have not received prior treatment with a fluoropyrimidine, L-OHP, and CPT-11.

Furthermore, the efficacy of nivolumab was evaluated primarily with the response rate, and no information on prolonged survival has been obtained in the present partial change application. Therefore, the "Precautions Concerning Indications" section should also include a cautionary statement to thoroughly consider the choice of alternative therapies, before deciding to initiate nivolumab therapy.

On the basis of the above, PMDA concluded that the indication should be "Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy," as proposed by the applicant, with the following statements in the "Precautions Concerning Indications" section.
- The efficacy and safety of nivolumab have not been established in patients who have not received prior treatment with a fluoropyrimidine, L-OHP, and CPT-11.
- The efficacy and safety of nivolumab in adjuvant therapy have not been established.
- Eligible patients must be selected by physicians with adequate knowledge in the efficacy and safety of nivolumab, after fully understanding the "Clinical Studies" section, and carefully considering the choice of alternative therapies.

7.1.R.4.2 MSI test
The applicant's explanation about the MSI test used to select intended patients for nivolumab therapy:
In Study 142, patients who were locally determined to have a dMMR or MSI-High (PCR) colorectal cancer were included in the efficacy and safety analysis sets. "MSI test kit (FALCO)," a companion diagnostic for nivolumab in which an application for partial change was filed, demonstrated to appropriately identify the patient population in which the efficacy and safety of nivolumab are expected based on the results of an equivalence study using colorectal cancer samples and other data.

From the above, it is appropriate to select patients for nivolumab therapy by using the "MSI test kit (FALCO)," marketed by FALCO biosystems Ltd., and this will be stated in the "Precautions Concerning Indications" section.

- Nivolumab should be administered to patients with a MSI-High cancer confirmed by tests performed by a thoroughly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic should be used in the test.

PMDA accepted the applicant's explanation.

7.1.R.4.3 Efficacy and safety of nivolumab by PD-L1 expression status, and intended patient population

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

The applicant's explanation:

In Study 142, PD-L1 expression status[17] in tumor tissue samples was assessed using the "PD-L1 IHC 28-8 pharmDx assay 'Dako' (Dako Japan Co., Ltd.)," and the (a) efficacy and (b) safety of nivolumab by PD-L1 expression status were evaluated in patients who had evaluable PD-L1 data.

(a) Efficacy

Table 6 shows the investigator-assessed response rates by PD-L1 expression status (cutoff values, 1% and 5%) in patients with evaluable PD-L1 data.

There were no clear differences in response rate between the PD-L1-positive and -negative populations at either cutoff value. Thus, the efficacy of nivolumab can be expected, regardless of PD-L1 expression status.

Table 6. Efficacy by PD-L1 expression status (Study 142)

Percentage of cells with PD-L1	Responders/N	Response rate [95% CI*](%)
<1%	13/45	28.9 [16.4, 44.3]
≥1%	6/21	28.6 [11.3, 52.2]
<5%	16/55	29.1 [17.6, 42.9]
≥5%	3/11	27.3 [6.0, 61.0]

* Clopper-Pearson method

(b) Safety

In patients with <1% PD-L1 and those with ≥1% PD-L1, the incidences of adverse events of any grade were 95.6% and 100%, respectively, the incidences of Grade ≥3 adverse events were 48.9% and 71.4%, and the incidences of serious adverse events were 42.2% and 52.4%, respectively. In patients with <5% PD-L1 and those with ≥5% PD-L1, the incidences of adverse events of any grade were 96.4% and 100%, respectively, the

17) Percentage of cells with PD-L1 expression in the tumor tissue

incidences of Grade ≥3 adverse events were 54.5% and 63.6%, and the incidences of serious adverse events were 43.6% and 54.5%, respectively.

Since the safety of nivolumab was not clearly different between PD-L1-positive and -negative populations at either cutoff value, nivolumab is considered tolerable, regardless of PD-L1 expression status.

The above results described in (a) and (b) indicated that response to nivolumab in patients with MSI-High colorectal cancer is independent of PD-L1 expression status.

Therefore, in nivolumab therapy for chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer, it is not necessary to identify the intended patient population according to PD-L1 expression status.

PMDA's view:
PMDA generally accepted the applicant's explanation. However, the applicant should continue to collect information on possible predictors of response to nivolumab other than PD-L1 expression, and appropriately communicate new findings to healthcare professionals.

7.1.R.5 Dosage and administration

The present partial change application had proposed the following dosage and administration for the treatment of MSI-High colorectal cancer: "The usual adult dosage of nivolumab is 240 mg administered as an intravenous infusion every 2 weeks" (unchanged from the previous approval), with the following statement to be included in the "Precautions Concerning Dosage and Administration" section of the package insert.

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

As a result of the discussions described in Sections "7.1.R.2 Efficacy," "7.1.R.3 Safety," and "7.1.R.4 Clinical positioning and indication," and the subsection below, PMDA concluded that the dosage and administration of nivolumab for the treatment of MSI-High colorectal cancer should be "The usual adult dosage of nivolumab is 240 mg administered as an intravenous infusion every 2 weeks," and that the statement (unchanged from the approved statement) should be included in the "Precautions Concerning Dosage and Administration" section of the package insert.

7.1.R.5.1 Dosage and administration of nivolumab

The applicant's explanation about the dosage and administration of nivolumab for the treatment of MSI-High colorectal cancer:
In Study 142, the dosage regimen was determined to be 3 mg/kg every 2 weeks based on the results of a foreign phase I study (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated November 18, 2015") and other data, and the study results showed the clinical benefit of nivolumab in the treatment of MSI-High colorectal cancer. Taking account of the study outcome, results of a population

pharmacokinetic (PPK) analysis, and other data (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg, dated July 26, 2018"), the dosage and administration of nivolumab for the treatment of MSI-High colorectal cancer was proposed to be "The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks" (unchanged from the previous approval).

PMDA accepted the applicant's explanation.

7.1.R.6 Post-marketing investigations

Post-marketing investigations in patients with MSI-High colorectal cancer will be described in Section 7.2.R.5, with those in patients with esophageal cancer.

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

The applicant submitted efficacy and safety evaluation data, in the form of result data from the following 2 clinical studies: a Japanese phase II study and a global phase III study (Table 7).

Table 7. Clinical studies on efficacy and safety

Data type	Region	Study identifier	Phase	Study population	Number of patients*	Brief description of dosage regimen	Main endpoints
Evaluation data	Japan	Study 07	II	Patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine-, platinum-, and taxane-based chemotherapy	65	Nivolumab 3 mg/kg intravenously every 2 weeks	Efficacy Safety
	Global	Study 473	III	Patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine- and platinum-based chemotherapy	388 (a) 193 (b) 195	(a) Nivolumab 240 mg intravenously every 2 weeks (b) Investigator's choice of therapy • DOC 75 mg/m^3 intravenously every 3 weeks • PTX 100 mg/m^2 intravenously on Days 1, 8, 15, 22, 29, and 36 of a 7-week cycle	Efficacy Safety

*, For Study 07, the number of patients who were enrolled and treated with nivolumab; for Study 473, the number of patients who were enrolled and randomized, excluding 31 patients with GCP deviations

A summary of the clinical studies is presented below. Major adverse events other than deaths reported in these studies are detailed in "7.3.2 Adverse events reported in clinical studies in patients with esophageal cancer."

7.2.1 Evaluation data

7.2.1.1 Japanese clinical study

7.2.1.1.1 Japanese phase II study (CTD 5.3.5.2.1, Study 07, ongoing since February 19, 2014 [data cutoff on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 8 study sites in Japan, to evaluate the efficacy and safety of nivolumab in patients with unresectable, advanced or recurrent esophageal cancer[18] who previously received fluoropyrimidine-, platinum-, and taxane-based chemotherapy (target sample size, 60 patients).

Patients received nivolumab 3 mg/kg intravenously every 2 weeks, until disease progression or a withdrawal criterion was met.

All 65 patients enrolled into the study and received nivolumab were included in the safety analysis set. Of these 65 patients, 64, excluding 1 with multiple primary cancers, were included in the full analysis set (FAS) and used for the efficacy analyses.

Table 8 presents efficacy results based on the primary endpoint, response rate as centrally assessed using RECIST ver. 1.1 (data cutoff on [redacted], 20[redacted]). The lower bound of the 95% CI for the response rate was higher than the prespecified threshold response rate (5.0%).[19]

Table 8. Best overall response and response rate (Study 07)
(RECIST ver. 1.1, FAS, central assessment, data cutoff on [redacted], 20[redacted])

Best overall response	Number of patients (%)
	n = 64
CR	3 (4.7)
PR	8 (12.5)
SD	16 (25.0)
PD	29 (45.3)
NE	8 (12.5)
Response (CR + PR) (Response rate [95% CI*] [%])	11 (17.2[9.9, 28.2])

*, Wilson method

Deaths, during the treatment period or within 28 days after the last dose, were reported in 6 of 65 patients (9.2%). The cause of death was disease progression in all 6 patients.

[18] Included squamous cell carcinoma, adenosquamous carcinoma, and adenocarcinoma, arising from the esophagus ranging from the cervical esophagus to the thoracic esophagus (including the gastroesophageal junction). However, the histological type of esophageal cancer was squamous cell carcinoma in all of the enrolled patients.

[19] With reference to the reported response rate with placebo for malignant tumors (2.7%) (*J Natl Cancer Inst.* 2003;95:19-29), the threshold response rate was set at 5% in the study.

7.2.1.2 Global clinical study

7.2.1.2.1 Global phase III study (CTD 5.3.5.1.1, Study 473, ongoing since December 14, 2015 [data cutoff on November 12, 2018])

An open-label, randomized, comparative study was conducted in patients with unresectable, advanced or recurrent esophageal cancer[20] who previously received fluoropyrimidine- and platinum-based chemotherapy [21] (target sample size, 390 patients) at 90 study sites in 8 countries or regions including Japan to compare the efficacy and safety of nivolumab with those of the investigator's choice of therapy (IC).

Patients in the nivolumab group received nivolumab 240 mg intravenously every 2 weeks. Patients in the IC group received docetaxel hydrate (DOC, 75 mg/m^2 every 3 weeks) intravenously or paclitaxel (PTX, 100 mg/m^2 on Days 1, 8, 15, 22, 29, and 36 of a 7-week cycle) intravenously. The study treatment was continued until disease progression or a withdrawal criterion was met.

A total of 419 patients (210 in the nivolumab group and 209 in the IC group) were enrolled and randomized. Of these 419 patients, 388 (193 in the nivolumab group and 195 in the IC group, including 136 and 138 Japanese patients, respectively) were included in the intention-to-treat (ITT) population and used for the efficacy analyses, and 31 (17 in the nivolumab group and 14 in the IC group) were excluded for GCP deviations[22]. Of the 388 patients in the ITT population, 2 received no study drug (1 in the nivolumab group and 1 in the IC group), and the remaining 386 (192 in the nivolumab group and 194 in the IC group, including 135 and 138 Japanese patients, respectively) were included in the safety analysis set.

The primary endpoint was OS. At the time of planning the study, an interim analysis was planned to determine early trial termination due to efficacy when 199 OS events had occurred, and the final analysis was planned when 331 OS events had occurred. However, because the results of Study 07 indicated the need of [redacted] for [redacted] at the planning of the study, the study protocol was amended to conduct an interim analysis on OS when 265 OS events had occurred (Protocol Amendment Version [redacted], dated [redacted], 20[redacted]). Subsequently, [redacted] was expected based on [redacted], and the interim analysis was omitted (Protocol Amendment Version [redacted], dated [redacted], 20[redacted]). The final analysis of OS was conducted when 331 OS events had occurred; however, the number of events became 307 at the time of final analysis of OS after excluding 31 patients for GCP deviations.

Table 9 shows the efficacy results based on the analysis of OS, the primary endpoint, while Figure 1 presents the Kaplan-Meier curves of OS. The results demonstrated the superiority of OS in nivolumab over IC. The OS

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[20] Included patients with squamous cell carcinoma and adenosquamous carcinoma, arising from the esophagus ranging from the cervical esophagus to the thoracic esophagus (including the gastroesophageal junction). However, the histological type of esophageal cancer was squamous cell carcinoma, in all of the enrolled patients.

[21] Included (a) patients who received chemotherapy as an adjunct to a surgical operation and (b) patients who achieved a complete response (CR) with initial chemotherapy or initial chemoradiotherapy, and experienced recurrence within 24 weeks after the last dose of the chemotherapy

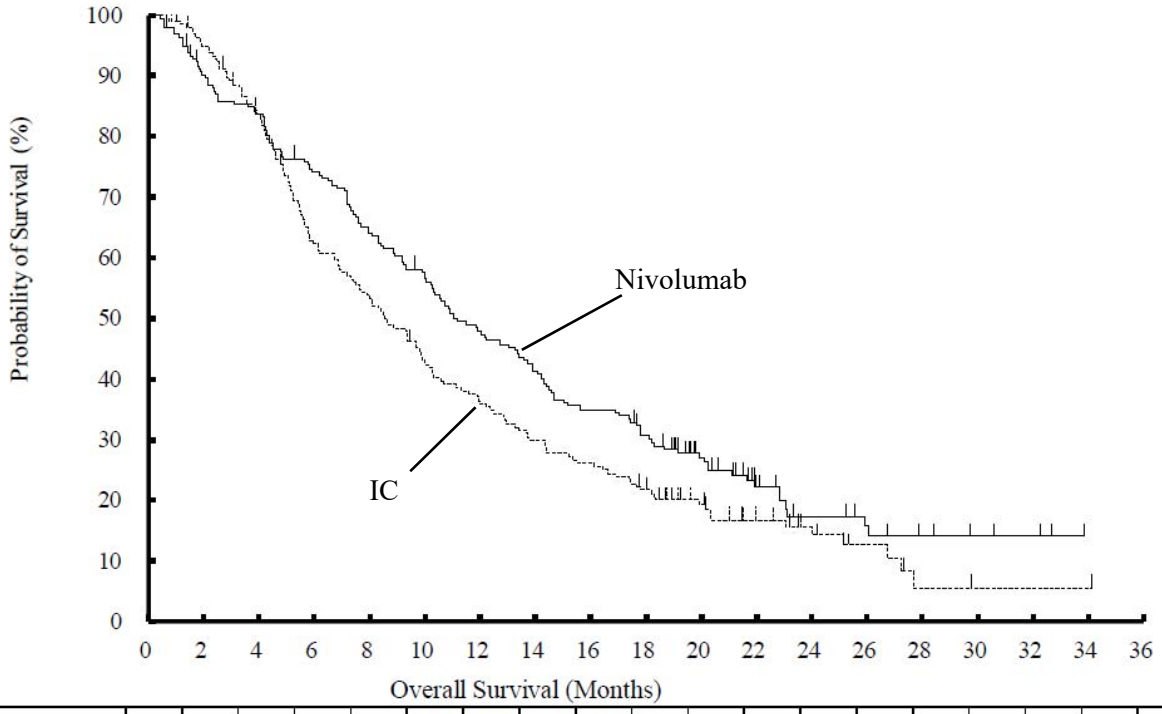
[22] One monitor prepared monitoring reports stating that study-related documents had been approved by the institutional review boards (IRBs), despite the fact that the documents had not been reviewed by the IRBs at 3 of the 6 study sites outside Japan, of which the monitor was responsible for. Due to such deviations, 31 patients enrolled at the 6 study sites were excluded.

(median [95% CI]) in the patient population before excluding the 31 patients with GCP deviations was 10.91 [9.23, 13.34] months in the nivolumab group and 8.38 [7.20, 9.86] months in the IC group. In addition, the hazard ratio [95% CI] of OS for the nivolumab group versus the IC group was 0.77 [0.62, 0.96] (*P*-value [2-sided] = 0.0189, stratified log-rank test).

Table 9. Results of OS analysis (ITT population, data cutoff on November 12, 2018)

	Nivolumab	IC
Number of patients	193	195
Number of events (%)	148 (76.7)	159 (81.5)
Median [95% CI] (months)	11.17 [9.99, 13.73]	8.54 [7.20, 9.89]
Hazard ratio [95% CI][*1]	0.79 [0.63, 0.99]	
P-value (2-sided)[*2]	0.0381	

*1, Stratified Cox regression model with geographic region (Japan, outside Japan), number of organs metastasized (≤1, ≥2), and PD-L1 expression status (≥1%, <1% or unmeasurable) as stratification factors; *2, Stratified Log-rank test with geographic region (Japan, outside Japan), number of organs metastasized (≤1, ≥2), and PD-L1 expression status (≥1%, <1% or unmeasurable) as stratification factors, with a 2-sided significance level of 0.05



At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Nivolumab	193	170	158	139	120	105	89	77	65	55	38	20	13	10	6	4	3	0	0
IC	195	182	157	116	100	79	66	55	48	39	26	16	11	6	2	1	1	1	0

Figure 1. Kaplan Meier curves for the OS analysis (ITT population, data cutoff on November 12, 2018)

Deaths, during the treatment period or within 28 days after the last dose, were reported in 13 of 192 patients (6.8%) (including 8 of 135 Japanese patients) in the nivolumab group and 9 of 194 patients (4.6%) (including 4 of 138 Japanese patients) in the IC group. The causes of deaths, other than disease progression (11 in the nivolumab group and 3 in the IC group), were metastases to lymph nodes and pneumonia in 1 patient each in the nivolumab group, and pneumonia in 2 patients, and unknown, spinal cord abscess, tumour haemorrhage,

and sudden death in 1 patient each in the IC group. A causal relationship to the study drug could not be ruled out for the spinal cord abscess and pneumonia in 1 patient each in the IC group. (The causes of the deaths other than disease progression in Japanese patients were spinal cord abscess and pneumonia in 1 patient each in the IC group; a causal relationship to the study drug could not be ruled out for either of these events.)

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

7.2.R.1 Efficacy

PMDA determined that, among the evaluation data submitted by the applicant, the important clinical study for evaluating the efficacy and safety of nivolumab was the global phase III study in patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine- and platinum-based chemotherapy (Study 473), and decided to evaluate the efficacy and safety of nivolumab in the treatment of esophageal cancer primarily based on the submitted results from Study 473.

Efficacy in Japanese patients was evaluated from the viewpoint of consistency between the entire study population and the Japanese subpopulation of Study 473, according to the "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), the "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated September 5, 2012), and the Guidelines on "General Principles for Planning and Design of Multi-Regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018).

On the basis of the discussion presented below, PMDA concluded that the efficacy of nivolumab has been demonstrated in patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine- and platinum-based chemotherapy.

7.2.R.1.1 Control group selection

The applicant's explanation about the control group selected in Study 473:

At the time of planning Study 473, the NCCN guidelines (esophageal and esophagogastric junction cancers) (v.3.2015) recommended the use of DOC and PTX, based on a report that DOC and PTX demonstrated high efficacy in the target patient population of Study 473 (*Lancet Oncol.* 2014;15:78-86 and *Ann Oncol.* 2007;18:898-902). In view of this recommendation and other findings, DOC or PTX, was selected by each investigator in the control group.

PMDA asked the applicant to explain the appropriateness of the dose of DOC (75 mg/m^2) selected for Study 473, which had not been approved for the treatment of esophageal cancer in Japan.

The applicant's explanation:

The dose of DOC selected for Study 473 (75 mg/m^2) was appropriate for the following reasons.

- The NCCN guidelines (esophageal and esophagogastric junction cancers) (v.3.2015) recommended the use of DOC at a dose of 75 to 100 mg/m^2 for patients with unresectable, advanced or recurrent esophageal cancer who previously receive chemotherapy. Further, the efficacy of DOC administered at a dose of 75

mg/m^2 was not expected to be inferior to that of DOC administered at the approved dose in Japan (70 mg/m^2).

- The results of the post-marketing use-results survey for DOC in Japan suggested that the safety profile of DOC administered at a dose of 75 mg/m^2 was not clearly different from that at a dose of 70 mg/m^2 in patients with esophageal cancer (see "Review Report for Taxotere 20 mg for I. V. Infusion, Taxotere 80 mg for I. V. infusion, dated September 28, 2010").

PMDA's view:

PMDA generally accepted the applicant's explanation. However, the possibility that the choice between the 2 different control drugs might affect the efficacy evaluation for nivolumab and should be assessed separately [see Section 7.2.R.1.2].

7.2.R.1.2 Efficacy endpoints and evaluation results.

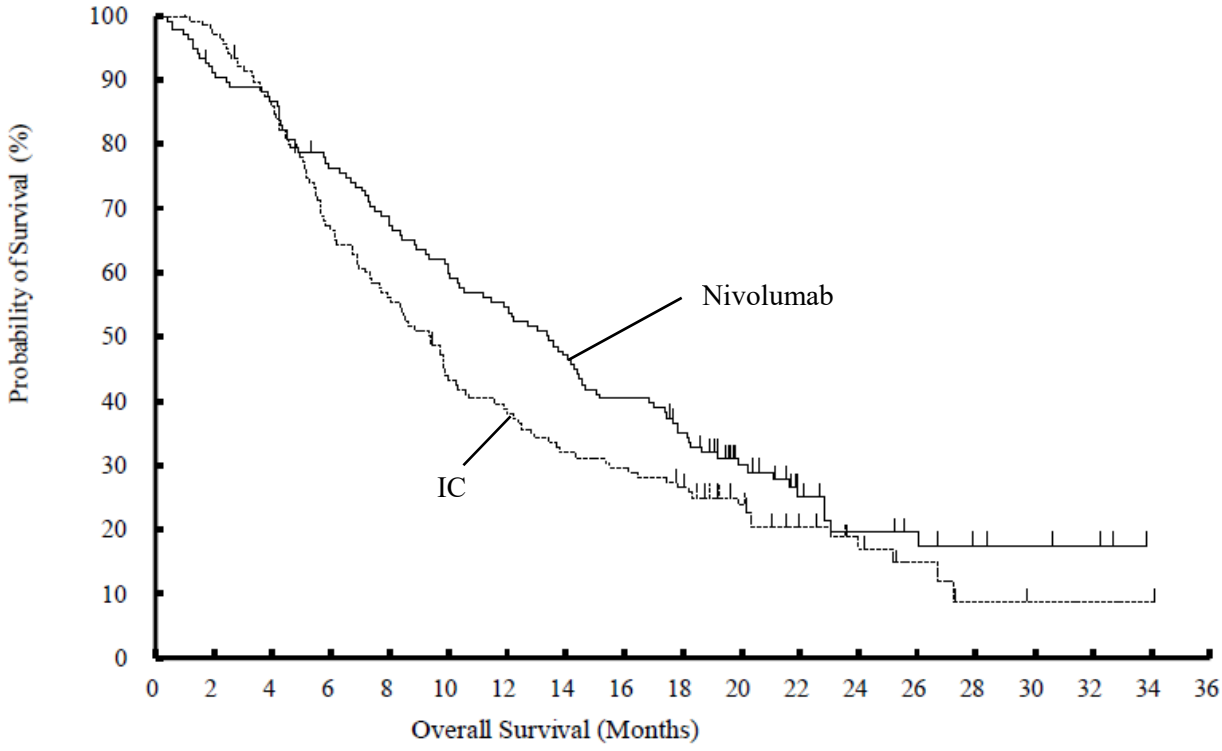
The results of Study 473 demonstrated the superiority of nivolumab in the primary endpoint of OS over IC [see Section 7.2.1.2]. The hazard ratios [95% CIs] of OS were 0.82 [0.58, 1.16] for nivolumab versus DOC and 0.76 [0.59, 0.98] for nivolumab versus PTX, providing no evidence that the choice between the 2 different control drugs affected the efficacy evaluation for nivolumab.

Table 10 shows efficacy results based on the OS analysis, while Figure 2 presents the Kaplan-Meier curves of OS in the Japanese subpopulation of Study 473.

Table 10. Results of OS analysis in Japanese patients (ITT population, data cutoff on November 12, 2018)

	Nivolumab	IC
Number of patients	136	138
Number of events (%)	101 (74.3)	109 (79.0)
Median [95% CI] (months)	13.40 [10.35, 15.05]	9.36 [7.39, 10.58]
Hazard ratio [95% CI]*1	0.77 [0.59, 1.01]	
P-value (2-sided)*2	0.0621	

*1, Non-stratified Cox regression; *2, Non-stratified log-rank test



At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Nivolumab	136	123	117	102	90	80	73	63	54	45	29	16	11	9	5	4	3	0	0
IC	138	133	116	89	75	58	50	42	39	34	23	14	10	5	2	1	1	1	0

Figure 2. Kaplan-Meier curves for the OS analysis in Japanese patients (ITT population, data cutoff on November 12, 2018)

In Study 473, GCP deviations were found after the clinical study report had been prepared, and a population of patients, after excluding the 31 patients involved in the GCP deviations (17 in the nivolumab group and 14 in the IC group), was defined as the ITT population used for the reanalyses of efficacy [see Section 7.2.1.2.1]. PMDA asked the applicant to explain the comparability of the nivolumab group and the IC group in the ITT population.

The applicant's explanation:

The imbalances in the patient background factors between the nivolumab group and the IC group in the ITT population were assessed using the Student's t-test for quantitative data such as age and body weight, and using Fisher's exact test for qualitative data such as race and ECOG performance status, at a 2-sided significance level of 0.05. The *P*-values were >0.05 for all the patient background factors, indicating no imbalances in the distribution of patient background factors between the nivolumab group and the IC group in the ITT population. Furthermore, the distribution of patient background factors in the ITT population was similar to that in the 419 patients who were enrolled and randomized in Study 473. Therefore, the comparability of the nivolumab group and the IC group was assured in the ITT population.

PMDA's view:

There are limitations to the above applicant's explanation on the comparability of the nivolumab group and the IC group in the population of patients after 31 patients with GCP deviations were excluded from 419 patients enrolled and randomized in Study 473. Nevertheless, PMDA concluded that the efficacy of nivolumab was demonstrated in patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine- and platinum-based chemotherapy, in view of the following findings.

- The study results confirmed the superiority of nivolumab in the primary endpoint of OS over IC.
- The study results from the Japanese subpopulation were not clearly different from those from the entire study population.

7.2.R.2 Safety [For adverse events, see "7.3.2 Adverse events reported in the clinical studies in patients with esophageal cancer."]

PMDA's view:

On the basis of the discussions in the subsections below, PMDA concluded that adverse events requiring particular attention with nivolumab therapy in patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine- and platinum-based chemotherapy are pancreatitis in addition to the events that were considered to require particular caution at the initial approval of nivolumab.[13)] Particular caution should be exercised against occurrence of such adverse events when nivolumab is administered for unresectable, advanced or recurrent esophageal cancer, as well as for the approved indications.

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

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

The applicant's explanation about the safety profile of nivolumab in patients with esophageal cancer, based on safety data from Studies 473 and 07:

Table 11 presents a summary of the safety data from Studies 473 and 07.

Table 11. Safety summary

	Number of patients (%)		
	Study 473		Study 07
	Nivolumab n = 192	IC n = 194	n = 65
All adverse events	172 (89.6)	192 (99.0)	56 (86.2)
Grade ≥3 adverse events	77 (40.1)	145 (74.7)	19 (29.2)
Adverse events leading to death	5 (2.6)	9 (4.6)	0
Serious adverse events	57 (29.7)	70 (36.1)	12 (18.5)
Adverse events leading to drug discontinuation	24 (12.5)	33 (17.0)	7 (10.8)
Adverse events leading to drug interruption	49 (25.5)	116 (59.8)	18 (27.7)

In Study 473, adverse events of any grade reported with a ≥5% higher incidence in the nivolumab group than in the IC group were hypothyroidism (19 patients [9.9%] in the nivolumab group, 3 patients [1.5%] in the IC group), dysphagia (15 patients [7.8%], 3 patients [1.5%]), and pruritus (23 patients [12.0%], 11 patients [5.7%]). The Grade ≥3 adverse events reported with a 2% higher incidence in the nivolumab group than in the IC group were hypercalcaemia (9 patients [4.7%], 3 patients [1.5%]) and blood creatine phosphokinase increased (4 patients [2.1%], 0%). The serious adverse event reported with a ≥2% higher incidence in the nivolumab group than in the IC group was pyrexia (5 patients [2.6%], 1 patient [0.5%]). No adverse events led to death, drug discontinuation or interruption, with a ≥2% higher incidence in the nivolumab group than in the IC group.

In Study 07, adverse events of any grade reported with a ≥10% incidence were diarrhoea (14 patients [21.5%]), decreased appetite (12 patients [18.5%]), lung infection (9 patients [13.8%]), cough (8 patients [12.3%]), and constipation, fatigue, nasopharyngitis, dysgeusia, and rash (7 patients [10.8%] each]). Grade ≥3 adverse events reported with a ≥3% incidence were lung infection (5 patients [7.7%]), and blood creatine phosphokinase increased, dehydration, hepatic function abnormal, hyponatraemia, and decreased appetite (2 patients [3.1%] each). Serious adverse events reported with a ≥3% incidence were lung infection (4 patients [6.2%]), and dehydration and ILD (2 patients [3.1%] each). Adverse event that led to drug discontinuation with a ≥3% incidence was ILD (3 patients [4.6%]). Adverse events that led to drug interruption with a ≥3% incidence were lung infection (5 patients [7.7%]), pneumonia (4 patients [6.2%]), and diarrhoea, malaise, hepatic function abnormal, and blood creatine phosphokinase increased (2 patients [3.1%] each).

The applicant's explanation about the differences in the safety profile of nivolumab between patients with esophageal cancer and patients treated for the approved indications:
Table 4 shows a comparison of the incidences of adverse events between patients treated with nivolumab for esophageal cancer in Study 473 and patients treated for the approved indications [see Section 7.1.R.3.1]. There were no adverse events of any grade reported with a ≥10% higher incidence in patients with esophageal cancer than in patients with any other type of cancer. There were no Grade ≥3 adverse events, serious adverse events, and adverse events that led to death, drug discontinuation or interruption, with a ≥3% higher incidence in patients with esophageal cancer than in patients with any other type of cancer.

Adverse events of any grade that had not been identified in patients treated for the approved indications, but were newly reported by ≥2 patients in Study 473 were glucose urine present, electrolyte imbalance, and oesophagobronchial fistula (2 patients each). The Grade ≥3 adverse event that were newly reported by ≥2 patients in Study 473 was oesophagobronchial fistula (2 patients). Serious adverse event newly reported by ≥2 patients was oesophagobronchial fistula (2 patients). There were no adverse events leading to death, drug discontinuation or interruption that were newly reported by ≥2 patients in Study 473.

Although the above comparison identified oesophagobronchial fistula as a new serious adverse event that had not been identified in patients treated with nivolumab for the approved indications, this event was attributable to the primary disease. Thus, the safety of nivolumab is not clearly different between patients with esophageal cancer and those treated for the approved indications.

The applicant's explanation about differences in the safety of nivolumab between Japanese and non-Japanese patients, based on the safety data from Study 473:
Table 12 presents a safety summary of nivolumab in the Japanese and non-Japanese subpopulations of Study 473.

Table 12 Safety summary

	Number of patients (%)			
	Japanese		Non-Japanese	
	Nivolumab n = 135	IC n = 138	Nivolumab n = 57	IC n = 56
All adverse events	119 (88.1)	137 (99.3)	53 (93.0)	55 (98.2)
Grade ≥3 adverse events	44 (32.6)	109 (78.9)	33 (57.9)	36 (64.3)
Adverse events leading to death	3 (2.2)	3 (2.2)	2 (3.5)	6 (10.7)
Serious adverse events	39 (28.9)	43 (31.2)	18 (31.6)	27 (48.2)
Adverse events leading to drug discontinuation	19 (14.1)	19 (13.8)	5 (8.8)	14 (25.0)
Adverse events leading to drug interruption	35 (25.9)	83 (60.1)	14 (24.6)	33 (58.9)

In the nivolumab group, there were no adverse events of any grade reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients. The adverse event that led to drug discontinuation with a ≥3% higher incidence in Japanese patients than in non-Japanese patients was ILD (5 patients [3.7%] in Japanese patients, 0% in non-Japanese patients). There were no Grade ≥3 adverse events, serious adverse events, and adverse events leading to death or drug interruption, with a 3% higher incidence in Japanese patients than in non-Japanese patients.

The onset of ILD led to discontinuation of nivolumab only in Japanese patients. However, ILD was also reported by 3 patients (2.2%) in the IC group, and the applicant considered that no nivolumab-associated adverse events were identified as requiring particular attention in Japanese patients.

PMDA asked the applicant to explain the differences in the incidences of adverse events between patients with and without prior radiotherapy:
The applicant's explanation:
In the nivolumab group, the incidences of adverse events of any grade were 91.1% in patients with prior radiotherapy (135 patients) and 86.0% in patients without prior radiotherapy (57 patients). The incidences of Grade ≥3 adverse events were 41.5% and 36.8%, and the incidences of serious adverse events were 32.6% and 22.8%, respectively.

There were no adverse events of any grade reported with a ≥10% higher incidence in patients with prior radiotherapy than in those without prior radiotherapy. The Grade ≥3 adverse event reported with a ≥3% higher incidence in patients with prior radiotherapy than in those without prior radiotherapy was hypercalcaemia (8 patients [5.9%] in patients with prior radiotherapy, 1 patient [1.8%] in patients without prior radiotherapy). The serious adverse event reported with a ≥3% higher incidence in patients with prior radiotherapy than in those without prior radiotherapy was pneumonia (7 patients [5.2%], 1 patient [1.8%]). No adverse events led

to death, drug discontinuation or interruption, with a ≥3% higher incidence in patients with prior radiotherapy than in those without prior radiotherapy.

Among adverse events reported only in patients with prior radiotherapy in the nivolumab group, the tracheal fistula, inappropriate antidiuretic hormone secretion, oesophagobronchial fistula, appendicitis, and pneumonia bacterial in 1 patient each were serious, Grade ≥3 adverse events for which a causal relationship to nivolumab could not be ruled out. Nevertheless, nivolumab is tolerable regardless of prior radiotherapy, for the following reasons.

- In the nivolumab group, a serious adverse event of pneumonia was more frequently reported in patients with prior radiotherapy than in those without prior radiotherapy. However, pneumonia was also reported in 6 patients (4.7%) who received previous radiotherapy in the IC group, and the incidence of pneumonia in patients with prior radiotherapy was not clearly different between the nivolumab group and the IC group.
- Although some serious adverse events for which a causal relationship to nivolumab could not be ruled out occurred only in patients with prior radiotherapy, each of these events were reported by 1 patient. It is thus difficult to conclude a relationship between the events and prior radiotherapy.

PMDA's view:

Most of adverse events reported more frequently in the nivolumab group than in the IC group of Study 473 were known adverse events of nivolumab. Patients with esophageal cancer reported serious adverse events that had not been identified in patients treated for the approved indications; however, most of these events were attributable to the primary disease. Therefore, nivolumab is also tolerable in patients with esophageal cancer, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through appropriate measures such as monitoring of adverse events, differential diagnosis and management of excessive immune-mediated adverse drug reactions, and interruption of nivolumab.

In Study 473, the incidence of adverse events in patients with prior radiotherapy did not tend to be clearly higher in the nivolumab group than in the IC group. However, nivolumab should be carefully administered to patients with esophageal cancer with prior radiotherapy, in view of (a) and (b) below, and for other reasons: (a) The incidences of some serious adverse events, such as pneumonia, tended to be higher in patients with prior radiotherapy than in those without prior radiotherapy; and, (b) serious adverse events were reported only in patients with prior radiotherapy. Nevertheless, PMDA concluded that nivolumab is also tolerable in patients with esophageal cancer with prior radiotherapy, as long as they are continuously monitored through clinical observation, imaging tests, etc. during nivolumab therapy, and appropriate measures, including the discontinuation of nivolumab therapy, are taken when an adverse event occurs, for the following and other reasons: The pneumonia, tracheal fistula, oesophagobronchial fistula, etc. reported in Study 473 were attributable to the primary disease or prior radiotherapy; and, nivolumab is intended to be used by physicians with sufficient knowledge and experience in chemotherapy for esophageal cancer.

In the following sections, PMDA focused on adverse events for which a causal relationship to nivolumab could not be ruled out in the post-marketing setting, and adverse events that tended to occur more frequently in the nivolumab group than in the IC group of Study 473.

7.2.R.2.2 Pancreatitis

The applicant's explanation about pancreatitis that has been reported in the post-marketing setting, etc. as adverse events for which a causal relationship to nivolumab cannot be ruled out:

As pancreatitis-related adverse events, events coded as the following MedDRA preferred terms (PTs) were counted: "alcoholic pancreatitis," "alcoholic pancreopathy," "pancreatitis viral," "cytomegalovirus pancreatitis," "pancreatitis mumps," "lupus pancreatitis," "hereditary pancreatitis," "pancreatitis necrotising," "traumatic pancreatitis," "pancreatitis acute," "ischaemic pancreatitis," "pancreatitis relapsing," "pancreatitis bacterial," "autoimmune pancreatitis," "haemorrhagic necrotic pancreatitis," "pancreatitis haemorrhagic," "pancreatitis fungal," "oedematous pancreatitis," "obstructive pancreatitis," "radiation pancreatitis," "pancreatitis chronic," "immune-mediated pancreatitis," "pancreatic phlegmon," "pancreatitis," "pancreas infection," "pancreatorenal syndrome," "pancreatic abscess," and "pancreatitis helminthic."

In foreign and Japanese clinical studies, and in the foreign and Japanese post-marketing settings for nivolumab, serious pancreatitis-related adverse events were reported in 396, 11, 204, and 54 patients, respectively. A causal relationship to nivolumab could not be ruled out in 288, 8, 182, and 46 patients, respectively.

Table 13 presents the details of patients who died from pancreatitis-related adverse events for which a causal relationship to nivolumab could not be ruled out, in Japanese and foreign clinical studies and post-marketing settings.

Table 13. A list of patients who died from pancreatitis-related adverse events (assessed as causally related to nivolumab)

Study, etc.	Age	Gender	Primary disease	Concomitant use of other antitumor drugs	PT (MedDRA ver.22.0)	Grade	Time of onset (Day)	Duration of the event (days)	Nivolumab therapy
CA209-277	56	Male	Malignant melanoma	None[*1]	Pancreatitis acute	3	19	ca. 70	Discontinued
CA209-169	74	Male	NSCLC	None	Pancreatitis acute	4	241	4	Discontinued
CA209-580	54	Male	NSCLC	None	Pancreatitis acute	5	539	4	Discontinued
Post-marketing	54	Male	NSCLC	None	Autoimmune pancreatitis	—	around Day 240	ca. 150	Discontinued
Post-marketing	64	Male	Pulmonary malignancy	None	Pancreatitis acute	—	2	5	Discontinued
Post-marketing	74	Male	Malignant melanoma	None	Pancreatitis acute	—	—	5	Discontinued
Post-marketing	45	Female	Lung cancer	None	Pancreatitis	—	4	—	Discontinued
Post-marketing	74	Female	RCC	None[*2]	Pancreatitis acute	—	446	3	Discontinued

—, Unknown; *1, The patient had received prior ipilimumab therapy, and a causal relationship to ipilimumab for the event could not be ruled out; *2, The patient started pazopanib therapy at 63 days after the last dose of nivolumab and experienced the event on Day 67 of pazopanib therapy.

PMDA's view:

Among the pancreatitis reported as adverse event for which a causal relationship to nivolumab cannot be ruled out, many cases were not identified as drug related, while multiple cases, including fatal ones, were serious for which a causal relationship to nivolumab was strongly suspected. Thus, nivolumab therapy requires particular attention to the onset of pancreatitis. The incidence of pancreatitis in clinical studies, measures to be taken at the onset of pancreatitis, and other relevant information should be properly communicated to healthcare professionals through the package insert and other materials.

7.2.R.2.3 Other adverse events

The applicant's explanation about (a) tumour haemorrhage and (b) fistula, which tended to be more frequently reported as Grade ≥3 or serious adverse events in the nivolumab group than in the IC group of Study 473:

(a) Tumour haemorrhage

As tumour haemorrhage-related adverse events, events coded as the following MedDRA PTs were counted: "intracranial tumour haemorrhage," "tumour haemorrhage," "tumour necrosis," "haemorrhagic tumour necrosis," "tumour perforation," and "tumour fistulisation."

Table 14 shows the incidences of tumour haemorrhage-related adverse events in Studies 473 and 07.

Table 14. Incidences of tumour haemorrhage (Studies 473 and 07)

PT (MedDRA ver.21.1)	Number of patients (%)					
	Study 473				Study 07	
	Nivolumab n = 192		IC n = 194		Nivolumab n = 65	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Tumour haemorrhage	3 (1.6)	3 (1.6)	1 (0.5)	1 (0.5)	0	0

In Study 473, no patients died from tumour haemorrhage-related adverse events in the nivolumab group, while 1 patient (0.5%) died from a tumour haemorrhage-related adverse event in the IC group, for which a causal relationship to the study drug was denied. Serious tumour haemorrhage-related adverse events were reported in 3 patients (1.6%) in the nivolumab group and 1 patient (0.5%) in the IC group; a causal relationship to nivolumab could not be ruled out in the 3 patients in the nivolumab group. Tumour haemorrhage-related adverse events led to drug discontinuation in no patients in the nivolumab group and 1 patient (0.5%) in the IC group. Tumour haemorrhage-related adverse events led to drug interruption in 2 patients (1.0%) in the nivolumab group and no patients in the IC group.

The median time to the onset of tumour haemorrhage-related adverse events (range) was 36.0 (19 to 66) days in the nivolumab group and 102 days in the IC group. Of the 3 patients with tumour haemorrhage-related adverse events in the nivolumab group, 2 had received prior radiotherapy.

(b) Fistula

As fistula-related adverse events, events coded as the following MedDRA PTs were counted: "lymphatic fistula," "mammary fistula," "perineal fistula," "arterioenteric fistula," "arteriovenous fistula," "oroantral

fistula," "oral cavity fistula," "pharyngeal fistula," "salivary gland fistula," "laryngeal fistula," "aortoenteric fistula," "aorto-oesophageal fistula," "female genital tract fistula," "uterine fistula," "fistula of small intestine," "enterocolonic fistula," "urogenital fistula," "urinary fistula," "ureteric fistula," "urethroperineal fistula," "urethral fistula," "atrio-oesophageal fistula," "acquired tracheo-oesophageal fistula," "diverticular fistula," "bronchial fistula," "bronchopleural fistula," "tracheal fistula," "tracheo-oesophageal fistula," "lacrimal fistula," "thyroglossal fistula," "male genital tract fistula," "fistula," "fistula inflammation," "fistula discharge," "rectoprostatic fistula," "rectourethral fistula," "ocular fistula," "dural arteriovenous fistula," "colonic fistula," "postauricular fistula," "anovulvar fistula," "intrahepatic portal hepatic venous fistula," "pulmonary arteriovenous fistula," "pulmonary fistula," "gastric fistula," "gastropleural fistula," "gastrosplenic fistula," "gallbladder fistula," "biliary-bronchial fistula," "biliary fistula," "biliary-vascular fistula," "pleural fistula," "pleurocutaneous fistula," "cerebrospinal fistula," "renal pelvis fistula," "vaginal fistula," "tumour fistulisation," "intestinal fistula," "enterocutaneous fistula," "enterovesical fistula," "peritoneocutaneous fistula," "vesical fistula," "vesicocutaneous fistula," "pancreatic fistula," "sinus perforation," "labyrinthine fistula," "jaw fistula," "oesophagobronchial fistula," "oesophageal fistula," "oesophagopleural fistula," and "bone fistula."

Table 15 presents the incidences of fistula-related adverse events in Studies 473 and 07.

Table 15. Incidences of fistula-related adverse events (Studies 473 and 07)

PT (MedDRA/J ver.21.1)	Number of patients (%)					
	Study 473				Study 07	
	Nivolumab n = 192		IC n = 194		Nivolumab n = 65	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Fistula	6 (3.1)	6 (3.1)	4 (2. 1)	2 (1.0)	0	0
Oesophagobronchial fistula	2 (1.0)	2 (1.0)	0	0	0	0
Tracheo-oesophageal fistula	1 (0.5)	1 (0.5)	0	0	0	0
Gastric fistula	1 (0.5)	1 (0.5)	0	0	0	0
Tracheal fistula	1 (0.5)	1 (0.5)	0	0	0	0
Aorto-oesophageal fistula	1 (0.5)	1 (0.5)	0	0	0	0
Fistula	0	0	1 (0.5)	1 (0.5)	0	0
Oesophageal fistula	0	0	1 (0.5)	1 (0.5)	0	0
Fistula inflammation	0	0	2 (1.0)	0	0	0

In Study 473, a fatal fistula was reported in 1 patient (0.5%; oesophagobronchial fistula) in the nivolumab group, for which its causal relationship to nivolumab was denied. Serious fistula were reported in 6 patients (3.1%; oesophagobronchial fistula in 2 patients, and tracheo-oesophageal fistula, gastric fistula, and tracheal fistula, and aorto-oesophageal fistula in 1 patient each) in the nivolumab group and 1 patient (0.5%; fistula) in the IC group. A causal relationship to the study drug could not be ruled out in the 2 patients (1.0%; oesophagobronchial fistula and tracheal fistula in 1 patient each) in the nivolumab group. Fistula leading to study drug discontinuation was reported in 2 patients (1.0%; oesophagobronchial fistula and tracheal fistula in 1 patient each) in the nivolumab group and 2 patients (1.0%; fistula and oesophageal fistula in 1 patient each) in the IC group. Fistula leading to drug interruption was reported in 3 patients (1.6%; oesophagobronchial

fistula, tracheo-oesophageal fistula, and aorto-oesophageal fistula in 1 patient each) in the nivolumab group and 1 patient (0.5%; fistula inflammation) in the IC group.

The median time (range) to the onset of fistula was 109.5 (6-196) days in the nivolumab group and 25.5 (18-92) days in the IC group. All of the 6 patients with onset of fistula in the nivolumab group had received prior radiotherapy.

PMDA's view:
Although the incidences of tumour haemorrhage and fistula were not clearly different between the nivolumab group and the IC group of Study 473, and no clear risk of tumour haemorrhage or fistula was identified in association with nivolumab therapy, some serious events for which a causal relationship to nivolumab could not be ruled out were reported. Therefore, the incidences of tumour haemorrhage and fistula during nivolumab therapy should be properly communicated to healthcare professionals through materials, etc. and the onset of tumour haemorrhage and fistula should be monitored in the post-marketing setting, and new information should be properly provided to healthcare professionals.

7.2.R.3 Clinical positioning and indication

The proposed indication for esophageal cancer in the present partial change application was "Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy," and the following statements were proposed in the "Precautions Concerning Indications" section.

- The efficacy and safety of nivolumab in first-line treatment have not been established.
- The efficacy and safety of nivolumab in adjuvant chemotherapy have not been established.

PMDA's view:
On the basis of the discussions in Sections "7.2.R.1 Efficacy" and "7.2.R.2 Safety," and the subsections below, PMDA concluded that the indication of nivolumab should be "Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy," and the following statements should be presented in the "Precautions Concerning Indications" section of the package insert, and the inclusion criteria of Study 473 and other relevant information should be included in the "Clinical Studies" section.

- The efficacy and safety of nivolumab in first-line treatment have not been established.
- The efficacy and safety of nivolumab in adjuvant therapy have not been established.
- Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of nivolumab presented in the "Clinical Studies" section.

7.2.R.3.1 Clinical positioning and intended patient population of nivolumab

In representative clinical practice guidelines and leading clinical oncology textbooks in and outside Japan, descriptions on nivolumab in the treatment of patients with esophageal cancer are as shown below. The US National Cancer Institute Physician Data Query (NCI-PDQ) (version dated July 3, 2019) has no description regarding nivolumab therapy for esophageal cancer.

Clinical practice guidelines

- NCCN Guidelines (Esophageal and Esophagogastric Junction Cancers) (v.2.2019):
  In Study 473, nivolumab significantly improved OS in chemotherapy-treated patients with esophageal cancer as compared with IC.
- Japanese clinical practice guidelines (esophageal cancer):
  The results of Study 07 showed the efficacy of nivolumab in the treatment of unresectable, advanced or recurrent esophageal cancer. However, the clinical application of nivolumab has to await the results of Study 473.

The applicant's explanation about the clinical positioning and indication of nivolumab for esophageal cancer:
Nivolumab therapy can be recommended for patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine- and platinum-based chemotherapy because Study 473 demonstrated the superiority of nivolumab in the primary endpoint of OS over the existing treatment (i.e., DOC or PTX) in such patients.

Although both Studies 473 and 07 were designed to enroll patients who had a documented squamous cell carcinoma, adenosquamous carcinoma, or other histological types of esophageal cancer, all of the enrolled patients were histologically categorized as having squamous cell carcinoma. Therefore, no clinical data are available to demonstrate the clinical benefit of nivolumab in patients with esophageal cancer of histological types other than squamous cell carcinoma. Nevertheless, in view of the following (a) and (b), administration of nivolumab to patients with esophageal cancer of histological types other than squamous cell carcinoma is acceptable, as long as it is determined by a physician with sufficient knowledge and experience in cancer chemotherapy, based on a good understanding of the clinical results for nivolumab: (a) Clinical practice guidelines in and outside Japan (e.g., NCCN guidelines [v.2.2019]) do not clearly distinguish treatment algorithms for esophageal cancer according to histological types; (b) Nivolumab has demonstrated its efficacy in the approved indications not only of the squamous type, but also of other histological types (gastric cancer [adenocarcinoma] and NSCLC [squamous and non-squamous cell carcinoma]).

In Study 473, patients with evident tumour invasion on the aorta, trachea, etc., or patients with an esophageal or tracheal stent were excluded; therefore, no clinical study results are available regarding nivolumab therapy in such patients. Although the risks of tumour haemorrhage, fistula formation, stent removal, due to tumor shrinkage associated with nivolumab therapy should be taken into account, the administration of nivolumab to patients with esophageal cancer who have evident tumour invasion on the aorta, trachea, etc. or who have an implanted esophageal or tracheal stent is considered to be acceptable, depending on individual patient conditions, if nivolumab is used by physicians with sufficient knowledge and experience in cancer chemotherapy.

PMDA's view:
PMDA generally accepted the applicant's explanation. However, the use of nivolumab in patients with esophageal cancer who have evident tumour invasion on the aorta, trachea, etc. or who have an implanted

esophageal or tracheal stent is not recommended, as no data are available from clinical studies evaluating the efficacy or safety of nivolumab in such patients. Further, the efficacy and safety of nivolumab as an adjuvant therapy have not been demonstrated. Accordingly, a precaution that the efficacy and safety of nivolumab in adjuvant therapy have not been established should be properly communicated to healthcare professionals.

On the basis of the above, PMDA concluded that the indication of nivolumab should be "Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy," and the "Clinical Studies" section of the package insert should include the target patient population of Study 473, as shown below, with a precaution in the "Precautions Concerning Indications" section for which appropriate patients must be selected based on a thorough understanding of the efficacy and safety of nivolumab after sufficiently understanding the "Clinical Studies" section.

- Patients who have previously received fluoropyrimidine- and platinum-based chemotherapy
- Patients who have no evident tumour invasion on the aorta, trachea, etc.
- Patients who have no implanted esophageal or tracheal stent

7.2.R.3.2 Efficacy and safety of nivolumab by PD-L1 expression status, and intended patient population

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

The applicant's explanation:

In Study 473, PD-L1 expression status[16)] in tumor tissue samples was assessed using the "PD-L1 IHC 28-8 pharmDx assay 'Dako' (Dako Japan Co., Ltd.)," and the (a) efficacy and (b) safety of nivolumab by PD-L1 expression status were evaluated in patients who had evaluable PD-L1 data.

(a) Efficacy

Table 16 and Figure 3 present the OS results by PD-L1 expression status (cutoff values, 1%, 5%, and 10%) in patients with evaluable PD-L1 data (data cutoff on November 12, 2018).

There were no clear differences in OS prolongation between the PD-L1-positive and -negative populations, at any of the cutoff values. Thus, the efficacy of nivolumab can be expected, regardless of PD-L1 expression status.

Table 16. OS results by PD-L1 expression status (Study 473, data cutoff on November 12, 2018)

PD-L1 expression*	Treatment	Number of patients	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
<1%	Nivolumab	103	11.0 [8.8, 13.9]	0.86 [0.63,1.18]	0.3421
	IC	102	9.4 [6.9, 12.0]		
≥1%	Nivolumab	90	11.5 [9.3, 14.4]	0.69 [0.50, 0.95]	
	IC	93	8.3 [5.8, 9.9]		
<5%	Nivolumab	129	11.2 [9.2, 14.3]	0.80 [0.61, 1.05]	0.7132
	IC	129	9.4 [7.4, 11.3]		
≥5%	Nivolumab	64	10.9 [7.6, 14.2]	0.74 [0.50, 1.08]	
	IC	66	7.7 [5.7, 10.3]		
<10%	Nivolumab	137	11.0 [9.2, 13.9]	0.81 [0.62, 1.05]	0.5539
	IC	143	9.3 [7.4, 10.7]		
≥10%	Nivolumab	56	11.5 [7.6, 14.2]	0.71 [0.46, 1.09]	
	IC	52	7.4 [5.2, 10.3]		

*, Non-stratified Cox regression

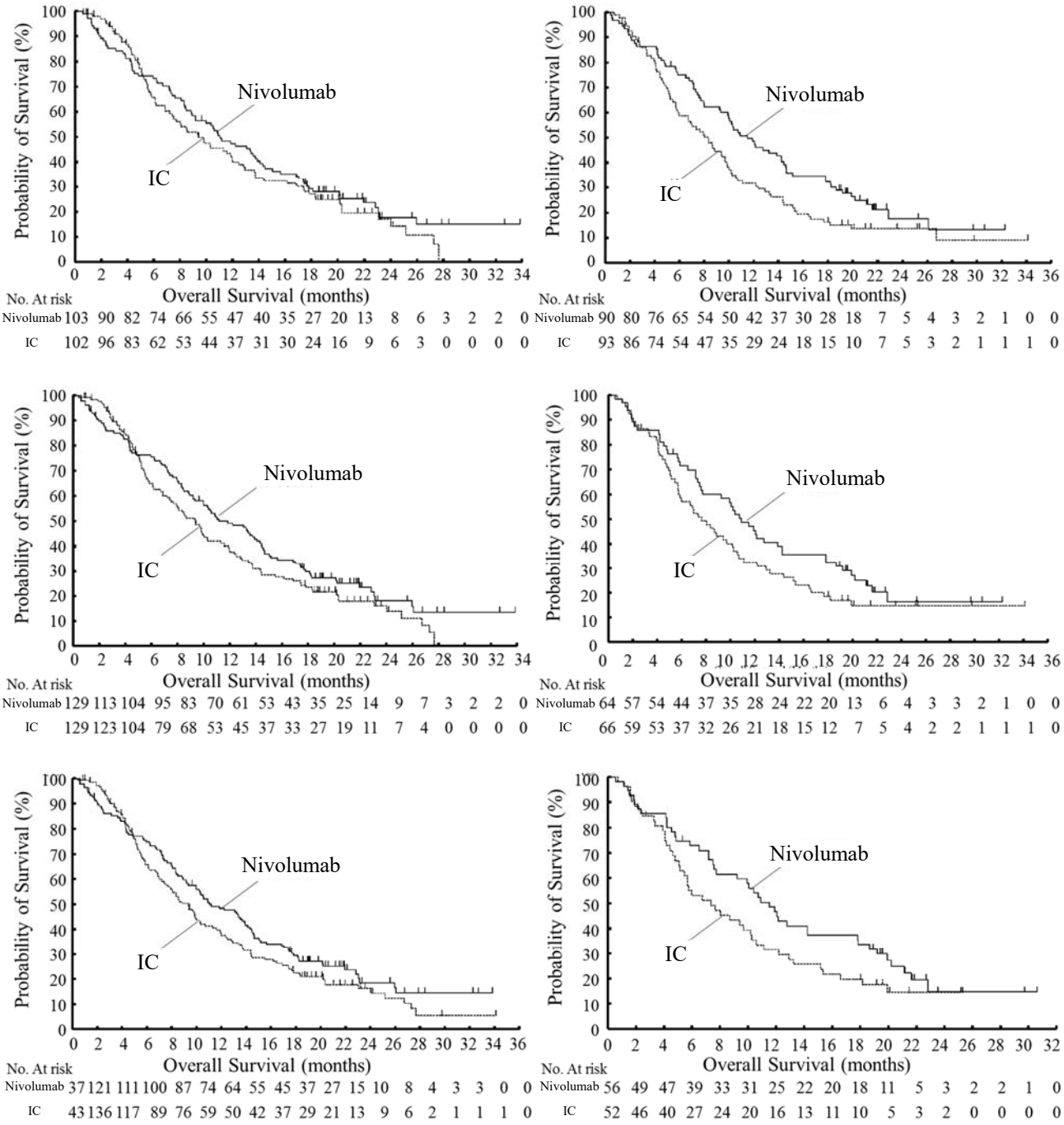


Figure 3. Kaplan-Meier curves of OS by PD-L1 expression status
(ITT population, data cutoff on November 12, 2018)
(Top left, <1%; top right, ≥1%; center left, <5%; center right, ≥5%; bottom left, <10%; bottom right, ≥10%)

(b) Safety

In the nivolumab group of Study 473, the incidence of adverse events of any grade was 93.1% in patients with <1% PD-L1 and 85.6% in those with ≥1% PD-L1. The incidence of Grade ≥3 adverse events was 38.2% and 42.2%, while the incidence of serious adverse events was 29.4% and 30.0%, respectively. The incidence of adverse events of any grade was 89.8% in patients with <5% PD-L1 and 89.1% in those with ≥5% PD-L1. The incidence of Grade ≥3 adverse events was 37.5% and 45.3%, while the incidence of serious adverse events was

27.3% and 34.4%, respectively. The incidence of adverse events of any grade was 90.4% in patients with <10% PD-L1 and 87.5% in those with ≥10% PD-L1. The incidence of Grade ≥3 adverse events was 37.5% and 46.4%, while the incidence of serious adverse events was 27.2% and 35.7%, respectively.

Since the safety of nivolumab was not substantially different between PD-L1-positive and -negative populations at any cutoff value, nivolumab is considered tolerable, regardless of PD-L1 expression status.

The discussions described in (a) and (b), above indicate that response to nivolumab in patients with esophageal cancer is independent of PD-L1 expression status.

Therefore, in nivolumab therapy for patients with unresectable, advanced or recurrent esophageal cancer who previously received fluoropyrimidine- and platinum-based chemotherapy, it is not necessary to identify the intended patient population according to PD-L1 expression status.

PMDA's view:
PMDA generally accepted the applicant's explanation. However, PMDA concluded that the applicant should continue to collect information on possible predictors of response to nivolumab other than PD-L1 expression, and appropriately communicate new findings to healthcare professionals.

7.2.R.4 Dosage and administration

In the present partial change application, the applicant proposed the following dosage and administration for the treatment of esophageal cancer: "The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks" (unchanged from the previous approval), with the following statement to be included in the "Precautions Concerning Dosage and Administration" section of the package insert.

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

PMDA's view:
As a result of the discussions in Sections "7.2.R.1 Efficacy," "7.2.R.2 Safety," and the subsection below, PMDA concluded that the dosage and administration of nivolumab for the treatment of esophageal cancer should be "The usual adult dosage of nivolumab is 240 mg administered as an intravenous infusion every 2 weeks," and that the statement proposed by the applicant should be included in the "Precautions Concerning Dosage and Administration" section of the package insert.

7.2.R.4.1 Dosage and administration of nivolumab

The applicant's explanation about the dosage and administration of nivolumab for the treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy:
In Study 473, a fixed dose of 240 mg every 2 weeks, rather than a body weight-based dose was selected based on data including the results of a PPK analysis (see "Review Report for Opdivo Intravenous Infusion 20 mg,

Opdivo Intravenous Infusion 100 mg, dated July 26, 2018"), and the results of the study demonstrated the clinically meaningful efficacy [see Section 7.2.R.1] and acceptable tolerability of nivolumab [see Section 7.2.R.2]. The dosage and administration of nivolumab for the treatment of esophageal cancer was therefore proposed as "The usual adult dosage of nivolumab is 240 mg administered as an intravenous infusion every 2 weeks."

PMDA accepted the applicant's explanation.

7.2.R.5 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plans for (a) MSI-High colorectal cancer and (b) esophageal cancer:

On the basis of the discussion below, it is not necessary to conduct post-marketing surveillance in patients treated with nivolumab for (a) MSI-High colorectal cancer or (b) esophageal cancer immediately after approval of the present applications.

(a) MSI-High colorectal cancer

- Considering that the safety profile of nivolumab in Study 142 was not clearly different from that in patients treated for the approved indications [see Section 7.1.R.3.1], administration of nivolumab to Japanese patients with MSI-High colorectal cancer, despite the lack of experience with such administration, is unlikely to raise new safety concerns [see Section 7.1.R.3.2].

(b) Esophageal cancer

- Oesophagobronchial fistula was newly reported as a serious adverse event in the nivolumab group of Study 473, as compared with patients treated for the approved indications. However, the oesophagobronchial fistula was attributable to the primary disease. Thus, the safety profile of nivolumab in Study 473 is not clearly different from that observed in patients treated for the approved indications [see Section 7.2.R.2.1].
- In Study 473, ILD was reported as an adverse event leading to treatment discontinuation only in Japanese patients. However, ILD was also reported in the IC group. There were no other adverse events attributable to nivolumab, which would require specific attention to Japanese patients treated with nivolumab [see Section 7.2.R.2.1].

PMDA's view:

As a result of discussions in "Section 7.1.R.3 Safety" and "Section 7.2.R.2 Safety," and considering that a certain amount of safety data on nivolumab therapy in Japanese patients is available from the post-marketing surveillances for the approved indications, there is little necessity to conduct post-marketing surveillances for the above (a) and (b) immediately after the approval of the present applications, and safety information may be collected through routine pharmacovigilance activities.

7.3 Adverse events reported in clinical studies

Deaths reported in clinical studies submitted as the safety evaluation data are presented in "Section 7.1.1 Evaluation data" and "Section 7.2.1 Evaluation data." Other main adverse events are shown below.

7.3.1 Adverse events reported in clinical studies in patients with MSI-High colorectal cancer

7.3.1.1 Japanese phase II study (Study 39)

Adverse events were reported in 1 of 2 patients (50.0%). Adverse events for which a causal relationship to nivolumab could not be ruled out were reported in 1 of 2 patients (50.0%). The adverse events reported were bronchitis, upper respiratory tract infection, lung infection, and pneumonitis in 1 patient (50.0%) each.

No serious adverse events were reported.

Pneumonitis, the adverse event that led to discontinuation of nivolumab, was reported in 1 of 2 patients (50.0%). A causal relationship to nivolumab could not be ruled out for this event.

7.3.1.2 Global phase II study (Study 275)

Adverse events were reported in 2 of 2 patients (100.0%). Adverse events for which a causal relationship to nivolumab could not be ruled out were reported in 1 of 2 patients (50.0%). The adverse events reported were anaemia, sinus bradycardia, abdominal pain, diarrhoea, enteritis, nausea, chills, fatigue, injection site reaction, oedema peripheral, subcutaneous abscess, upper respiratory tract infection, urinary tract infection, escherichia urinary tract infection, stoma site cellulitis, blood creatinine increased, lipase increased, blood alkaline phosphatase increased, dehydration, hypoalbuminaemia, hypokalaemia, anxiety, proteinuria, cough, rash maculo-papular, and suprapubic growth with abscess in 1 patient each.

Serious adverse events were reported in 1 of 2 patients (50.0%). The serious adverse events reported were diarrhoea, enteritis, stoma site cellulitis, and suprapubic growth with abscess in 1 patient (50.0%) each. A causal relationship to nivolumab was denied for all of these events.

There were no adverse events leading to discontinuation of nivolumab.

7.3.1.3 Global phase III study (Study 12)

Adverse events were reported in 1 of 1 patient (100.0%). Adverse events for which a causal relationship to nivolumab could not be ruled out were reported in 1 of 1 patient (100.0%). The adverse events reported were blood thyroid stimulating hormone decreased and urticaria in 1 patient (100%) each.

There were no serious adverse events or adverse events leading to discontinuation of nivolumab.

7.3.1.4 Foreign phase Ib study (Study 009)

Adverse events were reported in 2 of 2 patients (100.0%). Adverse events for which a causal relationship to nivolumab could not be ruled out were reported in 2 of 2 patients (100.0%). The adverse events reported were hypothyroidism, abdominal distension, abdominal pain, constipation, nausea, vomiting, fatigue, malignant neoplasm progression, sciatica, urinary retention, rash, and hypertension in 1 patient (50.0%) each.

No serious adverse events were reported.

Adverse events led to discontinuation of nivolumab in 1 of 2 patients (50.0%). The adverse events that led to discontinuation of nivolumab were abdominal distension and malignant neoplasm progression in 1 patient (50.0%) each. A causal relationship to nivolumab was denied for both of these events.

7.3.1.5 Foreign phase I/II study (Study 032)

Adverse events were reported in 7 of 7 patients (100.0%). Adverse events for which a causal relationship to nivolumab could not be ruled out were reported in 6 of 7 patients (85.7%). Adverse events reported with a ≥40% incidence were abdominal pain and fatigue in 5 patients (71.4%) each, and anaemia, diarrhoea, and pruritus in 3 patients (42.9%) each.

Serious adverse events were reported in 4 of 7 patients (57.1%). The serious adverse events reported were diarrhoea infectious, colitis, ALT increased, AST increased, anaemia, device-related infection, abdominal sepsis, transaminases increased, and epilepsy in 1 patient (14.3%) each. A causal relationship to nivolumab could not be ruled out for the ALT increased and AST increased in 1 patient each.

Adverse events led to discontinuation of nivolumab in 3 of 7 patients (42.9%). The adverse events that led to discontinuation of nivolumab were ALT increased, AST increased, colitis, and malignant neoplasm progression in 1 patient (14.3%) each. A causal relationship to nivolumab could not be ruled out for the ALT increased, AST increased, and colitis in 1 patient each.

7.3.1.6 Foreign phase II study (Study 142)

Adverse events were reported in 71 of 74 patients (95.9%). Adverse events for which a causal relationship to nivolumab could not be ruled out were reported in 51 of 74 patients (68.9%). Adverse events reported with a ≥20% incidence were diarrhoea in 32 patients (43.2%), fatigue in 31 patients (41.9%), anaemia in 27 patients (36.5%), nausea in 25 patients (33.8%), vomiting in 21 patients (28.4%), abdominal pain and cough in 19 patients (25.7%) each, pyrexia in 18 patients (24.3%), and constipation in 15 patients (20.3%).

Serious adverse events were reported in 31 of 74 patients (41.9%). Serious adverse events reported by ≥2 patients were malignant neoplasm progression in 6 patients (8.1%), abdominal pain, intestinal obstruction, and vomiting in 3 patients (4.1%) each, and diarrhoea, small intestinal obstruction, and pyrexia in 2 patients (2.7%) each. A causal relationship to nivolumab could not be ruled out for the diarrhoea in 1 patient.

Adverse events led to discontinuation of nivolumab in 6 of 74 patients (8.1%). The adverse events that led to discontinuation of nivolumab were abdominal pain, colitis, stomatitis, vomiting, ALT increased, malignant neoplasm progression, and acute kidney injury in 1 patient each. A causal relationship to nivolumab could not be ruled out for the colitis, stomatitis, ALT increased, and acute kidney injury in 1 patient each.

7.3.2 Adverse events reported in clinical studies in patients with esophageal cancer

7.3.2.1 Japanese phase II study (Study 07)

Adverse events were reported in 56 of 65 patients (86.2%). Adverse events for which a causal relationship to nivolumab could not be ruled out were reported in 40 of 65 patients (61.5%). Adverse events reported with a ≥15% incidence were diarrhoea in 14 patients (21.5%) and decreased appetite in 12 patients (18.5%).

Serious adverse events were reported in 12 of 65 patients (18.5%). Serious adverse events reported by ≥2 patients were lung infection in 4 patients (6.2%), and dehydration and ILD in 2 patients (3.1%) each. A causal relationship to nivolumab could not be ruled out for the lung infection, dehydration, and ILD in 2 patients each.

Adverse events led to discontinuation of nivolumab in 7 of 65 patients (10.8%). The adverse event that led to discontinuation of nivolumab in ≥2 patients was ILD in 3 patients (4.6%). A causal relationship to nivolumab could not be ruled out in all of these patients.

7.3.2.2 Global phase III study (Study 473)

Adverse events were reported in 172 of 192 patients (89.6%) in the nivolumab group and 192 of 194 patients (99.0%) in the IC group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 129 of 192 patients (67.2%) in the nivolumab group and 185 of 194 patients (95.4%) in the IC group. Table 17 shows the adverse events reported with a ≥15% incidence in either treatment group.

Table 17. Adverse events reported with a ≥15% incidence in either treatment group

SOC PT (MedDRA ver.21.1)	Number of patients (%)			
	Nivolumab n = 192		IC n = 194	
	Any grade	Grade ≥3	Any grade	Grade ≥3
All adverse events	172 (89.6)	77 (40.1)	192 (99.0)	145 (74.7)
Blood and lymphatic system disorders				
Anaemia	21 (10.9)	16 (8.3)	57 (29.4)	22 (11.3)
Neutropenia	1 (0.5)	0	36 (18.6)	27 (13.9)
Gastrointestinal disorders				
Diarrhoea	33 (17.2)	2 (1.0)	31 (16.0)	3 (1.5)
Constipation	31 (16.1)	0	39 (20.1)	0
Nausea	21 (10.9)	0	38 (19.6)	1 (0.5)
General disorders and administration site conditions				
Pyrexia	30 (15.6)	1 (0.5)	36 (18.6)	1 (0.5)
Fatigue	18 (9.4)	2 (1.0)	49 (25.3)	9 (4.6)
Malaise	13 (6.8)	0	48 (24.7)	0
Investigations				
Neutrophil count decreased	3 (1.6)	1 (0.5)	76 (39.2)	58 (29.9)
White blood cell count decreased	2 (1.0)	1 (0.5)	72 (37.1)	46 (23.7)
Metabolism and nutrition disorders				
Decreased appetite	36 (18.8)	4 (2.1)	66 (34.0)	10 (5.2)
Nervous system disorders				
Peripheral sensory neuropathy	1 (0.5)	0	48 (24.7)	1 (0.5)
Respiratory, thoracic and mediastinal disorders				
Cough	29 (15.1)	0	22 (11.3)	1 (0.5)
Skin and subcutaneous tissue disorders				
Rash	25 (13.0)	1 (0.5)	36 (18.6)	2 (1.0)
Alopecia	3 (1.6)	0	99 (51.0)	0

Serious adverse events were reported in 57 of 192 patients (29.7%) in the nivolumab group and 70 of 194 patients (36.1%) in the IC group. Serious adverse events reported by ≥5 patients in the nivolumab group were pneumonia in 8 patients (4.2%) and pyrexia in 5 patients (2.6%). Serious adverse events reported by ≥5 patients in the IC group were febrile neutropenia in 14 patients (7.2%), pneumonia in 12 patients (6.2%), and lung infection and decreased appetite in 5 patients (2.6%) each in the IC group. A causal relationship to the study drug could not be ruled out for the pyrexia in 5 patients and pneumonia in 1 patient in the nivolumab group, and the febrile neutropenia in 14 patients, lung infection and decreased appetite in 5 patients each, and pneumonia in 3 patients in the IC group.

Adverse events led to drug discontinuation in 24 of 192 patients (12.5%) in the nivolumab group and 33 of 194 patients (17.0%) in the IC group. Adverse events that led to drug discontinuation in ≥3 patients in the nivolumab group were ILD in 5 patients (2.6%) and pneumonitis in 4 patients (2.1%), while those in the IC group were pneumonia in 4 patients (2.1%) and ILD in 3 patients (1.5%). A causal relationship to the study drug could not be ruled out for the ILD in 5 patients and pneumonitis in 4 patients in the nivolumab group, and the ILD in 3 patients and pneumonia in 1 patient in the IC 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 there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.2-1.1, CTD 5.3.5.4-3.1, and CTD 5.3.5.4-5 [MSI-High colorectal cancer], and 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 clinical studies were suitably conducted in accordance with the GCP overall, and that there were no major obstacles to conducting its review based on the application documents submitted. The inspection revealed the following issues at some trial sites and the sponsor, although the issues had no significant impact on the overall assessment of the studies. The heads of the relevant study sites and the sponsor were notified of these issues requiring improvement.

Findings requiring corrective actions (MSI-High colorectal cancer)

Study sites

- Protocol deviations (noncompliance with the rules for reporting serious adverse events, noncompliance with the rules for administration of study drug)

Sponsor

- Failure to provide some safety information to the investigators and the heads of the study sites in a timely manner, before revising the Investigator's Brochure

Findings requiring corrective actions (esophageal cancer)

Study sites

- Protocol deviations (erroneous entry of stratification factors)
- Failure to obtain new written consent from some subjects, who were already participating in the clinical trial, using the revised Written Information

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

On the basis of the data submitted, PMDA has concluded that nivolumab has (a) a certain level of efficacy in the treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy, and (b) efficacy in the treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy, and that nivolumab has acceptable safety in view of its benefits. Nivolumab is clinically meaningful because it offers new treatment options for patients with MSI-High colorectal cancer and patients with esophageal cancer.

The clinical positioning, indications, post-marketing investigations, etc. of nivolumab need to be further investigated.

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

Review Report (2)

January 8, 2020

Product Submitted for Approval

Brand Name	Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg
Non-proprietary Name	Nivolumab (Genetical Recombination)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	March 28, 2019, May 30, 2019[23)]

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 Discussion, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of its review described in Sections "7.1.R.2 Efficacy" and "7.2.R.1 Efficacy" of the Review Report (1), PMDA has concluded the efficacy of nivolumab in the treatment of (a) microsatellite instability-high (MSI-High) colorectal cancer and (b) esophageal cancer as follows:

(a) In a global phase II study in chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer (Study 142), the investigator-assessed response rate [95% CI] (%) (the primary endpoint) was 31.1 [20.8, 42.9]. Taking into account the molecular pathology of MSI-High colorectal cancer [see Section 7.1.R.2.1] and other data, a certain level of efficacy of nivolumab has been demonstrated in the target study population of Study 142.

(b) The results of a global phase III study in patients with unresectable, advanced or recurrent esophageal cancer, who previously received fluoropyrimidine- and platinum-based chemotherapy (Study 473) demonstrated the superiority of nivolumab in overall survival (OS, the primary endpoint) over the investigator's choice. On the basis of the study results, the efficacy of nivolumab was demonstrated in the target study population of Study 473.

23) Applications for partial change in new indications for (a) MSI-High colorectal cancer and (b) esophageal cancer were filed on (a) March 28, 2019 and (b) May 30, 2019, respectively.

At the Expert Discussion, the expert advisors supported PMDA's conclusion. In the meantime, the following comment was raised by the expert advisors.

- In the present partial change application for MSI-High colorectal cancer, the efficacy of nivolumab was evaluated based mainly on response rate results, overall survival (OS) should continue to be collected and assessed.

Taking account of the above comment from the expert advisors, PMDA instructed the applicant to provide the results of an ongoing global phase IIIb study in patients with MSI-High colorectal cancer (Study CA2098HW) to healthcare professionals immediately, when they become available. The applicant agreed.

1.2 Safety

As a result of its review described in Sections "7.1.R.3 Safety" and "7.2.R.2 Safety" of the Review Report (1), PMDA has concluded that nivolumab therapy for (a) MSI-High colorectal cancer and (b) esophageal cancer requires particular attention to the onset of pancreatitis, in addition to the safety issues that were identified to require attention with nivolumab at the regulatory reviews for the approved indications.[24)] Patients should be closely monitored for these events when nivolumab is administered for the treatment of (a) and (b), as well as for the approved indications.

Although the use of nivolumab therapy should require attention to the above-mentioned adverse events, nivolumab is also tolerable in patients with (a) MSI-High colorectal cancer or (b) esophageal cancer, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through appropriate measures such as monitoring of adverse events, differential diagnosis and management of excessive immune-mediated adverse drug reactions, and interruption of nivolumab.

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

1.3 Clinical positioning and indications

As a result of its review described in Sections "7.1.R.4 Clinical positioning and indication" and "7.2.R.3 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the statements for (a) MSI-High colorectal cancer and (b) esophageal cancer presented in the table below should be included in the "Indications" and "Precautions Concerning Indications" sections of the package insert.

24) Intestinal lung disease (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, and tuberculosis (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg, dated July 26, 2018," etc.)

	Indications	Precautions Concerning Indications
(a)	Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy	• The efficacy and safety of nivolumab have not been established in patients who have not received prior treatment with a fluoropyrimidine, L-OHP, and CPT-11. • Nivolumab should be administered to patients with a MSI-High cancer confirmed by tests performed by a thoroughly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic should be used in the test. • The efficacy and safety of nivolumab in adjuvant therapy have not been established. • Eligible patients must be selected by physicians with adequate knowledge in the efficacy and safety of nivolumab, after fully understanding the "Clinical Studies" section, and carefully considering the choice of alternative therapies.
(b)	Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy	• The efficacy and safety of nivolumab in first-line treatment have not been established. • The efficacy and safety of nivolumab in adjuvant therapy have not been established. • Eligible patients must be selected by physicians with adequate knowledge in the efficacy and safety of nivolumab, after fully understanding the "Clinical Studies" section.

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

On the basis of the above, PMDA instructed the applicant to define the "Indications" and "Precautions Concerning Indications" sections as shown above. The applicant agreed.

1.4 Dosage and administration

As a result of its review described in Sections "7.1.R.5 Dosage and administration" and "7.2.R.4 Dosage and administration" of the Review Report (1), PMDA concluded that the dosage and administration should be "The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 weeks," and the following statement should be included in the "Precautions Concerning Dosage and Administration" section of the package insert.

Precautions Concerning Dosage and Administration

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

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

On the basis of the above, PMDA instructed the applicant to include the statements as shown above in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections. The applicant agreed.

1.5 Risk management plan (draft)

As a result of its review described in Section "7.2.R.5 Post-marketing investigations" of the Review Report (1), PMDA concluded that there is little necessity to conduct post-marketing surveillance in (a) patients with MSI-High colorectal cancer and (b) patients with esophageal cancer immediately after the approval of the present applications, and that safety information may be collected through routine pharmacovigilance activities.

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

Taking account of the review presented in Section "7.2.R.2 Safety" of the Review Report (1) and the above discussions, PMDA concluded that the risk management plan (draft) for nivolumab should include the safety specifications presented in Table 18, and that the applicant should conduct the additional risk minimization activities presented in Table 19.

Table 18. 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 • Hepatic failure, hepatic function disorder, hepatitis, cholangitis sclerosing • Endocrine disorders (thyroid dysfunction, pituitary dysfunction, adrenal disorder) • Neurological disorders • Renal disorders (including renal failure and tubulointerstitial nephritis) • Encephalitis • Severe skin disorders • Venous thromboembolism • Infusion reaction • Serious blood disorders • Tuberculosis • Haemophagocytic syndrome • Use of nivolumab in patients with a history of organ transplant (including haematopoietic stem cell transplant) • Pancreatitis	• Excessive immunisation reaction • Embryonic/fetal toxicity • Cardiac disorders (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles) • Aplasia pure red cell • Increased risk of severe complication associated with allogenic haematopoietic stem cell transplant after nivolumab therapy (haematologic neoplasm) • Tumour haemorrhage • Fistula	None
Efficacy specification (for the present partial approval applications)		
None		

Underline denotes specifications to be added after the present partial change approval. Wavy line denotes important identified risks to be added after the present partial change approval.

Table 19. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy investigations/studies	Additional risk minimization activities
• Use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Specified use-results survey in patients with unresectable, advanced or recurrent NSCLC (all-case surveillance) • Specified use-results survey in patients with unresectable or metastatic RCC (all-case surveillance) • Specified use-results survey in patients with relapsed or refractory cHL (all-case surveillance) • Use-results survey in patients with recurrent or metastatic head and neck cancer (all-case surveillance) • Use-results survey in patients with unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy • Specified use-results survey in patients with unresectable malignant melanoma (nivolumab/ipilimumab therapy) • Specified use-results survey in patients with unresectable malignant melanoma (nivolumab/ipilimumab therapy) • Specified use-results survey in patients with unresectable or metastatic RCC (nivolumab/ipilimumab therapy) • General use-results survey in patients with unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy • Post-marketing clinical studies (extension studies of Studies 05, 06, 08, 025, 12, 41, 473, 24E,* and 07)	• Use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Specified use-results survey in patients with unresectable, advanced or recurrent NSCLC (all-case surveillance) • Specified use-results survey in patients with unresectable or metastatic RCC (all-case surveillance) • Specified use-results survey in patients with relapsed or refractory cHL (all-case surveillance) • Use-results survey in patients with recurrent or metastatic head and neck cancer (all-case surveillance) • Use-results survey in patients with unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy • Post-marketing studies (extension studies of Studies 05, 06, 08, 025, and 12)	• Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients

Underline denotes activities to be performed for the newly added indications; *, A compassionate use trial with Study 473 as a pivotal clinical trial

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indications and modified dosage and administration, as shown below, with the following approval 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 sufficient knowledge and experience in cancer chemotherapy, at medical institutions capable of emergency response. The re-examination period for the present applications for partial change is the remainder of the ongoing re-examination period (until October 16, 2021).

Indications (Underline denotes additions.)

1. Treatment of malignant melanoma
2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer
3. Treatment of unresectable or metastatic renal cell carcinoma

4. Treatment of relapsed or refractory classical Hodgkin lymphoma
5. Treatment of recurrent or metastatic head and neck cancer
6. Treatment of unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy
7. Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy
8. Treatment of unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy
9. Treatment of unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy

Dosage and Administration (Underline denotes additions.)

1. Treatment of malignant melanoma
   The usual adult dosage of nivolumab (genetical recombination) is 240 mg administered as an intravenous infusion every 2 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.
2. 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.
   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.
3. Treatment of unresectable, advanced or recurrent non-small cell lung cancer, 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 microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy, or 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.

Approval Conditions

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.)

Unresectable, advanced or recurrent non-small cell lung cancer

1. The efficacy and safety of Opdivo have not been established in chemotherapy-naïve patients.

Unresectable or metastatic renal cell carcinoma

2. The use of Opdivo for the treatment of chemotherapy-naïve patients should be limited to IMDC[Note)] intermediate- or poor-risk patients.

Recurrent or metastatic head and neck cancer

3. The efficacy and safety of Opdivo have not been established in platinum-based chemotherapy-naïve patients.

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

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

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

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

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

6. 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.
7. 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.
8. 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.

Unresectable, advanced or recurrent non-small cell lung cancer, unresectable or metastatic renal cell carcinoma, recurrent or metastatic head and neck cancer, unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, or unresectable, advanced or

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

9. The efficacy and safety of Opdivo in adjuvant ~~chemo~~therapy have not been established.

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

10. The efficacy and safety of Opdivo in adjuvant therapy have not been established.

Malignant melanoma, unresectable, advanced or recurrent non-small cell lung cancer, unresectable or metastatic renal cell carcinoma, relapsed or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, or unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy

11. Eligible patients must be selected after being thoroughly familiar with the efficacy and safety of Opdivo presented in the "Clinical Studies" section.

Note) International Metastatic RCC Database Consortium

Precautions Concerning Dosage and Administration (Underline denotes additions.)

All indications

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

Unresectable or metastatic renal cell carcinoma

2. 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.

Unresectable, advanced or recurrent non-small cell lung cancer, 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 microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy, or unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy

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

Malignant melanoma

4. 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.

Appendix

List of Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
bevacizumab	bevacizumab (genetical recombination)
BIRC	blinded independent review committee
CI	confidence interval
CPT-11	irinotecan hydrochloride hydrate
CR	complete response
dMMR	mismatch repair deficient
DOC	docetaxel hydrate
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
IC	investigator's choice
IDMC	Independent data monitoring committee
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
ipilimumab	ipilimumab (genetical recombination)
IRB	institutional review board
IRRC	independent radiology review committee
ITT	intention-to-treat
Japanese clinical practice guidelines (esophageal cancer)	Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus 2017, edited by the Japan Esophageal Society
Japanese clinical practice guidelines (large intestine carcinoma)	Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines for the treatment of colorectal cancer 2019
KRAS	Kirsten rat sarcoma viral oncogene homolog
L-OHP	oxaliplatin
MedDRA	Medical Dictionary for Regulatory Activities
MLH1	mutL homolog 1
MSH2	mutS homolog 2
MSH6	mutS homolog 6
MSI	microsatellite instability
MSI-High	microsatellite instability-high
NCCN guidelines (colon cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Colon Cancer

NCCN guidelines (esophageal and esophagogastric junction cancers)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Esophageal and Esophagogastric Junction Cancers
NCCN guidelines (rectal cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Rectal Cancer
NCI-PDQ	National Cancer Institute Physician Data Query
NE	not evaluable
nivolumab	nivolumab (genetical recombination)
nivolumab/ipilimumab	A combination of nivolumab and ipilimumab
OS	overall survival
Partial change application	application for partial change
PCR	polymerase chain reaction
PD	progressive disease
PD-L	programmed cell death-ligand
pembrolizumab	pembrolizumab (genetical recombination)
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PMS2	postmeiotic segregation increased 2
PR	partial response
PS	performance status
PT	preferred term
PTX	paclitaxel
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
Q4W	quaque 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
regorafenib	regorafenib hydrate
SD	stable disease
SOC	system organ class
Study 001	Study CA209001
Study 003	Study CA209003
Study 009	Study CA209009
Study 01	Study ONO-4358-01
Study 017	Study CA209017
Study 025	Study ONO-4538-03/CA209025
Study 032	Study CA209032
Study 037	Study CA209037
Study 05	Study ONO-4538-05

Study 057	Study CA209057
Study 06	Study ONO-4538-06
Study 066	Study CA209066
Study 07	Study ONO-4538-07
Study 08	Study ONO-4538-08
Study 12	Study ONO-4538-12
Study 141	Study ONO-4538-11/CA209141
Study 142	Study CA209142
Study 15	Study ONO-4538-15
Study 205	Study CA209205
Study 238	Study ONO-4538-21/CA209238
Study 24E	Study ONO-4538-24E
Study 275	Study CA209275
Study 39	Study ONO-4538-39
Study 41	Study ONO-4538-41
Study 473	Study ONO-4538-24/BMS CA209473